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Contrast Media

Safety Issues and ESUR Guidelines

Third Edition
Preface to the Third Edition

Within 30 months of the release of both the first and second editions of *Contrast Media: Safety Issues and ESUR Guidelines*, the book had sold out, even though more copies were printed than is usual for a radiology book, and at a time when electronic media have increasing impact. There have been changes in the field of contrast media since the second edition, mainly because of increased knowledge about current agents rather than because new agents have been introduced. We therefore decided to update the book and have a new edition, instead of reprinting the second edition.

All of the chapters have been updated where appropriate and new chapters have been added. The chapter on non-gadolinium-based contrast agents has been omitted because the manganese- and iron-based agents are currently not marketed. There is a new chapter on the hot topic of off-label use of contrast media. Previously a contrast medium was approved, for example, for intravenous administration for all applications, but now it must also be approved for use in different parts of the body, based on efficacy data. All the currently available agents are not approved for imaging all parts of the body. The radiologist must know whether the agent which is to be used is approved for the particular examination that is to be undertaken. If the agent is not approved, special informed consent must be obtained in some countries. Another new chapter deals with the use of contrast media in pediatrics. Off-label use is often necessary in pediatrics because contrast media are not usually evaluated in children. Also, when administering contrast media to children, it is important to allow for some of the physiological differences between children and adults. A chapter on measurement of the glomerular filtration rate (GFR) has been added. Nowadays, this is an important topic because GFR decides which gadolinium-based agent can be used and whether or not there should be volume expansion before iodine-based contrast media are given. The CKD-EPI equation seems to be the best option for estimating GFR. The chapter on *Contrast Media Classification and Terminology* has been updated with more physicochemical data for the various commercially available agents. The chapter on prevention of acute contrast medium reactions has been rewritten to include the concept that hypersensitivity to contrast media may be allergic or non-allergic, and the increasing recognition of the fact that mild symptoms may follow CT and MR scans even when no contrast medium is given. The importance of recording acute reactions correctly is stressed, so that patients who have mild symptoms not requiring medical treatment are not inappropriately denied contrast medium in future. The chapters on late adverse reactions, contrast-induced nephropathy and nephrogenic systemic fibrosis have been revised. The European Society of Urogenital Radiology Contrast Medium Safety Committee (ESUR CMSC) recently reviewed the literature on these three topics and published update papers in European Radiology based on its conclusions. The conclusions are included in this book, and references to the guideline papers are given in Official publications from the Contrast Medium Safety Committee of the European Society of Urogenital Radiology.
We are very grateful to all the contributors to the book: without their support the project would not have been possible. We are also grateful to our academic colleagues in the ESUR CMSC for their continued and invaluable participation in our many debates and discussions. We thank Prof. Albert Baert and Prof. Maximilian Reiser as well as Corinna Schaefer and her colleagues at Springer Verlag, for supporting the book, which we hope will be an important source of reference on contrast media for all radiologists.

And finally, Henrik again thanks his wife Pia for her continuous support of this project since it started in 1996.

Herlev, Denmark
London, UK

Henrik S. Thomsen
Judith A. W. Webb
Preface to the Second Edition

A new edition of *Contrast Media: Safety Issues and ESUR Guidelines* has become necessary relatively soon after the first edition. Unusually for a book on contrast media (CM), the first edition sold out in 30 months. Since the first edition, nephrogenic systemic fibrosis, a serious adverse reaction after some of the gadolinium-based contrast agents, has been recognised, and this has necessitated a reappraisal of these agents.

This second, fully revised edition continues to provide a unique and invaluable source of information on the safety issues relating to CM. It contains a number of completely new chapters, for example, on gadolinium-based CM, meta-analyses in CM research and various regulatory issues. Comprehensive consideration is given to the many different safety issues relating to iodine-based, MR, barium and ultrasound CM. There are chapters on both acute and delayed non-renal adverse reactions and on renal adverse reactions. All the questions that commonly arise in radiological practice are addressed, and the latest version of the well-known European Society of Urogenital Radiology guidelines on CM is included. We hope that all radiologists will find this book helpful in their everyday practice.

We are very grateful to our academic colleagues in the European Society of Urogenital Radiology Contrast Medium Safety Committee for their invaluable help. They deserve thanks for their continuing involvement in our many debates and discussions. We also thank Prof. Albert L. Baert, as well as Ursula N. Davis and her colleagues at Springer Verlag, for their continuous support of this book.

Finally, Henrik thanks his wife, Pia, for endorsing this project again and again.

Herlev, Denmark

London, UK

Henrik S. Thomsen

Judith A. W. Webb
Preface to the First Edition

The European Society of Urogenital Radiology established its Contrast Media Safety Committee in 1994. Over the years, it has consisted of between 12 and 14 members, the majority of whom are experts in the field of contrast media research. There is currently one member from the scientific section of each of the pharmaceutical companies producing contrast agents (Bracco, Italy; GE Healthcare Diagnostics, USA; Guerbet, France; Schering, Germany). Although the members of the committee have diverse views, the Contrast Media Safety Committee works as one group for the good of patients. The committee benefits from the wealth of knowledge on contrast agents brought to it by the representatives of the pharmaceutical companies. However, the rules of the Contrast Media Safety Committee forbid any commercial promotion and the committee deals with all types of contrast agents based purely on objective analysis, sound scientific data, well-documented clinical experience and clinical common sense. Disagreement within the committee is discussed rationally and without commercial influence. All contrast media are referred to by their generic names, except when the generic name is confusing (e.g. ultrasound contrast agents). After 11 years of work, the committee has covered all the topics of clinical importance regarding the safe use of contrast media. The current book is mainly a collection of this work together with a few new chapters. The chapters have been prepared by the individual authors based on their original papers (see Appendix) when applicable and an up to date review of the literature. Some chapters are new and have never been published as papers by the committee. The chapters have not been circulated among or discussed by the members of the committee and have been edited by myself. In the appendix, the latest version of the ESUR guidelines agreed at the meeting of the committee in Copenhagen, February 2005, is presented. The ESUR guidelines have been well received by the radiological community. They are frequently cited in the literature. They have been incorporated into the protocols of many departments all over the world. They are also used by the health authorities in many countries as a reference for good radiological practice. Several of the guidelines have been translated into languages other than English, for example Spanish, Russian and Japanese.

I am sure the readers will agree that this book offers an invaluable, unique, practical and unparalleled resource dealing with safety issues related to radiographic, MR and ultrasound contrast media, and that it will ultimately benefit patients.

It has been a great honor for me to serve as chairman of this prestigious committee for 9 years. Special mention goes to the secretary of committee, Dr. Sameh Morcos, whose close cooperation has always been highly productive and inspirational. Without his energy and enthusiasm, we would never have accomplished what we have. Also, the past and current members of the committee deserve sincere thanks for their continuing involvement and for the outstanding discussions at the annual committee meeting.

Despite disagreements, we have always reached a consensus. A special thank you goes to Dr. Judith Webb, who has not only participated actively in our work but has also ensured that our manuscripts were published in correct English. Dr. Webb has revised
the English throughout this book and I am most grateful for her outstanding and continuous support.

We also thank Prof. Albert L. Baert, Editor-in-Chief of European Radiology and Editor-in-Chief of this book series, as well as Springer-Verlag for their immediate endorsement and support of the book.

Finally, I wish to thank my family, especially my wife Pia, for allowing me to invest so many hours of family time in this project.

Herlev, Denmark

Henrik S. Thomsen
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Part I
General Issues
Abstract

Current radiological imaging uses either electromagnetic radiation (X-rays or radiowaves) or ultrasound. Contrast agents may be used with all of these imaging techniques to enhance the differences seen between the body tissues on the images. This chapter deals with the classification of contrast agents and the terminology used to describe them.

1 Introduction

Current radiological imaging uses either electromagnetic radiation (X-rays or radiowaves) or ultrasound. X-rays have a frequency and photon energy several powers higher than that of visible light and can penetrate the body. The radiation that emerges from the body is detected either by analogue radiological film or by a variety of digital media (Thomsen et al. 2014). The radiowaves used in magnetic resonance imaging have a frequency and photon energy several powers lower than that of visible light. The radiowaves cause deflection of protons in the body, which have aligned in the magnetic field in the scanner, and as the protons relax back to their resting position, they emit radiowaves, which are used to generate the image (Thomsen et al. 2014). Ultrasound imaging uses sound (pressure) waves several powers higher than audible sound, which are reflected back from tissue interfaces in the body to generate the image (Dawson et al. 1999; Thomsen et al. 1999).

Contrast agents may be used with all of these imaging techniques to enhance the differences seen between the body tissues on the images. Contrast agents alter the response of the tissues to the applied electromagnetic or ultrasound energy by a variety of mechanisms (Dawson et al. 1999; Thomsen et al. 1999). The ideal contrast agent would achieve a very high concentration in the tissues...
without producing any adverse effect, but this has not yet been achieved and all contrast agents have adverse effects (Dawson et al. 1999; Thomsen et al. 1999, 2014). This chapter deals with the classification of contrast agents and the terminology used to describe them.

2 Radiographic Contrast Agents

Radiographic contrast media are divided into positive and negative contrast agents. The positive contrast media attenuate X-rays more than do the body soft tissues and can be divided into water-soluble iodine-based agents and non-water-soluble barium agents. Negative contrast media attenuate X-rays less than do the body soft tissues. No negative contrast agents are commercially available.

2.1 Iodine-Based Contrast Agents

Water-soluble iodine-based contrast agents that diffuse throughout the extracellular space are principally used during computed tomography (CT), angiography and other conventional radiography. They can also be administered directly into the body cavities, for example the gastrointestinal tract and the urinary tract.

All these contrast agents are based on a benzene ring to which three iodine atoms are attached. A monomer contains one tri-iodinated benzene ring and a dimer contains two tri-iodinated benzene rings (Fig. 1).

Iodine-based contrast agents can be divided into two groups, ionic and non-ionic, based on their water solubility (Dawson et al. 1999; Thomsen et al. 1999). The water in the body is polarized unevenly with positive poles around the
hydrogen atoms and negative poles around oxygen atoms. Ionic contrast agents are water soluble because they dissociate into negative and positive ions, which attract the negative and positive poles of the water molecules. Non-ionic contrast agents do not dissociate and are rendered water soluble by their polar OH groups. Electrical poles in the contrast medium OH groups are attracted to the electrical poles in the water molecules.

The osmolality of contrast agents affects the incidence of side-effects, particularly above 800 mosm kg\(^{-1}\). The early contrast media had very high osmolalities (1,500–2,000 mosm kg\(^{-1}\) and subsequently agents of lower osmolality have been developed (Fig. 2). Contrast agents may be divided into high-, low- and iso-osmolar agents (Table 1). An
indication of the osmolality of an agent is given by the contrast agent ratio, which is derived by dividing the number of iodine atoms in solution by the number of particles in solution:

\[
\text{Contrast agent ratio} = \frac{\text{Number of iodine atoms}}{\text{Number of particles in solution}}
\]

The higher osmolality agents have more particles per iodine atom and therefore have lower ratios. Thus, the ionic monomers have a ratio of 1.5 (three iodine atoms per two particles in solution), the non-ionic monomers and the ionic dimers have a ratio of 3 (three iodine atoms per particle in solution), and the non-ionic dimers have a ratio of 6 (six iodine atoms per particle in solution) (Fig. 3). The non-ionic dimers are iso-osmolar with blood (300 mosm kg\(^{-1}\)) at all concentrations.

Viscosities are a function of solution concentration, molecular shape, and weak interactions among the contrast agents and water molecules, including contrast media self-association. The move from ionic to non-ionic agents actually increased viscosity while decreasing osmolality and toxicity (Fig. 4). The new dimers continue this trend.

**Table 1** Iodine-based contrast agents: Ionicity, class, trade name and maximum g-Iodine/ml

<table>
<thead>
<tr>
<th>Contrast agent</th>
<th>Trade name</th>
<th>Structure</th>
<th>Charge</th>
<th>Class</th>
<th>Maximum g–Iodine/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diatrizoate</td>
<td>Renografin, Hypaque</td>
<td>Monomer</td>
<td>Ionic</td>
<td>HOCM</td>
<td>358–370</td>
</tr>
<tr>
<td>Amidotrizoate</td>
<td>Urografin</td>
<td>Monomer</td>
<td>Ionic</td>
<td>HOCM</td>
<td>300</td>
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<tr>
<td>Iothalamate</td>
<td>Conray</td>
<td>Monomer</td>
<td>Ionic</td>
<td>HOCM</td>
<td>370</td>
</tr>
<tr>
<td>Ioxithalamate</td>
<td>Telebrix</td>
<td>Monomer</td>
<td>Ionic</td>
<td>HOCM</td>
<td>350</td>
</tr>
<tr>
<td>Ioxaglate</td>
<td>Hexabrix</td>
<td>Dimer</td>
<td>Ionic</td>
<td>LOCM</td>
<td>320</td>
</tr>
<tr>
<td>Iopamidol</td>
<td>Iopamiro, Iovue</td>
<td>Monomer</td>
<td>Non–Ionic</td>
<td>LOCM</td>
<td>370</td>
</tr>
<tr>
<td>Iohexol</td>
<td>Omnipaque</td>
<td>Monomer</td>
<td>Non–Ionic</td>
<td>LOCM</td>
<td>350</td>
</tr>
<tr>
<td>Iomeprol</td>
<td>Iomeron, Imeron</td>
<td>Monomer</td>
<td>Non–Ionic</td>
<td>LOCM</td>
<td>400</td>
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<td>Iopentol</td>
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<td>LOCM</td>
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<td>Ioversol</td>
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<td>Iopromide</td>
<td>Ultravist</td>
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<td>Iotrolan</td>
<td>Isovist</td>
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<td>Iodixanol</td>
<td>Visipaque</td>
<td>Dimer</td>
<td>Non–Ionic</td>
<td>IOCM</td>
<td>320</td>
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</tbody>
</table>

HOCM High-osmolar contrast media, LOCM Low-osmolar contrast media, IOCM Iso-osmolar contrast media

**Fig. 2** Osmolality (mOsmol/kg) of iodine-based contrast media at a concentration around 300 mg/l/ml
**Fig. 3** Classification of iodine-based contrast agents

<table>
<thead>
<tr>
<th>FORMULA</th>
<th>MOLECULE</th>
<th>IODINE/MOL</th>
<th>CLASS</th>
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<tr>
<td>dimer</td>
<td><img src="image" alt="Dimer Structure" /></td>
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<tr>
<td>monomer</td>
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<tr>
<td>dimer</td>
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<td>monomer</td>
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**Fig. 4** Viscosity (mPa.s) of iodine-based contrast media at a concentration around 300 mg/l in ml⁻¹ and at 37 °C
2.2 Barium Contrast Agents

Barium sulphate preparations used to visualize the gastrointestinal tract consist of a suspension of insoluble barium sulphate particles, which is not absorbed from the gut. Differences between the different commercially available agents are very minor and relate to the additives in the different barium sulphate preparations.

3 MR Contrast Agents

Magnetic resonance (MR) imaging contrast agents contain paramagnetic or superparamagnetic metal ions, which affect the MR signal properties of the surrounding tissues. They are used to enhance contrast, to characterize lesions and to evaluate perfusion and flow-related abnormalities. They can also provide functional and morphological information.

Paramagnetic contrast agents are mainly positive enhancers that reduce T1 and T2 relaxation times and increase signal intensity on T1 weighted MR images (Thomsen et al. 2014). In most paramagnetic agents, the active constituent is gadolinium, a paramagnetic metal in the lanthanide series, which has a high magnetic moment and a relatively slow electronic relaxation time. Another paramagnetic ion is manganese, which has similar relaxivity properties to gadolinium, but, unlike gadolinium, occurs naturally in the body. It is one of the least toxic metal ions and is excreted by the hepatobiliary system. Agents containing manganese are no longer commercially available.

Superparamagnetic agents are extremely effective T2 relaxation agents, which produce signal loss on T2 and T2*-weighted images. They also have a T1 effect, which is substantially less than their T2 effect. However, superparamagnetic agents are no longer commercially available. Iron was used as the active ion in many agents. The iron agents were metabolized by the macrophages and the iron entered the body iron pool.

3.1 Gadolinium-Based Contrast Agents

In all paramagnetic agents which are given intravascularly, the gadolinium ion is bound to a ligand in a chelate to minimize its toxicity. Gadolinium is a heavy metal, which in its free form is very toxic and may cause liver necrosis, hematological changes etc. A human being would not survive 0.1 mmol kg⁻¹ free gadolinium injected into the circulation.

Gadolinium contrast agents may be considered in two categories: (1) non-specific extracellular gadolinium chelates (Fig. 5) and (2) high relaxivity agents/organ specific agents/protein bound agents (Fig. 6). The non-specific extra-cellular gadolinium chelates do not bind to protein and are excreted by the kidney only, while the high relaxivity agents show protein binding and are excreted to a varying extent through the bile as well as by the kidney. Nine gadolinium-based contrast agents are currently commercially available (Table 2).

Gadolinium-based agents are also classified by the chemical structure of the ligand to which the gadolinium is bound (Dawson et al. 1999; Thomsen et al. 1999, 2013). The ligands are either linear or cyclic, and may be ionic, which have a charge in solution, or non-ionic (Figs. 5 and 6). Their osmolality varies between 600 and 2,000 mosmol kg⁻¹ (Fig. 7). Unlike iodine-based contrast agents, high osmolality gadolinium-based agents do not cause more acute non-renal adverse reactions and discomfort than low osmolality agents. This is probably because the molar amounts of gadolinium-based agents used for the MR examinations are significantly less than the molar amounts of iodine-based agents used for radiography.

The stability of gadolinium contrast agents depends on their kinetic, thermodynamic and conditional stability (“Gadolinium Chelates and Stability”). Although these parameters do not directly relate to molecular structure, the contrast agents with cyclic ligands, in which gadolinium is caged in a preorganised cavity, are more stable than those with linear ligands.

The relaxivity \( r_1 \) of the extracellular gadolinium-based agents is almost identical at both 1.5 and 3T, since the change in field strength does not affect the relaxivity (Fig. 8). Protein binding increases the relaxivity of gadolinium-based agents, particularly at 1.5T.

Extracellular non-specific gadolinium-based contrast agents are given by bolus injection, and their biodistribution and pharmacokinetics are similar to those of iodine-based radiographic contrast agents. High relaxivity gadolinium-based contrast agents behave similarly to the extracellular non-specific agents immediately after intravascular injection. However, because of their protein binding and biliary excretion, their pharmacokinetics differ and the later liver uptake phase may be used for liver imaging. Of the available high relaxivity agents, gadobenate is mainly used as an extracellular agent, gadofosveset was specifically designed for MR angiography, and gadoxidate, which has the greatest biliary excretion, is mainly used for liver imaging.
**Fig. 5** Extracellular gadolinium-based contrast agents

<table>
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<tr>
<th>Chelate</th>
<th>Acyclic or linear</th>
<th>Cyclic</th>
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<tr>
<td>Ionic</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Gadopentetate dimeglumine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gadoterate</td>
<td></td>
</tr>
<tr>
<td>Non-ionic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gadodiamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gadoversetamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gadoteridol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gadobutrol</td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 6** High-relaxivity gadolinium-based contrast agents—all are ionic linear agents

Gadobenate dimeglumine  
Gadoxetate disodium  
Gadofosveset
Table 2 Gadolinium-based agents: brand names and characteristics (organ specific or extracellular, protein binding, biliary excretion)

<table>
<thead>
<tr>
<th>Name</th>
<th>Brand name</th>
<th>Organ specific</th>
<th>Extra-cellular</th>
<th>Hepato-biliary excretion</th>
<th>Protein-binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadodiamide</td>
<td>Omniscan</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Gadoversetamide</td>
<td>Optimark</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Gadopentetate dimeglumine</td>
<td>Magnevist</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Gadobenate dimeglumine</td>
<td>Multihance</td>
<td>Yes (Liver)</td>
<td>Mainly</td>
<td>Yes (1–4 %)</td>
<td>Yes (4 %)</td>
</tr>
<tr>
<td>Gadoxetate disodium</td>
<td>Primovist, Eovist</td>
<td>Yes (Liver)</td>
<td>No</td>
<td>Yes (42–51 %)</td>
<td>Yes (10 %)</td>
</tr>
<tr>
<td>Gadofosveset trisodium</td>
<td>Vasovist, Ablavar</td>
<td>Yes (Blood)</td>
<td>No</td>
<td>Yes (5 %)</td>
<td>Yes (90 %)</td>
</tr>
<tr>
<td>Gadobutrol</td>
<td>Gadovist, Gadavist</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Gadoteridol</td>
<td>Prohance</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Gadoterate meglumine</td>
<td>Dotarem, Magnescope</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Fig. 7 Osmolality (mOsmol/kg) of the gadolinium-based contrast media at their marketed concentrations (mmol/ml)

Fig. 8 Relaxivity ($r_1$, mM$^{-1}$s$^{-1}$) of gadolinium-based contrast media in plasma in 1.5 and 3T (37 °C)
4 Ultrasound Contrast Agents

Ultrasound contrast agents have previously been given the acronym USCA. In their 2012 Guidelines on contrast enhanced ultrasound, the European Federation of Societies for Ultrasound in Medicine and Biology uses the abbreviation UCA, which consequently will be used here (Claudon et al. 2012).

UCA are blood-pool agents, which produce their effect by increased back-scattering of sound compared to that from blood, other fluids, and most tissues. On grey-scale images, microbubble contrast agents change grey and dark areas to a brighter tone when the contrast medium enters in fluid or blood. The spectral Doppler intensity is also increased, with a brighter spectral waveform displayed and a stronger sound heard. Using color Doppler technique, ultrasound contrast agents enhance the frequency or the power intensity, giving rise to stronger color encoding. The level of enhancement of the Doppler signals may be in the order of up to 30 dB.

Ultrasound contrast agents can be used to enhance Doppler signals from most main arteries and veins. Specific UCA techniques have been developed and are widely available. These include second harmonic imaging, pulse inversion imaging and temporal maximum intensity projection technique (Wilson and Burns 2010).

UCA may be useful for imaging solid organs, e.g. liver, kidney, breast, prostate and uterus. They can also be used to enhance cavities, e.g. bladder, ureters, Fallopian tubes and abscesses.

4.1 Classification

Ultrasound contrast agents can be divided into five different classes: (1) Nonencapsulated gas microbubbles (e.g. agitated or sonicated), (2) stabilized gas microbubbles (e.g. with sugar particles), (3) encapsulated gas microbubbles (e.g. by protein, liposomes or in polymers), (4) microparticle suspensions or emulsions [perfluorooctyl bromide (PFOB), phase-shift], and (5) gastrointestinal (for ingestion). Products from all classes are not commercially available.

Ultrasound contrast agents can also be classified based on their pharmacokinetic properties and efficacy: (1) non-transpulmonary UCAs, which do not pass the capillary bed of the lungs following a peripheral intravenous injection, show on B-mode only in the right ventricle and have a short duration effect, (2) transpulmonary blood pool UCAs with a short half-life (<5 min after an intravenous bolus injection), which produce low signals using harmonic imaging at low acoustic power, (3) transpulmonary blood pool UCAs with a longer half-life (>5 min after an intravenous bolus injection), which produce high signals using harmonic imaging at low acoustic power, (4) transpulmonary UCAs with a specific liver and spleen phase, which can be short- or long-lived. They lodge in the small vessels of the liver or spleen, or are taken up by either the reticulo-endothelial system or by the hepatocytes (Dawson et al. 1999; Thomsen et al. 1999).

Agents that are currently available commercially are listed in Table 3.

Table 3 Some ultrasound contrast agents

<table>
<thead>
<tr>
<th>Product name</th>
<th>Constituents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definity™ (Luminity®)</td>
<td>Fluorocarbon gas in liposomes</td>
</tr>
<tr>
<td>SonoVue® (BR1)</td>
<td>Sulphur hexafluoride gas in polymer with phospholipid</td>
</tr>
<tr>
<td>Optison™ (FS069)</td>
<td>Octafluoropropane-filled albumin microspheres</td>
</tr>
<tr>
<td>Sonazoid™ (NC100100)</td>
<td>Perfluorinated gas-containing microbubbles</td>
</tr>
</tbody>
</table>

References

Thomsen HS, Muller RN, Mattrey RF (1999) Trends in contrast media. Springer, Heidelberg
Requests for Imaging Using Contrast Media: What Information Must be Provided
Sameh K. Morcos and Marie-France Bellin

Abstract
A questionnaire is proposed for any imaging examination requiring contrast agent administration. Information about important risk factors is essential and drug history is also important because of possible interactions between contrast agents and other drugs. This information should be available before the appointment, so that prophylactic measures can be planned or an alternative imaging technique not requiring contrast agent administration can be advised.

1 Introduction

There are potential risks associated with the administration of contrast agents and adverse reactions may occur. In addition, contrast agents may interact with some of the drugs and clinical tests used in the management of patients (Morcos and Thomsen 2001; Morcos et al. 2001, 2005; Morcos 2005a, b; Thomsen 2006). Although most serious reactions are observed after intravascular injection, adverse effects may also develop after oral or intra-cavitary administration, because some of the contrast medium molecules may be absorbed into the circulation (Morcos 2005). Reactions to contrast agents can be divided into non-renal and renal adverse reactions. Non-renal reactions may be acute (developing within 1 h of contrast agent administration) or delayed (developing after 1 h but less than a week) (Morcos and Thomsen 2001). Some reactions, such as thyrotoxicosis and nephrogenic systemic fibrosis, may occur after 1 week and are termed very late reactions. Patients at high risk of these reactions should be identified before contrast medium administration to ensure that all necessary measures are taken to reduce the risk.
2 Iodine-Based Contrast Media

2.1 Risk Factors for Acute Non-Renal Adverse Reactions

There is a 6-fold increase in incidence of severe reactions to both ionic and non-ionic contrast agents in patients with a history of previous severe adverse reaction to contrast agents. Asthma is also an important risk factor with a reported 6- to 10-fold increase in the risk of a severe reaction in such patients. Patients with a strong history of allergic reactions to different substances including those with a history of troublesome hay fever are also at risk (Morcos 2005a).

2.2 Risk Factors for Delayed Skin Reactions

A previous reaction to contrast medium is an important predisposing factor, increasing the risk of reaction by a factor of 1.7–3.3. A history of drug or contact allergy is a further risk factor, increasing the likelihood of a reaction by approximately a factor of two (“Late Adverse Reactions to Iodine-Based Contrast Media”). There is an increased incidence of delayed skin reactions to contrast agents in patients who have received non-ionic dimers or interleukin-2 (IL-2) (Webb et al. 2003; Morcos et al. 2005).

2.3 Risk Factors for Contrast Medium-Induced Nephropathy

Pre-existing renal impairment, indicated by serum creatinine >130 μmol l⁻¹ or preferably by an eGFR <60 ml min⁻¹ 1.73 m⁻², calculated using the Modification of Diet in Renal Disease (MDRD) study equation (Bostom et al. 2002), is an important risk factor for contrast medium-induced nephropathy (CIN). The risk of CIN is greater if renal impairment is associated with diabetes mellitus. The degree of renal insufficiency is a major determinant of the severity of CIN (Thomsen 2006). An eGFR of 30 ml min⁻¹ 1.73 m⁻² or less markedly increases the incidence and severity of CIN (McCullough et al. 1997; Morcos et al. 1999). Other risk factors include dehydration, congestive cardiac failure, concurrent use of nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs (NSAID) and aminoglycosides, hypertension, hyperuricemia, or proteinuria (McCullough et al. 1997; Morcos et al. 1999; Morcos 2004, 2005b).

Since pre-existing renal impairment is a critical risk factor for CIN, it is important to know the renal function before contrast agents are given, as precautions must be taken in patients with renal insufficiency. Measurement of serum creatinine is widely used for this purpose, but has several limitations for accurate assessment of renal function (Morcos 2005b; Thomsen et al. 2005). eGFR is a better test when serum creatinine is abnormal, but is not perfect as all the equations used to calculate it overestimate renal function to varying degrees.

2.4 Risk Associated with Concomitant Medications

Although contrast agents are not highly active pharmacologically, interaction with other drugs may occur with possible serious consequences to the patient (“Contrast Medium-Induced Nephropathy”, “Contrast Media and Interactions with Other Drugs and Clinical Tests”). This is an important topic which should be included in a questionnaire.

2.5 Patients with Thyroid Disease

Radiographic water-soluble iodine-based contrast media solutions contain small amounts of free iodide, which may cause thyrotoxic crisis in patients with Graves’ disease or with multinodular goiter and thyroid autonomy, especially if they are elderly and living in areas of iodine deficiency. Patients at risk of thyrotoxicosis should be closely monitored by endocrinologists after iodine-based contrast medium injection. Prophylaxis is generally not necessary, but in high-risk patients, particularly those in areas of dietary iodine deficiency, prophylactic treatment may be given by an endocrinologist (“Effects of Iodine-Based Contrast Media on Thyroid Function”).

3 MRI Contrast Agents

MR contrast agents include extracellular and organ-specific agents. All current agents for intravascular use are based on gadolinium.

3.1 Non-organ-specific Extracellular MRI Contrast Agents

Most adverse reactions to extracellular agents are mild and transient. Risk factors for acute reactions include a history of allergy, bronchial asthma, or previous reaction to gadolinium-based contrast media (Niendorf et al. 1993; Shellock and Kanal 1999).

CIN is rare with doses not exceeding 0.3 mmol kg body weight⁻¹ (Sam et al. 2003; Thomsen 2004; Briguori et al. 2006; Ergün et al. 2006; Zhang et al. 2006). However, patients with pre-existing severe renal impairment may be
at risk of CIN after administration of extracellular non-organ-specific gadolinium-based contrast media (Ergün et al. 2006). High doses of gadolinium agents used for X-ray procedures have a significant risk of inducing nephrotoxicity (Thomsen et al. 2002).

Nephrogenic systemic fibrosis has been reported in patients on dialysis or with a glomerular filtration below 30 ml min⁻¹, following administration of lower stability gadolinium-based contrast agents (“Nephrogenic Systemic Fibrosis and Gadolinium-Based Contrast Media”).

### 3.2 Organ-Specific MR Contrast Agents

The current MR organ-specific contrast agents are also gadolinium-based agents. Blood pool agents and liver-specific agents based on either iron or manganese are currently not commercially available. For the gadolinium-based blood pool agent and the liver-specific agents, the adverse reactions are the same as those seen after administration of the extracellular gadolinium-based agents (Bellin et al. 2005). Serious adverse reactions are rare. No specific risk factors have been identified for these reactions.

### 4 Discussion

Of all the potential adverse reactions to contrast agents, those which are most likely to have serious sequelae are severe anaphylactoid reactions and CIN. Also, patients with thyroid disease, particularly elderly patients living in regions with iodine deficiency, can be adversely affected by contrast media. In addition, it is important to be aware of the patient’s drug history as there is the possibility of interaction between contrast agents and other drugs.

It is proposed that the request for an imaging test which involves contrast agent administration should provide information about the important risk factors for the potential complications of giving the contrast agent. This information must be readily available before contrast agent administration, so that prophylactic measures can be planned, or an alternative imaging technique not requiring contrast agent administration can be advised. Some of the prophylactic measures, such as hydration or steroid prophylaxis, require time to produce the desired pharmacological effect. In emergency situations, the radiologist should try to obtain as much of this information as possible before contrast agent administration and should then, depending on the clinical problem under investigation, make a judgment of benefit against risk.

Demanding extensive information with the request is not practical and may not receive the cooperation of referring clinicians, and a questionnaire should therefore focus on important risk factors for serious complications that are most likely to be encountered in clinical practice. The ESUR contrast agent questionnaire offers a practical approach for identifying patients at high risk of contrast agent reactions without omitting important risk factors or being excessively demanding to use routinely. It should be considered as a supplement to the standard referral for imaging examinations, and the completed questionnaire should be sent with the request to the Imaging Department for any further action. The ESUR questionnaire can be found in “ESUR Guidelines on Contrast Media Version 8.1”.

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Off-Label Use of Medicines: Legal Aspects

June M. Raine

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2 Definition of a Medicine .................................................. 18
3 The European Regulatory System ....................................... 18
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Abstract

The use of medicines, including contrast media, outside the terms of a marketing authorization is acceptable within European legislation, subject to provisos. This takes account of the limited access to appropriately authorized medicines for certain patient populations and therapeutic areas, in particular medicines for use in children. The physician who prescribes an unlicensed or off-label medicine should be satisfied that such use reflects a favorable benefit–risk balance according to the scientific evidence, current clinical opinion and guidance. Prescribers should provide patients with appropriate information and explanation, and should report any suspected adverse reactions associated with unlicensed and off-label use to the national authority responsible for drug safety monitoring.

1 Introduction

In Europe, subject to certain exemptions explained below, no medicine can be marketed for human use without a Marketing Authorization granted either by a Member State competent authority or by the European Commission. The regulatory system exists to protect patients by ensuring that marketed medicines meet acceptable standards of safety, quality, and efficacy in their indications. Nonetheless, for a range of reasons use of medicines outside their authorized indications, commonly known as off-label use, and use of unlicensed medicines (i.e., medicines without a marketing authorization) are common. This chapter outlines the definition of a medicine and the current regulatory framework; reviews the legal position of prescribers of off-label use and the use of unlicensed medicines; considers special populations and therapeutic areas where off-label use or the use of unlicensed medicines is common; and provides some
general guidance for prescribers considering off-label use or the use of unlicensed medicines.

2 Definition of a Medicine

As diagnostic agents, contrast media fall within the definition of a medicine in European law, since the definition includes:

Any substance or combination of substances which may be used in or administered to human beings … with a view to … making a medical diagnosis.

The legislation also encompasses radiopharmaceuticals:

Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.

Marketing authorization is required for radionuclide generators, kits, radionuclide precursor radiopharmaceuticals, and industrially prepared radiopharmaceuticals. A marketing authorization is not required for a radiopharmaceutical prepared at the time of use by a person or by an establishment authorized, according to national legislation, to use such medicinal products in an approved health care establishment exclusively from authorized radionuclide generators, kits or radionuclide precursors in accordance with the manufacturer’s instructions.

European medicines legislation does not apply to the following:

• Medicines prepared in a pharmacy in accordance with a medical prescription for an individual patient (the “magistral formula”).
• Medicines prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and intended to be supplied directly to the patients served by the pharmacy (the “officinal formula”).
• Medicines for research and development trials [covered by the Directive 2001/20/EC on good clinical practice in the conduct of clinical trials for human use (“the Clinical Trials Directive”)].
• Intermediate products intended for further processing by an authorized manufacturer.
• Any radionuclides in the form of sealed sources.

3 The European Regulatory System

The European regulatory system governing the marketing of medicines for human use is set out in Directive 2001/83/EC as amended, Regulation (EC) No.726/2004 and associated legislation. The Regulation lays down Community procedures for the authorization, supervision and pharmacovigilance of medicines, establishes a European Medicines Agency, and sets up a scientific committee attached to the Agency, the Committee for Human Medicinal Products. It makes provision for medicines to be approved by the European Commission via centralized authorizations valid in all member states.

The centralized procedure must be used for certain specified categories of medicines and can also be used for medicines which contain a new active substance or which constitute a significant therapeutic, scientific, or technical innovation. It is therefore unsurprising that a number of new diagnostic imaging agents have been authorized by the centralized route. The Directive sets in place decentralized and mutual recognition systems, enabling authorizations to be granted nationally by Member States. For the foreseeable future, depending on the route by which a medicine has been authorized, differences may exist in Europe between Member States’ authorizations for the same product, and in availability of medicines. The result is that use may be within an authorization in one country and off label in another.

The terms in which a marketing authorization is granted are specified in the Summary of Product Characteristics (SPC), with which all advertising must comply. The SPC contains detailed provisions covering indications, recommended dosage, contra-indications, special warnings and precautions, and adverse effects associated with the medicine. Copies of SPCs are available from the marketing authorization holder, from the European Medicines Agency and from Member State competent authorities. The SPC also forms the basis for the Patient Information Leaflet (PIL) which accompanies the medicine and is written in terms which are understandable by patients. Clearly, a medicine which is unlicensed will not have an SPC or PIL. Marketing authorization holders are required to keep their authorizations up to date as new information accrues in clinical use, and there is naturally a particular focus on safety data. New evidence on efficacy may not be so readily identified and manufacturers may legitimately decline to market a medicine for a purpose they do not wish to support.

4 Definition of Off-Label Use

The term “off-label use” applies to prescribing or administration outside any of the terms of the marketing authorization, generally in relation to indications, dosage, or contra-indications. The expression relates to a term used in the US authorization process: the Food and Drug Administration (FDA) approves product labeling. A medicine which is prescribed off label will be accompanied by information which may not be consistent with its off-label
use, creating the potential for concern or confusion on the part of the patient, parent, or carer.

In the light of the regulatory framework, there are a number of situations where off-label use or the use of unlicensed medicines occurs:
- Products for which a marketing authorization application or variation has yet to be made. These include drugs in development and undergoing clinical trials.
- Medicines for which a marketing authorization application or variation has been refused.
- Medicines which no longer have a relevant marketing authorization because it has been suspended, revoked, not renewed, or compulsorily varied.
- Products prepared in formulations specially adapted to special populations such as lower strengths for children or liquids for the elderly, or without particular excipients for patients allergic to them.

The use of unlicensed medicines, and off-label use, may also occur in clinical trials; i.e., where use of the drug for a particular indication is still under development. The use of such medicines is subject to the provisions of the Clinical Trials Directive and is not dealt with in this chapter.

5 Special Populations and Special Therapeutic Areas

Off-label prescribing of medicines, and the prescribing of unlicensed medicines, is common in the areas of oncology, obstetrics, and infectious disease in particular in HIV/AIDS and is particularly common in the pediatric population. Hospital-based studies have shown that many drugs used in children are either not licensed or are prescribed off label. On general pediatric surgical and medical wards, 36% of children received at least one drug that was unlicensed or off-label during their in-patient stay. In pediatric intensive care, this figure was 70% and in neonatal intensive care 90%. A study of children’s wards in five European countries found almost half of all prescriptions were either unlicensed or off label. This is consistent with the UK licensing position on contrast media—of around 90 licensed products; about 50% are indicated in children.

This situation has resulted from practical, ethical, and commercial considerations relating to conducting clinical trials in children. There are difficulties in developing formulations appropriate for children, and funding for research into the pediatric use of established medicines has been lacking. Following initiatives taken by the FDA in 1997 and 1999 to create incentives and obligations to conduct trials in children, the position is changing.

Drawing on the experience of the US legislation, in 2007, Paediatric Regulation ((EC) No 1901/2006) came into force in Europe which established a system of incentives and requirements to improve the availability of licensed medicines for children. In order to generate data to support a pediatric indication, companies must submit a drug development plan known as a Pediatric Investigation Plan for agreement by the European Medicines Agency’s Pediatric Committee. The Committee may ask for long-term safety measures, for example in relation to a contrast agent being studied in very young children, as the renal system is not yet mature in the age subset from birth to less than 2 years of age. The decisions of the Pediatric Committee are published on the Agency website. Importantly, the European Regulation also contains provisions for research funding, improved information on the use of medicines in children and publication of information from clinical trials in children.

6 Legal Position of the Prescriber

The regulatory system aims to control the activities of pharmaceutical companies manufacturing, selling, or supplying medicines. It is not intended to impact on the practice of medicine. European legislation does not require Member States to prohibit the prescription or administration of medicines outside their authorized indications. Medicines prescribed outside the terms of the marketing authorization may be dispensed by pharmacists and administered by nurses or midwives. In addition, the legislation contains a specific exemption which enables Member States to permit the supply of unlicensed medicines for individual patients on the order of their doctor—Article 5 of Directive 2001/83/EC provides that: “A Member State may, in accordance with the legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorized health-care professional and for use by an individual patient under his direct personal responsibility”.

This provision is the basis for what is referred to as the “specials” regime. The exemption helps preserve clinical freedom to act in what is judged to be in the best interests of the individual patient.

The way in which European legislation is framed means that doctors can:
- Prescribe medicines off label.
- Prescribe unlicensed products for individual patients, either under the “specials” regime (i.e., when no suitable licensed alternative is available) or where they are specially prepared in a pharmacy.
- Supply another doctor with an unlicensed medicine, in accordance with the “specials” regime.
- Use unlicensed medicines in clinical trials.
• Use or advise the use of licensed medicines for indications or in doses or by routes of administration outside the recommendations given in the marketing authorization (i.e., off label).
• Subject to the points made below, prescribe or recommend the use of a medicine contrary to any warnings or precautions given in the marketing authorization.

While European legislation and the regulatory system permits the off-label use or, in certain circumstances, the use of unlicensed medicines, consideration also needs to be given to potential civil liability of the prescriber, in particular for negligence, in the event that such use results in an injury to a patient.

Even in relation to an unlicensed product, manufacturers retain a responsibility for the efficacy and safety of their product. The provision of information by the manufacturer, the prescriber, or another responsible body of medical professional opinion, is often the best way to obtain informed consent. This also reduces the risk of liability on individual prescribers in certain circumstances.

The second responsibility of prescribers undertaking off-label prescribing or the prescribing of unlicensed medicines is to ensure that the patient, parent, or carer is adequately informed about the risks and benefits of the medicine, in the absence of authorized product information. It has been recommended that when obtaining consent to treatment, the doctor should tell the patient of the drug’s marketing authorization status, and that for an unlicensed medicine its effects will be less well-known and understood than those of a licensed product. The provision of information by the prescriber is particularly important in relation to off-label use, where the PIL may provide conflicting information or information not relevant to such use, and in relation to unlicensed medicines, where no such leaflet is available. In relation to off-label use, the prescriber should have access to the up-to-date SPC, in order to give appropriate information and advice.

Providing a full verbal or written explanation to the patient and recording that in writing, helps ensure that the patient understands the risks involved and gives genuine and informed consent. This also reduces the risk of liability on the part of the prescriber in the event of injury to the patient.

Thirdly, prescribers have a professional responsibility for monitoring the safety of medicines and for submission of reports of any suspected adverse drug reactions to the competent authority of the Member State. In 2012, the European medicines legislation was extensively revised to strengthen public health protection and clarify roles and responsibilities. The definition of an adverse drug reaction has been simplified and extended; it is now simply specified as “any response to a medicinal product which is noxious and unintended”. This definition makes no reference to use within the terms of an authorized SPC and it therefore encompasses adverse drug reactions associated with use of unlicensed medicines and off-label use. Some Member States have introduced a legal requirement requiring health
professionals to report suspected adverse drug reactions, and this is also provided for (though not a requirement) in the revised European legislation. It should, however, be noted that all Member States are required to introduce systems for patients to report suspected adverse drug reactions, following initial experience in some EU countries which demonstrated the value of patients’ experience in identifying and characterizing drug safety issues.

8 Conclusion

The use of medicines according to the terms of the marketing authorization is supported by evidence of safety, quality, and efficacy which has satisfied regulatory authorities of Member States or the European Commission. It is generally understood and accepted that there are clinical situations where off-label use or the use of unlicensed medicines may be judged by the prescriber to be in the patient’s best interests, on the basis of the evidence available indicating a likely favorable benefit–risk balance. In such cases, the onus is on the prescriber to be familiar with the available evidence on risk and benefit, to make appropriate information available to the patient, parent or carer, and to monitor safety in use. If appropriate care is taken, information provided and decisions related to off-label use or use of unlicensed medicines recorded, the risk of a prescriber being found liable for any mishap should be minimized.
Off-Label Use of Contrast Media: Practical Aspects

Peter Reimer and Rolf Vosshenrich

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Abstract

The chapter deals with the practical aspects and extent of off-label use of medicines, particularly the off-label use of contrast agents. A number of MR and US contrast agents lack approval for some age groups or indications. Using a contrast agent off-label can be avoided in most cases by checking the label/Summary of Product Characteristics and using another contrast agent which is approved. The physician prescribing the contrast agent must be aware of the contrast agent label/Summary of Product Characteristics and is responsible for the administration of the contrast agent in accordance with current medico-legal regulations.

Abbreviations

EU European Union
MAH Marketing Authorization Holder
MR Magnetic Resonance
MRI Magnetic Resonance Imaging
SPC Summary of Product Characteristics
US Ultrasound

1 Definitions and Scope of Off-Label Use

The term “off-label use” applies to the prescription or administration of medicines outside any of the terms of the marketing authorization as described in “Off-Label Use of Medicines: Legal Aspects”. There are a number of ways in which off-label use or the use of unlicensed medicine may occur. For example, the European Medicines Agency (EMA) may not have given competent authority to the member state concerned, or drugs may still be in development or be undergoing clinical trials. An application for authorization of a drug may have been refused or a drug...
may no longer have an authorization. Also, there may not be authorization for particular population groups, such as children or allergic patients.

Short definitions of the most commonly used terms are as follows:

- A ‘labeled-use’ is a clinical use within a label as approved for given indications, doses, and route of administration. The ‘Summary of Product Characteristics’ (SPC), which is used in some countries rather than the term ‘label’, provides identical information.
- An ‘off-label use’ is a clinical use of an approved drug in a manner which has not been approved, or has not been addressed in the package insert, such as administering liver specific MR contrast agents to patients under the age of 18 years.
- A ‘compassionate use’ is a clinical use of a medicine that is not yet authorized, and is in the development process, which is made available to patients when there is no satisfactory alternative (EMEA 2010; Whitfield et al. 2010).
- An ‘unlicensed’ use is a clinical use without marketing authorization.
- A contraindication is a potential indication which is clearly stated as a contraindication by the manufacturer in the label/Summary of Product Characteristics approved by the Medicines Agency (Dresser 2008; Reimer and Vossenrich 2008).

During the approval process of a contrast agent, the manufacturer proposes a label/SPC, which describes the properties of the compound based on the results of preclinical and clinical studies. The approving agency may require changes to the label/SPC and will then approve the label/SPC together with the compound. The label/SPC describes the compound, including its chemical structure, physicochemical data, and clinical pharmacology. The preclinical testing in various species and the results of clinical trials are summarized. Clinical indications and usage are given, with a list of contraindications, and an explanation of warnings and precautions. A list of any adverse events observed follows. Use in the pediatric population and pregnant or lactating women are usually specified. The dosage and route of administration is stated and a dosage chart is usually provided. Information on the packaging sizes in which the compound is supplied and how it has to be stored is given (Reimer and Vossenrich 2008).

The label/SPC gives guidance for the use of a contrast agent with specific information on the dose range and indications such as imaging of a particular organ system. An MR contrast agent may be approved for contrast enhanced imaging of the central nervous system with a standard dose of 0.1 mmol/kg bodyweight and a maximum dose of 0.2 mmol/kg bodyweight, both for intravenous injection. If used for imaging of other organ systems or at a higher dose, or if administered intra-arterially, the administration is off-label. Other examples of off-label use are use in children when a contrast agent is only approved for adults >18 years of age, or in lactating or pregnant women. It is surprising how many contrast agents such as gadolinium chelates differ in their approved indications and how many are not approved for the current spectrum of clinical applications. Also, the approved indications differ from country to country. This poses a continuing problem for the user, which may result in legal problems or may affect reimbursement. Reimbursement based on labels/SPCs differs from country to country. To prevent liability shifting completely to the physician, he/she has to explain the reason for the off-label use, such as that “no product is available with this indication in the label” (Kairuz et al. 2007; Reimer and Vossenrich 2008). The legal and regulatory aspects are described in “Off-Label Use of Medicines: Legal Aspects”.

2 Magnitude of Off-Label Use

The off-label use of diagnostic or therapeutic medication is a daily problem. Prescription of an unlicensed medicine or of a medicine for off-label use increases the responsibility of prescribing the medicine, as described in “Off-Label Use of Medicines: Legal Aspects”.

A review of the current literature gives an idea in which areas and clinical disciplines off-label use is a substantial part of providing appropriate health care consistent with the current level of medical knowledge. Limited or absent approval is common in age or disease groups where clinical trials are difficult to perform or revenue from the sale of such medication may be limited, given the complex approval regulations.

An important example is the lack of testing of medication in children or teenagers, because clinical trials usually rule out any patients <18 years. Therefore, the label/SPC typically excludes administration to patients below 18 years of age. Furthermore, if some approval is given following clinical trials, it often does not include the full age range, for example often the newborn or younger children, such as below 2 years of age, are excluded. (Gavrilov et al. 2000; Regan and Alderson 2003; Askin 2006; Jain et al. 2008; Pasquali et al. 2008; Hsu and Brazelton 2009; Winterfeld et al. 2009; Oguz et al. 2012). The frequency of off-label prescriptions in children may be higher than 60–80 % (Bazzano et al. 2009).

In the current system, a contrast agent is approved for some indications and then, based on data in the peer-reviewed literature, the experience of colleagues, and professional guidelines, many radiologists use the agent off-label, in the interests of patient care. This off-label use has
increased over the years. Few severe adverse reactions have occurred, with no difference in adverse reactions between use for approved and unapproved body area indications.

Another important area is oncology because of the development of new drugs and the growing potential for combinations of drugs which have never been tested in controlled trials. Off-label prescribing in an acute hospitalized oncology population was reported to account for more than 20 % of all prescriptions for off-label or unlicensed medication (Poole and Dooley 2004; Scheinfeld 2004; Verhagen et al. 2008; Jansen and Gouws 2009; Roila et al. 2009; Sax 2009).

Pediatric and adult psychiatry is another specialty with a documented high rate of off-label prescriptions, of the order of 50 % or higher (Scheltema Beduin and de Haan 2010; Weiss et al. 2000; Regan and Alderson 2003; Barbui et al. 2004; Knoester et al. 2004; Haw and Stubbs 2005; and Winterfeld et al. 2009).

These three clinical specialties reflect the magnitude of the current problem of the use of off-label prescription. A study by Cras et al. 2007 concluded that 70 % of patients received at least one off-label medicine during their hospital stay. Most off-label prescriptions were related to an unapproved indication (75 %). The other main reasons were unapproved dosages (14 %) and dosing schedules (9 %). Anti-thrombotic and anti-ulcer agents accounted for more than 40 % of the off-label prescriptions. The problem of off-label prescription is immense and may require a change in policy by the regulatory agencies, because liability is currently almost entirely the problem of the physician responsible (Cras et al. 2007).

### 3 Off-Label Use of Contrast Agents

The off-label use of contrast agents is an important clinical problem, with limited or absent approval for certain age groups or indications. Current regulations for the approval of new contrast agents, age groups, or indications require specific testing in clinical trials with subsequent specific approval. Approval of a contrast agent within a given class of contrast agents such as low molecular weight gadolinium chelates (i.e., gadopentetate dimeglumine, gadoterate meglumine, gadodiamide, gadoteridol, gadobenate dimeglumine, gadobutrol) does not necessarily cover similar or identical approval for other contrast agents within that class (Runge and Knopp 1999; Knopp et al. 2001; Runge 2001; Heinemann and Lollgen 2007; and Reimer and Vosshenrich 2008). To obtain approval, the MAH would have to perform expensive phase 3 studies, which they are not motivated to do, because they are likely to already sell a lot of the agent for that use, and the potential increase in sales from an approval would never cover the costs.

Radiologists prefer a contrast agent to have general approval, because of concern that some patients (or even some local authorities) will question their judgment, when they see that the contrast agent being used for a scan is not approved for that particular body area by the Medicines Agency.

Since the physician prescribing the contrast agent is responsible for the correct use of the agent, he or she should be aware of the contrast agent label/SPC. As described in “Off-Label Use of Medicines: Legal Aspects”, the prescriber is responsible for deciding whether it is appropriate to use the contrast agent as proposed for the individual patient and has to consider the safety and efficacy of the product in relation to its proposed use.

#### 3.1 Special Populations

Most MR and US contrast agents are not systematically studied in patients <18 years (Reimer and Vosshenrich 2008, 2013). In this age group, there is inconsistent approval of medication including contrast agents (Conroy 2002; Olsson et al. 2011).

Among non-specific gadolinium chelates only three (gadopentetate dimeglumine, gadoterate meglumine, gadoteridol) had approval for use in the newborn in Germany in December 2012. Three of the approved MR contrast agents in Germany (gadoxetate disodium, ferumoxsil and gadoterate meglumine in a dilute preparation) are only approved for patients >18 years (Reimer and Vosshenrich 2013). Of these, only gadoxetate is for intravenous administration and is liver specific, and ferumoxsil and gadoterate meglumine in a dilute preparation are approved for oral intake and intraarticular injection, respectively. It is unlikely that it will be possible to collect enough studies with these agents to obtain approval in children. By comparison, iodine-based contrast agents are typically approved for use in children and the newborn, with specific recommendations for dosage.

#### 3.2 Special Indications

There are also contrast agents with approval for quite specific indications. These contrast agents should not be used like non-specific gadolinium chelates with a broad approval.

Examples of contrast agents with approval for special indications are gadoxetic acid approved only for hepatic MRI, ferumoxsil (Lumirem), approved only for the gastrointestinal tract, or gadofosveset trisodium for blood-pool MR angiography of arteries and veins of the body and peripheral vessels (Reimer and Vosshenrich 2013).
3.3 Limited Approval

Currently, approval of a contrast agent is given for certain indications based on clinical trials for those indications. The strategy of many companies is to try to enter the market with a first indication, which is subsequently broadened following further clinical trials. Whole body approval, which was granted for gadopentetate dimeglumine as the first MR contrast agent, was a historic decision of the authorities at that time (Knopp et al. 2001; Reimer and Vosshenrich 2008).

Coverage of the various applications is not complete among non-specific gadolinium chelates. Only three out of this group (gadopentetate dimeglumine, gadobutrol and gadodiamide) are approved for whole body administration in Germany, while in other countries gadoteridol and gadoterate meglumine are approved for whole body administration. Individual prescribers should check the label/SPC before administration and use approved contrast agents whenever possible (Reimer and Vosshenrich 2013).

Current approval in Europe varies among member states, and providing an overview of approval for contrast agents in Europe is therefore beyond the scope of this chapter. However, given the increase in EU wide regulations, it is likely that variations in approval will decrease.

3.4 Clinical Trials

The use of unlicensed medicines in clinical trials is subject to the provisions of the Clinical Trials Directive. Contrast agents used within clinical trials should not be used for patients outside the particular clinical trial and their administration must be monitored within the given clinical trial. However, the available evidence may be sufficient for some medications to extend the indications, for example to children, without further clinical studies. Discussion between the regulatory agencies and ethical committees aims to avoid unnecessary trial replication (Tafuri et al. 2009).

5 Conclusion

The off-label use of diagnostic or therapeutic medication is a daily problem in clinical medicine. Use of a contrast agent off-label, for example in special populations or for special indications, can be avoided in most cases by checking the label/SPC and using an alternative contrast agent which is approved. The prescriber must inform the patient adequately about the risks and benefits of a non-labeled contrast agent and obtain their informed consent before administering the contrast agent.

References

Off-Label Use of Contrast Media


Pharmacovigilance: When to Report Adverse Reactions to Contrast Media

Doris I. Stenver

Abstract
The main objective of pharmacovigilance is the early detection of new adverse drug reactions. Health care professionals play a key role in safety surveillance, as they are frontline observers if serious and unexpected adverse effects occur. They are obliged to report their observations and suspicions to the regulatory authorities, thereby enabling the authorities to react in an appropriate and timely manner.

1 Introduction
Effective drug safety surveillance—pharmacovigilance—is of the utmost importance for patients. A surveillance system should be in place for all kinds of medicinal products including contrast agents. The main objectives of pharmacovigilance are the early detection of new adverse drug reactions, risk assessment, risk minimization, and risk communication.

Health care professionals play a key role in safety surveillance, as they are frontline observers if serious and unexpected adverse reactions occur. They are obliged to report their observations and suspicions to the regulatory authorities, which can then react in an appropriate and timely manner.

Even before the administration of a medicinal product to the patient, the health care professionals play a crucial role. Before administration of any medicinal product to patients—whether for therapeutic, preventive, or diagnostic purposes—a careful risk/benefit assessment should always be undertaken. This assessment is the responsibility of the health care professionals.

1 Definitions: Adverse reaction. A response to a medicinal product which is noxious and unintended, Unexpected adverse reaction. An adverse reaction, the nature, severity, or outcome of which is not consistent with the summary of product characteristics.
It is important to be aware that drug safety surveillance is necessary for the entire life cycle of drugs, beginning in the pre-marketing phase and continuing throughout the post-marketing period. The condition nephrogenic systemic fibrosis (NSF) associated with the administration of gadolinium-based MR contrast agents to patients with renal impairment underlines this fact (Stenver 2008). Occasionally, it is necessary to monitor safety after marketing has ceased, for example, in the case of suspected late-onset adverse events, or to gather information on the outcome of observed events.

During the pre-marketing phase, information on risk is provided from the various pre-clinical and clinical studies. After marketing authorization, information on risk is collected from several sources, primarily through the spontaneous reporting system and from post-marketing safety studies.

2 The Adverse Drug Reaction Reporting System

For a number of decades the system for adverse drug reaction reporting has been a cornerstone and mainstay of drug safety surveillance.

The thalidomide tragedy in the 1960s (Lenz 1966) led to the establishment in many countries of national public institutions responsible for collecting, registering, and assessing adverse drug reaction reports (Finney 1965; Dukes 1985). Since then, the field of pharmacovigilance has undergone significant development, and is today primarily governed by internationally agreed legislative rules (Regulation 2012).

Originally, the key stakeholders in the spontaneous reporting system were health care professionals, national and international authorities, and marketing authorization holders. In 2012, the legal basis was provided for citizens and patients to report adverse drug reactions directly to the authorities (Regulation 2012).

Health care professionals are responsible for reporting suspected adverse reactions to the authorities. In some countries reporting of adverse drug reactions by health care professionals is voluntary and in other countries either mandatory or a mixture of mandatory and voluntary. In Denmark, for example, reporting is mandatory during the first 2 years of marketing, during which health care professionals should report all suspected adverse drug reactions they observe. Following the first 2-year period health care professionals in Denmark are obliged to report all suspected or serious unexpected adverse reactions they observe for the entire marketing period.

Ideally, health care professionals should report all suspected serious adverse drug reactions to the authorities, even though the adverse reaction may be known and appears in the labeling. Furthermore, health care professionals should also consider reporting known non-serious reactions, as the perceived frequency based on clinical trials may in fact differ from that observed in the post-marketing setting.

The authorities are responsible not only for registration of the reports in a national database, but also for forwarding the reports to the marketing authorization holder responsible for putting the product on the market. Following receipt of adverse drug reaction reports from health care professionals, the authorities are also obliged to forward the reports to the Eudravigilance database established at the European drug regulatory authority, EMA, and to the WHO. All adverse drug reactions classified as serious should be exchanged between authorities and marketing authorization holders (and vice versa) within 15 days after receipt. The reports are also submitted to the WHO database. Thus, through the reporting system all the observations made by health care professionals at a national level are in effect available to a large international community.

The assessment is undertaken by the authorities and marketing authorization holders in collaboration. The assessment is made on the basis of individual case reports when they are received, and also after individual reports have been included in the periodic safety update reports which marketing authorization holders are obliged to submit to the authorities at intervals after marketing has started.

Every assessment concludes with a decision about whether new safety data have been discovered, and—if this is the case—whether the safety profile of the product has changed. Every periodic safety update report should include a thorough assessment of the benefits and the risks as well as an integrated benefit/risk assessment of the product. The need to revise the labeling (Summary of Product Characteristics, Package Insert Leaflet) by introducing, for example, new contraindications, warnings or precautionary measures, or by adding new adverse drug reactions has to be considered. Whether further risk minimization measures are required, for example, a request for further studies or creation of registries, and whether new information should be provided to health care professionals and the public also need to be considered.

3 Reporting of Adverse Drug Reactions Makes a Difference

It is well known that underreporting of adverse drug reactions occurs all over the world. A variety of difficulties have been identified, such as insufficient time to fill out reporting forms, lack of knowledge about the impact of reporting, and the fact that the patient’s symptoms may not be recognized by the health care professionals to be drug-related.
The finding that the severe, disabling, and occasionally fatal condition of NSF is associated with the use of gadolinium-based MR contrast agents illustrates the challenges of drug safety surveillance. It is striking that gadolinium-based contrast agents had been used for more than a decade in a huge number of patients, and that the condition of NSF had been described in the literature for some years, before Grobner (2006) in 2006 finally realized that NSF and gadolinium could be linked. It is also noteworthy that many health care professionals seemed to be reluctant to report new suspected cases of NSF to the national regulatory authorities and instead preferred to publish small case series in scientific journals. This led to considerable delay in collecting sufficient data for the necessary regulatory actions to be taken to prevent further cases and to protect patients.

In addition, the adverse drug reaction reports led to increased understanding of the risk profile across the whole class of gadolinium contrast agents, and meant that it was possible to introduce measures to minimize risk. There can be no doubt that reporting of adverse drug reactions makes a difference and is in the interest both of individual patients and of society as a whole.

References

What is Required in Order to Get the Authorities to Approve a New Contrast Medium?

Doris I. Stenver

Abstract

The evaluation of diagnostic agents is governed by the same regulatory rules and principles as those for other medicinal products. This chapter summarizes relevant sections of the Guideline on Clinical Evaluation of Diagnostic Agents issued by the EMEA (2010). The requirements for authorization for completely new contrast agents may differ from those for contrast agents similar to contrast agents which have already been approved.

1 Introduction

The evaluation of diagnostic agents is governed by the same regulatory rules and principles as those for other medicinal products. The requirements for applications for Marketing Authorization for medicinal products in the EU, including all contrast agents, are provided in Directive 2001/83/EC as amended.

Several guidance documents have been developed to further amplify the requests laid down in the legislation.

The most important guidelines which give advice on clinical evaluation are the following:

- Guideline on Clinical Evaluation of Diagnostic Agents (EMEA 2010)
- Good Clinical Practice (International Conference for Harmonization, ICH, topic E6)
- Statistical Principles for Clinical Trials (ICH topic E9)
- Choice of Control Group in Clinical Trials (ICH topic E10)
- Structure and Content of Clinical Study Reports (ICH topic E3)

This chapter summarizes relevant sections of the Guideline on Clinical Evaluation of Diagnostic Agents (EMEA 2010), which outlines the principles for the clinical evaluation of diagnostic agents intended for in vivo
administration. Further details specific for imaging agents, which concern classification, efficacy criteria, methodological issues, and safety assessments, are outlined in the appendix to this Guideline.

The European Public Assessment Reports for the two latest approved gadolinium-containing MR contrast agents, gadofosveset trisodium (Vasovist®—the name was changed to Ablavar® on January 10th 2011) and gadoversetamid (Optivmark®) will be used to illustrate the non-clinical and clinical parts of the process of application for approval. On 18 October 2011, the European Commission issued a decision to withdraw the marketing authorization for Ablavar as requested by the Marketing Authorization Holder.

2 General Principles of Evaluation

The principles used for the evaluation of medicinal products with respect to quality, pharmacology, toxicology, pharmacochemistry, and safety also apply to diagnostic agents. However, since contrast agents are used to diagnose and monitor diseases or conditions and not for treatment, the clinical development programs have to be adapted accordingly. As for other medicinal products, the balance between benefits and risks should be taken into account when granting a marketing authorization.

In general, approval of a contrast agent is usually based on the clinical indications for its use rather than the general properties of a specific molecule. However, the general properties should be described in the application.

In practice, the requirements for authorization for completely new contrast agents may differ from those for contrast agents similar to contrast agents which have already been approved. Examples of the latter would be iodinated monomers or non-tissue-specific extracellular gadolinium chelates which share several similarities with an already approved contrast agent (such as chemical structure/class, pharmacokinetic profile, dose and dosing regimen of the active moiety), but frequently differ in the chemical structure of the carrier molecule. For such compounds, so-called non-inferiority comparative trials against a similar already approved agent are recommended. The aim is to show similar technical and diagnostic performances (sensitivity and specificity) as well as similar or better safety profile for the same patient population or indication. This relatively limited evidence for assessing the clinical benefit of these products is based on the claim(s) for the same indication which has already been granted to the similar approved contrast agent (the comparator). If the aim is to show superiority of the new contrast agent, this limited evidence may not be sufficient and, in addition to better technical and diagnostic performance, the impact on diagnostic thinking and patient management (see below) may need to be shown or at least discussed in the submission. However, if the impact of the diagnosis provided by the comparator contrast agent which has already been approved is widely accepted, better technical and diagnostic performance may be sufficient to support a claim of superiority.

If use for a new indication not approved for the similar contrast agent is claimed, the requirements for approval are identical to those required for a new product. It is then necessary to show adequate technical and diagnostic performance in relation to a standard of truth (for example, the histopathological diagnosis). In addition, when appropriate, technical and diagnostic performance should be compared to an established contrast agent in the clinical context in which the new agent is to be used.

3 Quality Aspects

Chemical, pharmaceutical, and biological aspects of the contrast agent should be presented in detail in the application.

A wide range of information about the active substance of the contrast agent should be provided, such as the composition and molecular structure and the administration form and dosage.

The stepwise manufacturing process should be adequately described, for example the chemical synthesis, purification steps, etc. Specifications for starting materials, reagents, catalysts, and solvents should be provided. Information on how the structure has been elucidated (e.g., elemental analysis, infrared spectroscopy, ultraviolet spectroscopy, optical rotation, mass spectrometry) should be given, together with data on how physico-chemical parameters (e.g., polymorphism, solubility, particle size) have been analyzed.

The active substance specification should include data on appearance, identification tests, purity control, and stability.

Also for the medicinal product the manufacturing process, product specification, and stability data should be provided.

4 Non-Clinical Evaluation

The non-clinical data comprises data on pharmacology, pharmacochemistry, and toxicology and studies should be performed in accordance with good laboratory practice requirements.

For example, when considering the pharmacological characteristics of magnetic resonance agents, the degree of albumin binding and the ability to alter proton relaxation times in vitro and in vivo are of the utmost importance. Depending on the claimed indication(s), other aspects such
as renal contrast enhancement, imaging performance in cerebral metastatic disease, and permeability of the blood–
brain barrier should be documented. Comparisons between
contrast agents with similar structure may facilitate the
evaluation. As an example, in vitro and in vivo investigations
of primary as well as secondary pharmacodynamics
were performed for the recently approved contrast agent
gadoversetamide in comparison with gadopentetate dimeglumine.

In vitro and in vivo safety pharmacology studies should
provide data on the effect on vital organ functions, such as
colloidal threshold and risk of QT-prolongation.

Ideally, the potential for pharmacodynamic drug inter-
actions should also be investigated. For example, for
gadofosveset trisodium a series of drug interaction studies were
performed to assess the ability to displace frequently used
drugs, such as digoxin and warfarin, from their binding sites
on human serum albumin. In addition, the potential effect of
commonly used drugs on MRI efficacy was examined. For
gadoversetamide, no studies on pharmacodynamic drug
interactions were available before the marketing authori-
zation was issued.

The pharmacokinetic data set should include data on
absorption, biodistribution or bioavailability, metabolism,
and excretion. The pharmacokinetic testing is typically
performed in two or more of the species used for toxicology
testing (rat, rabbit, dog, monkey) and using the adminis-
tration route intended for use in man.

The toxicology test program should as a minimum
include single dose toxicity, repeat dose toxicity, genotox-
icity, carcinogenicity, and reproduction toxicity.

Finally potential ecotoxic and environmental risks
should be assessed.

5 Clinical Evaluation

5.1 Good Clinical Practice (GCP) and Ethics

The clinical trials used to support the marketing authori-
zation application should be designed, conducted, recorded,
and reported in compliance with the GCP principles as laid
down in regulations and guidelines. In addition, all studies
should be conducted in accordance with the Declaration of
Helsinki.

5.2 Fundamental Requirements

According to the guideline on clinical evaluation of diag-
nostic agents (EMEA 2010), in order to establish an indi-
cation for a contrast agent, it is necessary to demonstrate its
benefit by assessing its technical performance (including
procedural convenience), diagnostic performance, impact
on diagnostic thinking, impact on patient management,
impact on clinical outcome and safety. In addition, a clin-
ical pharmacology study program should be performed
to provide data on safety, tolerance, pharmacokinetics,
and pharmacodynamic dose-related effects. EU and US
requirements are very similar, but there are a few differ-
ences. For example, the FDA requirements do not include
impact on diagnostic thinking, impact on patient manage-
ment, and impact on clinical outcome.

It is necessary to assess technical performance, for
example from image quality, but this on its own is not
enough to show the clinical benefit of a new contrast agent
and cannot be the sole basis for approval.

The diagnostic performance consists of the sensitivity
and specificity of a test. The trade-off between sensitivity
and specificity requires careful analysis in relation to the
intended applications and the implications for patient care.
The impact of disease prevalence should also be taken into
consideration, as co-morbidity, specificity, and sensitivity
may vary in different study populations.

The impact on diagnostic thinking refers to the impact of
a test result on post-test versus pre-test probability of a
correct diagnosis in a well-defined clinical context which
includes patient characteristics and other diagnostic proce-
dures. All diagnostic agents should have an impact on
diagnostic thinking (higher probability of correct diagnosis
after the test than before the test, or change in diagnosis).
Positive as well as negative predictive values are important
parameters which influence the impact on diagnostic
thinking in a given patient. Both negative and positive
predictive values depend on the prevalence of the disease in
the studied series and may not necessarily reflect the
prevalence of a disease in the overall population. The role
of a diagnostic test in the determination of the prognosis
may have significant impact on diagnostic thinking. Prog-
nostic value should be demonstrated by adequate statistical
methods such as multivariate analysis.

A description and quantification of the impact of the
diagnostic information obtained on the management of a
patient and of the clinical outcome are generally obtained
through an appropriate questionnaire or by sequential un-
blinding. Patient follow-up data should be available for this
purpose. Studies assessing patient outcomes may be
required if there is no standard of truth to compare. In all
other cases these studies are not mandatory, but, if per-
formed, can be the basis for a specific claim. An assessment
of the potential benefits and risks arising from the impact on
therapeutic decisions should be made. In particular, the
consequences of an incorrect diagnosis (false positive or
false negative) must be considered.

For each claim the contrast agent may be used alone or in
combination with other diagnostic procedures or medicinal
products necessary for the indication claimed. This should always be specified in the study protocol. If several indications or claims are planned for one imaging agent it may be considered necessary to perform separate clinical trials.

5.3 Methodological Considerations

In the phase III studies the protocol should describe the trial objectives or claim, the contrast agents and methods investigated (including the investigational agent, absolute or surrogate standard of truth, comparator and other clinical assessments and procedures if used), testing procedures, trial population, sample size calculation, endpoint justification, blinding, randomization, statistical considerations, principles for data presentation, issues related to collection and analysis of data, safety and any other relevant considerations.

Relevant data on the diagnostic performance of the contrast agent obtained from earlier phases of its clinical development (phase II studies) should be used to design subsequent confirmatory trials.

Special attention should be given to the trade-off between sensitivity and specificity, taking the intended clinical use into consideration, and to the justification of power calculations and acceptance limits in relation to clinical relevance. It is particularly important to design the trials in relation to the intended clinical use of the contrast agent. For example, different trials will be required if the contrast agent under investigation will be used to provide additional information when insufficient diagnostic information is obtained from established tests or if it will be used as an alternative to established standard tests.

Comparative studies are required both if the investigational contrast agent is being developed as an alternative or as an improvement over existing contrast agents. An appropriate comparator agent would be one which is widely accepted in the EU for the claimed indication and reflects current good medical practice. The choice of comparator must be justified and the corresponding procedures clearly described. The comparison should include evaluation of both efficacy and safety data.

For contrast agents the unenhanced procedure may serve as an appropriate comparator for evaluating the added value of the contrast agent. However, comparison with a marketed comparator contrast agent is ideal.

Two previously submitted marketing authorization applications illustrate the process. For gadoversetamide (Optimark®), the four submitted pivotal studies shared the same design, and were multicenter, randomized, double-blind, non-inferiority studies to evaluate the safety, tolerance, and efficacy of gadoversetamide compared to gadopentetate dimeglumine in CNS or liver lesions. For gadofosveset trisodium (Vasovist®), no head-to-head comparisons with currently available MRA contrast agents were carried out because no extracellular agent had European-wide approval for MRA during the development of gadofosveset trisodium.

5.4 Strategy and Design of Clinical Trials

In phase I studies the aim is to obtain pharmacokinetic and first human safety data assessments with single mass dose and increasing mass doses of the diagnostic agent. Phase I trials may be done in healthy volunteers or in patients.

In phase II studies the aim is to determine the mass dose or dosing regimen in patients to be used in the phase III studies, and to provide preliminary evidence of efficacy and safety, as well as to optimize the technique and timing of, for example, image acquisition. In addition, phase II studies are important for developing methods or criteria by which images or test results can be evaluated.

For gadofosveset trisodium, seven clinical phase I/II pharmacological studies were performed in healthy volunteers, in patients with renal or hepatic impairment, or in patients with vascular disease. For gadoversetamide, five phase I and one phase II study were performed in healthy volunteers and patients with various CNS or liver pathologies, as well as a variety of renal and hepatic dysfunction.

Phase III studies are large-scale trials which aim to establish the efficacy of the contrast agent in a well-defined target patient population, and in the step of the diagnostic decision-making process, where the contrast agent will be used in later clinical practice. The primary efficacy variable should be clinically relevant and evaluable or measurable in all patients. Multiple primary endpoints should be avoided. When approval for multiple indications is requested, studies may be done in different clinical settings, each corresponding to the particular claim and intended use.

The clinical phase III study program for gadofosveset trisodium consisted mainly of four studies performed in different vascular territories, and enrolled from 136 to 268 patients in each study. The clinical phase III study program for gadoversetamide comprised two pivotal CNS studies and two pivotal liver studies, and enrolled from 198 up to 208 patients in each study.

5.5 Clinical Safety

A serious safety concern may prevent marketing authorization if there are alternative and safer diagnostic methods. Marketing authorization will always be based on the benefit/risk ratio of the new contrast agent. In some cases a contrast agent will have to show a positive impact on
diagnostic thinking and patient management to support a marketing authorization claim.

Clinical safety assessments of contrast agents should be designed based on their characteristics and intended use(s) and on the results of other relevant clinical studies. Safety follow-up of patients should not be limited to the duration of the diagnostic procedure, but extended to a longer time period corresponding at least to the pharmacokinetic and pharmacodynamic properties of the product. Not only short term but also long-term safety data should be provided. An appropriate risk management plan should be established for agents accumulating in the organism (e.g. deposits of gadolinium in bones and skin). As well as risk(s) related to the agent itself (e.g. immunogenicity, allergic reactions), risks related to the potential for incorrect diagnosis following its use should be taken into consideration while assessing benefit/risk balance of the contrast agent.

Reference

A Critical Review of Meta-Analysis of Adverse Events After Contrast Media

Giuseppe Biondi-Zoccai and Giacomo Frati

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Abstract

Systematic reviews provide a point of view on a specific clinical topic by using explicit and structured methods for study search, selection, appraisal, and data extraction. When data pooling is performed using ad hoc statistical methods, a systematic review may also be described as a meta-analysis, although this type of analysis would more appropriately be described as a systematic review with meta-analysis. Adverse events after contrast agent administration are an ideal topic for systematic reviews, as they are uncommon. Any single randomized trial is unlikely to be adequately powered to accurately assess the incidence of adverse events and to compare adverse event rates between treatment groups while at the same time focusing on clinically relevant (i.e., hard) end-points. This chapter provides a concise but comprehensive overview of systematic reviews and meta-analyses, with particular focus on their application to adverse events after contrast agent administration.

1 Introduction

“If I have seen further it is by standing on the shoulders of giants” Isaac Newton

“The great advances in science usually result from new tools rather than from new doctrines” Freeman Dyson

“I like to think of the meta-analytic process as similar to being in a helicopter. On the ground individual trees are visible with high resolution. This resolution diminishes as the helicopter rises, and in its place we begin to see patterns not visible from the ground” Ingram Olkin

Systematic reviews and meta-analyses are achieving an ever increasing success among researchers and practitioners, because of the immediate appeal of a single piece of literature, which can apparently summarize diverse data on
a specific topic (Table 1 and Fig. 1) (Egger et al. 2001; Biondi-Zoccai et al. 2003, 2011).

However, systematic reviews and meta-analyses, despite their major strengths, may, like any other analytical and research tools, also have major weaknesses, especially when applied to a challenging topic such as adverse events after contrast agents. Adverse reactions or events following the administration of contrast media are ideal subjects for systematic reviews because of their diversity and their low incidence rates (Fig. 2).

The aim of this chapter is to provide a concise but sound framework to help critical reading of systematic reviews and meta-analyses, with a particular focus on adverse events after contrast agents.

### Table 1 Developmental milestones of systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Years</th>
<th>Individuals</th>
<th>Milestone</th>
</tr>
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<tbody>
<tr>
<td>1904</td>
<td>Karl Pearson (UK)</td>
<td>Correlation between inoculation of vaccine for typhoid fever and mortality across apparently conflicting studies</td>
</tr>
<tr>
<td>1931</td>
<td>Leonard Tippet (UK)</td>
<td>Comparison of differences between and within farming techniques on agricultural yield adjusting for sample size across several studies</td>
</tr>
<tr>
<td>1937</td>
<td>William Cochran (UK)</td>
<td>Combination of effect sizes across different studies of medical treatments</td>
</tr>
<tr>
<td>1970s</td>
<td>Robert Rosenthal, Gene Glass (USA); Archie Cochrane (UK)</td>
<td>Combination of effect sizes across different studies of, respectively, educational/psychological and clinical treatments</td>
</tr>
<tr>
<td>1980s</td>
<td>The global scientific community</td>
<td>Exponential development and use of meta-analytic methods; birth of The Cochrane Collaboration</td>
</tr>
<tr>
<td>1990s and 2000s</td>
<td>Heiner Bucher (Canada), Thomas Lumley (USA), and Anthony Ades (UK)</td>
<td>Development of methods for indirect meta-analysis, network meta-analysis, and mixed treatment comparisons</td>
</tr>
</tbody>
</table>

**Fig. 1** Histogram showing the ongoing exponential increase in published systematic reviews, systematic overviews, and meta-analysis. MEDLINE/PubMed search performed on January 11, 2013 with the following strategies: overview or review; “systematic review” or “systematic overview”; meta-analysis; meta-regression; ((indirect or network) and meta-analysis) or (“mixed treatment comparison”). *ITC* indirect treatment comparison or indirect meta-analysis, *MTC* mixed treatment comparison, and *NMA* network meta-analysis
2 Basic Concepts of Systematic Reviews and Meta-Analyses

2.1 Definitions

A **systematic review** provides a point of view on a specific clinical problem, be it therapeutic, diagnostic, or prognostic (Egger et al. 2001; Biondi-Zoccai et al. 2004). The term systematic means that all the steps underlying the reviewing process are explicitly and clearly defined, and so may be reproduced independently by other researchers. Thus, a formal set of methods is applied to study search (i.e., to the extensive search of primary or original studies), study selection, study appraisal, data abstraction and, when appropriate, data pooling according to statistical methods.

The term **meta-analysis** describes a statistical method which combines results from several different primary studies in order to provide more precise and valid results (Fig. 3). Thus, not all systematic reviews include a meta-analysis, as not all topics are suitable for sound and robust pooling of data. In addition, meta-analysis can be conducted outside the realm of a systematic review, without extensive and thorough literature searches, but then the results of the attempted meta-analysis are best viewed as generating a hypothesis only. This is mainly because meta-analyses outside the framework of a systematic review have a serious risk of selection bias, for example small study or publication bias. Additional definitions and pertinent examples useful for readers and writers of systematic reviews and meta-analyses are provided in Table 2.

A major recent development has been the introduction of indirect meta-analyses, network meta-analyses, and mixed treatment comparisons (Bucher et al. 1997; Lumley 2002; Lu and Ades 2004). These are specific types of meta-analysis which use randomized trial data from different treatments to generate indirect comparisons and weighted averages of direct and indirect (i.e., network) comparisons. They may be considered to be the ultimate step in systematic reviews because they are both comprehensive and statistically precise (Palmerini et al. 2012; Kwok et al. 2013). Finally, overview of reviews represents a novel but useful tool to summarize and compare results obtained from separate systematic reviews focusing on similar conditions (Kwok et al. 2013).

2.2 **Strengths**

Systematic reviews have several unique strengths, especially if they include meta-analytic pooling of quantitative data (Egger et al. 2001; Biondi-Zoccai et al. 2004). They use systematic literature searches and so allow the whole body of evidence about a specific clinical question to be retrieved. Their standardized methods for search, appraisal, and selection of primary studies facilitate reproducibility and objectivity. Thorough evaluation for internal validity and risk of bias in individual primary studies clearly identify the limitations of these studies. Often the greatest strength of systematic reviews is their ability to pinpoint weaknesses and fallacies in apparently sound primary studies (Lau et al. 1998).

Quantitative synthesis using meta-analysis also substantially increases statistical power, and yields narrower confidence intervals for statistical inferences. Assessing the effect of an intervention, including an exposure or diagnostic test, in different settings and at different times gives...
estimates and inferences of much greater external validity, which are more likely to be successfully applied in different conditions (Kandzari et al. 2005).

The huge sample sizes often achieved by systematic reviews may even provide the opportunity for testing post hoc hypotheses or for exploring the effects in selected subgroups (Thompson and Higgins 2002). Clinical and statistical variability (i.e., heterogeneity and inconsistency) may be exploited by advanced statistical methods such as meta-regression, with the possibility of testing new and hitherto untried hypotheses (Biondi-Zoccai et al. 2005). Meta-regression methods or more complex hierarchical models based on frequentist or Bayesian approaches can even be used to perform adjusted indirect comparisons, network meta-analyses, or mixed treatment comparisons (Bucher et al. 1997; Lumley 2002; Lu and Ades 2004).

2.3 Limitations

There are also significant drawbacks to systematic reviews and meta-analyses (Egger et al. 2001; Biondi-Zoccai et al. 2009). Since the first criticisms that they were “an exercise in mega-silliness” and inappropriately “mixing apples and oranges” (Glass 1976), there has been ongoing debate about the correct approach to choose. Meta-analytic pooling should be used when there is statistical homogeneity and consistency, and is not suitable when there is marked statistical heterogeneity (as evidenced by $p$ values < 0.10 at $\chi^2$ test) or significant statistical inconsistency (as evidenced by $I^2$ values > 50%) (Higgins et al. 2003).

While Canadian authors have suggested that systematic reviews and meta-analyses from homogenous randomized controlled trials represent the apex of the evidence-based medicine pyramid (Guyatt et al. 2002), others have maintained that very large and simple randomized clinical trials offer several major advantages, and, if available, are always preferable to systematic reviews (Cappelleri et al. 1996). It is also all too common to retrieve only a few studies on a given clinical topic from the literature, or to find studies of such low quality that including or even discussing them in the setting of a systematic review may be misleading. This drawback is only associated with small study bias, which is a major threat to meta-analysis validity (Egger et al. 2001). Especially when datasets are large, small primary studies are more likely to be reported, published, and quoted if their results are significant. Conversely, small nonsignificant studies often fail to reach publication or dissemination, and may thus be very easily missed, even after thorough literature searches. Combining results from these “biased” small studies with those of larger studies, which are usually published even if negative or nonsignificant, may inappropriately deviate summary effect estimates away from the true value. Unfortunately, despite the availability of several graphical and analytical tests (Peters et al. 2006), small study bias, which encompasses publication bias, is potentially always present in a systematic review and must not be forgotten (Biondi-Zoccai et al. 2008).

<table>
<thead>
<tr>
<th>Term</th>
<th>Characteristics</th>
</tr>
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<tbody>
<tr>
<td>Indirect meta-analysis</td>
<td>A meta-analysis providing indirect estimates of effect stemming from separate randomized trials which use one or more common comparators</td>
</tr>
<tr>
<td>Individual patient data meta-analysis</td>
<td>A study (not necessarily a review) using specific statistical methods for pooling data from separate datasets which use individual patient data</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>A study (not necessarily a review) using specific statistical methods for pooling data from separate datasets</td>
</tr>
<tr>
<td>Meta-regression</td>
<td>A study (not necessarily a review) using specific statistical methods for exploring interactions between dependent and independent variables (moderators) from a meta-analysis dataset</td>
</tr>
<tr>
<td>Mixed treatment comparison</td>
<td>As for network meta-analysis</td>
</tr>
<tr>
<td>Network meta-analysis</td>
<td>A meta-analysis providing weighted average estimates of effect using both direct and indirect comparisons</td>
</tr>
<tr>
<td>Overview</td>
<td>As for review</td>
</tr>
<tr>
<td>Overview of reviews</td>
<td>Deliberately uses a systematic approach to review search, selection, abstraction, appraisal and pooling</td>
</tr>
<tr>
<td>Qualitative review</td>
<td>A review which avoids a systematic approach</td>
</tr>
<tr>
<td>Quantitative review</td>
<td>A review which deliberately uses and reports quantitative methods to appraise or synthesize data</td>
</tr>
<tr>
<td>Review</td>
<td>A point of view on a given subject which quotes different primary authors or studies</td>
</tr>
<tr>
<td>Systematic review</td>
<td>A review which deliberately uses and reports a systematic approach to study search, selection, abstraction, appraisal and pooling</td>
</tr>
<tr>
<td>Viewpoint</td>
<td>As for review</td>
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</table>
Another common criticism is that systematic reviews and meta-analyses are not original research. The reader can form an independent opinion on this issue. Nonetheless, the main parameter for judging a systematic review should be its novelty and its usefulness for the reader, not whether it represents original or secondary research (Biondi-Zoccai et al. 2003). Also, the recent introduction of indirect and network meta-analyses and mixed treatment comparisons allows accurate predictions which can be tested by subsequent randomized trials, so making this type of research design highly scientific.

Finally, a burning issue is whether results from large systematic reviews and meta-analyses can ever be applied to the single individual under our care. There is no universal answer to this question, and judgment needs to be used about applying meta-analysis results to a particular patient. However, like the advocates of evidence-based medicine, we believe that all patients are likely to benefit similarly from a specific treatment or diagnostic strategy, unless proven otherwise, for example by a significant test for statistical interaction (Guyatt et al. 2002).

2.4 Systematic Reviews and Meta-Analyses: How to Do It Yourself

Even those who do not have to undertake a systematic review can get a helpful insight into this method of clinical research by understanding the key steps involved in the design, conduct and interpretation of a systematic review (Biondi-Zoccai et al. 2004).

Briefly, a systematic review should always stem from a specific clinical question (Fig. 4). Even if the experienced reviewer can probably guess the answer to this question, and judgment needs to be used about applying meta-analysis results to a particular patient. However, like the advocates of evidence-based medicine, we believe that all patients are likely to benefit similarly from a specific treatment or diagnostic strategy, unless proven otherwise, for example by a significant test for statistical interaction (Guyatt et al. 2002).

1. Definition of question and hypothetical solution
2. Prospective design of the systematic review
3. Problem formulation (Population, Intervention or exposure, Comparison, Outcome [PICO])
4. Data search
5. Data abstraction and appraisal
6. Data analysis ± quantitative synthesis (i.e. meta-analysis)
7. Results interpretation and dissemination

Fig. 4 Simplified algorithm for the design and conduct of systematic reviews in clinical research. This scheme may appear quite rigid, but the systematic review process in fact requires repeat piloting of several steps of the review process to adjust it to the limitations inherent in the primary literature, for example the lack of high-quality studies on a given topic undergoing digital subtraction angiography (P), with the intervention of interest being the administration of isosmolar contrast agents (I), the comparators being low-osmolar contrast agents (C), and the outcomes defined as risk of death or permanent hemodialysis within 30 days (O).

After these preliminary steps, the actual review begins with a thorough and an extensive search, encompassing several databases (not only MEDLINE/PubMed) with the help of library personnel experienced in literature searches. When a list of potentially pertinent citations has been retrieved, these should be assessed and included or excluded based on criteria, which stem directly from the PICO approach of defining the clinical question. The study assessment also includes a formal evaluation of study validity and of the risk of bias of primary studies. Data abstraction is generally performed by at least two independent reviewers with differences of opinion resolved by consensus and provides the quantitative data, which will eventually be pooled by meta-analysis (Higgins and Green 2008).

Provided that the studies are relatively homogenous and consistent, meta-analytic methods are employed to combine effect estimates from single studies into a unique summary effect estimate, with corresponding p values for effect and confidence intervals.

The last step relies on the interpretation and dissemination of the results, possibly by publication in a peer-reviewed journal. In many cases, the results may make the reviewer go back to the original research question and, very often, to revise his or her working hypothesis.
Appraising primary research studies, as well as systematic reviews and meta-analyses should be based on their internal validity and then, provided this is reasonably adequate, on their results and external validity (Guyatt et al. 2002). While the interpretation of the results and external validity of any research project is highly subjective and best left open to the individual judgment of the reader or decision-maker, internal validity can be appraised in a very structured and validated way.

Recent guidance on the appraisal of the risk of bias in primary research studies in the context of a systematic review has been provided by The Cochrane Collaboration, and includes separate assessment of the risk of selection, performance, and attrition and adjudication bias, as clearly given in Table 3 (Higgins and Green 2008). Other valid and complementary approaches, devised for specific study designs, have been proposed by advocates of evidence-based medicine methods (Guyatt et al. 2002).

The quality of a systematic review and meta-analysis also depends on a number of factors, which include the quality of the primary pooled studies. Nonetheless, the quality of the report, for example the compliance with current guidelines on drafting and reporting a meta-analysis, should be clearly characterized by internal validity (Moher et al. 1999; Biondi-Zoccai et al. 2006; Liberati et al. 2009). This can be low even in well reported reviews, but it is usually difficult to consider a poorly reported systematic review and meta-analysis as being of great value. Assessing the internal validity of a review is quite complex and based on several assumptions, including study search and appraisal, methods for data pooling, and approaches to the interpretation of study findings. Useful guidance was provided by Oxman and Guyatt with their well validated method (Table 4).

More recently, other tools for the appraisal of systematic reviews have been suggested, such as the a measurement tool to assess systematic reviews (AMSTAR), which however awaits further validation (Shea et al. 2007).

### 3 Appraising Primary Studies, Systematic Reviews and Meta-Analyses

Appraisal of primary research studies, as well as systematic reviews and meta-analyses should be based on their internal validity and then, provided this is reasonably adequate, on their results and external validity (Guyatt et al. 2002). While the interpretation of the results and external validity of any research project is highly subjective and best left open to the individual judgment of the reader or decision-maker, internal validity can be appraised in a very structured and validated way.

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### 4 Focus on Adverse Events After Contrast Agents

While systematic reviews and meta-analyses have several general limitations (Egger et al. 2001), a number of drawbacks and potential threats to validity are specifically relevant to research on adverse events after contrast agents. These include analytical issues associated with low event rates and the ensuing risk of alpha and beta errors, the common reliance on surrogate (thus softer) end-points, the impact of small study or publication bias, and, finally, the possibility that funding or conflicts of interest will affect the analysis. A detailed description of these threats to validity will be provided with some specific examples relevant to the contrast agent literature.
4.1 Analytical Challenges Caused by Low Event Rates

Adverse reactions to contrast agents are relatively uncommon, so low event rates often occur in primary research studies, unless they are extensively powered, for example by enrolling over 1,000 patients enrolled or by selectively recruiting very high-risk subjects. This fact may lead to null counts in one or more of the groups undergoing comparison in a controlled trial, and may cause severe difficulties in the analysis. Most statistical methods used for meta-analytic pooling require at least one event to have occurred in each study group. When this is not the case in one or more of the groups under comparison, bias may be introduced by the common practice of adding 0.25 or 0.50 to each group without events (Sweeting et al. 2004; Golder et al. 2006). In addition, when no event has occurred in any group, no comparison can be performed and data from such an underpowered study cannot be pooled for meta-analysis, as variance of the effect estimate approaches $\infty$.

4.2 Risk of Alpha Error

Alpha error is the risk of erroneously dismissing a null hypothesis despite it being true. Even when all groups being compared in a particular study have one or more events, the risk of biased estimates and alpha error may be present (Egger et al. 2001). Minor differences in few and rare events may provide nominally significant results (e.g., $p = 0.048$), which however may not be reliable. In such cases, we recommend reliance on the combined assessment of $p$ values and 95 % confidence intervals, or even pushing for 99 % confidence intervals. In other cases, a useful rule of thumb is only to trust meta-analyses which report on at least 100 pooled events per group being compared.

4.3 Risk of Beta Error

Beta error is the risk of erroneously accepting a null hypothesis despite it being false. This error is also common in systematic reviews and meta-analyses, especially when they include few studies with low event counts. This lack of statistical power (defined actually as 1-beta) is even more common with meta-regression analyses, which are usually underpowered because of the few studies included and because of regression to the mean phenomena (Thompson and Higgins 2002).

4.4 Reliance on Surrogate End-Points

Surrogates may help the design of clinical research, by increasing statistical power and giving an insight into more than one clinical outcome. However, choosing the example of contrast medium induced nephropathy (CIN), surrogates, such as a greater than 25 % increase in serum creatinine from baseline value, may be less clinically relevant than hard clinical end-points, such as death or a permanent need for hemodialysis (Guyatt et al. 2002). Usually, only surrogates which have a direct impact on patient well being and are clearly and independently associated with hard clinical end-points should be accepted in the design of clinical research studies.

A study with significant results for surrogate end-points but not for hard end-points should be considered as generating a hypothesis or, at best, underpowered.
4.5 Small Study and Publication Bias

Small study bias is always a potential threat to the results of a systematic review, because this type of problem affects all clinical topics and research study designs (Biondi-Zoccai et al. 2008). While this type of bias may have less impact in studies on recent and well financed drugs (e.g., fenoldopam) or devices, in other examples of cheaper interventions, publication bias may profoundly undermine the results of a systematic review. This applies particularly not only to the research evidence, which has now accumulated on acetylcysteine for the prevention of CIN (Biondi-Zoccai et al. 2006), but also to other commonly prescribed agents such as contrast media (Kwok et al. 2013).

4.6 Conflicts of Interest and Funding Issues

Another major threat to the validity of a systematic review, as to any other research project, is caused by conflicts of interest, including how studies are funded. It is recognized that reviewers with underlying financial conflicts of interest are more likely to draw conclusions that favor an intervention, which benefits the source of any financial gain (Barnes and Bero 1998). Most studies on contrast media were undertaken by investigators with either overt or probable conflicts of interest (Aspelin et al. 2003; Solomon et al. 2007). Whether these facts should just lead to more critical reading of their work or should stimulate a comprehensive re-evaluation of their whole research project is best left to the discretion of the reader. It also depends on the internal validity of the study, for example the blinding of patients, physicians, adjudicators, and analysts.

5 Conclusions and Future Perspectives

Systematic reviews and meta-analyses are powerful methods to assess the clinical effects of interventions in healthcare. They may be particularly helpful for assessing the risk of adverse effects after contrast agents and for comparing the risk of adverse effects with different contrast agents. However, more collaborative research effort is needed to set up international groups able to design, conduct, and disseminate individual patient data meta-analyses, which can combine the results from individual clinical trials in an unbiased and rigorous way (Antithrombotic Trialists’ Collaboration 2002). A further worthwhile goal is to foster collaboration to further develop and apply network meta-analytic methods, which identify the best preventive and management strategies for contrast medium-associated adverse events based on all the clinical evidence.

References


Part II

Iodine- and Gadolinium-Based Contrast Media: General Adverse Reactions
Acute Adverse Reactions to Contrast Media: Mechanisms and Prevention

Olivier Clement and Judith A. W. Webb

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Abstract

Acute adverse reactions are defined as reactions occurring within the hour following contrast medium injection. They may occur after any of the contrast agents used for radiography, ultrasound, or magnetic resonance imaging. The majority of reactions are mild, and some of the mild symptoms reported are not even caused by the contrast agent. However, severe and life threatening reactions may still occur. Hypersensitivity reactions after contrast medium may be allergic or non-allergic. The factors predisposing to acute reactions and the methods to reduce the incidence of acute reactions to both iodine- and gadolinium-based reactions are discussed in this chapter. The use of premedication is controversial, as the limited scientific basis for its use is now recognized. Even after premedication, adverse reactions may still occur.

1 Introduction

Acute adverse reactions are defined as reactions occurring within the hour following the contrast medium injection. They are traditionally divided into allergy-like (anaphylactoid or idiosyncratic) reactions, which are unpredictable and unrelated to the amount of contrast medium and non-allergy-like (chemotoxic or osmotoxic) reactions, such as pain, a sensation of heat, or pulmonary edema produced by the increased osmotic load, which are dose dependent. Fortunately, most reactions are mild and require no treatment. The fact that moderate and severe acute non-renal adverse reactions are infrequent after administration of non-ionic iodine-based contrast agents explains why most studies of acute non-renal adverse reactions were done in the last century, when the old ionic high-osmolar contrast agents were used.

The European Academy of Allergology and Clinical Immunology proposed Hypersensitivity (HS) as a general term for allergy-like reactions (Johansson et al. 2001; Rubio et al. 2010). HS reactions can be immune in origin (allergic...
Most of this chapter is concerned with acute hypersensitivity reactions to iodine-based contrast media, particularly the factors predisposing to these reactions and the measures that may be taken to prevent them. At the end of the chapter, acute reactions to gadolinium-based contrast media are also discussed ("Acute Adverse Reactions to Gadolinium-Based Contrast Media").

1.1 Lalli and Weber Effects

Not all symptoms experienced by patients in the hour following contrast medium injection are adverse reactions to the contrast agent: some of the symptoms may be explained by the so-called Lalli and Weber effects. In 1980, Dr. Lalli wrote in Radiology “The experience of investigating these deaths from contrast media has resulted in amplification of my previous opinions—that the most important factors in the production of contrast media reactions are the patient’s fear and apprehension. I now believe it possible to explain all reactions to contrast media through CNS mechanisms” (Lalli 1980). Four years later Weber (1984) showed that, when a new drug is first introduced, adverse effects after it are over-reported. Weber looked at non-steroidal antiinflammatory drugs (NSAIDs), but the phenomenon now called the Weber effect is not unique to NSAIDs. There is no doubt that both the Lalli and the Weber effects are seen after contrast media administration (Davenport et al. 2013; Thomsen and Webb 2012; Azzouz et al. 2013). The Weber effect is not only seen when a contrast agent is introduced, but also when a department changes from one agent to another.

Comparative studies of acute non-renal adverse reactions to contrast media must ensure that the different agents are given under identical conditions. In retrospective studies the Lalli and Weber effects are not controlled, so prospective randomized studies are the only way to obtain reliable data (Thomsen and Webb 2012).

2 Iodine-Based Contrast Media

2.1 Classifications of Reactions

Many patients who are given intravascular iodine-based contrast media experience some subjective sensations such as warmth, flushing, and altered taste. These common effects usually last for a few minutes and are not of clinical significance.

In the radiological literature, hypersensitivity or allergy-like reactions have been classified as mild or minor, moderate, or severe, depending on the type of treatment required (Bush and Swanson 1991). Mild or minor reactions usually do not need treatment and include nausea, mild vomiting, urticaria, and itching. Moderate reactions include more severe vomiting, marked urticaria, bronchospasm, facial or laryngeal edema, and vasovagal reactions. Severe reactions include hypotensive shock, pulmonary edema, respiratory arrest, cardiac arrest, and convulsions (“ESUR Guidelines on Contrast Media Version 8.1”). While this type of classification is widely used in clinical practice, it does not take the pathophysiological mechanisms into account, and is therefore of limited use to indicate the appropriate management when the patient requires contrast medium on a subsequent occasion.
Most acute reactions occur early after contrast medium administration. In Katayama et al.’s (1990) study of over 330,000 patients, over 70% of reactions to both ionic and non-ionic contrast media occurred in the first 5 min. In all 44 patients who died after intravascular contrast medium (reviewed by Shehadi 1985), the acute reaction to contrast medium started within 15 min of administration.

The general incidence of anaphylactic reactions is increasing (Resuscitation Council (UK) 2008). It is not known whether this is also the case for anaphylactoid reactions to contrast media.

Mild acute adverse reactions are the most frequent. The frequency of such reactions reported in the literature varies from 1 to 50%. The lowest figures are found in retrospective studies based on reviews of patient records. With prospective studies the frequency depends on whether adverse events were spontaneously reported or were sought by interview and on how detailed the interview was. When patients who have had CT or MR scans are interviewed a number who had the examinations without contrast medium report the same mild symptoms as patients who received intravenous contrast medium. (Azzouz et al. 2013).

### 2.2 Mechanisms of Acute Reactions

The exact mechanisms by which acute adverse reactions to iodine-based contrast medium occur are still unclear (Idee et al. 2005; Morcos 2005; Dewachter et al. 2006) and this makes prevention of reactions more difficult. True allergic hypersensitivity appears to account for some severe acute reactions (Brockow et al. 2009; Scherer et al. 2010; Nasser and Ewan 2010). Laroche et al. (1998) showed immediate marked rises in plasma histamine and tryptase levels in patients who had severe acute reactions, with the levels being proportional to the severity of the reaction. The timing and size of the increases were similar to those observed in known allergic hypersensitivity reactions, which suggested that immediate mast cell degranulation had occurred. Contrast-medium-specific IgE levels were higher in severe reactors than controls (Laroche et al. 1998). In some severe reactors, skin testing with contrast medium was positive (Laroche et al. 1998; Dewachter et al. 2009). Some cross-reactivity between contrast media has been shown in reactors, and in some patients non-cross-reacting contrast media were subsequently administered without problems (Dewachter et al. 2009).

How iodine-based contrast media act as antigens remains a problem, as they bind poorly to protein (Lasser et al. 1962). One suggestion, based largely on in vitro experiments, is that contrast media act as “pseudoantigens” that attach to the fixed Fc site on the IgE molecule rather than the variable Fab site of specific antigen binding (Lasser 2004).

When mast cells are activated, heparin is also released and can activate the contact system with the release of bradykinin (Lasser 1987, 2004). In addition, other mediators, such as prostaglandins, leukotrienes, and cytokines, are likely to be involved (Dewachter et al. 2006).

Complement levels in the blood decrease after contrast medium, both in control subjects and reactors, with the decreases being greater in the reactors (Eloy et al. 1991). Although contrast media may be able to activate the complement system, it is considered unlikely that this mechanism is responsible for acute reactions (Dewachter et al. 2006).

The immediate nonallergic effects of contrast media could be caused by direct chemotoxicity.

Nonallergic hypersensitivity could also relate to the nonspecific release of small amounts of histamine from mast cells and/or basophils, which occurs in up to 80% of patients in the minutes immediately after contrast medium (Eloy et al. 1991; Rodriguez et al. 2001; Dewachter et al. 2006). This effect relates to the nature of the contrast medium molecule as well as the dose and osmolality of the contrast agent.

### 2.3 Risk Factors for Acute Hypersensitivity Reactions

#### 2.3.1 Type of Contrast Agent

With the older high-osmolality ionic agents, the rate of reactions of all types was reported to be in the range 5–12% (Ansell et al. 1980; Witten et al. 1973; Shehadi 1975; Katayama et al. 1990; Cochran et al. 2001). Most reactions in these series were mild, with moderate reactions occurring in 1–2% and severe reactions in approximately 0.10–0.15% (Ansell et al. 1980; Witten et al. 1973). Mortality with the ionic agents is in the range 1 in 14,000 to 1 in 169,000 (Shehadi 1975; Katayama et al. 1990), with 1 in 75,000 an often quoted figure (Hartman et al. 1982).

With the newer low-osmolality non-ionic agents, the reaction rates are lower, by a factor of approximately 4–5 times (Katayama et al. 1990; Palmer 1988; Wolf et al. 1991; Bettman et al. 1997). Thus, in Katayama’s series of over 300,000 patients, the reaction rates for ionic and non-ionic agents were overall 12.66 and 3.13%, with severe reactions in 0.22 and 0.04%, respectively (Katayama et al. 1990). The Katayama study was an observational study so patients were not interviewed to ask about their symptoms. On the basis of a meta-analysis of all data published between 1980 and 1991, Caro et al. (1991) concluded that 80% of contrast media reactions could be prevented by using low-osmolality contrast media.
agents. This is probably valid for the most frequent mild reactions, but not for severe reactions, which unfortunately still occur despite the general use of non-ionic agents.

In Katayama et al.’s (1990) series there was no significant difference in mortality between the ionic and non-ionic agents, but other data suggest a lower mortality with non-ionic agents (Lasser et al. 1997).

In summary, although the incidence of acute reactions has generally decreased with the widespread use of low-osmolality agents, severe life threatening reactions may still occur, and the radiology department staff must be trained to institute the correct treatment.

2.3.2 Previous Contrast Medium Reaction
A previous reaction to an iodine-based contrast medium is the most important patient factor predisposing to an acute hypersensitivity reaction (Bettman et al. 1997). With ionic agents, the risk of a reaction in a patient who had reacted previously has been stated to be 16–35 % (Witten et al. 1973; Shehadi 1975) and to be 11 times greater than the risk in a non-reactor (Ansell et al. 1980). In these studies, however, the reactions were not evaluated to distinguish allergic from nonallergic hypersensitivity. In allergic HS, it is to be expected that reinjecting the culprit agent will again trigger a reaction, since the patient is truly allergic to the agent. In such patients the triggering agent should be avoided and a contrast agent to which the patient is not allergic should be used. In a nonallergic HS reaction, any iodine-based contrast agent could trigger this non-specific phenomenon and reproduce the initial symptoms. It is therefore very important to characterize acute reactions precisely using biological and allergological tests so that appropriate advice can be given before future injections.

2.3.3 Asthma
Asthma is a risk factor that is frequently cited. Shehadi (1975) found that 11 % of asthmatics had a reaction to ionic contrast media, and Ansell et al. (1980) stated that the risk of reaction to ionic agents was increased 5 times in an asthmatic. In patients with asthma, Katayama et al. (1990) described an 8.5 times increased risk with ionic agents and a 5.8 times increased risk with non-ionic agents.

The degree of control of the asthma appears to be more important than the fact that the patient is an asthmatic (Liccardi et al. 2009). If the asthma is unstable, and the patient has had an attack in the week before the proposed contrast medium injection, the contrast medium injection should be postponed until the asthma has been stabilized. If the asthma is stable, however, there is no need to give additional treatment before contrast medium administration (Vervloet et al. 2007).

2.3.4 Allergy
Several conditions, such as hay fever, eczema, allergy to foods, drugs, or other substances are associated with an increased risk of contrast medium reaction, usually by a lesser amount than a history of asthma (Ansell et al. 1980; Witten et al. 1973; Shehadi 1975; Katayama et al. 1990). These generally accepted statements in the radiological literature related to all patients with an apparent hypersensitivity reaction, but did not separate those with allergic from those with nonallergic hypersensitivity. Since there are no cross-allergic reactions between foods, drugs, and iodine-based contrast agents, it is more likely that these conditions are a risk factor for nonallergic hypersensitivity only (Dewachter 2006).

Allergy to foodstuffs that contain iodine, e.g., seafood, often causes particular anxiety. However, the available data suggest that allergy to seafood is no more significant than allergy to other foodstuffs (Witten et al. 1973; Shehadi 1975; Leder 1997).

Allergy to topical iodine skin preparations is a type of contact dermatitis and does not seem to predispose to acute idiosyncratic contrast medium reactions (Thomsen and Bush 1998).

2.3.5 Drugs
Whether ß-blockers affect the incidence of idiosyncratic contrast medium reactions is controversial. Greenberger et al. (1987) reported that neither ß-blockers nor calcium antagonists, given separately or together, increased the risk of reaction. Subsequently, however, Lang et al. (1991) found that ß-blockers did increase the risk of reaction. It is, however, agreed that the use of ß-blockers can impair the response to treatment if a reaction does occur (Thomsen and Bush 1998; Greenberger et al. 1987; Lang et al. 1991).

Since a large number of patients are receiving ß-blockers, and the probability of a severe reaction is very low, it does not seem warranted to stop beta blocking drugs before contrast medium injection.

Patients who are receiving or have received interleukin-2 are at increased risk of adverse events following iodine-based contrast media. Some of these adverse events appear to recall the side-effects of interleukin-2 (e.g., fever, nausea, vomiting, diarrhea, pruritus, and rash) (Zukiwski et al. 1990; Fishman et al. 1991; Oldham et al. 1991; Choyke et al. 1992). Reactions are often late, occurring more than 1 h after contrast medium, but can also occur within the first hour (Choyke et al. 1992; “Contrast Media and Interactions with Other Drugs and Clinical Tests”).

2.3.6 Other Factors
Female gender has been associated with an increased risk of acute reactions (Lang et al. 1995; Bettman et al. 1997).
Ethnicity may also increase the risk of acute reaction, with more reactions in the UK occurring in Indians and subjects of Mediterranean origin than in the indigenous white population (Ansell et al. 1980).

### 2.4 Extravascular Administration of Iodine-Based Contrast Media

Acute adverse reactions to iodine-based contrast media are almost always associated with intravascular administration. However, there are case reports of hypersensitivity reactions after administration of iodine-based contrast media into body cavities—for example, during cystography, retrograde pyelography, arthrography, and oral administration for evaluation of the gastrointestinal tract (Weese et al. 1993; Hugo et al. 1998; Miller 1997; Armstrong et al. 2005). In such cases, the reaction may occur later than after intravascular injection, because of the time needed for the contrast medium to enter the circulation.

### 2.5 Diagnosis of an Acute Hypersensitivity Reaction

Allergic and nonallergic hypersensitivity reactions can be differentiated using clinical, biological, and allergological evaluation:

- The clinical symptoms should be graded using the Ring and Messmer classification (Table 1): the more severe the reaction, the more chance it is truly allergic.
- Raised tryptase levels in blood samples taken after the reaction, preferably within 2 h, indicate a true allergic reaction. Raised histamine levels are less specific.
- Positive skin tests performed 1 month after the reaction with the triggering contrast agent indicate true allergy.

### 2.6 Prevention of Acute Hypersensitivity Reactions

In patients at increased risk of contrast medium reaction, especially if there has been a previous reaction to an iodine-based contrast agent, the possibility of obtaining the necessary diagnostic information from another test, not using iodine-based contrast medium (e.g., ultrasonography, magnetic resonance imaging), must be considered. If iodine-based contrast medium is still considered necessary, the use of an appropriate contrast medium is essential. The use of premedication remains controversial.

Because most severe reactions occur within the first 20 min after contrast medium injection (Hartman et al. 1982; Shehadi 1985), patients should remain in the Radiology Department or in a medical environment for at least this period (usually 30 min).

#### 2.6.1 Choice of Contrast Medium

The single most important method of reducing the risk of hypersensitivity contrast medium reactions is to use non-ionic, low-osmolality agents, which are associated with a 4–5 times lower risk of reactions (Katayama et al. 1990; Palmer 1988; Wolf et al. 1991; Bettman et al. 1997). In many countries, non-ionic agents are used for all intravascular administration of contrast material. Where this is not possible, selective use of non-ionic agents in patients at increased risk of reaction is recommended (King 1999).

When there has been a previous reaction to non-ionic iodine-based contrast medium, the use of a different agent may be helpful (Thomsen and Bush 1998; Dewachter et al. 2006). The decision to use another agent should be based on

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**Table 1** Ring and Messmer’s four-grade classification of hypersensitivity reactions gives a more detailed and reproducible documentation of acute hypersensitivity reactions (Laroche et al. 1998; Idee et al. 2005)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
<th>Abdomen</th>
<th>Respiratory tract</th>
<th>Cardiovascular system</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Pruritus, flush, urticaria, angioedema</td>
<td></td>
<td>Rhinorrhea, hoarseness, dyspnoea</td>
<td>Tachycardia (&gt;20 beats/min), BP change (&gt;20 mmHg systolic), arrhythmia</td>
</tr>
<tr>
<td>II</td>
<td>Pruritus, flush, urticaria, angioedema (not mandatory)</td>
<td>Nausea, Cramping</td>
<td>Laryngeal edema, bronchospasm, cyanosis</td>
<td>Shock</td>
</tr>
<tr>
<td>III</td>
<td>Pruritus, flush, urticaria, angioedema (not mandatory)</td>
<td>Vomiting, defecation, diarrhea</td>
<td>Respiratory arrest</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>IV</td>
<td>Pruritus, flush, urticaria, angioedema (not mandatory)</td>
<td>Vomiting, defecation, diarrhea</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Alternative contrast agents should also be tested (Dewachter et al. 2009; Torres et al. 2012).
the results of skin testing and on other allergological evidence obtained after the previous reaction.

2.6.2 Premedication: Possible Regimes and Evidence of Their Efficacy

A variety of premedication regimes have been used. Most frequently, steroids with or without additional H1 antihistamines have been recommended, and other drugs, such as ephedrine and H2 antagonists, have also been tried.

With ionic agents, there is good evidence that steroids reduce the rate of reactions. In a randomized study of 6,763 unselected patients, Lasser et al. (1987) showed a reduction in the incidence of reactions to ionic contrast media from 9 to 6.4 % when methylprednisolone was given 12 and 2 h before the contrast agent. In patients who have previously reacted to ionic contrast media, a combination of steroid and H1 antihistamine reduces the repeat reaction rate, estimated to be 16–35 % without premedication (Witten et al. 1973; Shehadi 1975). The addition of the H2 antagonist cimetidine to the steroid, antihistamine, and ephedrine premedication was associated with a higher risk of reaction (Greenberger et al. 1985). With the ionic low-osmolality agent meglumine ioxaglate, Bertrand et al. (1992) found that the antihistamine hydroxyzine reduced the risk of urticaria from 12.5 to 1.0 % in 200 subjects.

With the non-ionic, low-osmolality agents, there is less evidence of the value of premedication, but the available evidence suggests that premedication may further reduce the incidence of reactions. In a randomized study of 1,155 unselected patients, Lasser et al. (1994) found a statistically significant decrease in the total number of reactions from 4.9 to 1.7 % when patients given non-ionic contrast media were premedicated with methylprednisolone given 12 and 2 h before the contrast agent. The number of moderate and severe reactions was also less after steroids, but the numbers were small and no statistically significant difference was found. In previous reactors, Greenberger and Patterson (1991) found that the combined use of a non-ionic agent together with both prednisone and antihistamine or prednisone, antihistamine, and ephedrine reduced the repeat reaction rate to 0.5 % in 181 patients. In patients who had previously reacted, or who had a history of allergy or severe cardiopulmonary disease, H1 and H2 antagonists reduced the reaction rate to 1.57 % in 1,047 patients, as compared to a reaction rate of 4.37 % in those who were not pre-medicated (Fink et al. 1992).

When steroid premedication is used, the steroids should be given at least 12 h before the contrast medium. The minimal effective time interval between steroids and contrast medium is considered unlikely to be less than 6 h (Lasser et al. 1987; Morcos et al. 2001).

2.6.3 Premedication: Controversies

With the ionic agents, the higher risk of reaction and the stronger evidence for the value of premedication meant that steroid premedication was widely recommended and used (Greenberger et al. 1984; Lasser et al. 1987). With non-ionic agents, the use of premedication is more controversial and practice is variable (Dawson and Sidhu 1993; Lasser 1994, 1995; Dore et al. 1994, 1995; Lasser and Berry 1994; Seymour et al. 1994; Cohan et al. 1995; Dawson 2005; Radhakrishnan et al. 2005).

Since a systematic examination of hypersensitivity reactions with blood and skin tests has not yet been performed, the available literature provides very weak evidence for using premedication. Anaphylactic shock caused by true allergic hypersensitivity will never be prevented by premedication with antihistamines and steroids. However, a mild grade 1 cutaneous nonallergic HS reaction may be avoided if antihistamines are given.

After premedication has been given, the radiologist should not feel secure (Freed et al. 2001) because only mild skin reactions will potentially be avoided. The radiologist should always be ready to treat the patient if there is a severe adverse reaction, with the drugs and equipment for treatment readily available and the team trained in resuscitation. (“Management of Acute Adverse Reactions to Contrast Media”).

The ACR Committee on Drugs and Contrast Media (2012) states that the higher the risk of reaction, the stronger the case that can be made for premedication. The European Society of Urogenital Radiology guidelines indicate that opinion on this topic is divided, and therefore do not give a directive.

2.6.4 Pretesting and Injection Rate

The practice of pretesting—giving a small preliminary test dose of contrast medium intravenously before the full dose is given—has been shown to be of no value and is potentially dangerous (Shehadi 1975; Fischer and Doust 1972; Yamaguchi et al. 1991).

Injection rate does not appear to have any effect on the rate of adverse reactions (Jacobs et al. 1998).

2.7 Summary: Iodine-Based Contrast Media

To reduce the risk of an acute reaction to intravascular iodine-based contrast media, the important measures for all patients are as follows:

- Use non-ionic contrast media.
- Keep the patient in the Radiology Department or in a medical environment for 30 min after contrast medium injection.
• Have the drugs and equipment for resuscitation readily available.

There is an increased risk of an acute reaction to intravascular iodine-based contrast media in patients with a history of

• previous generalized reaction to iodine-based contrast medium, either moderate (e.g., urticaria, bronchospasm) or severe (e.g., hypotension, severe bronchospasm, pulmonary edema, cardiovascular collapse, convulsions).
• unstable asthma.
• an allergy requiring medical treatment.

In patients with an increased risk of a reaction to intravascular iodine-based contrast media
• Consider whether the use of iodine-based contrast medium is essential and whether another test (e.g., ultrasonography, magnetic resonance imaging) would give the diagnostic information needed.
• Consider the use of a different iodine-based agent for previous reactors to a contrast medium, with the help of skin tests performed by an allergist.
• Premedication for previous reactors to iodine-based contrast media and high-risk patients remains controversial and cannot prevent anaphylactic shock.

Note: Practice for the use of premedication is variable. If premedication is used, a suitable corticosteroid premedication regime is prednisone 30 mg orally (or methylprednisolone 32 mg orally) given 12 and 2 h before contrast medium. H1 antihistamines may also be used.

Since contrast media administered into body cavities may reach the circulation in small amounts, take the same precautions as for intravascular administration (“ESUR Guidelines on Contrast Media Version 8.1”).

3 Gadolinium-Based Contrast Media

3.1 Types of Reaction and Frequency

Adverse events following intravenous gadolinium-based contrast media are less common than with iodine-based agents and most are minor and self-limiting (Runge 2000). Less than 1 % of patients develop allergy-like or hypersensitivity reactions, and most of these are mild (Murphy et al. 1999; Li et al. 2006; Dilman et al. 2007). Anaphylactoid reactions occur within the first 30 min of contrast medium injection (Murphy et al. 1996). Fatal reactions, although extremely rare, have been described with all commercially available gadolinium-based chelates (Jordan and Mintz 1995; Hasdenteufel et al. 2008).

3.2 Risk Factors for Reactions

3.2.1 Type of Contrast Medium

There appears to be no significant difference between the incidence of reactions with the different gadolinium-based agents, both ionic and non-ionic (Kirchin and Runge 2003; “Acute Adverse Reactions to Gadolinium-Based Contrast Media”).

3.2.2 Patient Risk Factors

Patients with a history of previous reaction to iodine-based or gadolinium-based contrast media, or with a history of asthma or allergy, have an increased risk of acute reaction following administration of gadolinium-based contrast media (Nelson et al. 1995; Li et al. 2006; Dillman et al. 2007).

3.3 Prevention of Reactions

No evidence is available in the literature to indicate what measures should be taken to prevent a reaction to gadolinium-based contrast media. The measures to be taken when a patient has previously had a reaction to gadolinium-based contrast agent or is considered to be at high risk are therefore based on principles similar to those for iodine-based contrast agents (see ACR Manual 2012 and Sect. 3.4 below). However, premedication does not prevent all reactions, especially the severe ones. Even after corticosteroid and antihistamine administration, break-through reactions have occurred after gadolinium-based contrast agents (Dilman et al. 2008).

3.4 Summary: Gadolinium-Based Contrast Media

The risk of an acute reaction to gadolinium-based contrast media is very low, and lower than the risk of a reaction to iodine-based contrast media. Nonetheless, for all patients the following is recommended:

• Keep the patient in the Radiology Department or in a medical environment for 30 min after contrast medium injection.
• Have the drugs and equipment for resuscitation readily available.

The type of contrast medium, ionic, or non-ionic, does not appear to affect the incidence of reactions to gadolinium-based agents.

In patients with a previous reaction to a gadolinium-based agent or who are considered at very high risk:

• Consider whether the use of gadolinium-based contrast medium is essential, and whether an unenhanced scan or other test would give the diagnostic information needed.
• Choose a different gadolinium-based agent to that used when the patient had a previous reaction,
• Premedication is, as for iodine-based agents, controversial.

4 Records of Acute Adverse Reactions (CAVE or Warning)

It is very important that acute adverse reactions are properly noted in the patient’s records, so that the necessary information is available before the next examination and appropriate precautions can be taken. All reactions which require medical treatment should be recorded, but mild reactions not requiring any treatment should not be recorded, because they may not relate to the contrast medium. The only exception to this would be if a skin test has been done and shown evidence of allergic hypersensitivity. If minor symptoms, e.g., dizziness or nausea, which may be due to the examination and not the contrast agent, are recorded, the patient may in future be denied a clinically important enhanced examination.

References

ACR Committee on Drugs and Contrast Media (2012) ACR Manual on Contrast Media version 8.0. ISBN: 978-1-55903-009-0
Iodine-Based Contrast Medium Temperature and Adverse Reactions

Henrik S. Thomsen

Abstract

Warming changes the bolus kinetics of iodine-based contrast media and the pressure needed to inject them. It may also reduce the rate of acute non-renal adverse reactions.

1 Viscosity

The viscosity of a contrast medium formulation is of practical importance for hand injection, because more pressure is needed to deliver a high viscosity preparation through a needle or cannula. This has become less of a problem now that power injectors are almost invariably used in computed tomography, the current commonest indication for iodine-based agents. There are significant differences in the viscosities of the various commercially available agents, with the non-ionic dimer being the most viscous ("Contrast Media Classification and Terminology"). Viscosity is a function of solution concentration, molecular shape, and weak interactions among the contrast agent and water molecules, including contrast agent self-association (Thomsen et al. 2014).

Temperature strongly affects viscosity, and contrast agent viscosity may be markedly reduced by warming to body temperature before injection. Contrast agents are usually stored at room temperature (\(\sim 18–22 \, ^{\circ}C\)), which is much lower than body temperature, and injection at room temperature may cause the patient some discomfort. There is a non-linear inverse relationship between temperature and viscosity. At 14 \( ^{\circ}C \), the non-ionic dimer ioxixanol is twice as viscous as the non-ionic monomer ioversol and the ionic dimer ioxaglate, but at 40 \( ^{\circ}C \) iodixanol is only 27 % more viscous than the two other agents (Brunette et al. 2008).

Warming iodine-based contrast agents is generally regarded as best practice.
There is speculation that both osmolality and viscosity can affect kidney toxicity, contrast-induced nephropathy (CIN), because the contrast agents can be heavily concentrated in the renal tubules during excretion (Seeliger et al. 2012).

2 Acute Adverse Reactions and Heated Contrast Medium

One hundred patients were assigned in a double-blind fashion to receive ionic high osmolality contrast media either at room temperature (20–24 °C) or human body temperature (37 °C). When the anaphylactoid and nonanaphylactoid adverse event rates in the two groups were compared, no significant difference was found (Turner et al. 1982).

In a nonrandomized prospective study of 4,936 intravenous injections of iodine-based contrast media, each of four groups of patients received a specific contrast media and temperature combination (Vergara and Seguel 1996). One group received ionic contrast medium, with sodium meglumine as the cation, warmed to 35 °C before injection; one received the same contrast medium at room temperature; one received warmed, ionic contrast medium with pure meglumine as the cation, and one received warmed, non-ionic iopamidol. There was a statistically significant decrease (P<.05) in adverse reactions to ionic contrast material when it was warmed before administration. They concluded that, for CT, non-ionic, warmed contrast medium was the best option, because there were no severe reactions in the group which received this.

Recently, a major study of the effect of extrinsic warming on intravenous low osmolality non-ionic monomers was published (Davenport et al. 2012). In a retrospective analysis of 24,830 power-injections (<6 ml/s), the authors compared the rates of allergic-like reactions before and after the discontinuation of contrast media warming at a single institution for both iopamidol 300 and the more viscous iopamidol 370. Extrinsic warming to 37 °C did not appear to affect adverse event rates for intravenous injections of iopamidol 300 but was associated with a significant reduction in extravasation and overall adverse event rates for the more viscous iopamidol 370. The authors did not have any data which allowed the evaluation of the effect of extrinsic contrast media warming on patient comfort or physiological adverse events, such as nausea or a sensation of warmth.

3 Conclusion

Warming contrast medium before administering may reduce the rate of acute non-renal adverse reactions. However, the data on this are limited. Clinical observation suggests that patients are often more comfortable if the contrast medium is warmed before administration and contrast medium warming is widely regarded as best practice.

References

Management of Acute Adverse Reactions to Contrast Media

Henrik S. Thomsen

Abstract

This chapter describes the optimal first-line treatment of acute non-renal adverse reactions to contrast media. These reactions are infrequent and often occur unexpectedly. Prompt and effective treatment is very important and requires knowledge, training, and preparation.

1 Introduction

Improvements in the physicochemical properties of iodine-based contrast medium molecules, particularly the development of lower osmolality agents, were followed by a significant decrease in the frequency of acute adverse reactions (Pollack 1999; Thomsen and Morcos 2000). Similar acute adverse reactions may occur after gadolinium-based and ultrasound contrast media, with the incidence significantly lower with gadolinium-based contrast media than with iodine-based agents, and even lower with ultrasound agents. Nonetheless, serious reactions may still occur and remain a source of concern.

Much of the knowledge about first-line treatment of acute adverse contrast medium reactions derives from the time when high osmolar iodine-based ionic agents were used, and from the management of acute adverse reactions to drugs other than contrast media. With the current contrast agents, the incidence of acute adverse reactions is sufficiently low that it is difficult to collect study populations of sufficient size to evaluate treatment of reactions prospectively. The management of acute adverse reactions is identical whether they are caused by iodine- or gadolinium-based agents or by ultrasound agents.

A local audit in Australia demonstrated deficient acute management of anaphylactoid/anaphylactic reactions in radiology departments by both consultants and trainees (Bartlett and Bynevelt 2003). Six years later Lightfoot et al. 2009 reported similar problems in the USA and Canada.
They surveyed radiologists’ knowledge about the management of severe contrast-material-induced allergic reactions. No radiologist gave the ideal response, but 41% provided an acceptable drug administration route, concentration, and dose. Only 11% knew which concentration of epinephrine was available in their drug kit and/or crash cart and which equipment would be required to administer it to a patient. A poorly managed resuscitation situation and adverse outcome will be costly to practice as well as the individual in terms of financial loss and professional respect. All radiologists should be prepared to give immediate treatment for acute contrast medium reactions. Therefore, first-line management should be simple and suitable for the current era when acute adverse reactions are rare. The subsequent management of severe adverse reactions including administration of second-line drugs should be handled by the resuscitation team.

2 Risk Factors for Acute Reactions to Iodine-Based Contrast Media

The discussion of risk factors and incidence refer to iodine-based contrast agents about which much more data is available. A history of previous moderate or severe adverse reaction to iodine-based contrast media is an important risk factor (Katayama et al. 1990; Morcos et al. 2001). In Katayama et al.’s (1990) series of over 330,000 patients, there was a six-fold increase in reactions to both ionic and non-ionic contrast media following a previous severe adverse reaction. Asthma is also an important risk factor with a reported six- to ten-fold increase in the risk of a severe reaction in such patients (Katayama et al. 1990). Patients treated with interleukin-2 are at increased risk of adverse reactions to contrast media, whereas whether or not β-adrenergic blockers affect the incidence of idiosyncratic contrast medium reactions is controversial (Greenberger et al. 1987; Oldham et al. 1990; Fishman et al. 1991; Lang et al. 1991, 1993; Choyke et al. 1992; Vervloet and Durham 1998; Taylor 1998). Greenberger et al. (1987) reported that neither β-blockers nor calcium antagonists given separately or together increased the risk of reaction. Subsequently, however, Lang et al. (1991, 1993) found that β-blockers did increase the risk of reaction. Today, β-adrenergic blockers are seldom stopped before giving intravascular contrast medium (Morcos et al. 2001).

In patients who have had a previous severe reaction to iodine-based contrast medium, most radiologists avoid giving intravascular contrast media if at all possible (Morcos et al. 2001). If the examination is considered essential, non-ionic contrast media are the agents of choice on the basis of the evidence in the literature that with non-ionic agents the risk of reaction is reduced by a factor of 4–5 (Katayama et al. 1990). The potential risks of the procedure should be explained to the patient, and the resuscitation team should be present when the contrast medium is given (Morcos et al. 2001) (Resuscitation Council (UK) 2008). Reactions can be divided into mild, moderate, and severe. The mild reactions include flushing, nausea, arm pain, pruritus, vomiting, headache, and mild urticaria. They are usually of short duration and self-limiting, and generally require no specific treatment. Moderate reactions include more serious degrees of the above symptoms and/or moderate degrees of hypotension and bronchospasm. They usually respond readily to appropriate treatment. Severe life-threatening reactions include severe manifestations of all the symptoms included under mild and moderate reactions in addition to symptoms such as convulsions, unconsciousness, laryngeal edema, pulmonary edema, cardiac dysrhythmias and arrest, and cardiovascular and pulmonary collapse (Grainger 1997).

3 Acute Adverse Reactions

An acute adverse reaction is defined as an adverse event that occurs within 60 min of an injection of contrast medium. Most anaphylactic reactions occur within 20 min after intravenous injection. Acute adverse reactions may occur despite premedication (Dilman et al. 2008; Davenport et al. 2009).

4 Incidence of Acute Reactions to Iodine-Based Contrast Media

Mild adverse reactions are encountered in as many as 15% of patients after intravenous ionic, high osmolality, iodine-based contrast agents (1,000–2,000 mOsm kg⁻¹H₂O) and up to 3% of patients after non-ionic, low-osmolality contrast media (500–1,000 mOsm kg⁻¹H₂O). Severe and very severe reactions occur much less frequently, with an incidence of 0.22 and 0.04% (respectively) in patients after intravenous high-osmolality contrast media and 0.04 and 0.004% in patients after low-osmolality contrast media. Thus, the incidence of contrast reactions with low-osmolality contrast media is lower than with high-osmolality contrast media by a factor of 5 for mild reactions and by a factor of 10 for severe reactions. Fatal reactions to both types of contrast media are exceedingly rare (1:170,000), with no difference in mortality reported between the two types of agent (Katayama et al. 1990; Thomsen and Dorph 1993; Thomsen and Bush 1998). In a retrospective study, Hunt et al. (2009) found that medical treatment was necessary after 0.026% of 298,492 intravenous injections of an iodine-based contrast medium and after 0.009% of the 158,439 injections of a gadolinium-based contrast medium.
5 Mechanisms and Pathophysiology

Adverse reactions to drugs are generally classified into those that occur only in susceptible subjects and those that may occur in anyone. Reactions occurring in susceptible subjects include drug intolerance (low threshold to the normal pharmacological action of a drug), drug idiosyncrasy (a genetically determined, qualitatively abnormal reaction to a drug related to metabolic or enzyme deficiency), drug allergy (an immunologically mediated reaction, characterized by specificity, prior exposure, transferability by antibodies or lymphocytes, and recurrence on re-exposure), and pseudoallergic reactions which are similar to allergic reactions but lack immunological specificity (non-specific complement activation and non-specific histamine release mimicking type 1 allergic reactions) (Stacul 1999).

Although some reactions are difficult to categorize, most non-renal side effects of intravascular contrast media are considered idiosyncratic or pseudoallergic reactions. They are unpredictable and not dose-dependent, and may involve the release of histamine and other active biological mediators such as serotonin, prostaglandins, bradykinin, Leukotrienes, adenosine, and endothelin (Almen 1994). Activation and inhibition of several enzyme systems have also been implicated. There is no conclusive evidence to indicate that reactions to iodine-based contrast media are allergic in nature since antibodies against contrast media including IgE have not been consistently demonstrated (Almen 1994; Siegle 1999; Laroche et al. 1998).

Chemotoxic-type effects may also occur and are determined by dose, the molecular toxicity of each agent, and the physiological characteristics of the contrast agents (i.e., osmolality, viscosity, hydrophilicity, affinity to proteins, calcium-binding properties, and sodium content). Chemotoxic effects of iodine-based contrast media are more likely to occur in patients who are debilitated or medically unstable. High osmolality (osmotoxicity) causes shift of fluids from the intracellular to the extracellular space, leading to cell dehydration and an increase in intracellular fluid viscosity precipitating cellular dysfunction (Almen 1994; Siegle 1999). Low hydrophilicity may reduce the biological tolerance to iodine-based contrast media since it is associated with an increase in lipophilicity and higher affinity of the contrast medium molecule to plasma proteins and the cell membrane. High hydrophilicity of non-ionic contrast media is produced by hydroxyl (-OH) groups which are symmetrically distributed, thereby offering a good coverage of the benzene ring and restricting access to lipophilic areas of the iodinated contrast molecule (Bonnemann et al. 1990; Almen 1994; Siegle 1999).

6 Treatment

The vast majority of patients with severe anaphylactoid type reactions recover if they are treated quickly and appropriately. Most patients have reactions while they are still in the radiology department, and 94–100 % of severe and fatal reactions occur within 20 min of the contrast medium injection (Shehadi 1985). The ability to assess and treat the contrast reaction effectively is an essential skill that the radiologist should have and maintain. The first-line drugs and equipment should be readily available in rooms in which either iodine- or gadolinium-based contrast agents are injected, and a list of recommended drugs and equipment is given in “ESUR Guidelines on Contrast Media Version 8.1”. A survey has shown that most departments have these items available (Morcos et al. 2001).

The radiologist should remain near the patient for at least the first critical minutes following contrast medium injection and should remain in the immediate vicinity for the next 30–45 min. If there is an increased risk of an adverse reaction, venous access should be left in place.

Important first-line management includes establishment of an adequate airway, oxygen supplementation, administration of intravascular physiological fluids, and measuring the blood pressure and heart rate. Talking to the patient as you check their pulse rate provides useful initial information: breathing is assessed, the possibility of a vagal reaction (bradycardia) is determined, and a rough estimate of systemic pressure is obtained (a palpable radial artery pulse approximates to a systolic pressure of 80–90 mmHg).

6.1 Drugs, Fluid, and Oxygen

The first-line drugs and most important emergency equipment (“ESUR Guidelines on Contrast Media Version 8.1”) should be available either in or just outside the room where contrast media are given.

6.1.1 Oxygen

Oxygen by mask at relatively high rate (6–10 l min⁻¹) is very important in the initial treatment of all severe reactions to intravascular contrast media and for other emergencies unrelated to contrast media that occur in the radiology department or angiography suite (e.g., vagal reaction, hypotension, cardiac ischemia). Hypoxia can be a major complicating factor in all these situations, and can be induced by drugs such as adrenaline used for treating reactions. A “non-rebreather” mask is optimal; nasal “prongs” are much less effective and should be avoided in an acute
situation for preventing hypoxemia. Oxygen should be used for all patients; a history of chronic obstructive pulmonary disease or emphysema is not a contraindication to start oxygen therapy for an acute reaction.

6.1.2 Intravascular Fluid Administration
Intravascular fluid administration is very important, and it alone has been reported to be the most effective treatment for hypotension (van Sonnenberg et al. 1987). Starting intravenous fluid early before drug treatment is the highest priority in treating hypotension. There is no evidence to support the use of colloids over crystalloids in this setting. For initial resuscitation, 0.9 % saline is a suitable fluid.

6.1.3 Adrenaline
Adrenaline is an effective drug for treating certain serious contrast medium reactions. Although there are no randomized controlled trials, adrenaline is a logical treatment (Resuscitation Council (UK) 2008). There is consistent anecdotal evidence supporting its use to ease breathing difficulty and restore adequate cardiac output. The ω-agonist effects of adrenaline increase blood pressure and reverse peripheral vasodilatation. The vasoconstriction induced decreases angioedema and urticaria. The β-agonist actions of adrenaline produce positive inotropic and chronotropic cardiac effects (increase in strength and rate of cardiac contractions), and may increase intracellular cyclic adenosine monophosphate (AMP) (Smith and Corbascio 1970; Hoffman and Lefkowitz 1990). Increments in baseline cyclic AMP levels are generally considered to inhibit mediator release from inflammatory cells. There are β-2 adrenergic receptors on mast cells that inhibit activation.

The use of adrenaline demands careful attention (Bush and Swanson 1991). For example, in individuals with a fragile intracerebral or coronary circulation, the ω-agonist effects of a large dose of adrenaline may provoke a hypertensive crisis that could cause a stroke or myocardial ischemia (Barach et al. 1984). β-receptor sites usually respond to lower doses of adrenaline than ω-sites, but if a patient is on β-blockers, the refractory response that may occur might encourage the radiologist to increase the dose of adrenaline to the point that there are unwanted ω-effects. Patients with chronic asthma may simulate patients receiving β-blockers since they may have a systemic β-adrenergic hyporesponsiveness. When chronic asthmatics develop an anaphylaxis-like reaction with asthmatic symptoms requiring β-receptor stimulation, one option is to use isoproterenol as the primary adrenergic drug, combined with more conservative doses of adrenaline (Ingall et al. 1984; Bush 1996).

When possible, adrenaline should be avoided for treating a pregnant patient with a severe contrast medium reaction and hypotension (Entman and Mosie 1984). Because uterine vessels are sensitive to the ω-effect of adrenaline, the combination of hypotension plus adrenaline can cause harmful sequelae to the fetus. Ephedrine is a possible alternative.

Only one concentration (1:1,000) of adrenaline should be available in the radiology department to avoid confusion under stressful emergency conditions, where ampoules of different concentrations can be misidentified. The 1:1,000 preparations should be given intramuscularly only. Intravenous administration of adrenaline by inexperienced staff can be dangerous. The intramuscular route has several benefits: (1) there is a greater margin of safety (2) it does not require intravenous access, and (3) the intramuscular route is easier to learn. The best site for intramuscular injection is the anterolateral aspect of the middle third of the thigh. The needle used for injection needs to be sufficiently long to ensure that the adrenaline is injected into the muscle (Resuscitation Council (UK) 2008).

Dilution of adrenaline for intravenous use is time consuming and delays treatment. Only 43 % of the participants in an Australian audit knew the recommended dose of adrenaline (Bartlett and Bynevelt 2003). This reinforces the need for a standard dose such as 0.5 mg in adults and 0.3 mg in children between 6- and 12-years old (“ESUR Guidelines on Contrast Media Version 8.1”). Below 6 years of age, the Resuscitation Council in UK (2008) recommends 0.15 mg. If there is no improvement in the patient’s condition, the intramuscular adrenaline dose can be repeated at about 5 min intervals by non-specialists if the specialist resuscitation team has not arrived.

6.1.4 H2 Antihistamines and H2 Receptor Blockers
H2 antihistamines and H2 receptor blockers have a limited role in treating contrast media reactions. They are used primarily to reduce symptoms from skin reactions.

6.1.5 Corticosteroids
High-dose intravenous corticosteroids do not play a role in the first-line treatment of the acute adverse reaction. However, very high doses of corticosteroids may have an immediate stabilizing effect on cell membranes and may be used in the second-line treatment. Standard doses can be effective in reducing delayed recurrent symptoms, which can be observed for as long as 48 h after an initial reaction. It takes 6 h before corticosteroids are fully active (Lasser et al. 1977; Gillenberger et al. 1986).

6.1.6 Inhaled β-2 Adrenergic Agonists
Inhaled β-2 adrenergic agonists such as albuterol, metaproterenol, and terbutaline deliver large doses of bronchodilating β-2 agonist drugs directly to the airways with...
minimal systemic absorption and, therefore, minimal cardiovascular effects.

6.1.7 Atropine
Atropine blocks vagal stimulation of the cardiac conduction system. Large doses of atropine (0.6–1.0 mg) are indicated, since low doses (e.g., less than 0.5 mg) of atropine can be detrimental for treating bradycardia associated with contrast-media-induced vagal reactions (Chamberlain et al. 1967; Stanley and Pfister 1976; Brown 1990; Bush and Swanson 1991; Bush et al. 1993).

6.2 Treatment of Specific Reactions

6.2.1 Nausea and Vomiting
Nausea and vomiting, though usually self-limited, may be the first signs of a more severe reaction. With urography using ionic, high-osmolar iodine-based contrast agents, 15–20 % of fatal reactions began with nausea and vomiting (Lalli 1980). For this reason, the patient should be observed closely for systemic symptoms while intravenous access is maintained. The injection should be slowed or stopped. In severe, protracted cases, injection of an antiemetic may be used (“ESUR Guidelines on Contrast Media Version 8.1”).

6.2.2 Cutaneous Reactions
Treatment is usually not necessary if there are only a few scattered hives or pruritus. However, the patient should be observed closely for other systemic symptoms that may develop, and intravenous access should be maintained. Treatment should be given only if the urticaria is extensive or bothersome to the patient (“ESUR Guidelines on Contrast Media Version 8.1”).

6.2.3 Bronchospasm
Bronchospasm without co-existing cardiovascular problems should be treated with oxygen and inhaled bronchodilators (“ESUR Guidelines on Contrast Media Version 8.1”). Using a metered dose inhaler, treatment typically involves two to three deep inhalations. Adrenaline may be used if bronchospasm is not relieved by the inhaled bronchodilators.

6.2.4 Laryngeal Edema
Laryngeal edema does not respond well to inhaled β-2 agonists; they may actually worsen it. Therefore, careful clinical evaluation of the patient before beginning treatment is extremely important to differentiate laryngeal edema from bronchospasm. Adrenaline is the primary treatment for laryngeal edema (“ESUR Guidelines on Contrast Media Version 8.1”). Oxygen administration is also important in the management of this condition.

6.2.5 Hypotension
Profound hypotension may occur without respiratory symptoms. Normal sinus rhythm and tachycardia differentiate this reaction from the so-called vagal reaction (hypotension plus sinus bradycardia). Initially, the patient’s legs should be elevated, since this returns about 700 ml of blood to the central circulation (van Sonnenberg et al. 1987). Isolated hypotension is best treated first by rapid intravenous fluid replacement rather than vasopressor drugs (“ESUR Guidelines on Contrast Media Version 8.1”). A total volume of up to 3,000 ml may be required to reverse the hypotension.

6.2.6 Vagal Reaction
Vagal reactions are characterized by the combination of prominent sinus bradycardia (pulse rate <60 beats/min) and hypotension (systolic pressure <80 mmHg). Although their exact cause is unknown, vagal reactions seem to be elicited or accentuated by anxiety. Proper recognition of this reaction and the associated bradycardia is vital so that the correct treatment of increasing intravascular fluid volume plus reversing the vagal stimulation is used. Elevation of the patient’s legs and rapid infusion of intravenous fluids treat the vasodilatation and expanded vascular space. The bradycardia is treated by intravenous administration of atropine to block vagal stimulation of the cardiac conduction system (“ESUR Guidelines on Contrast Media Version 8.1”).

6.2.7 Generalized Anaphylactoid Reactions
These are acute, rapidly progressing, systemic reactions characterized by multisystem involvement with pruritus, urticaria, angioedema, respiratory distress (bronchospasm and/or laryngeal edema), and profound hypotension that require prompt response. Anaphylaxis is likely when one of the following three criteria are met: (1) sudden onset and rapid progression of symptoms (2) life-threatening airway and/or breathing and/or circulation problems, and (3) skin and/or mucosal changes (flushing, urticaria, angioedema) (Resuscitation Council (UK) 2008). Recent exposure to a contrast agent supports the diagnosis. Initial treatment includes maintenance of the airway, administration of oxygen, rapid infusion of intravenous fluids, and administration of adrenergic drugs (“ESUR Guidelines on Contrast Media Version 8.1”). Adrenaline is the drug of choice. Intramuscular injection of 0.5 ml of 1:1,000 adrenaline preparation is recommended in preference to intravenous administration, which requires careful electrocardiogram (ECG) monitoring and slow administration, ideally by people experienced in its use. According to the Project Team of the Resuscitation Council in the United Kingdom, adrenaline 1:1,000 should never be used intravenously because of the risk of arrhythmia, and subcutaneous administration is not helpful in acute life-threatening situations (Resuscitation Council (UK)
Hypoxia increases the risk of severe cardiac arrhythmias. Also, the amount of adrenaline should be limited in patients who are receiving non-cardioselective β-blocking medications (e.g., propranolol) as discussed above. Adrenaline should be avoided, if possible, in a pregnant patient experiencing an anaphylactoid reaction with hypotension. When adrenaline is contraindicated, bronchospasm can be treated with a β-2 agonist inhaler (β-2 with no α-effects).

7 Serum Tryptase Measurement after Acute Reactions to Contrast Agents

During anaphylaxis, tryptase is released from the mast cells into the blood. Blood tryptase levels peak at 1–2 h, and decline rapidly with a 2 h half-life. Whether or not collapse after contrast medium represented an anaphylactoid reaction may be important to future care of the patient. The UK Resuscitation Council recommends that blood samples for tryptase are taken following suspected anaphylaxis, so that the diagnosis can be established. The minimum recommendation is one sample 1–2 h after the reaction. Ideally, three samples should be obtained—the first once resuscitation is underway, the second at 1–2 h after the reaction, and the third at 24 h or during convalescence (Resuscitation Council (UK) 2008).

8 Be Prepared

Prompt recognition and treatment can be invaluable in blunting an adverse response of a patient to iodine- or gadolinium-based contrast agents and may prevent a reaction from becoming severe or even life threatening. Radiologists and their staff should review treatment protocols regularly (e.g., at 6–12 monthly intervals) so that each can accomplish his or her role efficiently (Gillenberger et al. 1986; Bush and Swanson 1991; Emergency Cardiac Care Committee and Subcommittees 1992; Berden et al. 1993; Bush et al. 1993; Cohan et al. 1996; Bartlett and Bynevelt 2003). Knowledge, training, and preparation are crucial for guaranteeing appropriate and effective treatment if there is an adverse contrast-related event.

References

Part III

Iodine- and Gadolinium-Based Contrast Media: Renal Adverse Reactions
Abstract

Because of the nephrotoxicity of iodine-based contrast media and the more recently accepted role of gadolinium-based contrast media in the etiology of nephrogenic systemic fibrosis, the renal function of patients undergoing contrast enhanced imaging studies must be known so that, if necessary, appropriate preventive measures can be taken. The risk of these two adverse reactions increases with decreasing glomerular filtration rate, which cannot be measured directly. Measurement of serum creatinine with calculation of the glomerular filtration rate is used to identify at-risk patients. The possible methods for measuring renal function using laboratory tests and the various equations for estimating glomerular filtration rate are reviewed, and questionnaires to replace serum creatinine measurement in outpatients at low risk are discussed.

1 History and Initiatives

Renal disease and the associated cardiovascular and cerebrovascular complications have been recognized as a major contributing factor to global healthcare costs for more than 50 years. In the early 1950s, the focus in patients with diagnosed renal failure was on the treatment of secondary effects, but nowadays prevention has a major role. The introduction and increasing use of dialysis reduced the impact of renal failure between 1970 and 1990, but the secondary morbidity and mortality associated with chronic hemodialysis stimulated the search for better treatments. Improvements in immunotherapy and renal transplantation technique gave hope of solving the problem of end stage kidney disease, but complications still occur and availability is limited for the majority of patients, emphasizing the importance of prevention of renal failure.

Effective measures to improve the outcome in patients with renal impairment require not only a proper understanding of the underlying pathophysiology but also the use
of clear nomenclature and staging of kidney disease. The US based National Kidney Foundation (NKF) took the first steps by focusing on outcome research and guidelines at a national level, which led in 1997 to the “National Kidney Foundation Kidney Disease Outcome Quality Initiative” (NKF K/DOQI) (Steinberg et al. 2000). In 2002, K/DOQI published a guideline on the definition, classification and evaluation of chronic kidney disease (CKD), which was refined recently (National Kidney Foundation 2012).

At an international level, the Kidney Disease Improving Global Outcome (KDIGO) was founded in 2003, to harmonize strategy and prepare global guidelines for renal failure prevention, diagnosis and treatment (Eknoyan et al. 2004). The original staging system for chronic kidney disease was recently refined by KDIGO (CKD Work Group 2013).

2 Indicators of Chronic Kidney Disease

Raised serum creatinine, proteinuria and hypertension are all related, either directly or indirectly, to chronic renal disease. Proteinuria is correlated to kidney injury, while raised serum creatinine, or data derived from it, such as a decreased estimated Glomerular Filtration Rate (eGFR), indicate impaired renal function. These indicators can occur separately or together. Hypertension may be the cause or the result of kidney disease (Levin et al. 2001; Weiner et al. 2004), and kidney disease is listed as an independent risk factor for cardiovascular disease in a position statement of the American Heart Association.

Laboratory tests, such as serum creatinine (s-creatinine) measurement, provide a straightforward method for assessing renal function and for staging renal disease. Glomerular filtration can be estimated from s-creatinine together with various individual factors, such as age, weight and gender, to provide the eGFR, which is the current recommended method for staging kidney disease. The urinary excretion of proteins, particularly albuminuria, and the degree of hypertension also give an indication of the stage of renal failure.

A system including all these criteria would be ideal for differentiating the various degrees of CKD, but eGFR is currently in general use because it is simple and is universally accepted.

3 Stages of Chronic Kidney Disease

Chronic kidney disease (CKD) includes many abnormalities of renal microstructure or renal function, which are sometimes related. It most often progresses over time, but may be stable and non-progressive. In the early stages of CKD, some patients have subclinical disease with normal laboratory tests, but are still at increased risk for secondary cardiovascular or cerebrovascular disease. Their CKD may not be detected until their laboratory tests become abnormal. Patients with subclinical CKD do not necessarily progress to renal failure and hemodialysis but they need specific care when they are given potentially nephrotoxic medication such as iodine-based contrast agents. Prognosis directly correlates with the stage of disease at the time of diagnosis and it is very important to recognize early CKD in order to prevent progressive disease, or at least to delay complications.

CKD encompasses a variety of clinical states, including normal, elevated or reduced eGFR. The cut-off eGFR value for diagnosing CKD is 90 ml min\(^{-1}\) 1.73 m\(^{-2}\), and all eGFR measurements less than this indicate renal insufficiency. However, renal damage may exist with normal or even with high eGFR values. When eGFR is normal, risk factors, such as proteinuria and hypertension, or abnormal imaging findings may indicate early CKD. Proteinuria is defined as a urine albumin-to-creatinine ratio (ACR) \(>30\) mg g\(^{-1}\) (Levey et al. 2009).

In 2008, the National Institute for Health and Clinical Excellence introduced a classification of CKD into five stages. This was subsequently updated by dividing CKD 3 into stages A and B (Table 1). In the 2013 position paper, K/DOQI recommended a similar classification, which is now used world-wide (CKD Work Group 2013).

4 Laboratory Testing for Renal Insufficiency

In renal insufficiency the kidney does not excrete water and the products of metabolism appropriately. The causes may be pre-renal, if the renal vascular supply is impaired, renal, if there is intrinsic renal disease, or post-renal, if there is obstruction to the passage of urine through the excretory system. As a result, excess water, salts and other metabolic end products are retained in the blood, which upsets metabolic balance and may affect many organs. Also, renal disease affects hematopoiesis by a hormonal mechanism.

Renal insufficiency tends to worsen steadily over time. While in the early stages symptoms may be absent or only mild, in the advanced stages many critical body functions are affected and the condition may become life-threatening. Subclinical disease can be diagnosed by laboratory testing, either of blood or of urine. Although optimal correlation of the diagnostic test with the stage of disease involves analysis of a 24 h urine sample, simple blood tests are easier to perform.
Naturally aging causes decreased renal function. The first sclerotic glomeruli can be seen by light-microscopy from the age of 18 years, but because of “activation” of sleeping glomeruli, the glomerular filtration rate does not decrease on average before the age of 40 years provided that reasons other than aging are not present. From approximately 40 years, renal function decreases slowly and at the age of 70 years, more than 25% of people have a glomerular filtration rate less than 60 ml min$^{-1}$ 1.73 m$^{-2}$.

### 4.1 Exogenous Markers

The accurate measurement of renal filtration capacity requires measuring the excretion of a substance which is freely filtered in the nephrons, and is not reabsorbed, secreted or metabolized (Work and Schwartz 2008).

#### 4.1.1 Inulin

Inulin, a very small sugar molecule with a molecular weight of approximately 5200 Da, is the acknowledged gold standard for determining glomerular filtration. After inulin has been administered to the patient, the urine must be collected over a defined time period, while the blood inulin level is in steady state, to determine the Inulin Clearance. Clearance is defined as the amount of urine which is cleared of a given substance within a defined time. Inulin clearance is a direct indication of kidney function and so of the Glomerular Filtration Rate (GFR), which represents the amount of urine filtered by all the glomeruli of both kidneys within a given time. GFR measurement requires catherization of the bladder and peripheral venous access for sampling over the test period. The method is invasive and time consuming, and so not suitable for routine clinical practice.

#### 4.1.2 Isotopes

Isotope methods give similar results to inulin clearance (Blaufox et al. 1996). The glomerular filtration rate is determined from one or more blood samples (more samples are needed if the patient has decreased renal function) and from scintigraphic measurements. $^{51}$Cr-EDTA is most often used and is available in Europe, but not in some countries, for example the USA. $^{99m}$Tc-DTPA can also be used. Small amounts of radioactive and non-radioactive iodine-based contrast media, too little for radiographic imaging, may also be used. However, isotope methods are also cumbersome and impractical for daily use in patients undergoing enhanced CT or MRI.

### 4.2 Endogenous Markers

#### 4.2.1 Creatinine

Determination of the clearance of endogenous metabolic substances, such as creatinine, has been used for many years. The clearance cannot be measured directly, but depends on the relationship between creatinine concentration in the serum and urine, multiplied by the urine flow rate. Creatinine Clearance is usually standardized to the body surface area and expressed per 1.73 m$^{2}$ body surface area. Measurements are based on a 24 h urine collection. This limits clinical use, especially in children and patients with limited compliance. Creatinine clearance measurement is not suitable for outpatients, and cannot resolve urgent concerns before an iodine- or gadolinium-based contrast agent is administered.

However, serum creatinine measurements take only a few minutes, are relatively inexpensive, and can be offered as fingerprick blood test to all patients if necessary. The standardized normal value of s-creatinine varies with age and gender, because creatinine is a product of muscle catabolism, and is directly dependent on muscle mass and on the level of activity of the subject (Cockcroft and Gault 1976). Short-term changes in the s-creatinine level may occur secondary to hematological and vascular disease, and also if the subject is dehydrated. Also, drug-induced changes in renal blood supply or glomerular function can affect the s-creatinine (White et al. 2008).

For many years, the s-creatinine value has been used to calculate the risk of contrast-induced nephropathy (CIN) in patients receiving iodine-based contrast media, to decide whether the patient should receive the contrast medium and,
if so, whether they require volume expansion before the contrast medium (“Contrast Medium-Induced Nephropathy” (CIN)). Exact cut-off values or standardized algorithms, based on kidney function, to calculate the dosage of nephrotoxic medication, such as iodine-based contrast media, cannot be derived from s-creatinine without taking other factors into account. The frequently quoted cut-off value of 132 \( \mu \text{mol l}^{-1} \) (1.5 mg dl\(^{-1}\)) s-creatinine may be suitable for a “standard” mature patient but is not applicable to elderly or very sick patients. Elderly patients with s-creatinine below 132 \( \mu \text{mol l}^{-1} \) (1.5 mg dl\(^{-1}\)) often have a glomerular filtration rate below 60 ml min\(^{-1}\) 1.73 m\(^{-2}\), while in patients aged 20 years, this GFR level only occurs in one out of 20. Also, serum creatinine becomes abnormal when there is a 50–60 % reduction in GFR.

4.2.2 Cystatin C

More than 15 years ago Cystatin C was proposed as an alternative endogenous marker for testing renal function. It is a small protein molecule which is continually produced by all nucleated cells at a constant rate, independent of muscle mass, sex, and age. It is freely filtered in the glomeruli and is secondarily reabsorbed, but then is completely catabolized in the tubular cells. Cystatin C is a reliable marker for GFR, especially in the early stages of CKD, but measuring it is more expensive than serum creatinine measurement and the test procedure is less standardized. Recently, further improvement in the measurement of GFR in pediatric patients was achieved using both the serum Cystatin C and creatinine levels (Bouvet et al. 2006; Herget-Rosenthal et al. 2007).

4.3 Serum Creatinine-Based Assessment of Glomerular Filtration Rate

The estimated GFR (eGFR) gives an approximation of the actual GFR from a standard s-creatinine measurement by using a mathematical formula which takes into account patient factors which affect renal function, such as age, sex and weight. This method is suitable for outpatients and emergency situations (Table 2).

Various different equations have been proposed: the Cockcroft-Gault formula (Cockcroft and Gault 1976), the MDRD formula (Levey et al. 1999), the CKD-EPI formula (Levey et al. 2009), and for children the Schwartz formula (Schwartz et al. 1976) and the Counahan-Barratt formula (Counahan et al. 1976). Radiologists have still not agreed about which equation should be used to calculate eGFR (White et al. 2008; Soliman et al. 2013), but CKD-EPI is the current preferred measurement in adults, particularly in the USA. The various formulae to be used in adults can be found in Table 3.

### Table 2
ACR and ESUR questionnaires on renal status (for iodine-based contrast media)

<table>
<thead>
<tr>
<th>ACR questionnaire (ACR Committee on Drugs and Contrast Media, 2012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60</td>
</tr>
<tr>
<td>History of renal disease, including:</td>
</tr>
<tr>
<td>Dialysis</td>
</tr>
<tr>
<td>Kidney transplant</td>
</tr>
<tr>
<td>Single kidney</td>
</tr>
<tr>
<td>Renal cancer</td>
</tr>
<tr>
<td>Renal surgery</td>
</tr>
<tr>
<td>History of hypertension requiring medical therapy</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ESUR questionnaire (“ESUR Guidelines on Contrast Media Version 8.1”)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>History of renal disease</td>
</tr>
<tr>
<td>Previous renal surgery</td>
</tr>
<tr>
<td>History of proteinuria</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Gout</td>
</tr>
<tr>
<td>Most recent measurement of serum creatinine (value/date)</td>
</tr>
<tr>
<td>Medication with nephrotoxic drugs</td>
</tr>
</tbody>
</table>

4.3.1 The Cockcroft-Gault Equation

The Cockcroft-Gault equation is the oldest formula for calculating creatinine clearance. It is based on laboratory data derived from 249 male inpatients who had creatinine clearances varying between 30 and 130 ml min\(^{-1}\). The equation includes weight, age and sex, but does not include the Body Mass Index (BMI). eGFR is generally slightly overestimated because the equation does not include tubular secretion (Cockcroft and Gault 1976) and because the muscle mass of the patients included was less than in the general population.

4.3.2 The MDRD Equation

The MDRD equation Modification of Diet in Renal Disease (MDRD) is based on a multicenter trial on the effect of dietary protein restriction and blood pressure control on the progression of renal disease (Klahr et al. 1994, Levey et al. 1999). More than 1,500 patients were included with the aim of developing a formula which would estimate GFR correctly. Several variants exist, but the so-called “4-variables”-MDRD formula (MDRD-short) is the most frequently used clinically. It includes age, sex, s-creatinine and ethnic group (white/black), based on the differences in muscle mass in the different groups. The longer variant of the MDRD formula (MDRD long) also
Table 3 Equations for estimating the glomerular filtration rate from serum creatinine level. Creatinine levels in μmol/L can be converted to mg/dL by dividing them by 88.4

<table>
<thead>
<tr>
<th>Creatinine Clearance $C_{Cr}$</th>
<th>Estimated creatinine clearance rate ($eC_{Cr}$) using Cockcroft-Gault formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{Cr} = \frac{U_{Cr} \times V}{P_{Cr}}$</td>
<td>$eC_{Cr} = \frac{(140 - \text{age}) \times \text{mass (in kilograms)} \times [0.85 \text{ if female}]}{72 \times SCr (\text{in mg/dL})}$</td>
</tr>
<tr>
<td>If serum creatinine is measured in μmol/L:</td>
<td>$eC_{Cr} = \frac{(140 - \text{age}) \times \text{mass (in kilograms)} \times \text{gender factor}}{SCr (\text{in μmol/L})}$</td>
</tr>
<tr>
<td>Gender factor is 1.23 for men and 1.04 for women</td>
<td></td>
</tr>
</tbody>
</table>

Estimated GFR (eGFR) using Modification of Diet in Renal Disease (MDRD) formula

The most commonly used formula is the “4-variable MDRD”, which estimates GFR using four variables: serum creatinine(SCr), age, race, and gender. The original MDRD used six variables with the additional variables being the blood urea nitrogen and albumin levels.

For creatinine in μmol/L:

\[
eGFR = 32788 \times SCr^{-1.154} \times \text{age}^{-0.203} \times [1.212 \text{ if black}] \times [0.742 \text{ if female}]
\]

For creatinine in mg/dL:

\[
eGFR = 186 \times SCr^{-1.154} \times \text{age}^{-0.203} \times [1.212 \text{ if black}] \times [0.742 \text{ if female}]
\]

A more elaborate version of the MDRD equation also includes serum albumin and blood urea nitrogen (BUN) levels:

\[
eGFR = 170 \times SCr^{-0.999} \times \text{age}^{-0.176} \times [0.762 \text{ if female}] \times [1.180 \text{ if black}] \times BUN^{-0.170} \times \text{Albumin}^{0.318}
\]

where the creatinine and BUN concentrations are both in mg/dL. The albumin concentration is in g/dL.

Estimated GFR (eGFR) using the CKD-EPI formula

The CKD-EPI equation, expressed as a single equation, is:

\[
eGFR = 141 \times \min(\text{SCr/k, 1})^a \times \max(\text{SCr/k, 1})^{-1.209} \times 0.993^{0.98} \times [1.018 \text{ if female}] \times [1.159 \text{ if black}]
\]

SCr serum creatinine (mg/dL), k is 0.7 for females and 0.9 for males, a is −0.329 for females and −0.411 for males, min indicates the minimum of SCr/k or 1, and max indicates the maximum of SCr/k or 1

includes measurements of serum albumin and urea, but the result is not very different from the short version.

In patients with CKD stages 3–5, the MDRD equation appears to be more precise than the Cockcroft-Gault formula. A criticism of the MDRD equation is that it is inaccurate in patients with CKD stages 1 and 2 (GFR > 60 ml min⁻¹) because it has not been validated in this group. Also inaccuracies have been claimed in patients over age 70, children, and patients with extremely high or low body weights (anorexia or bodybuilders, patients undergoing chemotherapy etc.).

4.3.3 The CKD-EPI Equation

Recently, the MDRD formula has been revised by using different weighting of the same four parameters as in the standard MDRD formula to derive a new equation called CKD-EPI (Chronic Kidney Disease Epidemiology Cooperation). Based on the data from more than one million adults with all stages of CKD from several cohort-studies, an improved estimation of GFR for the less severe stages of CKD (1 and 2) was obtained, without loss of accuracy in the more severe stages (Matsushita et al. 2012). This new equation appears preferable because it leads to less over-diagnosis of CKD stage 3 to stage 4 so that fewer patients require further medical investigation.

4.3.4 Schwartz Formula for Children

In the pediatric patient group, none of the equations already described is suitable. While the Cockcroft-Gault equation may be acceptable in patients over 12 years if the body surface area is taken into account, the MDRD formula has not been validated in patients below 18 years. In 1976, Schwartz et al. published a formula, which includes s-creatinine and patient size (height) and also a constant factor, which was determined empirically (Schwartz et al. 1976). This constant factor was varied in further studies and
compared to direct GFR determination studies in young patients, which led to the **Counahan-Barratt formula** (Counahan et al. 1976). These equations are very similar but the constant factor in the Schwartz formula differs for infants less than 1 year and for boys older than 13 years, while the Counahan-Barratt constant factor is identical for all ages and is lower than the Schwartz constant. There is a general trend to overestimate GFR by the Schwartz formula compared to the Counahan-Barratt formula (Bouvet et al. 2006; Grönroos et al. 2008; Schwartz et al. 2009).

## 5 When Should Serum Creatinine Be Measured and eGFR Calculated?

Contraindications of drug use and restrictions of drug dose which relate to renal function rely on proper evaluation of true kidney function. The medical support for eGFR determination as an accurate measure of renal insufficiency has been shown by its use in national drug regulations and international guidelines. For example, the ESUR guidelines on contrast media recommend the measurement of eGFR within 7 days before administration of iodine-based contrast medium in patients likely to be at risk of developing CIN (Thomsen et al. 2013).

The uncertainty which occurs when patients whose renal function is not known require contrast-enhanced radiography, DSA, CT, or MRI, is a common problem. The risk of CIN with iodine-based contrast media is to some extent dose-dependent, but it is more important to decide whether volume expansion should be undertaken before administration of contrast medium or whether an alternative test not using contrast medium should be used (“Contrast Medium-Induced Nephropathy”). For MR, the administration of gadolinium-based contrast agents (GBCA) is controlled by official restrictions and contraindications in the more severe stages of CKD, particularly if the least stable agents are used (“Nephrogenic Systemic Fibrosis and Gadolinium-Based Contrast Media”).

In all these at risk situations, measurement of the serum creatinine and subsequent calculation of eGFR is the most appropriate investigation.

### 5.1 Questionnaires

In 1998, Choyke et al. evaluated the accuracy of a questionnaire checking for evidence of kidney disease or increased risk of CIN compared to s-creatinine measurement. Based on the results, they recommended that s-creatinine should only be measured before the administration of iodine-based contrast media in patients with preexisting renal disease, proteinuria, prior kidney surgery, hypertension, gout and/or diabetes (Choyke et al. 1998). Questionnaires proposed by the American College of Radiology (ACR Committee on Drugs and Contrast Media 2012) and ESUR (Thomsen and Morcos 2006) concentrate on medical (renal) history, current and previous medication, and concomitant disease. There are only minor differences between the most commonly used questionnaires (Table 2). When the response to any question is positive, s-creatinine measurement and eGFR calculation are indicated.

However, a questionnaire cannot be used when official authorities, such as the EMA in Europe or the FDA in the United States of America, state that s-creatinine measurement and subsequent eGFR calculation is mandatory. Thus, s-creatinine must be measured and eGFR calculated before gadolinium-based contrast media considered to be at high-risk of inducing nephrogenic systemic fibrosis are administered (“Nephrogenic Systemic Fibrosis and Gadolinium-Based Contrast Media”). With the other gadolinium-based agents, GFR estimation is recommended but an alternative, at the discretion of the radiologist, is to use a questionnaire to save both time and money.

Ideally, the questionnaire should be completed by the referring clinician, but if the extra effort involved is considered too much, the patient may be asked to complete it. Alternatively, technicians or nurses can complete the questionnaire, with the advantage that they can explain the questions to the patient. Unfortunately, if people other than the referring physician complete the questionnaire, false positive answers may lead to unnecessary blood tests with their associated costs and delays.

In 2010, Ledermann et al. published a retrospective analysis of using the ESUR questionnaire in 1,766 consecutive outpatients scheduled for contrast enhanced CT. If a risk factor was identified, s-creatinine was determined on-site. The most frequently detected risk factor was hypertension (38 % of patients), followed by nephrotoxic medication (21 %). There were a variety of other risk factors, none in more than 10 %. A total of 45 % of the patients needed s-creatinine measurement and 6.6 % of the patients were found to have moderate to severe renal impairment. The two questions with the highest relative risk ratio and with the highest group-dependent odd ratios when comparing patients with eGFR < 60 ml min⁻¹ 1.73 m⁻² to patients with eGFR > 60 ml min⁻¹ 1.73 m⁻² were a history of renal disease and gout. Patient age over 70 years correlated best with the presence of moderate to severe kidney disease.

In an as yet unpublished study, presented at ECR 2012, Newerla et al. 2012 found in 1,304 patients who answered the ESUR questionnaire before contrast enhanced CT or MRI that only age above 70 years correlated strongly with renal impairment. None of the other data obtained from the questionnaire correlated significantly with a raised s-creatinine level. They recommended that s-creatinine should be...
measured in all elderly patients (above 70 years) and in patients who give a positive answer to the question as to whether they have a history of renal disease. This would speed up the process and still allow effective screening for CKD in a standard outpatient group. For hospital inpatients, a recent s-creatinine measurement remains the standard of care.

Whether gout should be included in the ESUR questionnaire is still under discussion (Filiopoulos et al. 2012; Murea 2012), but the combination of a raised serum urate, indicating renal impairment, together with the known increased cardiovascular morbidity and the frequent use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with gout, may combine to give a higher risk of renal disease (Abdellatif and Elkhalili 2012).

The ideal questionnaire does not exist.

6 Conclusion

Measurement of renal function is not simple. The best methods are time-consuming and not suitable for clinical radiological practice. At present, the CKD-EPI equation for estimating GFR seems to be the best choice whenever information about renal function is important before administration of contrast media in adults. In children the Counahan-Barratt formula should be used. GFR measurement using Cystatin C may have a role in the near future. Questionnaires may help to identify at-risk patients, but as yet there is no ideal questionnaire.

References

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Contrast Medium-Induced Nephropathy
Henrik S. Thomsen, Fulvio Stacul, and Judith A. W. Webb

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Abstract
A sudden drop in renal function after exposure to contrast media was first described more than 60 years ago. Contrast medium-induced nephropathy (CIN) is still considered an important acute adverse reaction. Despite both clinical and experimental research, its pathophysiology is still unclear. It occurs to the same extent after all non-ionic iodine-based contrast agents. Patients at increased risk are those with moderately and severely reduced renal function. Volume expansion seems to reduce the frequency, but no pharmacological manipulation has been proven to be helpful. This chapter reviews the recent information on CIN.

1 Introduction
Acute renal failure is a sudden and rapid deterioration in renal function which results in the failure of the kidney to excrete nitrogenous waste products and to maintain fluid and electrolyte homeostasis. It may be a result of intravascular administration of radiographic and magnetic resonance (MR) contrast media ("Radiography with Gadolinium-Based Contrast Media"). Despite increased awareness, contrast medium-induced nephropathy (CIN) is claimed to be the third most common cause of hospital-acquired kidney failure and was considered to be responsible for 11 % of cases in 2002 and 12 % in 1979 (Hou et al. 1983; Nash et al. 2002). The mortality rate in these cases was 14 %. Hoste et al. (2011)
found that CIN occurred in one out of six intensive care unit patients who received iodine-based contrast medium and was associated with both short- and long-term worse outcomes, such as need for renal replacement therapy, worse kidney function at discharge, increased length of stay in the intensive care unit and hospital, and mortality.

The term “contrast medium-induced nephropathy” is widely used to refer to the reduction in renal function seen after exposure to contrast media. It implies impairment in renal function (an increase in serum creatinine by more than 25 % or 44 μmol l⁻¹ (0.5 mg dl⁻¹)) that occurs within 3 days following the intravenous administration of contrast media in the absence of an alternative etiology (Morcos et al. 1999; Stacul et al. 2011). However, the two definitions of CIN—either an increase in serum creatinine by >44 μmol l⁻¹ (0.5 mg dl⁻¹), or >25 % from baseline—do not reflect the same changes in kidney function. The first definition is more sensitive for detecting CIN in patients with advanced renal impairment, whereas the second one is more sensitive in those with better pre-existing kidney function (Thomsen and Morcos 2009). In an analysis of 58,957 patients undergoing percutaneous coronary intervention, a rise in serum creatinine ≥44 μmol l⁻¹ (0.5 mg dl⁻¹) was superior to >25 % increase in serum creatinine for identifying patients at risk of adverse renal and cardiac events (Slocum et al. 2012). Classifications of acute kidney insufficiency such as the RIFLE (Bellomo et al. 2004) or the AKIN (Mehta et al. 2007) include, as minimal diagnostic criteria, changes in serum creatinine as low as 26 μmol l⁻¹ (0.3 mg dl⁻¹), and validation studies demonstrated that such marginal conditions are associated with worse outcomes (Chertow et al. 2005). The Kidney Disease Improving Global Outcomes group (KDIGO) (2013) defines acute kidney insufficiency as any of the following: (1) an increase in serum creatinine of ≥26 μmol l⁻¹ (0.3 mg dl⁻¹) within 48 h, (2) an increase in serum creatinine to >1.5 times the baseline that is known or presumed to have occurred within the prior 7 days, (3) urine volume <0.5 ml kg⁻¹ h⁻¹ for 6 h. The diversity in CIN definitions explains the differences across the studies. When the results of various studies are compared, it is important to ensure that the same definition of CIN is used in all of them. In the same study, the frequency of CIN ranged from 3.3 to 10.5 %, depending on the definition used (Jabara et al. 2009).

CIN is a diagnosis based on exclusion of other causes of the reduction in the renal function and not a diagnosis based on a specific and reproducible change. The reduction in renal function can easily have other causes e.g., cholesterol emboli due to catheter manipulation, cardiac dysfunction causing renal ischemia, and natural variations in S-creatinine levels. Thus, stating that all increases in s-creatinine levels after exposure to iodine-based contrast media with no clear cause are CIN may lead to over-estimation of its incidence. Serum creatinine levels are by no means an optimal expression of renal function because serum concentration depends on several factors (e.g., glomerular filtration rate, exercise, intake of food, hydration, and posture). CIN ranges in severity from asymptomatic, non-oliguric, transient renal dysfunction to oliguric, severe, acute renal failure necessitating dialysis. Luckily, the latter adverse reaction is the least frequent of them all. Serum creatinine often peaks within 3–4 days after the administration of contrast media (Katzberg 1997; Morcos 1998). Fortunately, most episodes of CIN are self-limited and resolve within 1–2 weeks. Some non-anuric episodes are probably undetected, because the serum creatinine is rarely measured after administration of contrast media if the patients have no symptoms, especially if they are outpatients who have received intravenous contrast medium. Permanent renal damage is very rare.

Diagnostic and interventional procedures using contrast media are performed with increasing frequency. The patient population subjected to these procedures is progressively older with more co-morbid conditions (Solomon 1998). Prevention is important to avoid the substantial morbidity and even mortality that may sometimes be associated with CIN. Even a small decrease in renal function may greatly exacerbate morbidity and mortality caused by coexisting conditions (Gruberg et al. 2000; McCullough et al. 1997). Patients with CIN have a higher mortality rate (31 %) than patients without it (0.6 %) after primary angioplasty for acute myocardial infarction (Marenzi et al. 2004). The 30-day mortality is higher in patients with CIN (16.2 %) than in those without (1.2 %), and the difference is maintained at 1 year (23.3 vs. 3.2 %) (Sadeghi et al. 2003). Sepsis, bleeding, coma, and respiratory failure are frequently observed in patients with acute renal failure. An important issue has been the recognition that even a small postprocedural decline in kidney function can have a dramatic impact on prognosis. In a retrospective analysis of 14,782 patients undergoing coronary angiography, the adjusted risk of 3-year mortality increased with growing severity of acute kidney injury (James et al. 2011). However, all this information derives from intra-arterial administration of contrast media for cardiac studies. As yet, there is no adequate information about whether CIN after an intravenous injection is associated with increased mortality and morbidity after 1 or more years. A recent study from Korea showed that intravenous contrast media used in the standard CT scan have no significant long-term effects (8 months follow-up) on renal function in CKD patients (Kim et al. 2012). From et al. (2008) performed a 2-year retrospective case matched cohort study at Mayo Clinic’s site in Rochester. A total of 809 patients who developed CIN were matched to 2,427 patients who did not develop CIN after contrast
medium exposure. CIN was significantly associated with 30-day mortality and overall mortality after adjustment for heart failure, hypertension, medications, total hydration, iodine load, prior contrast agent exposure, and all matched variables during the study period. The risk was higher in patients in whom contrast medium was administered intravascularly than in those in whom it was administered intravenously. However, the same has not been shown by other investigators, despite the fact that CIN is still widely investigated. More than 5,300 papers are listed in Pub-Med under “CIN” (June 1st 2013). The first example of CIN was published by Bartels et al. (1954), in a patient with myelomatosis.

2 Radiographic Features

A persistent nephrogram on plain radiography or computed tomography (CT) of the abdomen at 24–48 h after contrast medium injection (Fig. 1) has been described as a feature of CIN (Berns 1989; Love et al. 1994). However, its presence is not always associated with a reduction in renal function (Jakobsen et al. 1992; Yamazaki et al. 1997a). Also, opacification of the gallbladder (Fig. 2) is not necessarily related to the presence of CIN (Yamazaki et al. 1997b). However, if these signs are present, renal function should be assessed and the administration of further doses of contrast media should be avoided if the results are abnormal.

3 Incidence

CIN is rare in people with normal renal function, with the incidence varying from 0 to 2 % (Sholy et al. 2012; Morcos et al. 1999; McCullough et al. 1997; Rudnick et al. 1995). In acute myocardial infarction, CIN occurred after primary coronary angioplasty in 13 % of patients who had normal serum creatinine levels before the angioplasty (Marenzi et al. 2004). However, it is unclear whether it was the contrast medium or the cardiac dysfunction that reduced the renal function temporarily. Nearly all recent studies of CIN have involved arterial injection (coronary or peripheral angiography and angioplasty). Katzberg and Barrett (2007) found only 40 studies of the effects of intravenous injection, but there have been over 3,000 studies of the effects of intra-arterial injection. Heinrich et al. (2009) found 24 studies suitable for their meta-analysis, 8 of which involved intravenous injection, and 16 intra-arterial injection. Thus, angiographic studies are still the leading source of information on CIN. Pre-existing renal impairment increases the frequency of CIN. The incidence of CIN ranged from 3 to 33 % in several prospective controlled studies (Morcos et al. 1999; Solomon 1998; Rudnick et al. 1995; Bettmann 2005).

The incidence of CIN varied from 3 to 45 % in the control arms of prospective trials of acetylcysteine, and the contrast agent was given intra-arterially (Bettmann 2005; Sharma and Kini 2005; Solomon and Dumouchel 2006; Solomon 2005). In head-to-head trials of various contrast agents administered intra-arterially, the incidence varied between 3 and 26 %; the same range was found in patients with diabetic nephropathy (Thomsen et al. 2008a). The incidence is significantly higher in patients with diabetic nephropathy (19.7 %) than in patients with other types of nephropathy (5.7 %) (Rudnick et al. 1995). The most frequently used

![Fig. 1](image1.png) Appearances suggesting CIN on renal CT scan 24 h after conventional angiography in a patient with diabetic nephropathy and moderately reduced renal function. No contrast medium was administered for the CT scan. Note the persistent dense nephrogram, with obvious demarcation between cortex and medulla and no contrast medium in the renal pelves

![Fig. 2](image2.png) Calculus obstruction of the right ureter: appearances on a kidney CT scan 24 h after intravenous administration of iodine-based contrast medium. The persistent dense right nephrogram and contrast medium in the gall bladder do not indicate CIN. Contrast was still excreted by the left kidney, probably due to reabsorption along the right renal pelvis (pyelosinus backflow (not shown)). Serum creatinine was unchanged (normal), despite the unilateral obstruction
definition of CIN was an increase in serum creatinine of 44 \( \mu \text{mol l}^{-1} \) (0.5 mg dl\(^{-1} \)) or more, particularly in the most recent studies.

The incidence of CIN appears to be much lower after intravenous administration. Studies reported 0–2 % incidence of CIN, defined as an increase in serum creatinine level of 44 \( \mu \text{mol l}^{-1} \) (0.5 mg dl\(^{-1} \)) or more in an unselected group of patients with chronic kidney disease 3 and 4 (Barrett et al. 2006; Thomsen et al. 2008b). Kuhn et al. (2008) reported a 5 % incidence of CIN, defined as an increase of 25 % or more in serum creatinine in patients with diabetic nephropathy. In a group of cancer patients with underlying renal insufficiency receiving the contrast agent intravenously, 9.0 % developed CIN, defined as an absolute increase of 44 \( \mu \text{mol l}^{-1} \) or 25 % increase in serum creatinine level, with 4.8 % of patients developing irreversible renal damage (Cheruvu et al. 2007).

Based on a number of studies (Table 1) the best estimate of the incidence of CIN is around 5 % for both non-ionic monomers and dimers in patients with a glomerular filtration rate between 25 and 60 ml min\(^{-1} \). Below 25 ml min\(^{-1} \) the incidence is probably higher, but experience is extremely limited. Most referring physicians request an unenhanced examination in such patients.

### Table 1 Incidence of CIN in prospective randomized trials comparing intravenous iso- to low-osmolality contrast media in patients mainly with moderately reduced renal function

<table>
<thead>
<tr>
<th>Study</th>
<th>Low-osmolality CM (monomers)</th>
<th>Iso-osmolar CM (iodixanol)</th>
<th>Criteria</th>
<th>Statistical result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carraro et al. (1998)</td>
<td>0/32 (iopromide)</td>
<td>1/32</td>
<td>50 % ↑ SCr</td>
<td>No difference</td>
</tr>
<tr>
<td>Nguyen et al. (2008)</td>
<td>10/65 (iopromide)</td>
<td>3/61</td>
<td>44 ( \mu \text{mol l}^{-1} ) ↑ SCr</td>
<td>Iodixanol superior ( p &lt; 0.05 )</td>
</tr>
<tr>
<td>Kolehmainen et al. (2003)</td>
<td>4/25 (iobiditrol)</td>
<td>4/25</td>
<td>44 ( \mu \text{mol l}^{-1} ) ↑ SCr</td>
<td>No difference</td>
</tr>
<tr>
<td>Barrett et al. (2006)</td>
<td>0/77 (iopamidol)</td>
<td>2/76</td>
<td>44 ( \mu \text{mol l}^{-1} ) ↑ SCr</td>
<td>No difference</td>
</tr>
<tr>
<td>Thomsen et al. (2008b)</td>
<td>0/76 (iomeprol)</td>
<td>5/72</td>
<td>44 ( \mu \text{mol l}^{-1} ) ↑ SCr</td>
<td>Iomeprol superior ( p &lt; 0.05 )</td>
</tr>
<tr>
<td>Kuhn et al. (2008)</td>
<td>7/125 (iopamidol)</td>
<td>6/123</td>
<td>25 % ↑ SCr</td>
<td>No difference</td>
</tr>
<tr>
<td>Chuang et al. (2009)</td>
<td>1/25 (iohexol)</td>
<td>1/25</td>
<td>25 % ↑ SCr</td>
<td>No difference</td>
</tr>
<tr>
<td>TOTAL</td>
<td>22/425 (5.18 %)</td>
<td>22/418 (5.26 %)</td>
<td>No difference</td>
<td></td>
</tr>
</tbody>
</table>

SCr Serum creatinine

in equilibrium is generally reached within 2 h. Continuous elimination through the glomeruli also occurs. Less than 1 % is excreted extrarenally in patients with normal renal function (Thomsen et al. 1993). Following intravascular administration in patients with normal renal function, the elimination half-life of contrast media is about 2 h, and 75 % of the administered dose is excreted in the urine within 4 h (Katzberg 1997). After 24 h, 98 % of the injected contrast medium should have been excreted. After approximately 150 min, the concentration of contrast medium decreases in a mono-exponential way in patients with normal renal function, but in patients with severely reduced renal function this phase is delayed (Almén et al. 1999). In such patients it takes weeks before the contrast agent is completely eliminated from the body.

### 5 Pathophysiology of Contrast Medium-Induced Nephropathy

In spite of the clinical importance of CIN, our understanding of the pathophysiology behind CIN is still incomplete. Mechanisms underlying CIN include direct cytotoxic effects, auto-, and paracrine factors that upset renal hemodynamics, altered rheological properties that affect renal hemodynamics and tubulodynamics, and regional hypoxia (Seeliger et al. 2012). Taken together, there appear to be three relatively distinct mechanisms or pathways for the pathophysiology of CIN: (1) reduced renal perfusion (hemodynamic effects), (2) toxicity directly affecting the tubular cells, and (3) endogenous biochemical disturbances (Katzberg 2005). Most clinical attention has focused on the hemodynamic effects of contrast media.
because tubular hypoxic injury is considered to play a central role in the renal dysfunction (Heyman et al. 2005). The mechanisms responsible for hemodynamic effects are believed to involve tubular and vascular events. The importance of direct effects of contrast media on tubular cells is debated, although evidence of direct tubular cell toxicity of the contrast agents independent of either hemodynamic mechanisms or osmolality has been reported (Heinrich et al. 2005). An increase in oxygen-free radicals or a decrease in antioxidant enzyme activity triggered by contrast medium administration as the third potential pathway is speculative. There has been no clinical substantiation of the suggestion that the liberation of oxygen-free radicals is the mechanism of CIN (Katzberg 2005). Osmolar and viscous properties of contrast media can aggravate the cytotoxic and vasoactive effects of contrast media, and can also trigger pathophysiological mechanisms on their own. High viscosity reduces glomerular filtration and medullary oxygenation and impedes urine flow, so leading to renal retention of the contrast medium (Seeliger et al. 2012).

Although several studies have been undertaken during the last 5 years, our knowledge about the pathophysiologic mechanism has not improved. The lack of understanding of the cause of CIN makes prevention difficult.

### 6 Predisposing Factors

Patients at the highest risk for developing contrast medium-induced acute renal failure are those with pre-existing renal impairment (serum creatinine $>132$ μmol l$^{-1}$ (1.5 mg dl$^{-1}$) or GFR $<60$ ml min$^{-1}$ 1.73 m$^{-2}$), particularly when the reduction in renal function is secondary to diabetic nephropathy (Morcos et al. 1999; Rudnick et al. 1995). Diabetes mellitus alone without renal impairment is not a risk factor (Rudnick et al. 1995). The degree of renal insufficiency present before the administration of contrast media to a great extent determines the severity of CIN. Baseline renal insufficiency in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention is associated with markedly increased mortality as well as bleeding and restenosis (Sadeghi et al. 2003). The extent to which the contrast medium contributes to the clinical deterioration is unknown, since for ethical reasons the studies did not include a control group.

Large doses of contrast media and multiple injections within 72 h increase the risk of developing CIN. Repeat exposure to iodine-based contrast media within a short time increased the risk of CIN, even in subjects with relatively preserved renal function. In a small prospective study on 28 subjects with baseline eGFR $>60$ ml min$^{-1}$ 1.73 m$^{-2}$, who underwent a second contrast medium exposure after a mean interval of 20 days there was a significant increase in mean serum creatinine and decline in eGFR after the second exposure, and 4 subjects (14.3 %) developed CIN (Trivedi and Foley 2010). In a prospective series of 747 patients who had a total of 944 procedures, repeated contrast medium administration was found to be an independent predictor of CIN with an odds ratio of 2.8 (Balemans et al. 2012).

Knowledge about multiple injections of iodine-based contrast medium within a short period of time is limited. There are cases where the patients received more than 1 L of iodine-based contrast medium during a single procedure without any effect on kidney function (Thomsen and Reimer 2014).

Although there are no trials directly comparing intravenous and intra-arterial CM, increasing data supports a higher risk of renal complications, including CIN, after intra-arterial administration above the level of the renal arteries than after intravenous administration. Intravenous contrast medium for enhanced computed tomography (CT) is usually given in lower doses than for arteriography and lower concentrations of contrast medium reach the kidneys. Also, with enhanced CT, there are usually fewer hemodynamically unstable patients, and dislodged atheroemboli, which may occur during intra-arterial procedures, and result in cholesterol embolization that can mimic CIN, are not a risk. Thus, the route of administration is also important, and procedures requiring intravenous contrast medium administration involve a lower risk of nephrotoxicity than procedures in which contrast medium is given intra-arterially into the renal arteries or the aorta proximal to the origin of the renal blood vessels (Stacul et al. 2011; Stratta et al. 2013).

Dehydration and congestive cardiac failure are risk factors because they are associated with a reduction in renal perfusion, which enhances the ischemic insult of the contrast media. The concurrent use of nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) and aminoglycosides potentiates the nephrotoxic effects of contrast media. Renal dysfunction is found more frequently in patients with hypertension, hyperuricemia, or proteinuria than in patients without these conditions (Choyke et al. 1998). The type of contrast medium is also an important predisposing factor. High-osmolality contrast media are more nephrotoxic than low- and iso-osmolality contrast media (Morcos 1998; Katzberg 1997; Rudnick et al. 1995). Except for a low hematocrit, no new risk factors have come to our attention this century.

Multiple myeloma was considered in the past to be a risk factor for CIN. However, if dehydration is avoided, contrast medium administration rarely leads to acute renal failure in patients with myeloma (McCarthy and Becker 1992). Pahade et al. (2011) recently studied retrospectively 46 patients with multiple myeloma who had 80 examinations.
Their average creatinine level before contrast enhanced CT was 85 μmol l⁻¹ (0.97 mg dl⁻¹). CIN (serum creatinine >25 % or >44 μmol l⁻¹) (0.5 mg dl⁻¹) occurred within 7 days of the examinations in 12 patients (15 %). They concluded that the incidence of CIN in patients with multiple myeloma with a normal creatinine level is low and is correlated to β2-microglobulin levels. The administration of contrast agents to patients with myeloma appears to be safe but should still be based on an assessment of the potential benefit of the examination versus an expected low risk of developing CIN.

7 Identifying Patients at Risk of Contrast Medium-Induced Nephropathy

Patients with pre-existing renal impairment are at particularly high risk of CIN. Serum creatinine has often been used to determine the renal function and to identify high-risk patients. Several studies have shown that, despite its many limitations, serum creatinine is a relatively satisfactory marker for identifying patients at the greatest risk of developing CIN because patients with severely reduced renal function are at the greatest risk (Rudnick et al. 1995; McCullough et al. 1997; Parfrey et al. 1989; Thomsen et al. 2005, 2008a). However, renal function can be considerably reduced (Chronic Kidney Disease stage 3 (30–60 ml min⁻¹)) when the serum creatinine levels are within the normal range (<132 μmol l⁻¹ (1.5 mg dl⁻¹)). More than 25 % of older patients have normal serum creatinine levels but reduced glomerular filtration rates. Unfortunately, serum creatinine is a rather poor marker for glomerular filtration rate. Serum creatinine is determined by the interplay of creatinine production, glomerular filtration, and the kinetics of creatinine distribution among the body’s fluid compartments. Because of the exponential relationship between serum creatinine and glomerular filtration rate, serum creatinine is very insensitive in patients with normal pre-existing renal function. Also, serum creatinine is notoriously insensitive to rapid changes in the glomerular filtration rate such as the immediate drop in glomerular filtration rate induced by contrast media (Seeliger et al. 2012).

The most precise method of measuring renal function is the inulin clearance, and isotope methods give similar results (Blaufox et al. 1996). However, both methods are cumbersome and impractical for daily use. Also, a single determination of the glomerular filtration rate does not exclude acute renal insufficiency.

The best method in routine clinical practice is to measure the serum creatinine level and then calculate the estimated GFR using the CKD-EPI equation either in all patients or only in those patients who give an affirmative answer to questions indicating reduced renal function (“Chronic Kidney Disease, Serum Creatinine and Estimated Glomerular Filtration Rate (eGFR)”). However, even the eGFR is not ideal, because one of the components in the equations is the insensitive serum creatinine, but it is much better than nothing.

7.1 Validation of eGFR Measurements

Serum creatinine is not an ideal marker of renal function (Blaufox et al. 1996). The serum creatinine level depends on muscle mass and is not usually raised until the glomerular filtration rate has fallen by at least 50 %. Endogenous serum creatinine clearance as a measure of glomerular filtration rate is also inaccurate, especially when renal function is low, because of a compensatory increase in tubular secretion of creatinine which limits its validity as a glomerular filtration marker. Radionuclide techniques are preferable (Blaufox et al. 1996) but labor intensive and, therefore, are not suitable to use in all patients receiving contrast medium. Alternatively, renal function can be estimated using specially derived predictive equations. The most accurate results are obtained with the Cockcroft-Gault equation, while the most precise formula is the Modification of Diet in Renal Disease (MDRD) study equation (Cockroft and Gault 1976; Levey et al. 1999). However, the predictive capabilities of these formulae are suboptimal for ideal patient care (Bostrom et al. 2002). In addition, they are not useful for patients with a glomerular filtration rate above 60 ml min⁻¹ (Stevens et al. 2006). Even below this level, they do not always result in the same glomerular filtration rate (Stevens et al. 2006; Band et al. 2007; Eken and Kilicaslan 2007) (Fig. 3). For instance, a 43-year old, 70-kg male patient with a creatinine level of 132 μmol l⁻¹ has a glomerular filtration level of 63 ml min⁻¹ if calculated by the Cockcroft-Gault equation. The same patient will have a glomerular filtration level of 66 ml min⁻¹ if he is African-American and 54 ml min⁻¹ if he is Caucasian, if it is calculated by the MDRD equation. Nonetheless, these equations provide a better assessment of renal function than does serum creatinine measurement.

In 2009, a third equation—CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)—was published (Levey et al. 2009). It was developed in an effort to create a more accurate formula than the MDRD formula, especially when actual GFR is greater than 60 ml min⁻¹ 1.73 m⁻². Pooled data from 10 studies including 8254 patients were used to validate the new equation. Sixteen additional studies, which included 3896 participants, were used for external validation. The CKD-EPI equation performed better than the MDRD (Modification of Diet in Renal Disease Study) equation, especially at higher GFR, with less
bias and greater accuracy. Michels et al. (2010) concluded that the absolute bias of all formulae is influenced by age. The CKD-EPI and MDRD formulas are also influenced by GFR, and the Cockcroft-Gault equation is additionally influenced by body weight and BMI. In general, CKD-EPI gives the best estimation of GFR, although the performance is close to that of MDRD (“Chronic Kidney Disease, Serum Creatinine and Estimated Glomerular Filtration Rate (eGFR)”).

Another possibility is to use cut-off values for serum creatinine to indicate several levels of renal impairment. However, low cut-off levels will include some patients with normal renal function and high cut-off levels will exclude some patients with renal impairment (Couchoud et al. 1999).

The timing of serum creatinine determinations after the procedure is another topic of debate. The AKIN criteria suggest a period of 48 h for diagnosing CIN to ensure that the process being diagnosed is acute and representative (Molitoris et al. 2007). Waikar and Bonventre (2009) agreed with this time period. They emphasized that patients with subacute rises in serum creatinine may not be identified, but noted that the significance and prognosis of such subacute rises is unknown.

The number of serum creatinine measurements within the given period also affects the findings and requires some standardization. Reddan et al. (2009) analyzed data published by Davidson et al. (1989) and showed that a single 24-h measurement would have missed 58.2% of the CIN cases that were detected by the 48-h measurement. McCullough and Sandberg (2003) found that serum creatinine typically peaks 3–5 days after contrast medium administration and returns to baseline or near baseline within 1–3 weeks.

### 7.2 In Which Patients Should eGFR be Measured?

A questionnaire designed to elicit a history of renal disorders as well as additional risk factors for CIN may be used to identify patients with normal serum creatinine in whom blood testing would be unnecessary (Choyke et al. 1998). The majority of patients (85%) in Choyke et al.’s. (1998) study had normal serum creatinine values (<114 μmol l⁻¹ (1.3 mg dl⁻¹) for women, 123 μmol l⁻¹ (1.4 mg dl⁻¹) for men). All except two patients (99%) who gave negative answers to the questionnaire had serum creatinine levels...
<150 \mu \text{mol l}^{-1} (1.7 \text{ mg dl}^{-1}). There was a strong association between raised serum creatinine values and a history of renal disease, proteinuria, prior kidney surgery, hypertension, gout, and diabetes. Only 6% of patients with negative answers to the six questions had abnormal serum creatinine levels.

In a study of 2,034 consecutive outpatients referred for CT examinations, only 3.2% (66 patients) had a raised serum creatinine level (>176 \mu \text{mol l}^{-1} (2.0 \text{ mg dl}^{-1})) and the majority of these patients (97%) had risk factors for CIN (Tippins et al. 2000). Two of the 66 patients with a raised serum creatinine (0.1% of the total number of patients) had no identifiable risk factors. Serum creatinine was measured in a prospective study of 640 consecutive adult patients presenting to the emergency department with a clinical indication for intravenous administration of iodine-based contrast medium (Olsen and Salomon 1996). A total of 35 (5.5%) patients had abnormal serum creatinine levels (>141 \mu \text{mol l}^{-1} (1.6 \text{ mg dl}^{-1})). Of these 35 patients, 77% (27) were considered to have risk factors for renal insufficiency. The remaining eight patients (1.3% of the total number) had no identifiable risk factors for renal insufficiency.

A retrospective analysis of using the ESUR questionnaire in 1766 consecutive outpatients scheduled for contrast enhanced CT was undertaken by Ledermann et al. (2010). If a risk factor was identified, s-creatinine was determined on-site. The most frequently detected risk factor was hypertension (38% of patients), followed by nephrotoxic medication (21%). There were a variety of other risk factors, none in more than 10%. A total of 45% of the patients needed serum creatinine measurement and 6.6% of the patients were found to have moderate to severe renal impairment. The two questions with the highest relative risk ratio and with the highest group-dependent odd ratios when comparing patients with eGFR <60 ml min\(^{-1}\) 1.73 m\(^{-2}\) to patients with eGFR >60 ml min\(^{-1}\) 1.73 m\(^{-2}\) were a history of renal disease and gout. Patient age over 70 years correlated best with the presence of moderate to severe kidney disease.

Thus, most patients at risk of CIN may be identified by appropriate questions, but a questionnaire does not exclude the presence of renal insufficiency.

### 7.3 Risk Stratification

Risk stratification of patients to identify those susceptible to CIN has not been fully evaluated. On the basis of two cohorts (one derivation cohort (1993–1998) and one validation cohort (1999–2002)) of 20,479 patients, Bartholomew et al. (2004) proposed a CIN risk score with good predictive ability for identifying patients in whom preventive strategies are indicated. Independent variables (with weighted scores) include estimated creatinine clearance <60 ml min\(^{-1}\) (2), urgent percutaneous coronary intervention (2), intra-aortic balloon pump use (2), diabetes mellitus (1), congestive heart failure (1), hypertension (1), peripheral vascular disease (1), and contrast medium volume >260 ml (1). The incidence of CIN after percutaneous coronary intervention increased with each unit increase in score. No patient with a score <1 developed CIN, whereas 26% of patients with a score >9 developed CIN.

Mehran et al. (2004) also developed a simple risk score for CIN after percutaneous coronary intervention. On the basis of a study of 8,357 patients they identified eight variables, which were assigned a weighted integer: hypertension (5); intra-aortic balloon pump (5); congestive heart failure class III/IV by New York Heart Association classification and/or a history of pulmonary edema (5); age >75 years (4); anemia (3); diabetes (1); contrast medium volume (1 for each 100 ml); serum creatinine >132 \mu \text{mol} l^{-1} (1.5 \text{ mg dl}^{-1}) (4); or estimated creatinine clearance <20 ml min\(^{-1}\) 1.73 m\(^{-2}\) (6), 20-40 ml min\(^{-1}\) 1.73 m\(^{-2}\) (4), and 40-60 ml min\(^{-1}\) 1.73 m\(^{-2}\) (2). In patients with a risk score <5 the risk of CIN was 7.5% and the risk of dialysis was 0.04%, whereas the figures for patients with a risk score >16 were 57.3 and 12.6%, respectively. Fu et al. (2013) developed a risk score for CIN in 668 elderly patients; 105 (15.7%) developed CIN. There were 9 risk factors for CIN (with weighted integer): estimated glomerular filtration rate (eGFR) <60 ml min\(^{-1}\) 1.73 m\(^{-2}\) (4), diabetes (3), left ventricular ejection fraction <45% (3), hypertension (2), age >70 years (2), myocardial infarction (2), emergency percutaneous coronary intervention (PCI) (2), anemia (2), and contrast agent volume >200 mL (2). The incidence of CIN was 3.4%, 11.9%, 36.9, and 69.8% in the low risk (<4), moderate risk (5–8), high risk (9–12), and very-high-risk groups (>13). A problem with these proposals for risk score is that they include factors (like volume of contrast medium and intra-aortic balloon pump), which are unknown before the procedure.

Kim et al. (2011) attempted to develop a risk stratification nomogram for CIN in patients having emergency abdominal contrast enhanced CT. Nephropathy was observed in 34 out of 750 patients. Age and baseline serum creatinine appeared to be risk factors. The risk of nephropathy could be predicted by the nomogram based on these two risk factors, but this nomogram has not been tested in other studies.

Methods of stratifying patients being given contrast media appear to have potential but need further evaluation, particularly when contrast medium is injected intravenously.
8 Measures to Reduce the Incidence of CIN

A number of measures (Table 2) have been recommended to reduce the incidence of CIN (Sholy et al. 2012; Thomsen 1999; Morcos 2004, 2005). The main methods are extracellular volume expansion, administration of non-ionic contrast media, and the use of a variety of drugs, all of which are discussed in this section. Other measures that have been tried include hemodialysis, hemofiltration, and use of gadolinium-based contrast media instead of iodine-based agents, and they are discussed in “Dialysis and Contrast Media” and “Radiography with Gadolinium-Based Contrast Media”.

### 8.1 Extracellular Volume Expansion

Extracellular volume expansion is the most effective of all the measures used to prevent CIN (Morcos et al. 1999; Mueller et al. 2002; Trivedi et al. 2003; Allaqaband et al. 2002; Solomon et al. 1994; Taylor et al. 1998; Thomsen et al. 2008a). Early studies of CIN often described those affected as dehydrated. Intravascular volume expansion may increase kidney blood flow, reduce vasoconstriction in the kidney, reduce the dwell time of contrast medium within the kidney, improve tubular clearance of uric acid and cast material, and exert variable neurohormonal effects that reduce the rate of CIN. In addition, diuresis produced by effective hydration is associated with an increased intrarenal production of prostacyclin, leading to vasodilation in the vulnerable region of the renal medulla.

During the last 20 years, only a few randomized trials examining prophylactic fluid therapy have been published (Table 3). They include patients with normal and decreased kidney function. The fluid has been administered orally, intra-arterially, and intravenously. The study sample size has varied from 18 to 1,620, but not more than 2,500 patients (in total) have participated in these trials. It is clear that forced diuresis by adding mannitol or furosemide to hypotonic saline does not work (Dussol et al. 2006; Solomon et al. 1994; Weinstein et al. 1992). The same applies to a rapid bolus of isotonic saline (250–300 ml) at the time of contrast medium exposure (Bader et al. 2004; Krasuski et al. 2003). Unrestricted access to water for 12 h before contrast medium administration does not appear to be effective either (Trivedi et al. 2003). The potentially effective measures are (1) hypotonic (0.45 %) saline at 1 ml kg\(^{-1}\) h\(^{-1}\), starting 12 h before and continuing for 12 h after contrast medium exposure (Solomon et al. 1994); (2) isotonic saline at 1 ml kg\(^{-1}\) h\(^{-1}\) 4 h before and continuing for 12 h after contrast medium exposure (Mueller et al. 2002); (3) oral hydration (1,000 ml over 10 h) followed by hypotonic saline (300 ml h\(^{-1}\)) starting 0.5 h before contrast medium exposure and continuing for 6 h in total (Taylor et al. 1998).

Intravenous infusion of 0.9 % saline solution at a rate of 1 ml h\(^{-1}\) kg\(^{-1}\) body weight starting 6 h before contrast medium administration and continuing for 6 h afterwards seems to be effective (“ESUR Guidelines on Contrast Media Version 8.1”). In areas with a hot climate more fluid should be given. This regime is suitable for patients who are not in congestive heart failure and are not allowed to drink or eat before undergoing an interventional or surgical
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention regimen</th>
<th>Control regimen</th>
<th>Number of participants</th>
<th>Mean baseline kidney function</th>
<th>Outcome measure</th>
<th>Results</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bader et al. 2004</td>
<td>LOCM/IV</td>
<td>2 l IV fluid (12 h pre/12 h post)</td>
<td>39</td>
<td>eGFR 110 ml min⁻¹</td>
<td>Mean change in GFR by contrast clearance at 48 h</td>
<td>−34.6 v. −18.3 ml min⁻¹</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Mueller et al. 2002</td>
<td>LOCM/IA</td>
<td>1 ml kg⁻¹ h⁻¹ IV 0.9 % saline (24 h from morning of procedure)</td>
<td>1,383</td>
<td>eGFR 84 ml min⁻¹ 50 kg lean mass</td>
<td>SCr increase by &gt;44 µmol l⁻¹ (0.5 mg dl⁻¹) within 48 h</td>
<td>5 (0.7 %) v. 14 (2 %)</td>
<td>p = 0.04</td>
</tr>
<tr>
<td>Taylor et al. 1998</td>
<td>Multiple/IA</td>
<td>1 l water PO (over 10 h pre), 300 ml h⁻¹ IV 0.45 % saline (6 h from call to lab)</td>
<td>36</td>
<td>eGFR 48 ml min⁻¹</td>
<td>Mean maximal change in SCr within 48 h</td>
<td>0.21 v 0.12 mg dl⁻¹</td>
<td>p = NS</td>
</tr>
<tr>
<td>Trivedi et al. 2003</td>
<td>LOCM/IA</td>
<td>Unrestricted oral fluids</td>
<td>53</td>
<td>eGFR 79.6 ml min⁻¹</td>
<td>SCr increase by &gt;44 µmol l⁻¹ (0.5 mg dl⁻¹) within 48 h</td>
<td>1 (3.7 %) v. 9 (34.6 %)</td>
<td>p = 0.005</td>
</tr>
<tr>
<td>Krasuski et al. 2003</td>
<td>?/IA</td>
<td>250 ml 0.9 % saline (pre) and 1 ml kg⁻¹ 1.045 % saline (12h post)</td>
<td>63</td>
<td>eGFR ~45 ml min⁻¹</td>
<td>SCr increase by &gt;44 µmol l⁻¹ (0.5 mg dl⁻¹) within 48 h</td>
<td>0 (0 %) v. 4 (10.8 %)</td>
<td>p = NS</td>
</tr>
<tr>
<td>Dussol et al. 2006</td>
<td>LOCM/IA or IV</td>
<td>1 g per 10 kg weight salt and unrestricted water PO (2 days pre)</td>
<td>153</td>
<td>eGFR 34 ml min⁻¹ 1.73 m⁻²</td>
<td>SCr increase by &gt;44 µmol l⁻¹ (0.5 mg dl⁻¹) within 48 h</td>
<td>5 (6.6 %) v. 4 (5.2 %)</td>
<td>p = NS</td>
</tr>
<tr>
<td>Merten et al. 2004</td>
<td>LOCM/ Multiple</td>
<td>3 ml kg⁻¹ h⁻¹ (1 h pre), 1 ml kg⁻¹ h⁻¹ (6 h post) IV sodium bicarbonate 154 mmol l⁻¹</td>
<td>119</td>
<td>eGFR 41–45 ml min⁻¹ 1.73 m⁻²</td>
<td>SCr increase by &gt;25 % within 48 h</td>
<td>1 (1.7 %) v. 8 (13.6 %)</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>Briguori et al. 2007</td>
<td>IOCM/IA</td>
<td>1 ml kg⁻¹ h⁻¹ 0.9 % saline, (12 h pre and 12 h post) plus NAC</td>
<td>220</td>
<td>eGFR 32–35 ml min⁻¹ 1.73 m⁻²</td>
<td>SCr increase by &gt;25 % at 48 h</td>
<td>2 (19 %) v. 11 (9.9 %)</td>
<td>p = 0.01</td>
</tr>
<tr>
<td>Recio-Mayoral et al. 2007</td>
<td>LOCM/IA</td>
<td>1 ml kg⁻¹ h⁻¹ 0.9 % saline IV (12 h post) plus NAC 600 mg PO q12 h X 2 next day</td>
<td>111</td>
<td>eGFR 75 ml min⁻¹ 1.73 m⁻²</td>
<td>SCr increase by &gt;44 µmol l⁻¹ (0.5 mg dl⁻¹) within 3 days</td>
<td>1 (1.8 %) v. 12 (21.8 %)</td>
<td>p = 0.0009</td>
</tr>
<tr>
<td>Clavijo et al. 2006</td>
<td>HOCM or LOCM/IA</td>
<td>Not specified</td>
<td>976</td>
<td>eGFR 44 ml min⁻¹</td>
<td>SCr increase by &gt;44 µmol l⁻¹ (0.5 mg dl⁻¹) between 24 and 72 h post</td>
<td>2 (14 %) v. 47 (5.7 %)</td>
<td>p = 0.03</td>
</tr>
</tbody>
</table>

(Adapted from Thomsen et al. 2008a)

RCT Randomized controlled trial; HOCM High-osmolar contrast media; LOCM Low-osmolar contrast media; IOCM Iso-osmolar contrast media; IA Intraarterial; IV Intravenous; NAC N-acetylcysteine
procedure. If there is no contraindication to oral administration, free fluid intake should be encouraged. At least 500 ml of water or soft drinks orally before and 2,500 ml during the 24 h following contrast medium administration is recommended.

The use of sodium bicarbonate instead of sodium chloride has been advocated. It is suggested that the resulting urine alkalinisation reduces the generation of free radicals. Bicarbonate appears capable of scavenging reactive oxygen species, as well as increasing urine flow. Also, the large amounts of chloride in isotonic saline may cause constriction of the renal vasculature (Joannidis et al. 2008). Merten et al. (2004) published the first trial comparing infusion of sodium bicarbonate (154 mEq l\(^{-1}\) in dextrose 5 % water) with sodium chloride. Infusion was started 1 h before the CM injection at a rate of 3 ml kg\(^{-1}\) h\(^{-1}\) and continued for 6 h after at a rate of 1 ml kg\(^{-1}\) h\(^{-1}\). A number of further trials followed and their results have been pooled in recent meta-analyses (Joannidis et al. 2008; Merten et al. 2004; Brar et al. 2009; Hogan et al. 2008; Meier et al. 2009; Navaneethan et al. 2009; Weisbord and Palevsky 2008). These suggest that sodium bicarbonate may provide better protection against CIN than normal saline. However, in all these meta-analyses, study heterogeneity was reported and there was even publication bias in some studies. When heterogeneity is present, meta-analysis is not the right tool for summarizing data (Biondi-Zoccai et al. 2006). However, a more recent meta-analysis showed no evidence of heterogeneity or publication bias and favors hydration with sodium bicarbonate (Trivedi et al. 2010). The reduced risk of CIN after sodium bicarbonate does not seem to translate into decreased mortality or a reduced need for hemodialysis, but the incidence of these complications is low and a pooled analysis is probably underpowered to detect significant differences (Meier et al. 2009). The safety of sodium bicarbonate in cardiac patients might be a source of concern, but sodium bicarbonate does not appear to cause deterioration in congestive heart failure or to trigger acute pulmonary edema (Navaneethan et al. 2009). In a multicenter trial, Gomes et al. (2012) showed that sodium bicarbonate in patients with a glomerular filtration rate below 50 ml min\(^{-1}\) or serum creatinine below 106 \(\mu\)mol l\(^{-1}\) (1.2 mg dl\(^{-1}\)) was not superior to saline, with CIN rates after saline and bicarbonate of 6 and 6.1 %, respectively. It appears that sodium bicarbonate provides equal protection to isotonic saline.

For sodium bicarbonate, the most widely used regimen (3 ml kg\(^{-1}\) h\(^{-1}\) for 1 h before contrast medium followed by 1 ml kg\(^{-1}\) h\(^{-1}\) for 6 h after) seems appropriate (“ESUR Guidelines on Contrast Media Version 8.1”), although the dose of sodium bicarbonate should be increased until urine alkalinisation is achieved (Meier et al. 2009). The sodium bicarbonate protocol is quicker than the optimal isotonic saline regimen and might be useful for outpatients. Additional studies are required to assess whether a single bolus of sodium bicarbonate administered just before contrast medium administration is effective as Tamura et al. (2009) suggested, as this protocol would be extremely useful in daily practice.

Prolonged intravenous fluid therapy is difficult to administer for outpatient procedures. A novel fast strategy of infusing 1 l of 5 % dextrose immediately before cardiac catheterization was associated with a lower rate (1.4 %) of CIN than in the comparison group (5 %) in a retrospective study of high-risk patients. Further studies are required to test this approach (Clavijo et al. 2006).

Marenzi et al. (2012) looked at the effect of furosemide-forced diuresis and intravenous saline infusion matched with urine output, using a novel dedicated device designed for CIN prevention (RenalGuard®). A total of 170 consecutive patients with chronic kidney disease undergoing coronary procedures were randomized to either furosemide with matched hydration or to standard isotonic saline hydration. Only 4.6 % of the patients in the furosemide group developed CIN (>25 % or >44 \(\mu\)mol l\(^{-1}\) (0.5 mg dl\(^{-1}\)) rise in serum creatinine) versus 18 % in the control group. However, this procedure may be difficult to use during a short CT procedure and seems more appropriate for use during conventional angiography.

### 8.2 Non-ionic Contrast Media

The type of contrast medium used is an important risk factor for the development of CIN, with iso-osmolar contrast media (IOCM) and low-osmolar contrast media (LOCM) being less nephrotoxic than high-osmolar contrast agents in patients with pre-existing renal impairment (Morcos 1998; Morcos et al. 1999; Katzberg 1997; Rudnick et al. 1995; Thomsen et al. 2008a; Sholy et al. 2012). Therefore, low-osmolar or iso-osmolar non-ionic contrast media are recommended in high-risk patients to reduce the risk of CIN. Time has shown that there is no difference in nephrotoxic potential between the non-ionic monomers and the non-ionic dimer.

A total of eight non-ionic monomeric LOCM (iohexol, iomeprol, iopamidol, iopentol, ioxilan, iopromide, ioversol, and iobitritol), one ionic dimer LOCM (ioxaglate), and one non-ionic dimer IOCM (iohexanol) are approved for intravascular use (“Contrast Media Classification and Terminology”). Their approved use varies from country to country.

Several studies have compared LOCM with IOCM, and in most cases the contrast agents were given intra-arterially. Aspelin et al. (2003), in a randomized trial in 129 patients with moderate chronic kidney disease and diabetes mellitus, showed a significantly higher incidence of CIN, defined as
an absolute increase in serum creatinine greater than 44 μmol l\(^{-1}\) (0.5 mg dl\(^{-1}\)), within 72 h with intra-arterial iohexol than with iodixanol (26 vs. 4 %). The two groups differed significantly with regard to interventional procedures and duration of diabetes, but were otherwise comparable. Laskey et al. (2009) repeated Aspelin et al.’s study in a larger group of similar patients; no difference between the monomer (iopamidol) and the dimer (iodixanol) was found. Using the same endpoint as Aspelin et al. (2003) and Laskey et al. (2009), Jo et al. (2006) did not find a significant difference overall between the IOCM iodixanol and the LOCM ionic dimer ioxaglate in 275 patients with chronic kidney disease undergoing coronary procedures; but in some subgroups, e.g., patients with diabetic nephropathy, there was a significant difference. At least eight other angiographic studies showed no significant difference between IOCM and LOCM (Table 4). In a retrospective study of 225 patients with moderate to severe kidney disease, Briguori et al. (2006) could not find differences in CIN rates between iohexol and the LOCM, non-ionic monomer iobitridol. Neither Solomon et al. (2007) nor Wessely et al. (2008) found a difference between iopamidol and iodixanol in their prospective randomized studies of 414 and 334 patients with kidney disease, respectively.

Comparisons between studies that compared a variety of LOCM with the IOCM iodixanol have raised the possibility of differences in nephrotoxic potential between the different LOCM (Bettmann 2005; Solomon and Dumouchel 2006). Since the higher nephrotoxic potential of the LOCM iohexol compared to the IOCM iodixanol (Aspelin et al. 2003) was not replicated in studies using other LOCM, the possibility was raised of a difference in nephrotoxic potential between iohexol and the other non-ionic monomers (Bettmann 2005; Sharma and Kini 2005; Solomon and Dumouchel 2006). Solomon and Dumouchel (2006) conducted a systematic analysis of published papers and the Food and Drug Administration (FDA) reports of adverse events, and found that the risk of CIN was higher in patients following administration of iohexol than of another non-ionic monomer, iopamidol. Bettmann (2005) and Sharma and Kini (2005) analyzed control arms of studies of patients with chronic kidney disease receiving no premedication and showed that the average incidence of CIN after iopamidol administration was significantly lower than after iohexol, whereas the incidence after iodixanol varied from 3 to 33 %. Thus, it is possible that there may be a difference in the nephrotoxic potential between the various LOCM. Although there are no important differences in the physicochemical properties between the different non-ionic monomeric LOCM, it may be argued that it is inappropriate to put all non-ionic monomers together in any review or meta-analysis. In a retrospective multicenter observational study including 107,994 patients not on hemodialysis who underwent invasive coronary angiography (ICA) and/or percutaneous coronary intervention (PCI) with either iohexol, iopamidol or ioversol, death in hospital, need for hemodialysis, and readmission for CIN were all uncommon, with no apparent clinical advantage among these three agents (LaBounty et al. 2012).

Also, after intravenous injection, there is no difference in the nephrotoxic potential between LOCM and IOCM (Table 1). Thomsen et al. (2008a) reported 7 % CIN after intravenous injection of 40 g I iodixanol (320 mg I ml\(^{-1}\)) and 0 % CIN after 40 g I iomeprol (400 mg I ml\(^{-1}\)) in patients with reduced kidney function \((p < 0.05)\). Also, using the same endpoint as in the NEPHRIC study (Aspelin et al. 2003), Barrett et al. (2006) showed a 2.6 % CIN rate after intravenous injection of iodixanol for CT and 0 % after injection of iopamidol in a randomized, multicenter trial. Kuhn et al. (2008) found no difference between iopamidol and iodixanol in patients with diabetic nephropathy. Previous smaller studies by Carraro et al. (1998) and Kolehmainen and Soiva (2003) in patients with chronic kidney disease did not show any difference between iodoxanol and their respective comparators (iopromide and iobiditrol) either (Table 1). On the other hand, Nguyen et al. (2008) found iopromide to be inferior to iodixanol in a randomized study of 117 patients with average GFR of 52 ml min\(^{-1}\). It is surprising that 18.5 % developed CIN after only 100 ml of 370 mg I ml\(^{-1}\) iopromide. In 41 patients who did not receive acetylcysteine (control arm), Tepel et al. (2000) reported a 21 % rate of CIN after intravenous injection of 75 ml iomeprol of 300 mg I ml\(^{-1}\). In both studies the same endpoint (\(>44 \mu\)mol l\(^{-1}\) (0.5 mg dl\(^{-1}\)) was used. Pugh et al. (1993) compared iopromide and iodixanol for femoral arteriography; according to McCullough et al. (2006a, b) they found a lower rate of CIN after iopromide than after iodixanol. Chen et al. (2012) did not find any difference in nephrotoxicity between iopromide and iodixanol in patients undergoing coronary angiography who had moderately reduced renal dysfunction. These conflicting results are typical of this topic. They apply to all agents and this indicates that there is no difference in nephrotoxic potential between agents. The variable results are likely to be due to natural fluctuations in serum creatinine.

A number of reviews have recommended that the non-ionic iso-osmolar dimer should be used rather than the non-ionic monomers in patients at risk of developing CIN (Gleeson and Bulugahapitaya 2004; Cavusoglu et al. 2004; Maeder et al. 2004; Nikolsky and Mehran 2003; Mitchell et al. 2004; Asif and Epstein 2004; Andrew and Berg 2004; Nicholson and Downes 2003; Erdogan and Davidson 2003). However, there is no conclusive evidence of a difference in the nephrotoxic potential between the various monomers and the dimer. Based on a more recent meta-analysis,
Table 4 Prospective randomized trials comparing intra-arterial iso- to low-osmolality contrast media

<table>
<thead>
<tr>
<th>Low-osmolar CM</th>
<th>N</th>
<th>Iso-osmolar CM</th>
<th>N</th>
<th>Examination</th>
<th>Pre-procedural SCr μmol l⁻¹ (mg dl⁻¹)</th>
<th>Diabetes Mellitus (%)</th>
<th>Statistical result</th>
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<tr>
<td>Iohexol</td>
<td>48</td>
<td>Iodixanol</td>
<td>54</td>
<td>Coronary</td>
<td>273 (3.1)</td>
<td>35</td>
<td>No difference</td>
<td>SCr ≥ 25 % from baseline</td>
<td>Chalmers and Jackson (1999)</td>
</tr>
<tr>
<td>Iohexol</td>
<td>65</td>
<td>Iodixanol</td>
<td>64</td>
<td>Arteriography</td>
<td>132 (1.5)</td>
<td>100</td>
<td>Iodixanol superior</td>
<td>SCr increase ≥ 44 μmol l⁻¹ (0.5 mg dl⁻¹)</td>
<td>Aspelin et al. (2003)</td>
</tr>
<tr>
<td>Iopamidol</td>
<td>263</td>
<td>Iodixanol</td>
<td>263</td>
<td>Diagnostic and/or therapeutic coronary angiographic procedures</td>
<td>138 (1.57)</td>
<td>100</td>
<td>No difference</td>
<td>SCr increase ≥ 44 μmol l⁻¹ (0.5 mg dl⁻¹)</td>
<td>Laskey et al. (2009)</td>
</tr>
<tr>
<td>Ioxaglate</td>
<td>135</td>
<td>Iodixanol</td>
<td>140</td>
<td>Coronary</td>
<td>117 (1.34)</td>
<td>48</td>
<td>Iodixanol may be superior in certain subgroups</td>
<td>SCr increase ≥ 44 μmol l⁻¹ (0.5 mg dl⁻¹)</td>
<td>Jo et al. (2006)</td>
</tr>
<tr>
<td>Iopamidol</td>
<td>204</td>
<td>Iodixanol</td>
<td>210</td>
<td>Coronary</td>
<td>128 (1.45)</td>
<td>41</td>
<td>No difference</td>
<td>SCr increase ≥ 44 μmol 1⁻¹ (0.5 mg dl⁻¹)</td>
<td>Solomon et al. (2007)</td>
</tr>
<tr>
<td>Iopamidol</td>
<td>48</td>
<td>Iodixanol</td>
<td>54</td>
<td>Coronary</td>
<td>&lt;176 (2)</td>
<td>100</td>
<td>SCr ≥ 25 % from baseline</td>
<td>Second endpoint: SCr increase ≥ 44 μmol 1⁻¹ (0.5 mg dl⁻¹) or ≥ 25 % increase from baseline</td>
<td>Hardiek et al. (2008)</td>
</tr>
<tr>
<td>Iopamidol</td>
<td>41</td>
<td>Iodixanol</td>
<td>46</td>
<td>Coronary artery stenting</td>
<td>CrCL &lt; 60 ml min⁻¹</td>
<td>19</td>
<td>No difference</td>
<td>SCr increase ≥ 44 μmol 1⁻¹ (0.5 mg dl⁻¹) or ≥ 25 % increase from baseline</td>
<td>Jingwei et al. (2006)</td>
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<tr>
<td>Ioxaglate</td>
<td>74</td>
<td>Iodixanol</td>
<td>75</td>
<td>Percutaneous coronary diagnostic or interventional procedures</td>
<td>161 (1.83)</td>
<td>45</td>
<td>No difference</td>
<td>SCr increase ≥ 44 μmol 1⁻¹ (0.5 mg dl⁻¹)</td>
<td>Mehran et al. (2009)</td>
</tr>
<tr>
<td>Iopromide</td>
<td>278</td>
<td>Iodixanol</td>
<td>284</td>
<td>Cardiac Catherization</td>
<td>124 (1.41)</td>
<td>30</td>
<td>No difference</td>
<td>First endpoint: SCr increase &gt;50 % Second endpoint: SCr increase ≥ 44 μmol 1⁻¹ (0.5 mg dl⁻¹) or ≥ 25 % increase from baseline</td>
<td>Chen et al. (2012)</td>
</tr>
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<td>Iomeprol</td>
<td>162</td>
<td>Iodixanol</td>
<td>162</td>
<td>Coronary angiography</td>
<td>120 (1.36)</td>
<td>37</td>
<td>No difference</td>
<td>SCr increase ≥ 44 μmol 1⁻¹ (0.5 mg dl⁻¹) or ≥ 25 % increase from baseline</td>
<td>Wessely et al. (2008)</td>
</tr>
</tbody>
</table>

SCr Serum creatinine
Heinrich et al. (2009) concluded that the iso-osmolar iodixanol is not associated with a reduced risk of CIN compared to LOCM after intravenous administration. In patients with renal insufficiency given contrast media intra-arterially, low-osmolar iohexol was associated with a greater risk of CIN than iodixanol, but no significant difference between iodixanol and other LOCM was found. Why the nephrotoxicity of iohexol should differ from the other monomers is still unclear.

It is important to remember that all these agents are potentially nephrotoxic, although the risk associated with them is less than that with the old, high-osmolar contrast agents.

### 8.3 Avoidance of Nephrotoxic Drugs

The use of nephrotoxic drugs is likely to increase the risk of developing CIN. This is supported by experimental observations (Morcos 2005), but clinical data are lacking. A trend toward a higher incidence of CIN in patients receiving loop diuretics, nonsteroidal anti-inflammatory drugs, coxibs, aminoglycosides, or amphotericin B has been reported (Alamartine et al. 2003). CIN in patients treated with cisplatinum has also been described. Conflicting data have been reported on angiotensin-converting enzyme (ACE) inhibitors, with some suggesting an increased risk of CIN, and others suggesting a decreased risk. A more comprehensive list of nephrotoxic drugs has been published; it includes drugs that have not been reported in the medical history of patients who developed CIN (Naughton 2008; Pannu and Nadim 2008). Withdrawal of nephrotoxic drugs at least 24 h before CM administration in at-risk patients was suggested in the first guideline from the ESUR CMSC (Morcos et al. 1999). Current literature supports this advice, but the recommendation is poorly followed in clinical practice (Fishman and Reddan 2008; Reddan and Fishman 2008). It seems reasonable to continue the use of ACE-inhibitors, loop diuretics, and small doses of nonsteroidal anti-inflammatory drugs (NSAIDs) for antiplatelet treatment in patients with stable renal function, because temporary cessation may be more harmful for the patient.

Possible withdrawal of nephrotoxic drugs before contrast medium in patients at risk of CIN should be discussed with the referring physician and the judgment should balance the relative benefits and harms (“ESUR Guidelines on Contrast Media Version 8.1”).

### 8.4 Pharmacological Manipulation

In recent years, it has been claimed that various substances or drugs may protect the kidney against CIN. However, no intervention has proven efficacious beyond doubt. Strongly positive initial trials have often not been replicable.

Acetylcysteine is an antioxidant and scavenger of oxygen-free radicals. It enhances the biologic effect of the endogenous vasodilator nitric oxide by combining with nitric oxide to form S-nitrosothiol, which is a more stable and potent vasodilator than nitric oxide. Acetylcysteine also increases the expression of nitric oxide synthase, the enzyme responsible for the endogenous production of nitric oxide in the body (Safirstein et al. 2000). Nitric oxide is crucial for maintaining the perfusion of the kidney, particularly in the vulnerable region of the renal medulla. Therefore, acetylcysteine might reduce the nephrotoxicity of contrast medium through antioxidant and vasodilatory effects (Meschi et al. 2006). The results of an initial trial were dramatic, but the event rate in the controls was unexpectedly high for patients given a low dose, intravenous, low-osmolality contrast medium (Tepel et al. 2000). Subsequent trials have largely involved patients with reduced kidney function having cardiac angiography. Some have shown benefit and others have not; many are limited by low power and a lack of blinding (Fishbane et al. 2004; Brigouri et al. 2004a; Liu et al. 2005; Pannu et al. 2006; Marenzi et al. 2006). The dose of acetylcysteine used in most trials has not been chosen on the basis of pharmacologic principles. Two trials comparing doses of acetylcysteine have suggested that higher doses may be required, especially if higher doses of contrast medium are being used (Brigouri et al. 2004b; Marenzi et al. 2006). There have been several meta-analyses of trials of acetylcysteine (Alonso et al. 2004; Pannu et al. 2004; Fishbane et al. 2004; Liu et al. 2005; Zagler et al. 2005; Kshirsagar et al. 2004; Bagshaw and Ghali 2004; Bagshaw et al. 2006; Vaikus and Brar 2007; Biondi-Zoccai et al. 2006). The results of these meta-analyses must be interpreted with caution given the heterogeneous results of the individual trials, and the possibility of publication bias, with small negative studies under-represented (Bagshaw et al. 2006; Vaikus and Brar 2007; Biondi-Zoccai et al. 2006). A recent meta-analysis on the role of acetylcysteine in preventing CIN in patients undergoing peripheral angiography showed that there is insufficient evidence to recommend prophylactic acetylcysteine in these patients (O’Sullivan et al. 2013). Also, the effect of acetylcysteine on outcomes other than minor changes in serum creatinine is largely unknown. Indeed, studies in healthy volunteers have suggested that acetylcysteine might have an effect on creatinine levels unrelated to an effect on GFR (Hoffmann et al. 2004; Curham 2003). Poletti et al. (2007) found no effect of acetylcysteine when they used Cystatin C as the measure of glomerular filtration rate, but they found a significantly lower CIN rate in the acetylcysteine group than in the control group when they used serum creatinine as the measure of renal function.
Cystatin C is not secreted by the tubular cells, whereas creatinine is. Thus, there is no conclusive evidence that acetylcysteine provides consistent protection against CIN and its routine use for prophylaxis is not recommended.

Theophylline and aminophylline (nonselective adenosine receptor antagonists) have the potential to reduce CIN through antagonizing adenosine-mediated vasoconstriction. Adenosine is an important intrarenal mediator, which can induce a decrease in the glomerular filtration rate through vasoconstriction of the afferent arterioles and contraction of the mesangial cells of the glomeruli (Oldroyd et al. 2000). Adenosine also induces vasoconstriction in the renal cortex and vasodilatation in the renal medulla, increases the generation of oxygen-free radical cells, and is a mediator of the tubuloglomerular feedback (TGF) response. Clinical studies have given conflicting results. In one study, administration of 200 mg theophylline intravenously had a preventative effect (Huber et al. 2002), but in another study 810 mg theophylline orally daily for 3 days did not offer additional protection compared to hydration alone (Erley et al. 1999). In a recent study Dai et al. (2012) found no beneficial effects of theophylline in patients with high baseline creatinine values (>132 μmol l⁻¹ (1.5 mg dl⁻¹)). Meta-analyses found that the mean rise in serum creatinine was significantly, but only slightly, lower at 48 h after contrast medium administration among those receiving active therapy compared to placebo (Ix et al. 2004; Bagshaw and Ghali 2005). The clinical importance of this finding is not clear (Thomsen et al. 2008a; Goldenberg and Matetzky 2005). There was heterogeneity among studies with regard to changes in serum creatinine. There is potential for adverse effects with theophylline particularly in patients with ischemic heart disease in whom it may induce cardiac arrhythmias (Morcos 2004). The optimal dose for preventing CIN has not been established. Further studies using a selective adenosine receptor (A1) antagonist are warranted. The effectiveness of theophylline in preventing CIN remains uncertain.

The antioxidant ascorbic acid has been tested in two randomized trials of patients undergoing cardiac angiography (Briguori et al. 2007; Spargias et al. 2004). In the first study, CIN occurred in 11 (9 %) of patients given ascorbic acid compared to 23 (20 %) given placebo (p = 0.02) (Spargias et al. 2004). However, these results are difficult to interpret, as the baseline serum creatinine level was lower in the placebo group and both groups reached a similar level after contrast medium administration. In the more recent trial, ascorbic acid given with acetylcysteine and saline was associated with the same rate of CIN as when acetylcysteine and saline alone were given (Briguori et al. 2007).

Calcium channel blockers prevent the influx of calcium ions through voltage-operated channels, so causing a vasorelaxant effect in all vascular beds including the kidney. In one study, 3 days treatment with 20 mg nitrendipine prevented the development of CIN in patients with moderate renal impairment (Neumayer et al. 1989), but in another study a single dose (20 or 10 mg) given 1 h before contrast medium administration failed to prevent CIN (Carraro et al. 1996). The incidence of CIN was 6.5 % with 20 mg nitrendipine, 3.7 % with 10 mg nitrendipine, and 8.3 % in the control group, and the differences were not statistically significant. Thus, the role of calcium channel blockers remains uncertain and their protective effect in patients with advanced renal impairment has not been proven. In addition, these drugs are not suitable in patients with heart failure.

The use of the vasodilators dopamine and atrial natriuretic peptide may be harmful in patients with diabetic nephropathy. The frequency of CIN in patients who were pretreated with either drug plus hydration was 83 %, whereas the frequency in the control group, who received only hydration, was 43 % (Weisberg et al. 1994).

The selective dopamine-1 receptor agonist, fenoldopam, in contrast to dopamine, increases both cortical and medullary blood flow. Fenoldopam has the advantage of not stimulating β- and β-adrenergic receptors or dopamine-2 receptors, which can produce renal vasoconstriction. One study has shown that fenoldopam offers some protection against CIN (Kini et al. 2002), but two studies indicated that it offered no protection (Allaqaband et al. 2002; Stone et al. 2003). In addition, fenoldopam has the disadvantages that it has to be given intravenously and it induces hypotension, so regular monitoring of the blood pressure is necessary (Morcos 2004).

Experimental studies have indicated that the potent endogenous vasoactive peptide endothelin may play an important role in mediating CIN (Oldroyd et al. 1995). Therefore, it was suggested that endothelin antagonists (Benigni and Remizzi 1999) would reduce the incidence of CIN in humans. However, Wang et al. (2000) found that a nonselective endothelin receptor antagonist and intravenous hydration were associated with a CIN rate of 56 % compared to 29 % in the hydration only group. In addition, hypotension was more frequent in the treated group. Wang et al.’s (2000) study has been criticized (Haylor and Morcos 2000) because the choice of a nonselective endothelin receptor antagonist, which blocks both endothelin-A and the endothelin-B receptors, was not appropriate. Endothelin-B receptors are responsible for vasodilatation and clearance of endothelin, and blocking them abolishes the vasodilatory effect and prolongs the vasoconstrictor effect of endothelin, which is released in response to contrast medium. Also, the endothelin receptor antagonist was given only 12 h after contrast medium injection so that there was no sustained drug cover.
Two studies of captopril as a prophylactic agent yielded divergent results (Gupta et al. 1999; Toprak 2006; Toprak et al. 2003). In the first trial, serum creatinine rose by more than 0.5 mg dl$^{-1}$ (44 μmol l$^{-1}$) in 2 (6 %) patients given captopril for 3 days vs. 10 (29 %) given placebo ($p < 0.02$) (Gupta et al. 1999). In the second study, CIN was reported as occurring in five (10 %) patients given captopril vs. one (3 %) given placebo ($p = 0.02$) (Toprak 2006; Toprak et al. 2003).

Several other interventions have been proposed to reduce the risk of CIN, but data to support them are limited. Forced diuresis with furosemide, mannitol, dopamine, or a combination of these given at the time of the contrast medium exposure has been associated with similar or higher rates of CIN when compared to prophylactic fluids alone (Solomon et al. 1994; Weinstein et al. 1992; Stevens et al. 1999; Gare et al. 1999; Hans et al. 1998). Negative fluid balance might underlie some of the detrimental effects.

In summary, none of the many proposed pharmacological manipulations has been proven to be of consistent benefit in reducing the incidence of CIN.

9 Recommendations During the Last 15 Years

In 2006, Barrett and Parfrey (2006) reviewed the literature and recommended using intravenous saline therapy and the lowest possible dose of low-osmolality contrast media. They also indicated that NSAIDs and diuretics should be withheld for at least 24 h before and after exposure to contrast medium and that N-acetylcysteine was not recommended routinely, given the inconsistent results of clinical trials. Their recommendations were in accordance with ESUR guidelines from 1999 (Morcos et al. 1999). Thomsen and Morcos (2006) evaluated a plethora of reviews and guidelines on prevention of CIN. They concluded that guidelines should be prepared after careful study of published literature and with a thorough understanding of the subject, and recommendations should be evidence-based whenever possible, relying on consistent results of well-structured, large studies. Recommending a change in clinical practice based only on a single study cannot be justified, particularly in the field of CIN, since inconsistency of results of clinical studies is a real problem. Clinical investigation of CIN regularly faces the problem of finding a perfectly matching control group, as there are many variables that can influence renal function. In addition, it is important to emphasize that meta-analysis of inconsistent study results cannot provide confident recommendations about treatment (Higgins et al. 2003). There is a great need for randomized clinical trials. Guidelines should be based on proven clinical practice. In areas of contention, a consensus among experts on the subject should be sought. Guidelines should be concisely and clearly written using accurate terminology and avoiding vague recommendations. The ESUR guidelines on the prevention of CIN (Morcos et al. 1999), which required 3 years of preparation and involved wide consensus, remain valid in spite of the large number of new studies reported in the literature since their publication in 1999. They have recently been updated (Stacul et al. 2011).

Recently KDIGO (Fliser et al. 2012) produced a guideline on CIN, which is summarized in this paragraph. Overall, it does not differ from the ESUR guidelines (“ESUR Guidelines on Contrast Media Version 8.1”). They use the same definition of CIN as for acute kidney insufficiency (Kidney Disease: Improving Global Outcomes (KDIGO) 2013). They recommend that before an intervention which involves a risk of CIN, a baseline serum creatinine should be measured and, for high-risk patients, a repeat serum creatinine 12 and 72 h after administration of contrast medium. In individuals who develop changes in kidney function after intravascular contrast media, not only CIN but also other possible causes of acute kidney injury should be considered. The risk of CIN should always be weighed against the benefit of administering contrast medium. Alternative imaging methods not requiring contrast medium should always be considered in patients at increased risk of CIN, as long as these give the same diagnostic accuracy. For example, the potential risk of CIN must be balanced against the potential diagnostic loss from not giving contrast medium, such as overlooking a resectable tumor. The risk of CIN increases with decreasing baseline GFR, particularly in the presence of diabetes and dehydration. Several drugs have a prolonged nephrotoxic action because of long-lasting accumulation in the renal cells. To minimize the risk of kidney damage, these drugs would have to be stopped for days or even weeks, not just hours, before contrast medium administration. The rationale for stopping loop diuretics is mainly based on their detrimental effect when used as prophylaxis against CIN. Volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions in patients at increased risk for CIN is recommended. Hydration may be given orally, provided that there is adequate intake of fluid and salt. When adequate oral fluid and salt intake is not possible in patients at increased risk of CIN, hydration should be given intravenously. Prophylactic intermittent hemodialysis (IHD) or hemofiltration (HF) to prevent CIN only is not recommended.

10 Residual Function

It is essential to preserve residual renal function in dialysis patients as long as possible. Among the suggested prophylactic strategies are angiotensin-converting enzyme (ACE)
inhibitors or angiotensin II receptor blockers, use of biocompatible dialysis solutions, prevention of peritonitis, and avoidance of nephrotoxic drugs such as aminoglycosides, nonsteroidal anti-inflammatory agents and iodine-based contrast media (Lameire 1997; Suzuki et al. 2004). Patients on dialysis are never included in the major prospective trials mentioned above—for obvious reasons. Dittrich et al. (2006) looked at residual renal function in 10 patients treated with continuous ambulatory peritoneal dialysis (CAPD) who electively received intravenous or intra-arterial administration of contrast medium for diagnostic purposes (median dose 107.5 ml/patient). Eight CAPD patients who did not receive contrast medium acted as the control group. There was no significant difference between the two groups in age, gender, diabetes, duration of dialysis, and renal clearance at baseline. In the study group, a temporary but statistically significant decline in residual renal clearance was observed. On day 30, clearances were not significantly different from baseline. This is in agreement with several retrospective studies, which either showed no long-term influence of intravenous contrast medium on the decline of residual renal function in patients on peritoneal dialysis or did not consider this aspect (Dittrich et al. 2006).

Residual function is of less importance in hemodialysis. Whether CIN occurs in patients with residual function who are treated with chronic hemodialysis is unclear, as there may be other factors causing renal function to stop. In patients without residual function, CIN is not an issue.

### 11 Is CIN Just a Result of Natural Fluctuations in Serum Creatinine?

Newhouse et al. (2008) reported that hospitalized patients who were not exposed to contrast medium had rates of increased serum creatinine similar to the reported rates of CIN after contrast medium. For a long time, only two studies (Cramer et al. 1985; Heller et al. 1991) comparing these two groups had been published and in neither study did contrast medium produce renal dysfunction in more patients than in patients who did not receive contrast medium. Over the last 5 years, another 11 studies with control groups have been published (McDonald et al. 2013a). They constitute only 0.9% of the 1489 studies dealing with nephrotoxicity following intravenous contrast medium administration. A meta-analysis of these 13 studies showed a similar incidence of acute kidney injury, dialysis, and death in the contrast medium group and the control group (McDonald et al. 2013a). Four studies were prospective and the rest retrospective. McDonald et al. (2013b) looked at all contrast medium enhanced and unenhanced abdominal, pelvic, and thoracic CT scans from a 10-year period and classified patients according to their renal function. A total of 167,140 scans were performed in 53,439 patients. Counterfactual analysis revealed no significant difference in acute kidney injury incidence following enhanced and unenhanced CT scans in the same patients. They concluded that, after adjustment for presumed risk factors, the incidence of CIN was not significantly different from contrast medium independent acute kidney injury, and that these two phenomena were clinically indistinguishable using established serum creatinine criteria. This suggests that intravenous iodine-based contrast media may not be the cause of reduced renal function after contrast medium administration. Davenport et al. (2013) did a similar study based on examinations performed over 10 years. A one-to-one propensity-matched cohort analysis with multivariate analyses of effects was performed with post CT acute kidney injury as the primary outcome measure (10,121 unenhanced and 10,121 unenhanced CT examinations in 20,242 patients). They found that intravenous low-osmolality iodine-based contrast medium is a nephrotoxic risk factor, but not in patients with a stable serum creatinine level less than 132 μmol l⁻¹ (1.5 mg dl⁻¹). There is no doubt that in the past natural fluctuations in serum creatinine have been identified as CIN and that the incidence of CIN has, therefore, been overestimated. However, severe cases, for example those with acute anuria cannot be explained as natural serum creatinine fluctuations. The truth is very likely somewhere in between and the overwhelming majority (>95%) of patients are not at increased risk of CIN during routine CT.

One of the major problems in these studies is the control group. Optimal randomization is not possible. For example, a patient with suspected liver metastasis cannot be randomized to receive or not to receive contrast medium. The opposite applies to a patient referred for an unenhanced examination such as MR of the knee. For proper randomization, all patients need a needle in an arm vein and apparently identical contrast medium or saline has to be prepared without contact with the personnel doing the scan. If the scan is performed enhanced and unenhanced, the two examinations must be relatively close so that the disease does not change between them. The possibility of increased radiation dose to the patient must be considered. Other problems relate to whether younger patients should be included and whether patients will consent to participate. Retrospective studies suffer from the fact that someone decided not to give contrast medium. The reason for this is often unclear and may have been that the patient had impaired renal function. It is difficult to establish an ideal control group.

Becker et al. (2013) looked at measured GFR in relation to injection of three non-ionic monomers and the non-ionic dimer in patients at low risk of CIN (<123 μmol l⁻¹ (1.4 mg dl⁻¹)). They concluded that the four agents were
comparable in their lack of a significant effect on measured GFR. They suggested that renal function formulas offer little because they are creatinine driven and result in an estimate that has limited relation to measured GFR (Botev et al. 2011). Recent research appears to minimize the problem of CIN, particularly in patients with moderately reduced renal function. Using better measurements of GFR than eGFR, it may be possible in the near future to reduce the cut-off level for being at low risk of CIN after an intravenous injection of an iodine-based contrast medium to 30 ml min\(^{-1}\) 1.73 m\(^{-2}\).

12 Metformin and Contrast Media

In non-insulin dependent diabetes mellitus not controlled by diet and exercise, the biguanide metformin is the first line drug of choice (Bolen et al. 2007; NICE Clinical guideline CG87 2009). The risk of lactic acidosis with another biguanide, phenformin, was considered unacceptable and phenformin was withdrawn in the late 1970s. Although the risk of lactic acidosis with metformin was recognized to be much lower than with phenformin (Bailey and Turner 1996), concern persisted. More recent data indicate that the risk of metformin causing lactic acidosis in diabetics is very low, between 4.3 and 9 cases per 100,000 patient years (Stang et al. 1999; Salpeter et al. 2010), and that the risk of metformin-associated lactic acidosis is no greater than the risk with sulphonylurea (Cryer et al. 2005; Salpeter et al. 2010).

12.1 Metformin Pharmacokinetics

Metformin is readily absorbed from the gut and blood levels peak at 2.5 h (Electronic Medicines Compendium 2012a). Renal excretion of metformin is rapid with 90 % excreted by glomerular filtration and tubular secretion in the first 12 h (Bailey and Turner 1996). In slow release metformin tablets, a polymer layer around the metformin slows absorption, and blood levels peak later, at 7 h, but excretion is then identical to immediate release metformin (Electronic Medicines Compendium 2012b).

12.2 Impaired Renal Function and Metformin Contraindications

When renal function is reduced, metformin is excreted more slowly. Metformin clearance was reduced by 23–33 % in mild renal impairment and by 74–78 % in severe renal impairment, with associated increases in blood metformin concentration (Sambol et al. 1995). Since increased metformin blood levels potentially increase the risk of lactic acidosis, renal impairment has been considered to be a contraindication to metformin, with manufacturers recommending that it should not be given if eGFR is less than 60 ml min\(^{-1}\) 1.73 m\(^{-2}\) (Electronic Medicines Compendium 2012a, b).

Despite this, the increasing recognition of the low incidence of lactic acidosis in diabetics taking metformin has led to metformin being given to patients with CKD3 (eGFR 30–59 ml min\(^{-1}\) 1.73 m\(^{-2}\)) (Holstein and Stumvoll 2005; Shaw et al. 2007; Warren et al. 2007). There was only one case of lactic acidosis in approximately 2,500 patients in whom a variety of contraindications to metformin were not observed (Holstein and Stumvoll 2005). The most recent guidelines from the UK National Institute of Clinical Excellence (NICE) (2009) state that metformin can be given to patients with eGFR >45 ml min\(^{-1}\) 1.73 m\(^{-2}\), that the metformin dose should be reviewed if eGFR <45 ml min\(^{-1}\) 1.73 m\(^{-2}\), and that metformin should be stopped if eGFR <30 ml min\(^{-1}\) 1.73 m\(^{-2}\) (NICE Clinical guideline CG 87 2009).

Metformin is contraindicated in conditions associated with lactic acidosis, especially liver disease and conditions causing hypoxia, such as cardiac and respiratory failure and severe infection (Bailey and Turner 1995).

12.3 Iodine-Based Contrast Media

Diabetics with reduced renal function have an increased risk of CIN compared to nondiabetics with similar renal function (Parfrey et al. 1989; Rudnick et al. 1995; McCullough et al. 2006a, b). The possibility that diabetics with renal impairment might develop CIN after intravascular iodine-based contrast media, and so be at risk of metformin retention and lactic acidosis, led to restrictions on the administration of metformin when iodine-based contrast agents were given.

There is insufficient evidence in the literature on which to base guidelines for the administration of iodine-based contrast media to patients taking metformin and guidelines have therefore had to be produced by expert consensus based on the pharmacokinetics of metformin and the pathophysiology of CIN (Goergen et al. 2010; Thomsen et al. 2010). The early guidelines recommended that metformin was stopped for 48 h before iodine-based contrast media and only restarted 48 h after contrast medium if renal function was normal (Thomsen et al. 1999). As the guidelines for the use of metformin in patients with impaired renal function have relaxed, so have the guidelines for use of metformin when iodine-based contrast media are given.

The current ESUR guidelines state that patients with an eGFR of 45 ml min\(^{-1}\) 1.73 m\(^{-2}\) or greater can continue to
take metformin normally if they receive intravenous iodine-based contrast medium. Patients receiving intra-arterial iodine-based contrast medium with eGFR $30–59 \text{ ml min}^{-1} \text{ 1.73 m}^{-2}$ and those receiving intravenous iodine-based contrast medium with eGFR $30–44 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ should stop taking metformin 48 h before contrast medium. Renal function should be measured 48 h after contrast medium and metformin should only be restarted if there has been no further deterioration in renal function. In patients with eGFR less than 30 ml min$^{-1}$ 1.73 m$^{-2}$ (CKD 3 and 4), and patients with conditions predisposing to lactic acidosis (liver failure and hypoxia), metformin is contraindicated and iodine-based contrast medium should be avoided (Stacul et al. 2011).

### 12.4 Gadolinium-Based Contrast Media

CIN has been described after gadolinium-based contrast media but appears to be very rare if approved contrast medium doses are used (Thomsen 2004). No special precautions are necessary when patients on metformin are given gadolinium-based contrast media.

### 13 Summary

A major problem in the prevention of CIN is that, after 50 years of research, the pathophysiological mechanism of the condition is still not known. Recently, it has even been claimed that some patients diagnosed as having CIN have only had natural fluctuations in serum creatinine, not caused by the contrast medium.

Current practice for preventing CIN still relies on identifying patients at increased risk. Estimated glomerular filtration rate (eGFR) has replaced serum creatinine in the routine determination of renal function. In patients with reduced renal function, the possibility of an alternative imaging method not using contrast medium should be considered. If an investigation using iodine-based contrast medium is considered essential for patient management, a number of measures that have been proved to reduce the incidence of CIN should be instituted. These are extracellular volume expansion with either normal (0.9 %) saline or sodium bicarbonate, the choice of low- or iso-osmolar non-ionic contrast medium, and use of the lowest contrast medium dose consistent with a diagnostic conclusion or a therapeutic goal. Kidney function should not be used as a guide to the amount of contrast medium that can safely be given. Pharmacological manipulation with the drugs so far evaluated cannot be recommended. Even when the recommended prophylactic measures are used, CIN remains a risk after administration of iodine-based contrast media.

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Dialysis and Contrast Media

Sameh K. Morcos

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Abstract

Extracellular water soluble contrast media, whether gadolinium- or iodine-based, can be removed from the circulation by hemodialysis and less efficiently by peritoneal dialysis. Hemodialysis has no role in prevention of contrast-induced nephropathy and patients on hemodialysis do not need to receive dialysis shortly after administration of iodine-based contrast media. The administration of low stability gadolinium-based contrast media to patients receiving dialysis has been associated with development of nephrogenic systemic fibrosis. Only highly stable gadolinium-based contrast agents at the smallest possible dose should be used if contrast enhanced MR is considered essential in patients receiving dialysis. Patients already on hemodialysis should undergo a hemodialysis session as soon as practically possible after administration of gadolinium-based contrast agents.

1 Introduction

Contrast-induced nephropathy (CIN) remains an important cause of hospital-acquired acute renal failure. Pre-existing renal impairment, especially diabetic nephropathy, and the dose of the contrast medium are major risk factors in the development of CIN (Morcos et al. 1999; Morcos 1998, 2004). It is generally agreed that if contrast medium injection is clinically necessary prophylactic measures should be used to reduce the risk (Morcos et al. 2002). Prophylactic hemodialysis has been proposed to prevent CIN in patients with renal impairment, but has not obtained general acceptance. In addition, there is misunderstanding about whether intravascular iodine-based contrast medium injection in patients on dialysis should be scheduled in relation to the time of the hemodialysis session (Morcos et al. 2002). In this chapter, the use of hemodialysis and peritoneal dialysis in the elimination of water-soluble,
iodine- and gadolinium-based contrast agents in patients with end-stage renal disease will be outlined. The value of hemodialysis in preventing CIN in patients with pre-existing renal impairment, and whether hemodialysis has a role after gadolinium-based contrast media in patients with pre-existing renal impairment will be discussed.

2 Hemodialysis in the Removal of Iodine-Based Contrast Media

The pharmacokinetic properties of water-soluble, iodine-based contrast media are such that they are distributed in the extracellular fluid only, protein binding is minimal, they are not metabolized and excretion is mainly by glomerular filtration. The half-life of iodine-based contrast media in patients with a normal glomerular filtration rate is approximately 2 h but in patients with severe renal dysfunction it can be prolonged to over 30 h depending on the extent of renal impairment. Therefore, in patients with end-stage renal failure the plasma contrast medium concentration remains high for a long period of time. Such patients are at risk of central nervous system reactions such as convulsions and respiratory depression, which may be due either to contrast media or to uremia (Morcos et al. 2002). Delayed severe skin disorders including vasculitis and salivary gland swelling have also been reported in chronic renal failure patients after high-dose urography (Furukawa et al. 1996).

To reduce the risk of these complications, it has been suggested that contrast media should be removed from the body as soon as possible.

Several factors influence the elimination of contrast media by hemodialysis (Table 1) (Waaler et al. 1990; Moon et al. 1995; Furukawa et al. 1996; Ueda et al. 1996; Matzkies et al. 1999; Sterner et al. 2000). The first factor is the size and weight of the contrast media molecules; the smaller the solute molecule, the easier it moves across the membrane. Comparisons of dialysance (\(\text{Dialysance} = \frac{\text{blood flow rate of the hemodialysis}}{\text{X extraction ratio}}\)) values of contrast media from one study to another are usually meaningless as the time period between contrast medium injection and starting dialysis, and the dialysis conditions, are likely to vary from one study to another. In one study, under the same conditions the dialysance of non-ionic, monomeric contrast media was slightly higher than that of ionic, dimeric contrast media, partly because of the lower molecular weight and size of the former (Furukawa et al. 1996). However, in another study the elimination by hemodialysis of the non-ionic monomer iohexol was similar to that of the non-ionic dimer iodixanol which has a molecular mass almost twice that of iohexol (Sterner et al. 2000). Second, binding to the plasma proteins, which have large molecular size, also decreases the efficiency of hemodialysis of contrast media. The hydrophilicity of non-ionic contrast media is an important factor in determining the protein binding of their molecules.

The higher the hydrophilicity, the lower the affinity of the molecules to proteins. The elimination by hemodialysis of the non-ionic dimer iodixanol which has high hydrophilicity and low protein binding was similar to that of the non-ionic monomer iohexol (Sterner et al. 2000). The protein binding of the ionic dimer ioxaglate on the other hand is relatively high and amounts to 7.6 ± 1.5 %, compared to the value for iohexol of 1.5 ± 0.3 % determined by means of equilibrium dialysis. This difference might be partly responsible for the fact that iohexol was more easily eliminated than ioxaglate (Furukawa et al. 1996). Another possible factor is the molecular aggregation that occurs with ioxaglate, leading to the formation of large particles which are less permeable by hemodialysis. The electrical charge of the molecule also influences dialysance. Ioxaglate is almost completely dissociated in plasma and is negatively charged. As the cellulose diacetate membrane is slightly negatively charged, solutes with a negative charge such as ioxaglate move less easily across the membrane (Furukawa et al. 1996).

The degree of hepatic and renal excretion (in patients who are not anuric) may also affect the elimination rate of contrast media during hemodialysis in patients with chronic renal failure (Waaler et al. 1990; Ueda et al. 1996).

The elimination of contrast media is not dependent on the pore size of the membrane during dialysis. Under clearly defined conditions, the mean clearance rate for the non-ionic monomer iopromide was 108 ml min\(^{-1}\) for high- and low-flux membranes, both with a surface area of 1.3 m\(^2\) (Matzkies et al. 1999). The clearance rate of contrast agents for polyacrylonitrile membranes is 1.5–3 times higher than

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that of cuprophane membranes (Matzkies et al. 2000), whereas there is no difference between polyamide and hemophane membranes (Matzkies et al. 1999).

Blood flow does not seem to have an important effect. Removal of contrast agents can be performed at low blood flow rates without loss of efficacy and this is preferable in uremic patients who are prone to develop disequilibrium syndrome because of the rapid removal of the low molecular weight products during intensive dialysis (Moon et al. 1995). The osmotic process contributes to the elimination. Greater amounts of substance are transported across the dialysis membrane when it is exposed to higher concentrations. Thus, fast reduction of contrast medium concentrations can be achieved by dialysis in patients with high initial plasma levels. A short dialysis time of 2 h can be sufficient for contrast medium removal (Matzkies et al. 1999).

3 Elimination of Iodine-Based Contrast Media by Peritoneal Dialysis

Three patients with chronic renal failure (serum creatinine 389–804 μmol l⁻¹) underwent coronary angiography with iohexol. Intermittent automated peritoneal dialysis (36–60 l dialysis fluid) was able to remove 43–72 % of the iohexol over 16–18 h (Moon et al. 1995). In another study, intermittent peritoneal dialysis for 64 h removed 56 % of the injected meglumine diatrizoate (Brooks and Barry 1973). Continuous ambulatory peritoneal dialysis (CAPD) removed 54 % (range 36–80 %) of the administered dose of iopamidol 300 mgI ml⁻¹ (30 ml) over 7 days using 8 l of dialysis fluid daily. During the same period, 27 % (range: 36–80 %) of the injected contrast medium was excreted in the urine (Donally et al. 1992). Thus, peritoneal dialysis is also effective for removing contrast agents from the body, but takes longer than hemodialysis. No side effects of the contrast agents were reported in the three studies and this is important since the residual renal function in these patients must be protected.

4 Prophylactic Hemodialysis in the Prevention of Contrast-Induced Nephropathy

A variety of approaches have been suggested to prevent CIN, including saline hydration, administration of agents that cause increased renal blood flow or diuresis (Morcos et al. 1999; Morcos 1998, 2004) and hemodialysis. In an early study, ten patients on regular hemodialysis (three times a week) who had received between 40 and 225 ml of non-ionic iodine-based contrast media were followed up by laboratory tests and clinically. No significant adverse effects were seen and no patient required emergency dialysis. It was concluded that postprocedural dialysis was not warranted routinely (Younathan et al. 1994). Further, larger studies have demonstrated that hemodialysis does not offer any protection against CIN (Dehnarts et al. 1998; Vogt et al. 2001; Huber et al. 2002). The additional cost of hemodialysis and the associated risks including venous cannulation and the possibility of heparin-induced bleeding could only be justified if hemodialysis were shown to prevent CIN (Morcos 2004).

Thirty patients with reduced renal function (mean serum creatinine concentration 212 ± 14 μmol l⁻¹) were randomly assigned to receive either hemodialysis for 3 h starting as soon as possible (63 ± 6 min) or conservative treatment with no hemodialysis after administration of a non-ionic monomeric contrast medium (Dehnarts et al. 1998). All patients received intravenous infusion of 0.9 % saline at the rate of 83 ml h⁻¹ beginning 12 h before injection of the contrast medium (350 mgI ml⁻¹, mean dose 3 ml kg⁻¹ body weight). In the control group, only the infusion of saline was continued for another 12 h after the radiographic procedure. Serum concentrations of the contrast agent and creatinine were followed for up to 14 days. Both the groups were treated with calcium channel antagonists (nitrendipine 10 mg 12 hourly). The incidence of CIN in the hemodialysis group was 53 % and in the control group was 40 %, so hemodialysis treatment did not decrease the incidence of CIN. The poor efficacy of hemodialysis in preventing CIN, despite the fact that the patients were hemodialyzed as early as possible after contrast medium, relates to the rapid onset of renal injury after administration of contrast medium (Morcos 1998).

Of 113 patients with chronic renal impairment and serum creatinine above 200 μmol l⁻¹, 55 were randomly assigned to hemodialysis and 58 to non-hemodialysis after injection of non-ionic monomeric contrast media (Vogt et al. 2001). The mean dose of contrast medium injected in the non-hemodialysis group was 143 ± 15 and 210 ± 19 ml in the hemodialysis group. The baseline serum creatinine levels were 316 ± 16 and 308 ± 15 μmol l⁻¹, respectively. All patients received saline infusion following the same protocol as the previous study. The hemodialysis began 30–280 min after the radiographic procedure (median time 120 min). The incidence of CIN in the hemodialysis group was 24 % and in the non-hemodialysis group was 16 %. There was no significant difference between the two groups in relation to clinically important events (stroke, pulmonary edema, myocardial infarction, and death). The higher incidence of nephropathy in the hemodialysis group could be attributed to the larger doses of contrast medium used in these patients than in the control group. In addition, hemodialysis may cause deterioration of the renal function through activation of inflammatory reactions with the
release of vasoactive substances that may induce acute hypotension. Although a recent study suggested that prophylactic hemodialysis after coronary angiography (dialysis was initiated 81 ± 32 min after the angiography) is effective in improving renal outcome in patients with advanced renal impairment (creatinine clearance 13 ml min⁻¹) (Lee et al. 2007), the general consensus is that performing prophylactic hemodialysis immediately after administration of contrast media in patients with reduced renal function does not diminish the rate of complications, including the complication of CIN (Morcos 2004; Cruz et al. 2006; Rodby 2007). A recent systematic review also concluded that hemodialysis does not reduce the risk of CIN and suggested that hemodialysis actually appears to increase the risk of this complication (Cruz et al. 2012).

5 Elimination of Gadolinium-Based Contrast Media by Dialysis

Good hemodialysability of MRI gadolinium-based contrast agents has been reported (Joffe et al. 1998; Okada et al. 2001). After three consecutive hemodialysis sessions over 6 days, 97 % of the initial blood concentration of gadodiamide was eliminated (Joffe et al. 1998). In another study of 70 patients, no early side effects were noted (Okada et al. 2001), nor were there side effects in the six patients in whom hemodialysis was performed 3 days after the contrast medium injection. A total of four routine hemodialysis sessions was required to achieve nearly complete removal of gadolinium-based contrast from the blood (Okada et al. 2001).

Continuous ambulatory peritoneal dialysis (CAPD) for 20 days eliminated 69 % of the total amount of injected gadodiamide (Joffe et al. 1998) reflecting the low peritoneal clearance. The slow removal is probably a consequence of altered apparent volume of distribution because of dialysis fluid in the peritoneal cavity and of the limitations of the peritoneum as a dialysis membrane. The peritoneal clearance of gadopentetate dimeglumine in patients undergoing CAPD was about 5 ml min⁻¹. No side effects were recorded during a 1 week observation period (Tombach et al. 2001). Injection of gadolinium-based contrast media for MRI examinations (0.1–0.3 mmol kg⁻¹ BW) caused no significant change in renal function (Dörsam et al. 1995; Joffe et al. 1998; Okada et al. 2001; Tombach et al. 2001).

6 Prophylactic Hemodialysis after Gadolinium-Based Contrast Media

In normal subjects, the half-life of a nonspecific extracellular gadolinium-based contrast agent is about 1.5 h and 90 % of the injected dose is removed via the kidneys within the first 24 h. The elimination half-time of gadolinium-based contrast media in patients with significant reduction in renal function can be prolonged to several hours depending on the degree of renal impairment. Over 80 % of the administered dose is usually excreted within 7 days in such patients. It may take several days/weeks before the remainder is completely eliminated. The extrarenal elimination of gadolinium is very small and less than 2 % of the injected dose is excreted in the feces within 5 days of injection (Joffe et al. 1998).

In patients with end-stage renal disease, including those on dialysis, low stability gadolinium-based agents are contra-indicated, because the slow elimination of these agents allows dissociation of the gadolinium-chelate complex with release of free gadolinium, which may lead to nephrogenic systemic fibrosis (NSF) (“Nephrogenic Systemic Fibrosis and Gadolinium-Based Contrast Media”). If enhanced MR is essential for clinical management in patients with end-stage renal failure on dialysis, one of the most stable gadolinium-based agents should be used. Although there is no evidence about the ability of hemodialysis to prevent NSF, current understanding of the pathophysiology of NSF suggests that such patients should have a hemodialysis session as soon as is practically possible after the contrast agent is given to reduce the possibility of release of gadolinium.

7 Conclusion

Hemo- and peritoneal dialysis are effective for eliminating iodine- and gadolinium-based contrast media. Relating the time of iodine-based contrast medium injection to the dialysis schedule is unnecessary since it does not offer any protection against contrast-induced nephropathy and may increase the risk of this complication. There is as yet no convincing evidence to show that hemodialysis prevents the development of nephrogenic systemic fibrosis. However, current knowledge about the pathophysiology of NSF supports the recommendation that, for patients already on hemodialysis, a dialysis session should be scheduled as soon as possible after a gadolinium enhanced MRI examination.

References


Part IV

Iodine- and Gadolinium-Based Contrast Media: Other Adverse Effects
Abstract

Iodine-based contrast media can be given during pregnancy. Neonatal thyroid function should be checked during the first week because of the potential for depressed thyroid function. Lactating women who receive iodine-based contrast media can breastfeed normally. The most stable macrocyclic agents should be used if gadolinium-based contrast media are given to pregnant women. Although only small amounts of gadolinium-based contrast media reach the milk, if a lactating woman receives one of the lower stability agents, breastfeeding should be discontinued for 24 h.

1 Pregnancy

Radiological investigations using iodine-based contrast medium are not often done during pregnancy to avoid exposing the fetus to ionizing radiation (Bury 2002). Occasionally, however, such investigations may be necessary for the mother’s health (e.g., CT head scan, CT pulmonary angiogram) and the potential additional hazard to the fetus from the contrast medium has to be considered. While magnetic resonance imaging avoids the risks of ionizing radiation, the possibility of harmful effects of gadolinium-based contrast media during pregnancy needs to be considered. In particular, the potential for small amounts of gadolinium to be retained in the body of the fetus or infant for long periods after gadolinium-based contrast agents are given, especially with the lower stability agents, is a cause for concern.

1.1 Mutagenicity and Teratogenicity of Contrast Media

No mutagenic effects have been shown with ionic iodine-based contrast media in vitro (Nelson et al. 1982). No
1.2 Placental Transfer of Contrast Media

In the human placenta, there is only a single layer of chorionic epithelium separating maternal blood from fetal connective tissue (Broughton-Pipkin et al. 1994). Most drugs traverse the chorionic epithelium by diffusion. Current iodine-based non-ionic monomers and gadolinium-based contrast agents, which are water-soluble and have molecular weights in the range 500–850 Da, would be expected to traverse the placenta less easily than lipid-soluble or smaller water-soluble molecules (Bloomfield and Hawkins 1991).

The human placenta is structurally similar to the placentas of rabbits, mice, and rats, and pharmacokinetic studies of contrast media have been done in these animals. Only small amounts of iobitridol and iohexol, non-ionic iodinated agents, crossed the placenta of rabbits in 24 h following injection (Bourrinet et al. 1995). When gadodiamine meglumine (0.5 mmol kg$^{-1}$) was given to pregnant mice, the maximum placental concentration of gadolinium was 0.15 % of the injected dose, at 10 min after injection. The maximum fetal gadolinium concentration was 0.077 % of the injected dose, at 30 min after injection and this decreased to traces at 48 h (Muhler et al. 2011). In pregnant rats given 0.3 mmol kg$^{-1}$ of gadodiamide, 0.01 % of the injected dose was found in the fetus at 5 min (Okazaki et al. 1996) and in pregnant rabbits given 0.1 mmol kg$^{-1}$ of gadopentetate dimeglumine, only small amounts of gadolinium were found in the fetal tissues (Novak et al. 1993). Gadolinium uptake into the placenta was sufficient for placental imaging in 11 women at 16–37 weeks of pregnancy after 0.1 mmol kg$^{-1}$ gadopentetate dimeglumine (Marcos et al. 1997).

1.3 Iodine-Based Contrast Media during Pregnancy

1.3.1 Pharmacokinetics

Iodine-based contrast agents which cross the placenta into the fetal blood are then excreted by the kidneys into the bladder. When the bladder empties, urine containing the contrast agents enters the amniotic fluid. In later pregnancy, fetal urine is the main source of amniotic fluid, with a lesser contribution from fluid secreted by the lung and a minor contribution from transudation across the umbilical cord and fetal skin and from fetal metabolism (Beall and Ross 2009). The entire amniotic fluid volume turns over on a daily basis. Resorption of fluid occurs by an intramembranous pathway across the amnion into the fetal vessels and also by fetal swallowing (Beall and Ross 2009).

It has been known for many years that intravenous ionic contrast media given to the mother could result in a neonatal pyelogram, or opacification of the neonatal gut (Thomas et al. 1963; Kelleher et al. 1979). Opacification of the neonatal gut has also been described after the non-ionic agents iohexol (Moon et al. 2000), iopromide (Vanhaesebrouck et al. 2005), and ioversol (Hill et al. 2007; Saigal and Abdenour 2007) had been given to the mother in late pregnancy. Contrast media injected into the amniotic fluid have been used to opacify the fetal gut before intrauterine transfusion (Raphael et al. 1967). Assays of amniotic fluid for iodine when amniocentesis was done following maternal intravenous urography showed large amounts of iodine 24 h after urography, and much lower amounts 22 days later (Etling et al. 1979). This suggests that contrast media diffuse out through the placenta into the mother as well as passing from the mother into the fetus.

1.3.2 Effect of Iodine-Based Contrast Media on the Fetal Thyroid

The most important potential harmful effect of iodine-based contrast media which cross the placenta is depression of the fetal thyroid. By 12 weeks’ gestation, thyroid stimulating hormone (TSH) is detectable, and the fetal thyroid is trapping iodide and synthesizing thyroxine (T4). The levels of TSH and T4, however, remain low until 20 weeks gestation, and then until term thyroid iodide uptake and T4 and T3 secretion increase markedly (Nader 2009). At birth, there is a TSH surge in the neonate, with the TSH returning to normal within days, and an accompanying increase in T3 and T4 which decrease to adult levels in the first 4–6 weeks (Nader 2009). Fetal thyroid function is essential for the normal development of the central nervous system (Semba and

mutagenic or teratogenic effects were found in vivo with non-ionic iodine-based contrast media tested in animals (Felder 1984; Shaw and Potts 1985; Ralston et al. 1989; Krause et al. 1994; Morisetti et al. 1994; Fujikawa et al. 1995; Heglund et al. 1995; Donandieu et al. 1996). Abnormal micronuclei indicating chromosomal damage have been detected in lymphocytes following radiological investigations using iodine-based ionic and non-ionic agents (Norman et al. 1978; Cochrane et al. 1980; Cochrane and Norman 1994). This effect, however, appears to be cytotoxic rather than genetic, and only to occur in cells circulating in the blood at the time of the examination (Norman et al. 1978, 2001).

No evidence of either teratogenic effects or chromosomal damage has been shown with gadopentetate dimeglumine either alone or together with magnetic resonance imaging in mice or rats (Rofsky et al. 1994, 1995). No teratogenic effects have been shown in animals with gadoteridol, gadobenate dimeglumine or gadoversetamide (Soltys 1992; Morisetti et al. 1999; Wible et al. 2001).
Delange 2001; Delange et al. 2001). Medicines containing iodine are usually considered contraindicated during pregnancy because of the potential for iodide uptake depressing the fetal thyroid (Bloomfield and Hawkins 1991).

When amniography was carried out using a mixture of lipiodol (iodized ethyl esters of the fatty acids of poppy seed oil) and water-soluble agents, elevated TSH levels were found in most of the neonates in the first week (Rodesch et al. 1976). Several infants subsequently developed hypothyroidism (Rodesch et al. 1976; Stubbe et al. 1980). The fat-soluble agent lipiodol is deposited on the vermix and can then be absorbed by the fetus over a long period. In rabbits, lipiodol crosses the placenta and accumulates in the fetal thyroid (Bourrinet et al. 1997). Lipiodol persists in the body when given intramuscularly. It is used to treat iodine deficiency and results in increased urinary iodine levels for over 12 months (Leverge et al. 2003).

When water-soluble iodine-based contrast media were used alone for amniography, no abnormalities in cord blood T4 and T3 were detected (Morrison et al. 1973). The decline in amniotic fluid iodine levels over time after water-soluble iodine-based contrast agents were given to the mother suggests diffusion of contrast agents back across the placenta into the mother (Etling et al. 1979). With water-soluble agents, the free iodide is the potentially harmful component (van der Molen et al. 2004). In a contrast agent with 300 mg I ml\(^{-1}\), the upper level of free iodide allowed immediately after production is 50 μg ml\(^{-1}\) and at 3–5 years after production is 90 μg ml\(^{-1}\). In practice, the free iodide concentration is usually one-tenth of these amounts (van der Molen et al. 2004). If the free iodide content of a contrast agent is 50 μg ml\(^{-1}\), and if 150 ml of the agent is used for CT pulmonary angiography in a pregnant woman, the total free iodide dose is 7,500 μg. Although there are no data about the pharmacodynamics of the free iodide, it is likely to traverse the placenta readily in both directions so that the fetal thyroid is only exposed to the iodide for a short period of time.

In four recent studies which included a total of 503 neonates whose mothers had received iodine-based contrast agents during pregnancy, neonatal thyroid function was normal in 501 (Atwell et al. 2008; Bourjeily et al. 2010; Kochi et al. 2012; Rajaram et al. 2012). One neonate had an abnormal TSH at birth which had returned to normal by day 6 (Bourjeily et al. 2010) and one which had been born very prematurely at 25 weeks had a low T4 level (Kochi et al. 2012).

In pregnant women with impaired renal function, blood levels of contrast medium and free iodide remain higher for longer, and exposure of the fetus is therefore likely to be longer. An early study on the effect of a high dose of iopamidol (1500 mg I kg\(^{-1}\)) in the first month of life found no effect on thyroid function (Bona et al. 1992). A recent systematic review of 11 studies of thyroid function in neonates who had received iodine-based contrast media found a trend towards increased TSH and decreased T4, although it was considered that all studies were highly affected by bias (Ahmet et al. 2009). 8.3 % of term infants and 18.2 % of premature infants needed treatment for hypothyroidism (Ahmet et al. 2009), consistent with the recognized greater susceptibility of premature infants to iodine induced hypothyroidism (Brown 2003).

### 1.3.3 Other Clinical Data
There are no reports of other adverse effects when iodine-based contrast media are given during pregnancy. When arteriography and amniography were undertaken with ionic agents, no harmful effects were reported (Raphael et al. 1967; Wholey 1967; Blumberg et al. 1967).

### 1.3.4 Conclusion
In summary, when water-soluble iodine-based contrast media are given intravascularly to pregnant women, the most important risk to the fetus is depression of the thyroid. However, fetal exposure to the contrast agent and any associated free iodide is short-lived. Nonetheless, it is recommended that, following exposure, neonatal thyroid function is checked during the first week of life. Although in many countries it is standard pediatric practice to check neonatal thyroid function (Klein and Mitchell 2000), it is mandatory that this is done when the mother has received an iodine-based contrast agent during pregnancy (“Contrast Media Use in Pediatrics: Safety Issues”).

### 1.4 Gadolinium-Based Contrast Media During Pregnancy

#### 1.4.1 Pharmacokinetics
Animal studies support the suggestion that gadolinium-based contrast media are handled very similarly to iodine-based agents during pregnancy. In mice at 16 weeks gestation, corresponding to the third trimester of human pregnancy, who received gadoterate meglumine in a dose of 0.5 mmol kg\(^{-1}\), fetal gadolinium concentration was maximal at 30 min, when it was 0.077 % of the injected dose. The mean half-life of gadolinium in the fetus was 4 h and at 24 h the fetal concentration was 0.006 % of the injected dose. The amniotic fluid gadolinium concentration was maximal at 30 min, and the mean half-life of gadolinium in the amniotic fluid was 5 h (Muhler et al. 2011). In pregnant
rabbits, gadopentetate dimeglumine 0.1 mmol kg\(^{-1}\) given intravenously to the mother reached peak concentration in the placenta at 5 min and then decreased up to 60 min. Concentrations in fetal muscle, brain, heart, and liver remained stable from 5 to 60 min, while the concentration of the contrast agent in the kidneys increased up to 60 min (Novak et al. 1993). In pregnant rats, radio-actively labeled gadodiamide given in a dose of 0.3 mmol kg\(^{-1}\) crossed the placenta in small amounts. Concentrations in the placenta and most fetal tissues decreased from 5 min onwards, while concentrations in the amniotic fluid, brain, and kidney peaked at 4 h. At 4 h, the amount of contrast medium in the fetus was estimated to be 0.01 % of the maternal dose, and only traces remained at 24 h (Okazaki et al. 1996).

### 1.4.2 Nephrogenic Systemic Fibrosis

In 2006, nephrogenic systemic fibrosis (NSF), in which there are fibrotic changes in skin, muscle, and the internal organs in patients with severe renal impairment, was linked to previous administration of gadolinium-based contrast media (Grobner 2006; Marckmann et al. 2006). NSF has been described after administration of the linear agents gadodiamide, gadoversetamide, and gadopentetate. In gadolinium-based contrast media, the gadolinium is bound to a chelating agent to prevent exposure of the body to free gadolinium, which is toxic. The current hypothesis for the etiology of NSF suggests that the slow excretion of the gadolinium-based contrast media in patients with severe renal impairment allows the release of gadolinium from the less stable linear contrast media (Morcos 2007). Gadolinium has been detected in the skin biopsies of affected patients (High et al. 2007; Boyd et al. 2007).

### 1.4.3 Neonatal Renal Function

Neonatal renal function is immature. In normal neonates aged 1 week, mean GFR is 40 ml min\(^{-1}\) 1.73 m\(^{-2}\), at age 2–8 weeks mean GFR is 65 ml min\(^{-1}\) 1.73 m\(^{-2}\) and over the age of 8 weeks mean GFR is 95 ml min\(^{-1}\) 1.73 m\(^{-2}\) (K/DOQI Clinical Practice Guidelines 2002). Neonates may therefore have a risk of NSF if they receive the less stable gadolinium-based contrast media, and concerns have been raised that this may also apply to the fetus.

### 1.4.4 Retention of Gadolinium in the Tissues

Residual gadolinium was detected in the bone and liver of mice and rats 14 days after exposure to gadolinium-based contrast media (Tweedle et al. 1995). The amount of residual gadolinium was greater with the linear agents gadopentetate and gadodiamide than with the macrocyclic agents gadoteridol and gadoterate (Tweedle et al. 1995). Sieber et al. (2008) gave repeated injections of 2.5 mmol kg\(^{-1}\) of gadolinium-based agents to rats, for which this is not a high dose because they clear the agents very rapidly; the equivalent dose in man would be 0.3–0.4 mmol kg\(^{-1}\). In rats the T\(\frac{1}{2}\) is only 20 min, whereas in man it is between 90 and 120 min. The highest concentrations of gadolinium in the skin, liver, and femur occurred with gadodiamide. With gadopentetate there was 10 times less gadolinium in skin and with gadoterate and gadobutrol there was 30 times less (Sieber et al. 2008). When skin gadolinium concentrations were measured in rats up to 1 year after repeated injections of gadolinium-based contrast media (2.5 mmol kg\(^{-1}\)) small amounts of gadolinium were still present at 1 year, with the amounts greatest with the non-ionic linear agents and least with the macrocyclic agents (Pietsch et al. 2009).

Retention of gadolinium in bone has also been shown in patients, with four times greater retention after gadodiamide than after gadoteridol (White et al. 2006). Abraham et al. (2008) showed that in NSF patients the amount of gadolinium in the skin increased over time, leading to the suggestion that gadolinium which has been stored in the bone may be released over time.

### 1.4.5 Clinical Reports

There are relatively few clinical reports of the effect on neonates of giving gadolinium-based contrast media to the pregnant mother. No adverse effects on the infants were detected in a total of 57 cases reported when the pregnant mother had been given gadopentetate dimeglumine in doses of 0.1–0.2 mmol kg\(^{-1}\) (Barkhof et al. 1992; Shoenu et al. 1993; Marcos et al. 1997; Spencer et al. 2000; Birchard et al. 2005; de Santis et al. 2007).

### 1.4.6 EMA Recommendations

In July 2010, the European Medicines Agency (EMA) updated their recommendations on the use of gadolinium-based contrast media (Commission Decision of 1-7-2010). The recommendations state that high risk gadolinium-based contrast media should not be given to neonates less than 4 weeks old, because of their immature renal function, and should be restricted to the minimum recommended dose in infants less than one year old. No specific recommendations about pregnant women are made, but it would seem prudent to follow the recommendations for neonates to protect the fetal kidneys.

### 1.4.7 Conclusion

Animal data indicate that a relatively small proportion of a gadolinium-based contrast agent given intravascularly to a pregnant female traverses the placenta (Novak et al. 1993, Okazaki et al. 1996; Muhler et al. 2011) and the first ESUR guideline stated that gadolinium-based contrast media could be safely given to the pregnant female (Webb et al. 2005). The recognition since then of NSF, and the fact that fetal renal function, like that of the neonate, is likely to be
immature, together with the evidence indicating long-term retention of small amounts of gadolinium in the bone and other tissues after gadolinium-based contrast media, have led to more restrictive recommendations (Kanal et al. 2007; Thomsen et al. 2013).

It is recommended that:

Gadolinium-based contrast media should only be given to pregnant women when there is a very strong clinical indication.

One of the more stable, macrocyclic gadolinium agents (gadoterate meglumine, gadoteridol, or gadobutrol) should be used in the lowest dose consistent with a diagnostic result.

2 Lactation

The excretion of drugs into the milk is facilitated when the drugs are lipid-soluble and bind readily to plasma and milk proteins (Wilson et al. 1980). Both iodine- and gadolinium-based contrast media are water-soluble with minimal protein-binding suggesting that they are likely to enter milk with difficulty.

2.1 Iodine-Based Contrast Media in Milk

Early reports suggested that excretion of iodine-based contrast media into the milk was very low or not detectable after intravenous ionic agents and an intrathecal non-ionic agent (Fitzjohn et al. 1982; Ilett et al. 1981). Even after fat-soluble cholecystographic agents, iodine excretion in the milk was very low (Holmdahl 1956). A detailed study of larger doses (350 mg I kg⁻¹) of the non-ionic agent iohexol and the ionic agent metrizoate showed that small amounts of these contrast agents reached the milk (Nielsen et al. 1987). It was calculated that with a milk intake of 0.15 l kg⁻¹ day⁻¹ the infant would have received 1.7 mg I kg⁻¹ with iohexol and 0.7 mg I kg⁻¹ with metrizoate, corresponding to 0.5 and 0.3 % of the maternal dose, respectively (Nielsen et al. 1987). For pediatric urography, the recommended dose is 900 mg I kg⁻¹ for babies less than 6.5 kg, and 600 mg I kg⁻¹ for babies 7.0 kg or more (Jorulf 1983). The dose of iohexol received in the milk over 24 h is only 0.002 % of the dose recommended to be given intravenously for urography. Only very small amounts of iohine-based contrast agents in the gut are absorbed into blood. When the non-ionic agent metrizamide was given as an oral contrast agent, a total of 0.8 % of the dose was excreted into the urine by the end of the third day (Johansen 1978).

2.1.1 Conclusion

The evidence indicates that only a very small amount of iodine-based contrast medium reaches the infant’s blood when a lactating mother is given one of these agents intravascularly. The amounts entering the neonatal blood are tiny compared to the amounts of iodine-based contrast media given to infants during imaging. The very low risk to the neonate suggests that the potential disruption to the mother and baby if breastfeeding is stopped for 24–48 h after iodine-based contrast medium is not warranted (“ESUR Guidelines on Contrast Media Version 8.1”). As with all drugs and foodstuffs, the baby may notice a change in the taste of the milk.

2.2 Gadolinium-Based Contrast Media in Milk

2.2.1 Excretion of Gadolinium into Milk and Absorption from the Gut

Only very small amounts of gadolinium-based contrast media reach the milk after intravenous administration to the mother. In 20 lactating women who received 0.1–0.2 mmol kg⁻¹ of gadopentetate, less than 0.04 % of the intravenous dose was excreted into the milk over 24 h (Kubik-Huch et al. 2000). In two further case reports, the cumulative excretion of gadolinium-based contrast media into the milk over 24 h was 0.011 and 0.023 % of the intravenous dose of gadopentetate (Schmiedl et al. 1990; Rofsky et al. 1993). Doses of gadopentetate and gadodiamide of 0.1–0.2 mmol kg⁻¹ are considered to be well-tolerated intravenously in infants under 6 months (Marti-Bonmati et al. 2000; Tsai-Goodman et al. 2004). The amount of gadolinium-based contrast medium reaching the neonatal gut is, therefore, less than 1 % of the recommended intravenous dose for an infant after the lactating mother has received a gadolinium-based agent intravenously (Kubik-Huch et al. 2000).

When gadolinium-based contrast media are given orally, dissociation in acid gastric content is theoretically possible (Cacheris et al. 1990) but there is no data on the extent to which this occurs in vivo. However, when gadolinium-based contrast media are given orally, very little is absorbed. Over 99 % of gadopentetate given orally is excreted in the feces (Kaminsky et al. 1991). When adults were given gadopentetate (0.005 or 0.01 mmol kg⁻¹) orally with mannitol, no change in the signal intensity of the urine was detected indicating that significant gadolinium absorption was unlikely (Lanaido et al. 1988).

2.2.2 EMA Recommendations

The EMA updated its recommendation about gadolinium-based contrast media in lactating women in July 2010 (Commission Decision of 1-7-2010). The current recommendation states that if a high-risk gadolinium-based contrast medium is given to a lactating woman, breastfeeding should be discontinued for at least 24 h after the
patient receives the contrast medium. For medium and low-risk agents, the decision about whether to stop breastfeeding for 24 h or to continue normally should be discussed by the mother and the doctor.

2.2.3 Conclusion
The previous ESUR guideline indicated that when gadolinium-based contrast media were given intravascularly to the pregnant woman, breastfeeding could continue normally (Webb et al. 2005). However, the new information already discussed in the pregnancy section about the potential harmful effects of retained gadolinium, combined with immature neonatal renal function, indicate that despite the very tiny amounts of gadolinium-based contrast media likely to be absorbed into the blood by the breastfed infant, breastfeeding should be discontinued for 24 h if the lactating mother receives a high risk intravascular gadolinium-based contrast agent (gadodiamide, gadoversetamide, gadopentetate dimeglumine). The decision about whether or not breastfeeding should be temporarily discontinued after a medium or low risk gadolinium-based agent (gadobenate dimeglumine, gadoxetate disodium, gadofosveset trisodium, gadobutrol, gadoteridol, gadoterate meglumine) should be made by the mother in consultation with her doctor (“ESUR Guidelines on Contrast Media Version 8.1”).

References


Pheochromocytoma and Contrast Media

Judith A. W. Webb

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Abstract

Patients with catecholamine-producing tumors (pheochromocytomas and paragangliomas) do not need any special preparation before they receive non-ionic iodine-based contrast medium or any gadolinium-based contrast medium intravenously. It is recommended that such patients should receive oral α- and β-adrenergic blocking drugs before they are given non-ionic iodine-based contrast media intra-arterially.

1 Introduction

Pheochromocytomas are relatively rare tumors which originate from chromaffin cells in the adrenal medulla and secrete the catecholamines adrenaline and noradrenaline (epinephrine and norepinephrine). Less frequently, catecholamine-secreting tumors arise from extra-adrenal chromaffin tissue in and around the sympathetic and parasympathetic chains (paragangliomas). Secretion of catecholamines by pheochromocytomas and paragangliomas may be continuous or intermittent. Typical clinical presentations include hypertension resistant to conventional treatment and intermittent crises—attacks of hypertension, headache, sweating, anxiety, and pallor or flushing. Crises occur when catecholamines are released from the tumor, and may be spontaneous or precipitated by drugs or by physical compression of the tumor (Bouloux and Fakeeh 1995).

When symptoms suggest the presence of a catecholamine-producing tumor, assays of catecholamines or their metabolites in the urine or plasma are used to confirm the diagnosis (Bouloux and Fakeeh 1995; Lenders et al. 2002). Once the diagnosis has been established biochemically, the tumor is localized by imaging—anatomical (CT or MR) or functional (123I-metaiodobenzylguanidine [MIBG] tomography (FDG PET)). Full CT evaluation necessitates the use of enhancement with intravenously injected...
iodine-based contrast medium and if MR is used, a gadolinium-based contrast agent may be given intravenously.

Adrenal masses are not infrequently incidentally detected during abdominal imaging with CT, MR, or ultrasound. Incidental adrenal masses occur in 5–9% of the general population at autopsy (Ilias and Pacak 2004). The majority are non-functioning adrenocortical adenomas of no clinical significance (Grumbach et al. 2003). They can be identified on unenhanced CT by their low density (<10 HU), and/or by typical washout behavior after iodine-based contrast medium (Korobkin 2000). However, a proportion of incidentally detected adrenal masses are pheochromocytomas and some pheochromocytomas have as low density as adenomas on unenhanced CT (Blake et al. 2003). Full evaluation of incidentally detected adrenal masses often involves administration of iodine-based agents during CT.

In patients with adrenal masses incidentally detected on CT, it was considered unsafe to characterize them fully using enhancement with iodine-based contrast medium before catecholamine assay.

More recently, the effects of intravenous lower osmolality non-ionic iodine-based contrast medium have been studied in patients with pheochromocytoma or paraganglioma. Mukherjee et al. (1997) studied ten patients with pheochromocytoma or paraganglioma and six controls. The patients were under full \( \alpha- \) and \( \beta- \) adrenergic blockade and had received phenoxybenzamine intravenously 24 h before contrast medium. No significant differences were detected in the plasma noradrenaline or adrenaline levels between the patients and controls in the 60 min after either iohexol or saline. However, plasma catecholamine levels in several patients fluctuated throughout the study and one patient with high basal levels (indicating a highly secretory tumor) showed both an increase in plasma catecholamine after saline and a delayed increase in plasma catecholamine at 60 min after contrast medium, considered to be spontaneous. Although catecholamine release had not been precipitated by the contrast medium, Mukherjee et al. (1997) recommended that it would be prudent to give all patients with biochemically proven catecholamine-producing tumors oral \( \alpha- \) and \( \beta- \) adrenergic blockade before intravenous non-ionic contrast medium, but that intravenous phenoxybenzamine was no longer necessary. No special preparation was recommended before intravenous contrast medium was given to evaluate incidentally detected adrenal masses. The previous ESUR guideline was based on these recommendations.

Baid et al. (2009) evaluated 22 patients with pheochromocytoma, 11 of whom were taking blocking drugs (7 under \( \alpha- \) and \( \beta- \) blockade, 2 each taking \( \alpha- \) and \( \beta- \) blockers only). They found no significant changes in plasma catecholamines in the patients or in 8 control subjects after intravenous iopamidol, but noted labile blood pressure changes in several of the patients. A retrospective review of 25 patients with one or more pheochromocytomas or paragangliomas found no adverse effects recorded after intravenous iohexol or iopamidol. None of the patients had received blockading medication (Bessell-Browne and O’Malley 2006).

The data presented indicates that intravenous non-ionic iodine-based contrast media do not cause catecholamine release from pheochromocytomas and paragangliomas. It is current clinical practice to give these agents intravenously both to patients with biochemically diagnosed catecholamine-producing tumors and with incidentally detected adrenal masses without adrenergic blockade and the ESUR guideline has been modified to reflect this. However, before intraarterial iodine-based contrast medium, especially if it is given selectively into the renal or adrenal arteries, \( \alpha- \) and \( \beta- \) adrenergic blockade using oral drugs is still recommended.

## 2 Iodine-Based Contrast Media

In the 1960s, adrenal angiography with ionic iodine-based agents, usually following alpha-blockade with phenoxybenzamine, was reported to be relatively safe (Rossi et al. 1968; Alfidi et al. 1969). However, in some patients who had not received alpha-blockers, ionic iodine-based contrast media used for selective angiography and adrenal venography caused significant increases in blood pressure (Meaney and Buonocore 1966; Alfidi et al. 1969; Gold et al. 1972). The contrast media were presumed to have caused catecholamine release from the tumors.

This was supported by plasma catecholamine measurement after the ionic contrast medium meglumine iothalamate was given intravenously (Raisanen et al. 1984). The mean change in plasma noradrenaline at 10 min after contrast medium was not significantly different between eight patients with pheochromocytomas and 12 controls. However, in five of the patients the increase in plasma noradrenaline at 10 min was considered sufficient to have produced a rise in blood pressure if they had not already been under alpha-adrenergic blockade (Raisanen et al. 1984). It became standard practice for all patients with biochemically proven pheochromocytoma to have full alpha- and beta-adrenergic blockade (e.g., by oral phenoxybenzamine and propranolol) for at least 1 week before contrast medium injection, and to have further phenoxybenzamine intravenously in the 24 h before the procedure (Francis et al. 1992; Bouloux and Fakeeh 1995).

While this approach was safe, it had several disadvantages. The preparation for imaging localization in biochemically proven pheochromocytoma was time consuming. Also, intravenous phenoxybenzamine could interfere with subsequent MIBG imaging (Patel et al. 1995) so that this had to be delayed for at least 10 days after CT.

The data presented indicates that intravenous non-ionic iodine-based contrast media do not cause catecholamine release from pheochromocytomas and paragangliomas. It is current clinical practice to give these agents intravenously both to patients with biochemically diagnosed catecholamine-producing tumors and with incidentally detected adrenal masses without adrenergic blockade and the ESUR guideline has been modified to reflect this. However, before intra-arterial iodine-based contrast medium, especially if it is given selectively into the renal or adrenal arteries, \( \alpha- \) and \( \beta- \) adrenergic blockade using oral drugs is still recommended.
3  Gadolinium-Based Contrast Media

There is no specific information about the effects of gadolinium-based contrast agents on catecholamine-producing tumors. Some of these agents are ionic with higher osmolality while others are non-ionic with lower osmolality (Kirchin and Runge 2003). However, the volumes of gadolinium-based contrast agents injected are usually at least five to ten times less than the volumes of iodine-based contrast media. Thus, even with the ionic agents, the osmolar load is less than the osmolar load given with a non-ionic iodine-based agent for CT. Since the increase in plasma catecholamines caused by iodine-based contrast media appears osmolality-related (Mukherjee et al. 1997), it seems very unlikely that the small osmolar load with the gadolinium-based agents will cause a rise in plasma catecholamines.

The previous ESUR guideline, which recommended α-and β-adrenergic blockade before intravenous gadolinium-based agents are given to patients with catecholamine-producing tumors, has been modified in parallel with the guidance for iodine-based agents. The current guideline states that no special preparation is required before gadolinium-based agents are given intravenously to patients with adrenal tumors, including those which produce catecholamine (“ESUR Guidelines on Contrast Media Version 8.1”).

References

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Contrast Media and Interactions with Other Drugs and Clinical Tests

Sameh K. Morcos

Abstract

Water soluble contrast media may interfere with the pharmacokinetics or pharmacodynamics of other drugs, as well as with some biochemical assays and with isotope imaging. These topics are reviewed in this chapter, with the aim of raising the awareness of both radiologists and clinicians to the possibility of these problems.

1 Introduction

Iodine-based water-soluble contrast media in clinical use are high-osmolar ionic monomers, low-osmolar ionic dimers, low-osmolar non-ionic monomers and iso-osmolar non-ionic dimers. Nowadays, high-osmolar contrast media are rarely used intravascularly in the developed world. Currently, available magnetic resonance imaging (MRI) contrast agents are all gadolinium-based. Some of the gadolinium preparations are ionic and have high-osmolality; others are non-ionic with varying osmolality (600–2,000 mOsmol kg$^{-1}$ H$_2$O). Ultrasound contrast agents are microbubbles which produce acoustic enhancement. They are pharmacologically almost inert and safe (Jakobsen et al. 2005).

The use of contrast media is continuously growing in a wide range of imaging and interventional procedures. Also, the patient population receiving contrast media has changed, and many older patients with multiple medical problems, who are receiving a variety of drugs, are now actively investigated with imaging techniques which require contrast agent administration.

A drug interaction is defined as a drug’s possible capacity to influence the pharmacological action of another drug. Such interactions between contrast agents and therapeutic medications have not been widely investigated (Morcos et al. 2005). Although contrast agents are not highly active pharmacologically, interaction with other drugs may occur with possible serious consequences to the patient.
In this chapter, potential interactions between drugs and contrast agents are presented with the help of an extensive review of the literature. The interactions are grouped together according to clinical importance and the body system involved. In addition, the effects of contrast media on isotope studies as well as the danger of mixing contrast media with other drugs before intravascular use are highlighted. Contrast media may also interfere with biochemical assays of body fluids. The aim of this chapter is to raise the awareness of both radiologists and clinicians to the possibility of such events.

2 Classification of Contrast Media Interactions

The interactions between drugs and contrast agents are subdivided into the following:

- Drugs which will be retained in the body if there is reduction in renal function induced by contrast media.
- Drugs which enhance the renal effects of contrast media.
- Drugs which enhance the renal effects of contrast media and will be retained in the body because of reduction in renal function.
- Drugs which enhance allergy-like reactions to contrast media.
- Drugs which interfere with the hematological effects of contrast media.
- Contrast media and drugs acting on the nervous system.
- Drugs which enhance the effects of contrast media on the heart.
- The effects of contrast media on isotope studies.
- Mixing contrast media with other drugs.
- The effects of contrast media on biochemical assays.

2.1 Drugs Which Will be Retained in the Body if There is Reduction in Renal Function Induced by Contrast Media

Contrast media may interfere with the pharmacokinetics (distribution, metabolism and elimination of the drug) of other drugs, particularly those which are eliminated from the body through the kidneys. One of the important potential, but rare, pharmacodynamic effects of iodine-based contrast media is reduction of renal function, particularly in patients with pre-existing reduced renal function. This leads to the retention of drugs which are excreted exclusively through the kidneys. A good example is the indirect interaction between contrast media and metformin (Thomsen et al. 1999). Significant reduction of renal function can be induced by contrast agents in the presence of pre-existing kidney disease, particularly diabetic nephropathy (Morcos 1998; Morcos et al. 1999; Thomsen and Morcos 2003). If renal function is reduced after contrast medium administration, metformin will be retained, with the potential for the serious complication of lactic acidosis. This subject is reviewed in “Contrast Medium-Induced Nephropathy”. Drugs which cause diuresis and natriuresis can be hazardous and should be avoided in patients receiving lithium. Although iodine-based contrast media, especially those of high osmolality, can induce significant diuresis and natriuresis, their potential for increasing the toxicity of lithium has not been studied widely.

2.2 Drugs Which Enhance the Renal Effects of Contrast Media

Nephrotoxic drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) have the potential to increase the renal effects of iodine-based contrast media. This class of drugs inhibits the intrarenal synthesis of vasodilatory prostaglandins, so augmenting the renal vasoconstrictor effect of iodine-based contrast media, and may facilitate the development of contrast media nephrotoxicity (Morcos 1998; Morcos et al. 1999). Other nephrotoxic drugs such as gentamicin, cyclosporine and cisplatin may also augment the nephrotoxic effects of contrast media (Morcos et al. 1999). Diuretics such as acetazolamide, furosemide and spironolactone may augment the diuretic effect of iodine-based contrast media, particularly those of high osmolality, leading to dehydration, increased risk of contrast medium nephropathy, electrolyte imbalance and hypotension (Swanson et al. 1990).

2.3 Drugs Which Enhance the Renal Effects of Contrast Media and are Retained in the Body Because of Reduction in Renal Function

Methotrexate (MTX) is nephrotoxic, particularly when a high dose is used and, if iodine-based contrast medium is given, there is potential for an additive nephrotoxic effect. MTX is eliminated from the body by the kidney. The nephrotoxicity induced by the contrast medium and MTX causes retention of MTX in the body, leading to MTX toxicity which includes bone marrow suppression, mucositis, encephalopathy, dermatitis and hepatitis. The intravascular administration of iodine-based contrast media is contraindicated in patients receiving a high dose of MTX who have a serum concentration of the drug of >0.1 μmol l⁻¹. If the serum MTX is less than 0.1 μmol l⁻¹, iodine-based contrast media should be used with extra care and the smallest possible dose of iso- or low-osmolar contrast agent should be used. Intravenous hydration with
normal saline (100 ml h\(^{-1}\)) for at least 6 h before and after the contrast medium injection should also be offered (Harned and Mascarenhas 2007).

### 2.4 Drugs Which Enhance Allergy-Like Reactions to Contrast Media

In general, the rate of allergy-like reactions after administration of non-ionic iodine-based contrast media is very low. Patients receiving \(\beta\)-receptor blockers, interleukins or interferon have an increased tendency to develop allergy-like reactions following the administration of contrast media. Delayed reactions to iodine-based contrast media are more likely to develop in patients who received interleukin-2 (IL-2) treatment (Choyke et al. 1992). In addition, patients on hydralazine treatment, which can induce a systemic lupus erythematosus (SLE) like syndrome, may develop cutaneous vasculitis several hours after intra-vascular administration of non-ionic iodine-based contrast medium. Hypersensitivity reactions to iodine-containing compounds have also been described in patients with SLE. It has been suggested that injection of iodine-based contrast media should be avoided in patients receiving hydralazine as they may provoke severe reactions (Reynolds et al. 1993).

#### 2.4.1 \(\beta\)-Blockers

Anaphylaxis-like reactions that may occur following the administration of contrast media require aggressive treatment including adrenaline. However, if the patient is receiving \(\beta\)-receptor blockers the effectiveness of the sympathomimetic drugs, which are crucial in a potentially lethal situation, will be reduced. \(\beta\)-Blockers selectively block the \(\beta\)-adrenergic effects of adrenaline and inhibit adenylate cyclase activity which leads to increased release of ana\-phylactoid mediators. \(\beta\)-Blockers are often prescribed for hypertension, angina, arrhythmias and after myocardial infarction. Eye-drop preparations are used for the treatment of glaucoma. To avoid the risk of exacerbating angina, acute myocardial infarction and malignant tachycardia and causing sudden death, \(\beta\)-blockers should not be stopped suddenly. Gradual withdrawal over 10–14 days is recom-\mended (Laurence and Bennett 1992).

Whether or not \(\beta\)-blockers affect the incidence of idio-\syncratic reactions is controversial. Greenberg et al. (1987) reported that neither \(\beta\)-blockers nor calcium antagonists given separately or together increased the risk of reaction to iodine-based contrast media. Subsequently, however, (Lang et al. 1991, 1993) found that patients on \(\beta\)-blockers, including the ophthalmic preparations, who were given iodine-based contrast media were three times more likely to have an anaphylactoid reaction than matched controls. They also found an increased risk of contrast media induced bronchospasm, particularly in asthmatics (Lang et al. 1991, 1993). Anaphylaxis-like reaction in these patients is more refractory to conventional treatment because of low reacti-\vity to emergency medication. Adrenaline may be ineffective or promote undesired \(\alpha\)-adrenergic or vagal effects. Anaphylaxis associated with \(\beta\)-blockers was nine times more likely to result in hospitalization than in matched controls (Lang et al. 1991, 1993).

#### 2.4.2 Interleukin-2

IL-2 is a lymphokine, produced by helper T cells, which acts as an antineoplastic agent. Alone or in combination with lymphokine-activated killer cells, it can induce partial or complete responses in more than 20 % of patients with advanced melanoma or renal cell carcinoma (Choyke et al. 1992). In a prospective study of patients undergoing CT who had received IL-2 and intravenous non-ionic low-osmolar or oral high-osmolar iodine-based contrast media, or both, there were immediate urticarial reactions in 1.8 % of the patients within an hour of contrast medium administration. No acute reactions were observed in a control group who received contrast media but had not been treated with IL-2. Delayed reactions (erythema, rash, fever, flushing, pruritus and flu-like symptoms) developed in 12 % of IL-2 patients and in only 4 % of the control group. Two of the IL-2 patients required admission to hospital.

The mean onset of symptoms was 4.5 h after injection of contrast media and the mean duration of reaction was 16.4 h. The patients had no risk factors for delayed reactions other than IL-2 therapy and all had had previous uneventful exposure to contrast media. None of the patients with immediate reactions developed delayed reactions. The average time since IL-2 therapy was 6 months (range 24 days–2.4 years). The main concern with delayed side effects is that the patient may be out of hospital when the reaction occurs. Previous iodine-based contrast media reaction in an IL-2 patient should be considered a relative contraindication to further contrast media administration (Choyke et al. 1992). An increased risk of contrast reactions may remain for 2 years after stopping IL-2 treatment.

The administration of iodine-based contrast media may also precipitate IL-2 toxicity. Fever, diarrhea, nausea and vomiting have been observed 2–4 h after CT scanning enhanced with non-ionic low-osmolar contrast media. The exact mechanism is not clear and immunologic interactions are probable. Con-\trast media may generate the release of endogenous IL-2 or reactivate the IL-2 receptors (Abi-Aad et al. 1991). Patients who develop these reactions should avoid further exposure to contrast media and imaging techniques such as MRI or CT without contrast media injection should be considered for monitoring response to treatment (Abi-Aad et al. 1991).
2.5 Drugs Which Interfere with the Hematological Effects of Contrast Media

2.5.1 Effects of Contrast Media on Coagulation
It is well established that iodine-based contrast media interact with the coagulation mechanism, platelet activation and degranulation and with thrombolytic drugs (Frohlich 2001). Ionic iodine-based contrast media inhibit both the intrinsic and extrinsic coagulation cascades at several levels. They act as direct inhibitors of thrombin production. They also inhibit both platelet activation and aggregation, increase the bleeding time and cause enzyme inhibition of fibrinolysis. Iodine-based ionic contrast media are more effective than non-ionic agents at increasing the clotting time and give a fourfold increase in the whole blood clotting time when compared to non-ionic agents (Frohlich 2001). Non-ionic contrast media cause less significant alteration of clotting by inhibiting the coagulation cascade after the generation of thrombin at the step of fibrin monomer polymerization (Parvez et al. 1982; Massee et al. 1991). Thus, both ionic and non-ionic iodine-based contrast media can prolong clotting time and may exaggerate the effects of anticoagulant and antiplatelet drugs (Frohlich 2001). In addition, clotting times will be falsely prolonged after the administration of iodine-based contrast media and should only be performed 6 h or more after contrast media have been given (Parvez et al. 1982).

2.5.2 Effects of Contrast Media on Fibrinolysis
Iodine-based contrast media impede fibrinolysis and delay the onset of lysis by recombinant tissue-type plasminogen activator (rt-PA), urokinase and streptokinase (Dehmer et al. 1995). This effect is reduced by increasing the concentration of the lysis agent. Contrast media cause fibrin to form in long/thin fibrils which have a lower mass/length ratio and are more resistant to fibrinolysis (Parvez et al. 1982). In vitro studies have shown that diatrizoate and iohexol delay the onset of lysis induced by all the lysis agents. However, ioxaglate delayed the onset of lysis by rt-PA and urokinase but not by streptokinase (Dehmer et al. 1995). In vivo studies in dogs showed that alteplase-induced thrombolysis could be inhibited by iohexol and amidotrizoate (Pislaru et al. 1998).

In clinical practice, if coronary angiography is performed before thrombolysis, the recent administration of iodine-based contrast media may reduce therapeutic success. Reocclusion of coronary arteries was more common after contrast media administration despite concomitant aspirin and heparin therapy (Pislaru et al. 1998). The hematological effects of iodine-based contrast media are described in detail in “Effects of Iodine-Based Contrast Media on Blood and Endothelium”.

2.6 Contrast Media and Drugs Acting on the Central Nervous System
Cerebral angiography may lower the fit threshold in patients receiving antipsychotics such as phenothiazines, (chlorpromazine, perphenazine, prochlorperazine, thioridazine), antihistamines (promethazine, tramiprosate), thioxanthenes (chlorprothixene, haloperidol, thiothixene) or tricyclic antidepressants (amitryptiline, desipramine, doxepin, imipramine, protryptiline), butyrophenones, or analeptics (amphetamine, methamphetamine, cocaine, methylphenidate) (Frohlich 2001). During the time when high-osmolar iodine-based contrast media were in general use, it was suggested that these drugs should be discontinued for 48 h before and 24 h after cerebral angiography. However, discontinuation of antipsychotics may lead to an increased rate of suicides. Since the routine use of modern non-ionic iodine-based contrast media for angiography, antipsychotic drugs are no longer stopped.

2.7 Drugs Which Enhance the Effects of Contrast Media on the Heart
Calcium channel blockers prevent influx of calcium ions into the cell, so affecting the tone of heart and vascular smooth muscle cells and leading to vasodilatation and negative inotropic effects on the myocardium. Patients receiving calcium channel blockers may develop hypotension after left ventriculography with ionic high-osmolar iodine-based agents since the contrast agents can also induce peripheral vasodilatation and have a negative inotropic effect on the heart. These effects are not significant with modern low-osmolar non-ionic iodine-based contrast media which are less vasoactive and have minimal negative inotropic effect on the myocardium (Higgins et al. 1983; Morris et al. 1985; Morcos et al. 1998).

A harmful synergism between high-osmolar iodine-based contrast media and digitalis has also been suggested following experimental studies in the rat (Fischer and Morris 1980). However, there are no human data supporting this observation.

2.8 Effects of Contrast Media on Isotope Studies
The administration of iodine-based contrast media interferes with both diagnostic scintigraphy and radiiodine treatment. The reduced uptake of the radioactive tracer is caused by the free iodide in the contrast medium solution. A delay before
undertaking scintigraphy of 4–6 weeks for water-soluble and 12 weeks for cholangiographic contrast media is advocated, depending on the indication for scintigraphy and whether the patient is euthyroid or hyperthyroid. A more detailed discussion of the effects of contrast media on the thyroid gland can be found in “Effects of Iodine-Based Contrast Media on Thyroid Function”.

Intravascular administration of iodine-based contrast media shortly after injection of isotope material (99mTc-pyrophosphate) for bone imaging can interfere with the body distribution of the 99mTc-pyrophosphate. Increased uptake of the isotope material in kidneys and liver with low uptake in bones was observed. The diuretic effect of contrast media may increase the elimination of the isotope material in urine, so less is available for deposition in skeleton. The increased uptake in the liver is not fully explained (Crawford and Gumerman 1978).

Intravascular administration of iodine-based contrast media may also interfere with red blood cell labeling with isotope material. 99mTc labeling of red blood cells should not be performed within 24 h after contrast media injection. How contrast media interfere with red blood cell labeling is not fully understood (Tatum et al. 1983).

## 2.9 Mixing Contrast Media with Other Drugs

Contrast media should not be mixed with other drugs before intravascular use (Kim et al. 1992) because this may change the stability of the drugs. It is also advisable not to inject other drugs through the same venous access used for contrast media injection. If the same venous access is used, there should be adequate flushing with normal saline first.

## 2.10 Effects of Contrast Media on Biochemical Assays

Measurements of clotting time and other coagulation factors can be falsely increased after the intravascular administration of iodine-based contrast media. Therefore, clotting tests should be avoided for 6 h or more after injection of contrast media (Parvez et al. 1982). Iodine-based contrast media in the urine may also interfere with some of the protein assay techniques leading to false-positive results (Morcos et al. 1992). Care must be exercised in interpreting tests for proteinuria for 24 h after injection of contrast media.

Gadodiamide and gadoversetamide may cause spurious hypocalcemia, particularly at doses of 0.2 mmol kg⁻¹ or higher in patients with renal insufficiency (Prince et al. 2003; Choyke and Knopp 2003). These contrast media interfere with calcium measurements obtained by assay using the ortho-cresolphthalein complexone (OOC) method but not with the assays using the Arsenazo III method (Normann et al. 1995; Proctor et al. 2004). The false measurements of serum calcium did not occur with gadopentetate dimeglumine or gadoteridol (Choyke and Knopp 2003). In very high concentrations, Gd-DTPA may interfere with calcium determination when methylthymolblue is used (Junge and Troge 1991). It is important to be aware of this effect on calcium measurements of some MRI contrast agents so as to avoid incorrect and potentially hazardous treatment (Prince et al. 2003). Iodine-based contrast media may interfere with the determination of bilirubin, copper, iron, phosphate and proteins in blood (Junge and Troge 1991). Caution should be exercised when using colorimetric assays for angiotensin-converting enzyme, calcium, iron, magnesium, total iron-binding capacity and zinc in serum samples from patients who have recently received gadolinium-based contrast media (Proctor et al. 2004). Therefore, biochemical assays are better performed before contrast media injection or delayed for at least 24 h afterwards, or longer in patients with renal impairment. Urgent laboratory tests performed on specimens collected shortly after contrast media injection should be carefully assessed. Accuracy of unexpected abnormal results should be ascertained and discussed with colleagues from the hospital laboratories.

## 3 Conclusion

Contrast media have the potential for interaction with other drugs and may interfere with biochemical assays. Awareness of these interactions is important to avoid misinterpretation of biochemical data and to reduce the risk of causing harm to the patient following imaging and interventional procedures. Proper documentation of intravascular use of contrast media should be included in the patient’s records (Barrs 2002).

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Contrast Media Extravasation Injury

Jarl Å. Jakobsen

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Abstract

Extravasation of contrast medium during injection, especially when doing contrast-enhanced CT, is now a common problem. The risk factors include patient factors, the class of contrast medium used, and the injection technique. The mechanisms discussed are effects of osmolality, cytotoxicity, volume, and compression. The clinical picture varies from no subjective complaints to pain, ulcers, and compartment syndrome. However, nearly all cases can be effectively handled by simple conservative treatment with a cold pack and elevation of the arm. The treatment and follow-up of the patient must be documented.

1 Introduction

Subcutaneous extravasation is a well-recognized complication of intravenous administration of iodine-based contrast media (Pond and Dorr 1993; Cohan et al. 1996; Federle et al. 1998; Cochran et al. 2001; Runge et al. 2002; Wang et al. 2007). The incidence of extravasation after mechanical bolus injection is higher than that reported for hand-injection or drip-infusion techniques, but there seems to be no relation between injection rate, volume, and extravasation frequency (Pond and Dorr 1993; Jacobs et al. 1998; Wienbeck et al. 2010). The clinical presentation is variable. Most extravasations involve small volumes of contrast material and cause minimal swelling or localized erythema, which diminish rapidly. Pain is the most common subjective symptom (Wang et al. 2007). Extensive tissue necrosis and severe skin and subcutaneous ulceration are rare and usually follow high-volume extravasations (Cohan et al. 1996; Ayre-Smith 1982).
2 Risk Factors

2.1 Patient Factors

Infants, small children, and unconscious patients are more likely to develop extravasation (Cohan et al. 1996) because they are unable to complain of pain at the injection site. Patients undergoing chemotherapy are at a higher risk because chemotherapy may induce fragility of the vein wall. Extravasation injuries are also more severe in patients with low muscle mass and atrophic subcutaneous tissue. In addition, patients with arterial insufficiency (e.g., atherosclerosis, diabetes mellitus, or connective tissue diseases) or compromised venous drainage (e.g., thrombosis) or lymphatic drainage (e.g., radiation therapy, surgery, or regional node dissection) are less able to tolerate extravasation than those with unimpaired circulation.

2.2 Class of Iodine-Based Contrast Medium

Extravasation of low-osmolar contrast media is better tolerated than extravasation of high-osmolar media. However, five severe injuries have been reported with non-ionic contrast media, one of them in a 22-month-old child. None of them required reconstructive surgery (Pond et al. 1992; Memolo et al. 1993; Young 1994; Benson et al. 1996; Wang et al. 2007).

2.3 Volume

The majority of extravasations involve small volumes of contrast material and symptoms resolve completely within 24 h (Sistrom et al. 1991; Cohan et al. 1996, 1997; Federle et al. 1998; Jacobs et al. 1998). Severe skin ulceration and necrosis have been seen after extravasation of volumes as small as 10 mL, but this is very rare (Ayre-Smith 1982). Large volume extravasation may lead to severe damage to the extravascular tissues and is most likely to occur when contrast medium is injected with an automated power injector and the injection site is not closely monitored (Cohan et al. 1996, 1997). However, it is difficult to find reports about the relationship between compartment syndrome and the compartment in the arm where extravasation occurred.

2.4 Access Site

The site of injection appears to be important. Seventy-eight percent of 36 patients who had contrast medium injected through a dorsal vein of the great toe for lower limb phlebography developed extravasation (Gothlin 1972). The use of tourniquets and the presence of edema increase the risk of extravasation with lower limb phlebography (Cohan et al. 1996). Injections into the dorsum of the hand are also frequently associated with extravasation injury (Gault 1993; Wienbeck et al. 2010).

2.5 Injection Rate

Mechanical power injection for CT studies is probably responsible for most extravasation injuries today. The frequency of extravasation with power injection rates between 1 and 2 mL s$^{-1}$ varies from 0.2 to 0.4 % (Cohan et al. 1990a; Miles et al. 1990; Sistrom et al. 1991; Kaste and Young 1996; Federle et al. 1998). In a large study where injection rate was recorded in 421 patients who had extravasation, 27 % were injected at a rate of less than 2 mL s$^{-1}$, 50 % at 2–3 mL s$^{-1}$, and 23 % at more than 3 mL s$^{-1}$ (Wang et al. 2007). Jacobs et al. (1998) found that the extravasation rate (0.6 %) did not differ significantly between groups of patients receiving contrast media at different injection rates. A prospective study of 4.457 patients undergoing MDCT with various contrast medium concentrations, injection rates, catheter sizes, and injection sites did not show any correlation between the injection rate and the incidence of extravasation (Wienbeck et al. 2010).

2.6 Indwelling Cannulas or Lines

The type of venous access also affects the frequency of extravasation. In 40 % of one series of patients with contrast medium extravasation, indwelling intravenous lines were used (Sistrom et al. 1991). Extravasations are more frequent with metal needles than with plastic cannulae (Gothlin 1972).

Injection through indwelling peripheral intravenous lines that have been in place for more than 24 h and multiple punctures into the same vein are associated with an increased risk of extravasation (ACR Manual 2012).

3 Mechanisms and Toxicity

3.1 Osmolality

The osmolality threshold for significant tissue injury is estimated to be 1.025–1.420 mOsm kg$^{-1}$ water (Cohan et al. 1990a, b; Elam et al. 1991). Both radiographic and MR contrast agents of low osmolality are better tolerated than high-osmolar iodine-based contrast agents (Sistrom et al. 1991). With gadolinium-based contrast agents, the
osmotic loads and the volumes that are administered are markedly less than with iodine-based agents. However, in rats, extravasation of dimeglumine gadopentetate (1960 mmol kg$^{-1}$ water) was associated with a higher incidence of necrosis, hemorrhage, and edema than gadoteridol (789 mmol kg$^{-1}$ water) (Cohan et al. 1991; Runge et al. 2002). Gadoteridol, in a concentration of 0.5 mol L$^{-1}$, was no more toxic than 0.9 % saline. Runge et al. (2002) also showed, after extravascular injection of 0.3 mL of MR contrast medium in the hind limb of rats, that higher osmolality agents, such as gadopentetate dimeglumine and gadoversetamide (1110 mmol kg$^{-1}$ water), had more harmful consequences than lower osmolality agents, such as gadodiamide (789 mmol kg$^{-1}$ water) and gadoteridol (630 mmol kg$^{-1}$ water).

3.2 Cytotoxicity

The cytotoxicity of the contrast media may be important, although when ionic and non-ionic contrast media are compared, the literature is conflicting. In rats, extravasated iodine-based ionic contrast media produced acute inflammation followed by a chronic inflammatory process, with fibrosis and adjacent muscle atrophy detected at the injection site by 8 weeks (McAlister and Palmer 1971).

The acute inflammatory response, including histologic changes, peaks at 24–48 h after extravasation (Cohan et al. 1990b). While the same authors also found that ionic contrast media were more toxic than non-ionic agents, no difference was found by Jacobs et al. (1998). The presence of meglumine as a cation may also play a role in the cytotoxicity of ionic contrast media (Kim et al. 1990).

3.3 Volume and Compression

The volume of contrast medium extravasated seems to be important. Mechanical compression caused by large volume extravasations may lead to compartment syndrome (Pond et al. 1992; Memolo et al. 1993; Young 1994; Benson et al. 1996).

Although severe skin lesions have been described following extravasation of less than 15 mL, the majority occurred with large volume extravasations (Upton et al. 1979).

3.4 Indwelling Catheters

Extravasation from indwelling intravenous lines is often due to phlebitis that develops in veins that have previously been cannulated (Cohan et al. 1996). Thrombosis increases vascular resistance in the same way as an injection does. Other mechanisms include the inadequate placement of the catheter in the vein, multiple punctures of the same vein, and high injection pressure, which can rupture the vessel wall. Theoretically, using central venous access may increase the risk, especially if the catheters are not approved for high pressure and flow.

4 Clinical Picture

The presentation of the extravasation of iodine-based and gadolinium-based contrast media varies from minor erythema and swelling to tissue necrosis associated with progressive edema and skin ulceration as well as the compartment syndrome. The injuries may heal or rarely may lead to long-term sequelae including hypoesthesia, marked weakness, and pain (Federle et al. 1998).

4.1 Symptoms and Signs

Symptoms of extravasation are very variable and many patients complain of stinging or burning pain. Although unconscious patients, the elderly, and infants cannot complain of pain, others, who are able to complain, often do not experience any discomfort and remain asymptomatic. On physical examination, the extravasation site appears swollen, red, and tender. Most extravasation injuries resolve spontaneously in 2–4 days. At the initial examination, it is not possible to predict whether the injury will resolve or will result in ulceration or necrosis and soft tissue damage. Some clinical findings which suggest severe injury justify seeking the advice of a surgeon. These include skin blistering, altered tissue perfusion, paresthesiae, and increasing or persistent pain after 4 h (Cohan et al. 1996).

When extravasation results in an acute compartment syndrome, tense and dusky forearms, with swelling and diminished arterial pulses and reduced sensibility may occur. Compartment syndrome may necessitate emergency fasciotomy to relieve neurovascular compromise (Pond et al. 1992; Memolo et al. 1993; Young 1994; Benson et al. 1996). Fortunately, this complication is rare.

Extravasation injuries must be distinguished from other local reactions to injected fluid, including hypersensitivity reactions and local irritative effects of iodine-based contrast agents on the vessel wall. In these reactions, edema and erythema are absent and the catheter is well positioned in the vein. Transient, local pain has been reported in 2–5 % of patients following intravenous administration of ionic iodine-based contrast material while delayed arm pain at or above the injection site has been reported in 0.1–14.0 % of
patients who received iodine-based contrast material (Shehadi 1975; McCullough et al. 1989). The pain may last for several days (mean, 3 days; range, 1–30 days) and may progress to phlebitis in rare cases (Panto and Davies 1986).

4.2 Imaging Findings

Extravasated iodine-based contrast medium can be seen on radiographs as a dense, confluent mass at the injection site (Chew 2010; Schummer et al. 2010; Earhart and McMahon 2011). With CT, the tissue compartments and other details can be visualized (Fig. 1).

Extravasated gadolinium-based contrast medium is also easily demonstrated. It may produce a zone of signal void on short relaxation time MR images because of the high local concentration (Carrier et al. 1993). The precise depth of the extravasation into soft tissue can also be assessed (Fig. 2).

5 Prevention, Treatment, and Information to the Patient

There is no consensus about the best approach for the management of extravasation (Katayama et al. 1990; Park et al. 1993; Yucha et al. 1994; Cohan et al. 1996; Federle et al. 1998). The following recommendations are taken from the papers referred to in this chapter, as well as guidelines from the American College of Radiology, the Royal College of Radiologists, an earlier publication from European Society of Urogenital Radiology (ESUR) (Bellin et al. 2002), and the most recent ESUR guidelines (“ESUR Guidelines on Contrast Media Version 8.1”).

5.1 Aborting the Contrast Medium Injection

The injection of contrast medium should be stopped immediately when extravasation is suspected, either by the radiographer observing the injection site during injection, or by the patient. Ideally, to detect extravasation early, there would be a trained radiographer or nurse beside the patient, but exposure to ionizing radiation makes such close observation difficult when scanning starts immediately after the start of the injection. New devices to detect extravasation are under evaluation. In a study of 500 patients (Birnbaum et al. 1999), an extravasation detection accessory (EDA) had a sensitivity of 100 % and a specificity of 98 % for detecting clinically relevant extravasation (>10 mL). The device was easy to use, safe, and accurate for monitoring intravenous injections for extravasation, and could prove especially useful in high flow rate CT applications. Other devices are currently being evaluated, including those using Doppler ultrasonography (Hoff et al. 2008).

5.2 Choice of Injection Site, Catheter Size and Contrast Medium

High risk injection sites, such as the back of the hand, the ankle, or the neck should be avoided, if possible. Veins that have recently had multiple recent punctures should not be used. Smaller catheters (22 G) have a higher risk than the wider ones (18G–16G) (Wienbeck et al. 2010). High-osmolar contrast media should be avoided, because the evidence in the literature indicates that low-osmolar agents produce less tissue damage if they extravasate.
5.3 Inspect and Plan

The first thing to do when extravasation has occurred is to inspect the injection site. Changes in the normal contours indicate the volume which has extravasated into the tissues. Any color change or blisters should be noted and the peripheral pulse in the affected limb should be palpated. While the patient is being examined, he/she should be asked about pain, numbness, etc. Appropriate treatment can then be planned and can be discussed with the patient.

5.4 Elevation of the Affected Limb

Elevation is often useful in order to reduce edema by decreasing the hydrostatic pressure in the capillaries.

5.5 Topical Application of Heat or Cold

Heat produces vasodilatation and helps resorption of extravasated fluid and edema, while cold produces vaso-constriction and limits inflammation. The immediate application of warm compresses reduced the volume of extravasated fluid in healthy volunteers (Hastings-Tolsma et al. 1993). In an experimental study, application of cold compresses was associated with a decrease in the size of skin ulcers produced by extravasation of iothalamate and diatrizoate (Elam et al. 1991). No significant difference was found at the injection site in untreated rats, rats treated with warmth, and rats treated with cooling (Cohan et al. 1990a). In patients, cooling can easily be produced with ice packs placed at the injection site for 15–60 min three times a day for 1–3 days or until symptoms resolve. The application of a cold pack is now the main advice in the major guidelines.

To prevent secondary infections, many plastic surgeons recommend applications of silver sulfadiazine ointment if there is blistering (Heckler 1989). However, this has not become common practice.

5.6 Drugs, Aspiration of Fluid, and Surgery

Local subcutaneous injection of hyaluronidase, which breaks down connective tissue, has frequently been used in patients with large extravasations of high- or low-osmolality contrast medium and of chemotherapeutic agents (Laurie et al. 1984). It should be administered within 1 h of the extravasation of the contrast medium.
extravasation. Dose recommendation is variable, and efficacy has not been convincingly shown. Some animal and clinical studies suggest a beneficial effect (Laurie et al. 1984; Heckler 1989; Cohan et al. 1996), while McAlister and Palmer (1971) reported that hyaluronidase injected into rat tissues with contrast media was associated with a more marked inflammatory reaction.

Corticosteroids, vasodilators, and a variety of other agents have been proposed for treating extravasation, but most studies either failed to demonstrate any value of these agents or evaluated extravasation of drugs other than contrast media. The usefulness of fluid aspiration from the extravasation site is controversial, as it usually removes only a small amount of extravasated fluid and in addition carries a risk of infection.

Most plastic surgeons believe that the majority of extravasation injuries heal without surgery and recommend conservative treatment (Cohan et al. 1990a). Surgical drainage or emergency suction applied within 6 h can be effective (Loth and Jones 1988) and the use of emergency suction alone or combined with saline flushing has also been helpful (Gault 1993; Vandeweyer et al. 2000). However, these measures do not seem in practice to be used to any extent.

5.7 Follow-up of the Patient

Observation of the patient for 1–2 hrs in the department, with a final inspection of the injection site before discharge should be considered, and, if done, should be noted in the patient’s records. However, the usefulness of this does not appear to have been published.

The patient should be given information about the incident, preferably in writing. This information should include signs that may indicate the need for further contact with a physician and contact details. Examples of forms from Duke University Hospital and from Addenbrooke’s Hospital, Cambridge, can be found on their homepages (http://radiology.duke.edu/modules/duke_rad_clinicalsvs/index.php?id=55; http://www.cuh.org.uk/resources/pdf/patient_information_leaflets/PIN2856_contrast_medium_extravasation.pdf).

The incident should be recorded in the patient’s hospital or radiology records, as well as in the written report to the referring physician.

6 Conclusion

Extravasation of contrast material is a frequent complication of enhanced imaging studies. Although severe damage has been reported, the consequences are usually minor and easily treated. Early identification is important and conservative management is effective in most cases.

References


Part V

Iodine-Based Contrast Media
Late Adverse Reactions to Iodine-Based Contrast Media

Fulvio Stacul and Marie-France Bellin

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Abstract

The most commonly reported late adverse reactions to iodine-based contrast media are headache, skin rash, itching, nausea, dizziness, urticaria, fever, arm pain and gastrointestinal disturbances. When late reactions to enhanced and unenhanced CT were compared, only skin reactions occurred more frequently in the group who received contrast medium (non-ionic monomer or dimer) and skin reactions appear to account for the majority of true late reactions. Late skin reactions occur three to four times more commonly with the non-ionic dimer iodixanol than with the non-ionic monomers. Most reactions are self-limiting, resolve by 3–7 days, and appear to be T-cell mediated.

1 Introduction

Late adverse reactions to intravascular iodine-based contrast media are defined as reactions occurring between 1 h and 1 week after contrast medium injection. They were first recognized in the mid-1980s (Panto and Davies 1986) and since then have been widely studied, particularly the reactions to low osmolality contrast media. However, many aspects remain controversial and there is widespread uncertainty among radiologists about the incidence, pathophysiology, significance and management of late reactions.

2 Reaction Type and Severity

In reports of late reactions, the symptoms most commonly described are headache, skin rash, itching, nausea, dizziness, urticaria, fever, arm pain and gastrointestinal disturbances. When late reactions to enhanced and unenhanced CT were compared, only skin reactions occurred more frequently in the group who received contrast medium (non-ionic monomer or dimer) (Schild 1996; Yasuda and
Munechika 1998; Schild et al. 2006) and skin reactions appear to account for the majority of true late reactions (Loh et al. 2010). The types of late skin reactions and their relative frequencies are similar to those which occur with many other drugs (Bigby et al. 1986). Maculopapular rash is observed in more than 50 % of the affected patients (Hosoya et al. 2000). Other frequently occurring skin reactions are angioedema, urticaria, erythema, macular exanthema and scaling skin eruption (Bigby et al. 1986; Rydberg et al. 1998; Christiansen et al. 2000; Sutton et al. 2001, 2003; Vernassiere et al. 2004; Kanny et al. 2005). Lesser-known delayed skin reactions have been discussed by Böhm and Schild (2006).

In most cases, skin reactions are mild or moderate, i.e., they may cause discomfort and may require specific treatment (steroids, antihistamines, topical emollients) (Rydberg et al. 1998; Hosoya et al. 2000; Sutton et al. 2001, 2003; Munechika et al. 2003). In most cases, they are self-limiting. Depending on their site, these reactions cause some discomfort, the most troublesome being those affecting the palms, soles of the feet or face (Sutton et al. 2001). Severe delayed reactions needing hospital treatment and/or leading to persistent disability or death have been reported, but are very rare. In the eight cases Christiansen et al. (2000) collected from the literature, four had underlying serious medical conditions (Goodfellow et al. 1986; Savill et al. 1988; Reynolds et al. 1993; Sadi et al. 1995) and there are only a few other case reports of serious reactions (Conroy et al. 1994; Rosado et al. 2001; Vavricka et al. 2002; Atasoy et al. 2003; Laffitte et al. 2004).

3 Pathophysiology

A number of pathophysiological mechanisms have been proposed for late skin reactions; however, the cellular and molecular mechanisms of these reactions remain poorly documented. Although the pathogenesis is still not fully understood, it appears that many are type IV hypersensitivity reactions, i.e., they are T-cell mediated (Christiansen et al. 2000; Christiansen 2002; Brockow et al. 2005; Kanny et al. 2005; Guéant-Rodriguez et al. 2006; Brockow et al. 2009). The skin reactions often show typical features of late hypersensitivity, including exanthematous rash, positive skin tests and lymphocyte rich dermal perivascular infiltrate, sometimes accompanied by eosinophils on skin biopsy (Savill et al. 1988; Hari et al. 2001).

Much information about the pathophysiology of late adverse reactions has been obtained from studies of skin tests using diluted contrast medium (Idée et al. 2005; Romano et al. 2008; Torres et al. 2008; Brockow et al. 2009; Khachman et al. 2009; Torres et al. 2012). Such skin tests include skin prick and delayed reading intradermal tests which can identify both IgE and T-cell mediated mechanisms, as well as patch tests which only identify T-cell mediated reactions. These tests are carried out on patients who have reacted to contrast media, so-called “reactors”.

The recent literature suggests that a T-cell mediated mechanism, involving CD4+ and CD8+ lymphocytes is the pathophysiological basis of delayed reactions (Torres et al. 2008; Seitz et al. 2009; Torres et al. 2012). These T-cells also demonstrate cross-reactivity with similar contrast media, which occurs among ionic and non-ionic, and monomeric and dimeric agents (Kanny et al. 2005; Lerch et al. 2007; Brockow et al. 2009). In patients who have had late adverse reactions to iodine-based contrast media, skin tests showed significant cross-reactivity with other iodine-based contrast media, but there was rarely a reaction with inorganic iodine (Seitz et al. 2009; Scherer et al. 2010). This suggests that the whole contrast medium molecule has an immunogenic role but free iodine rarely does (Scherer et al. 2010). The observation that peripheral blood lymphocytes from patients who have previously had late adverse reactions are activated in vitro when exposed to contrast medium provides support for this putative immunogenic role (Torres et al. 2008). Further support comes from evidence that dendritic cells from reacting patients are involved in the recognition and presentation of contrast medium molecules to cells of the immune system and influence T-cell proliferation and cytokine production (Antunez et al. 2011).

4 Frequency

Determining the true frequency of late adverse reactions to contrast media from the literature is difficult. First, a variety of different methodologies have been used, with different methods of data collection (questionnaires, patient interviews in person or by phone), different starting points (at a variety of times from 30 min after contrast medium injection) and different data collection periods (from 1 to 7 days).

A further problem is the fact that the greater the time interval between the contrast medium injection and the onset of symptoms, the more difficult it is to be sure that the symptoms are contrast medium induced. This has been highlighted by the studies on “background noise” by several investigators who have shown a high incidence of late symptoms after radiological investigations not using contrast medium (Loh et al. 2010). In one study, late adverse reactions occurred in 12.4 % of patients who had contrast medium enhanced CT, and in 10.3 % who had unenhanced CT (Yasuda and Munechika 1998), and in another study approximately 50 % of late adverse reactions were found to be unrelated to contrast media (Beyer-Enke and Zeitler...
Ueda et al. (2001) reported late reactions in 8.4% of patients having enhanced CT, and in 7.9% having plain CT, while Loh et al. (2010) reported late reactions in 14.3% of patients having iohexol-enhanced CT, and in 2.5% having plain CT. Schild (1996) reported more late adverse reactions following plain CT than enhanced CT, with the exception of skin reactions which were more common after enhanced CT. Recently, Böhme et al. (2011) assessed the causative agent in adult patients with hypersensitivity reactions that occurred during and after contrast medium-enhanced procedures. In 28/38 patients, the hypersensitivity reactions were induced by the contrast medium and in 6/38 cases the reaction was partly contrast-medium related. Four patients had reactions that were not contrast medium-related.

In most studies, it appears that skin rashes account for the majority of true late reactions to iodine-based contrast media (Loh et al. 2010). In 1996, Schild et al. considered 895 patients who underwent CT after injection of a dimeric or a monomeric agent or without contrast material injection. They found that the overall rates of delayed reactions were comparable in all the three study groups (53.1, 50.8, and 48.4%, respectively), and again skin reactions were more common after enhanced CT.

The frequency of late adverse reactions to non-ionic monomers has been reported to be between 0.52 and 50.8% (Higashi and Katayama 1990; Choyke et al. 1992; Yoshikawa 1992; Cochran et al. 1993; Mikkonen et al. 1995; Pedersen et al. 1998; Rydberg et al. 1998; Yasuda and Munechika 1998; Bartolucci et al. 2000; Hosoya et al. 2000; Ueda et al. 2001; Munechika et al. 2003; Schild et al. 2006; Loh et al. 2010.) Several studies suggest that the incidence in the 1–24 h period is 4% or less (Choyke et al. 1992; Beyer-Enke and Zeitler 1993; Pedersen et al. 1998) and in four large studies the frequency of late skin reactions was 1–3% over a period of 7 days (Rydberg et al. 1998; Yasuda and Munechika 1998; Munechika et al. 1999; Hosoya et al. 2000). There do not appear to be significant differences in the incidence of late reactions between ionic and non-ionic monomers (McCullough et al. 1989; Panto and Davies 1986; Yamaguchi et al. 1992; Pedersen et al. 1998), nor between the different non-ionic monomers (Panto and Davies 1986; Yamaguchi et al. 1992; Pedersen et al. 1998). No significant differences have been found between the non-ionic monomers and the ionic dimer ioxaglate either (Bertrand et al. 1995; Mikkonen et al. 1995; Oi et al. 1997).

The available evidence suggests that late skin reactions are more common with non-ionic dimers (Lapi et al. 2008). In two studies conducted by the same group, late skin reactions occurred three to four times more commonly with the non-ionic dimer iodoxanol than with the non-ionic monomers iopamidol and iomeprol and the ionic dimer ioxaglate (Sutton et al. 2001, 2003). Schild et al. (2006) did not find a significant difference in the overall incidence of delayed reactions between the non-ionic dimer iotrolan and the non-ionic monomer iopromide, but they found a higher incidence of cutaneous symptoms (itching or skin rash) in the dimeric group. In another study, the frequency of late skin reactions with iodoxanol was similar to that with non-ionic monomer, but more of the iodoxanol patients were treated with hydrocortisone or antihistamine (Rydberg et al. 1998). Fransson et al. (1996), however, found no difference in the frequency of late skin reactions between iodoxanol and ioxaglate. The non-ionic dimer iotrolan was withdrawn in 1995 because of the high incidence of late reactions, particularly skin reactions, initially reported from Japan but subsequently also from the USA (Niendorf 1996; Hosoya et al. 2000).

## 5 Reaction Onset and Duration

Late skin reactions after contrast medium develop within 1–7 days, with the majority occurring within the first 3 days (Hosoya et al. 2000). Most reactions are self-limiting and resolve by 7 days, with up to three-quarters resolving within 3 days (Yoshikawa 1992; Hosoya et al. 2000).

## 6 Predisposing Factors

A number of factors appear to predispose a person to the development of late adverse reactions. A previous reaction to contrast medium is an important predisposing factor, increasing the risk by a factor of 1.7–3.3 (Yoshikawa 1992; Mikkonen et al. 1995; Hosoya et al. 2000). However, there is no evidence that patients with a previous late reaction are at increased risk for a subsequent immediate anaphylactic reaction (Yamaguchi et al. 1992; Yoshikawa 1992; Hosoya et al. 2000). A history of allergy is a further risk factor (Higashi and Katayama 1990; Yoshikawa 1992; Oi et al. 1997; Munechika et al. 1999, 2003; Hosoya et al. 2000; Schild et al. 2006), increasing the likelihood of a reaction approximately two-fold. A history of drug and contact allergy especially seems to predispose to late skin reactions after contrast medium exposure (Aoki and Takemura 2002; Vernassiere et al. 2004; Kanny et al. 2005). A seasonal variation in the incidence of late skin reactions has been described with 45% of the reactions occurring in the period April to June in Finland (Mikkonen et al. 2000). A relation to the pollen season and/or to the possible photosensitizing effect of contrast media has been postulated. A significantly higher incidence of late adverse reaction during the pollen season was confirmed by Munechika et al. (2003). Females are more likely to develop late adverse reactions than males (Higashi and Katayama 1990; Mikkonen et al. 1995;
Oi et al. 1997; Bartolucci et al. 2000; Hosoya et al. 2000; Schild et al. 2006). Patients of Japanese descent may be more susceptible to late reactions (Christiansen et al. 2000) Coexisting diseases also appear to predispose to late reactions, especially renal disease, but also cardiac and liver disease and diabetes mellitus (Mikkonen et al. 1995; Bartolucci et al. 2000; Hosoya et al. 2000). Some of the most severe skin reactions reported occurred in patients with systemic lupus erythematosus or in patients who were taking hydralazine, which induces a lupus-like syndrome in some patients (Goodfellow et al. 1986; Savill et al. 1988; Reynolds et al. 1993). Bone marrow transplantation patients were reported to be another risk group for severe contrast medium induced skin eruptions (Vavricka et al. 2002).

The increased incidence of late reactions to contrast media in patients who have received interleukin-2 (IL-2) immunotherapy is well documented, with an increased frequency of two to four times (Oldham et al. 1990; Zukiwski et al. 1990; Fishman et al. 1991; Choyke et al. 1992; Shulman et al. 1993). Skin rash, pruritus and flu-like syndrome were all more frequent in patients who had received IL-2 (Choyke et al. 1992). Interestingly, both IL-2 and pre-existing stimulation of the immune system in systemic lupus erythematosus reduce the threshold for T-cell activation by enhanced cytokine secretion or monocyte activation (Schnyder et al. 1998; Christiansen 2002).

7 Management

Management of late adverse reactions is symptomatic and similar to the management of other drug-induced reactions. Oral antihistamines, topical steroids and emollients have been used (Sutton et al. 2003; Schild et al. 2006).

8 Skin Testing

If there is doubt about whether contrast medium is responsible for a skin reaction, skin testing (patch and delayed intradermal tests) may be indicated (Schick et al. 1996; Akiyama et al. 1998; Courvoisier and Bircher 1998; Gall et al. 1999; Watanabe et al. 1999; Brockow et al. 1999, 2005; Kanny et al. 2001, 2005; Sedano et al. 2001; Bohm and Schild 2006; Bellin et al. 2011). However, it should be noted that some patients who have had late adverse reactions to a contrast agent do not have a positive skin test with the agent. Goksel et al. (2011) reported that the sensitivities of delayed readings of intradermal tests and patch tests were 14.3 and 25 %, respectively, while the specificity for both these tests was 100 %. The positive predictive value (PPV) was 100 % for both of these tests, and the negative predictive values (NPV) were 85.4 and 82.4 %, respectively. In a recent study of 161 subjects, Torres et al. (2012) found that patients with non-immediate reactions to contrast medium were identified by skin testing in 43.6 % and by drug provocation testing in 56.4 %. Despite this, most recent studies suggest that if a patient with a confirmed late adverse reaction to a contrast medium needs further administration of contrast medium, skin testing may be useful for choosing an alternative contrast agent (Brockow et al. 2005; Seitz et al. 2009).

9 Prophylaxis

Given the relatively low rate of occurrence of late adverse reactions and the fact that they are usually mild and self-limiting, it does not seem appropriate to warn patients with no special risk factors about the possibility of a late reaction. However, it is recommended that patients who have had a previous late skin reaction after contrast medium administration, who suffer from major drug or contact allergy or who have received interleukin-2 are warned about the possibility of a late skin reaction and told to contact a physician if they have a problem. Steroid prophylaxis has been proposed in the literature (Watanabe et al. 1999), but its value is unclear and drug prophylaxis is generally not recommended (Bellin et al. 2011).

If patients who have previously had a late skin reaction to iodine-based contrast medium require further contrast medium, it is recommended that an alternative contrast medium is chosen. Skin testing may be useful for choosing an alternative agent. Patch and delayed reading intradermal tests can help confirm a late skin reaction to contrast medium and can be helpful to study cross-reactivity patterns with other agents. To reduce the risk of repeat reaction, it is recommended that a contrast agent other than the agent which precipitated the first reaction is used, and that agents which have shown cross-reactivity on skin testing are avoided (Bellin et al. 2011).

10 Conclusion

Late adverse reactions to iodine-based contrast media have been recognized for 20 years. They are mainly mild or moderate skin reactions which develop from 1 h to 7 days after contrast medium administration and usually resolve within 3–7 days. The majority of these cutaneous reactions are T-cell mediated allergic reactions. A simple guideline has been produced by the Contrast Media Safety Committee (“ESUR Guidelines on Contrast Media Version 8.1”)


Abstract
The effects of contrast agents on red blood cells and white blood cells have been shown not to be clinically important. High-osmolar contrast media can induce thrombosis after injection, mainly because of endothelial injury. However, all contrast media have anticoagulant properties, especially the ionic agents. There is general consensus that good technique is the most important factor to reduce thrombotic complications following angiography.

1 Introduction

Iodine-based contrast media are widely used either to visualize blood vessels (angiography) or to enhance the density of the parenchyma of different organs. In both instances, they are administered intravascularly and ideally their effects on blood and endothelium should be minimal. However, all contrast media have some effects on the endothelium, blood, and its constituents. There is a vast literature on these effects both in vitro and in vivo. The present chapter summarizes the effects from a clinical perspective and discusses whether there are important differences between different iodine-based contrast media in current clinical use.

Iodine-based contrast media may be either ionic or non-ionic and they all produce various effects on blood components. These effects are thought to be caused by the chemical nature of contrast media, their electrical charge, and by the viscosity and the osmolarity of the solution in which they are given. Different contrast media have varying effects on the many components of the blood.

The hematologic effects of iodine-based contrast media have been divided into the following categories: red blood cells, white blood cells, endothelium, platelets, coagulation, and fibrinolysis.
2 Red Blood Cells

The effect of contrast media on red blood cells can be divided into the effects on morphology, aggregation, and rheology (flow properties of the blood). When iodine-based contrast media come into contact with red blood cells, the normal discoid shape of the red blood cells changes (Aspelin et al. 1980; Nash and Meiselman 1991). Extraction of water may cause either shrinkage of the red blood cells, producing a dessicocyte, or changes in shape, called echinocyte or stomatocyte deformation.

2.1 Red Blood Cell Morphology

Dessicocyte formation is an in vitro effect of dehydration of the red blood cell and is proportional to the osmolality of the contrast media to which it is exposed (Aspelin et al. 1980). It is observed only in a fraction of the red blood cells exposed to almost undiluted high-osmolar contrast medium.

Echinocyte formation in vitro is dependent on the chemotoxicity (including electrical charge, pH, or salt concentration) (Chronos et al. 1993) and not on the osmolality of the contrast agent. All contrast media including the iso-osmolar dimers may induce some degree of echinocyte formation (Aspelin et al. 1987; Hardeman et al. 1991; Jung et al. 2008; Mrowietz et al. 2008, 2012).

2.2 Red Blood Cell Aggregation

Contrast media in vitro cause disaggregation of red blood cell rouleaux and not aggregation as sometimes believed (Aspelin et al. 1987). The reason for the misunderstanding could be that contrast media make red cells more rigid causing precapillary stasis, which can be mistaken for increased red blood cell aggregation (Aspelin and Schmid-Schonbein 1978; Aspelin 1992).

2.3 Blood Rheology

The combined effect of dessicocyte, echinocyte, and stomatocyte formation is reduced plasticity of the red blood cells compared to normal red blood cells (Aspelin and Schmid-Schonbein 1978; Aspelin 1992; Losco et al. 2001; Katsanos et al. 2008). Plasticity is essential for the smooth flow of red blood cells through small capillaries and when it is lost there is a decrease in blood flow especially after intra-arterial injections (Dawson et al. 1983; Le Mignon et al. 1988; Strickland et al. 1992b; Pugh 1996; Jung et al. 2012). Pure echinocyte and stomatocyte formation without any dehydration of red blood cells produces only minor rheological change (Aspelin et al. 1980; Nash and Meiselman 1991). However, the overall in vivo effect is a mixture of the effect of contrast media on red blood cell morphology, rigidity, viscosity, and vascular tone. Contrast media can induce both vasoconstriction and vasodilatation in different organs (Mills et al. 1980; Almén et al. 1980; Liss et al. 1996; Morcos et al. 1998). In the pulmonary circulation, contrast media can induce red cell rigidity and pulmonary arterial vasoconstriction, leading to an increase in pulmonary vascular resistance (Almén et al. 1980; Mills et al. 1980; Pugh 1996; Morcos et al. 1998). In the kidney, contrast media can reduce the blood flow in the vasa recta in the medulla (Liss et al. 1996). It is not clear whether in vivo this effect is mainly caused by stasis due to vasoconstriction or by increased red blood cell aggregation. The morphological red cell changes may also affect the capacity for oxygen delivery and pH buffering (Galtung et al. 2002). However, these effects have not been proven to be of importance in clinical studies (Strickland et al. 1992a).

The overall effect of contrast media on red blood cells has not been shown to be of clinical importance.

2.4 Sickle Cell Disease

HbSS in the red cells of patients with sickle cell anemia is susceptible to polymerization, causing the cells to become flattened and rigid (sickling). Sickled cells undergo more hemolysis than normal red blood cells and the impaired passage of sickled cells through the microcirculation may lead to small vessel occlusion, with resultant infarction. Sickling may be precipitated by hypoxia, acidosis, dehydration, or hyperosmolality.

There were a number of reports of vascular occlusions and hemolytic episodes after hyperosmolar iodine-based contrast media were given to patients with sickle cell disease (Losco et al. 2001; Campbell et al. 2012). In vitro, the ionic agent meglumine iothalamate caused greater increases in mean corpuscular hemoglobin concentration (MCHC) and more irreversibly sickled cells in blood from patients with sickle cell anemia than did the non-ionic agent iopamidol (Rao et al. 1982). Losco et al. (2001) compared the effects of the ionic agent sodium/meglumine diatrizoate, the non-ionic monomer iohexol, the ionic dimer ioxaglate, and the non-ionic dimer iodixanol on blood from sickle cell disease patients in vitro. The degree of red cell shrinkage induced was proportional to the osmolality of the contrast agent. The isosmolar iodixanol produced no significant change in red cell volume at any concentration, and the other agents all caused a reduction in mean corpuscular volume (MCV), with the ionic agent producing the greatest
effect. In patients with sickle cell disease, a retrospective review found no increase in the rate of adverse events compared to the general population following a variety of low or iso-osmolar iodine-based contrast agents (Campbell et al. 2012). Hydration before contrast medium administration was associated with a reduced incidence of adverse events (Campbell et al. 2012).

With gadolinium-based contrast media, the smaller doses given compared to iodine-based agents suggest that contrast medium osmolality is unlikely to be a significant problem in sickle cell disease patients. However, it was postulated that sickle cell alignment perpendicular to the magnetic field might be increased by gadolinium agents, so increasing the risk of vascular occlusions or hemolysis. There have been no reports of vessel occlusion or hemolysis following gadolinium-based contrast media (Dillman et al. 2011). A retrospective review of patients with sickle cell disease who received gadolinium-based contrast media found no significant increase in adverse events in the week following contrast medium compared to sickle cell disease patients who had unenhanced MR (Dillman et al. 2011).

3 White Blood Cells

The function of the white blood cells is mainly host defense, but their interactions with the endothelial cells and platelets are also important. White blood cells must be able to adhere to the endothelium and migrate through the vessel wall in order to phagocytose and inactivate toxic products. This involves adherence, chemotaxis, degranulation, and phagocytosis. In vitro studies have shown that all these processes are affected by contrast media.

3.1 Phagocytosis

Contrast media reduce the ability of white blood cells to exhibit phagocytosis (Rasmussen et al. 1988, 1992b; Rasmussen 1998). This effect has been studied only with ionic, high-osmolar contrast media. It may also be caused by calcium chelating agents in the solution. The clinical importance of these in vitro observations is not known.

3.2 Chemotaxis, Granulocyte Adherence, and Inflammation

Contrast media have been shown in vitro to inhibit the chemotoxic response of white blood cells. In vivo studies have not shown this finding to be significant (Rasmussen et al. 1992c). All contrast media decrease the adherence property of white blood cells (Rasmussen et al. 1992a; Zhan et al. 1998; Blann et al. 2001; Barani et al. 2002). Contrast media may interfere with the inflammatory response of white blood cells in the body (Hernanz-Schulman et al. 2000; Fanning et al. 2002; Laskey and Gellman 2003; O’Donnell et al. 2010).

There are no clinical data to suggest that any of these interactions between contrast media and white blood cells are of clinical importance.

4 Endothelium

Endothelial cells contribute to the regulation of many aspects of vascular homeostasis, including coagulation, fibrinolysis, and platelet function. In addition, they are important modulators of vascular tone, primarily by the regulated secretion and rapid clearance of powerful vasoactive mediators such as prostacyclin, nitric oxide, endothelin, and adenosine. The endothelium also controls solute permeability and leukocyte movement during the generation of inflammatory and immune responses (Pearson 1991).

Endothelial cells are exposed transiently to high concentrations of contrast media following intravascular administration. The endothelial effects of contrast media may contribute to the hemodynamic disturbances, thrombosis, and pulmonary edema associated with the intravascular use of these agents.

Modulation of the production of endothelial vasoactive substances plays an important role in mediating the hemodynamic effects of contrast media particularly in the kidney (Morcos 1998). Contrast media can increase the release and expression of the potent vasoconstrictor peptide endothelin by the endothelial cells (Oldroyd and Morcos 2000; Franke et al. 2009). In addition, contrast media may decrease the endothelial production of nitric oxide by reducing the activity of the enzyme nitric oxide synthase which is responsible for the endogenous synthesis of this vasodilator (Schwartz et al. 1994; Heyman et al. 1998). How contrast media increase the release of endothelin or reduce the production of nitric oxide is not fully understood.

Contrast media, particularly high-osmolality ionic agents, have cytostatic and cytotoxic effects on endothelial cells which may precipitate thrombosis (Laerum 1983; Morgan and Bettmann 1989; Wilson and Sage 1994; Barstad et al. 1996; Fauser et al. 2001; Gabelman et al. 2001; Sumimura et al. 2003). In addition, contrast media can induce apoptosis (programmed cell death) of endothelial cells (Zhang et al. 2000). An increase in the frequency of apoptosis in the endothelium may alter vascular homeostasis, including coagulant and thrombotic properties, permeability and tone of the blood vessel wall, as well as vessel growth and angiogenesis (Zhang et al. 2000).
The biocompatibility of contrast media is influenced both by osmolality and chemical structure, particularly the presence of carboxyl groups in the molecules of the ionic agents. In non-ionic contrast media, the absence of carboxyl groups and the presence of many hydroxyl groups that increase hydrophilicity markedly improve biocompatibility and significantly reduce cytotoxicity (Eloy et al. 1991; Albanese et al. 1995; Heptinstall et al. 1998; Labarthe et al. 2003). Ionic contrast media, in particular high-osmolar agents, have greater effects on enzymes and higher affinity to proteins and lipids compared to non-ionic media, and can induce injury to cell membranes and interfere with cell metabolism (Krause and Niehues 1996; Dawson 1996). In addition, contrast media can penetrate endothelial cells, forming dense granules on the luminal surface, and pino-cytotic vesicles (Nordby et al. 1989).

Ionic contrast media may increase vascular endothelial permeability leading to pulmonary edema (Sendo et al. 2000; Emery et al. 2001; Furuta et al. 2001, 2002; Tominaga et al. 2001; Morcos 2003). Subclinical pulmonary edema without obvious signs or symptoms of respiratory distress is thought to be common after intravascular contrast media but its true incidence is difficult to establish (Idée et al. 2002). Pulmonary edema produced by contrast media could also be responsible for the increase in the pulmonary vascular resistance (PVR) caused by these agents (Morcos 2003). Experimental studies have shown that ioxaglate induced the largest increase in PVR of the isolated rat lung preparation and more marked pulmonary edema compared to other classes of contrast media (Sendo et al. 2000; Emery et al. 2001; Furuta et al. 2001, 2002; Tominaga et al. 2001). However, these experimental observations have not been confirmed in larger clinical studies (Idée et al. 2002).

The endothelial effect of high-osmolar ionic contrast media is of clinical importance in phlebography because after this procedure there is an increased frequency of thrombosis.

5 Platelets

Briefly, platelets adhere to exposed collagen, von Willebrand factor, and fibrinogen at the site of arterial injury (adhesion step). Adherent platelets are then activated by mediators such as thrombin, collagen, adenosine diphosphate (ADP), serotonin, etc. (activation step). Activated platelets degranulate and secrete chemotaxins, clotting factors, and vasoconstrictors, thereby promoting thrombin generation, vasospasm, and additional platelet accumulation (aggregation step) (Ferguson et al. 2000; Becker 2001). Therefore, when the interaction of contrast media with platelets is assessed, each of these stages in platelet physiology should be evaluated separately.

5.1 Experimental Effects

5.1.1 Platelet Adhesion

Grabowski et al. (1991a, b) showed that in vitro platelet adhesion/aggregation was inhibited in the order diatrizoate > ioxaglate > iohexol > saline. However, these effects were rapidly diminished because of hemodilution. In a baboon study (Markou et al. 2001), contrast media were found to inhibit platelet deposition on stents in the order ioxaglate > iohexol = iodoxanol > saline. Thus, all contrast media inhibit platelet adhesion, with ionic agents being more potent than non-ionic ones.

5.1.2 Platelet Activation by Thrombin

In vitro platelet activation by thrombin was inhibited by low-osmolar ionic contrast media, whereas non-ionic monomeric and dimeric contrast media did not affect it (Li and Gabriel 1997).

5.1.3 Direct Platelet Activation

Direct activation of platelets (i.e., degranulation and release of the procoagulant content of dense bodies and z-granules) was induced in vitro by non-ionic monomeric contrast media. Lesser activation was caused by high-osmolar ionic contrast media and there was no activation by low-osmolar ionic and non-ionic dimeric contrast media (Chronos et al. 1993; Corot et al. 1996). Chronos et al. (1993) showed that blood from patients anticoagulated with heparin and pretreated with aspirin in preparation for percutaneous coronary angioplasty (PTCA) showed the same pattern of non-ionic monomeric contrast medium-induced platelet activation as normal subjects.

5.1.4 Platelet Aggregation

An inhibitory effect of contrast media on platelet aggregation was first described by Zir et al. (1974) and has been widely investigated since. Both high- and low-osmolar ionic contrast media inhibit in vitro platelet aggregation (induced by mediators such as thrombin, ADP, or collagen) more than do non-ionic agents (monomeric or dimeric) (Eloy et al. 1991; Heptinstall et al. 1998). Potentiation of the antithrombotic effects of clopidogrel, an antiaggregant drug, has been found in rats with an ionic low-osmolar contrast medium but not with a non-ionic monomer (Labarthe et al. 2003).

5.2 Clinical Pharmacology Studies

Clinical pharmacology studies comparing the different categories of contrast media have produced more equivocal conclusions than in vitro and animal studies.

In one study of patients, no significant platelet activation (P-selectin expression) was found following left
ventriculography or coronary angiography with iohexol (Albanese et al. 1995). Similarly, Arora et al. (1991) and Brzoko et al. (1997) did not find a significant difference between ionic and non-ionic contrast media when platelet degranulation markers were measured in peripheral venous samples. Polanowska et al. (1992) reported an increase in the venous level of P-thromboglobulin following angiography with a high-osmolar contrast agent.

Conversely, following cardiac catheterization, Jung et al. (2002) found no platelet activation with ioxaglate, whereas serotonin release was detected following injection of a non-ionic monomer. Jaumdally et al. (2007) showed that iomeprol produced a minimal effect on soluble and physical indices of platelets within the coronary artery, primarily due to plasma volume expansion. Most of these studies, with the exception of those of Albanese et al. (1995) and Jaumdally et al. (2007), evaluated peripheral venous and not blood samples from close to the injection site. It is known that arterial catheterization itself may activate platelets.

Most clinical pharmacology studies of platelet aggregation have shown a higher antiaggregatory effect for ionic agents than non-ionic monomers, as confirmed by Eloy et al. (1991) and Dalby et al. (2002). However, Stormorken et al. (1991a, b) did not find a significant difference between ionic and non-ionic agents.

The clinical impact of these in vitro and experimental in vivo changes is debatable and is discussed in the section on coagulation.

In summary, there are no clinical data to suggest that the effect of non-ionic contrast media on platelets induces increased coagulation. The mechanisms responsible for the effects of contrast media on platelets are still unclear and clinically significant effects have not been shown.

6 Coagulation

6.1 In Vitro Effects of Contrast Media

All contrast media inhibit blood coagulation but to different extents. Prothrombin time, reptilase time, activated partial thromboplastin time, and recalcification clotting time are significantly increased in proportion to the dose of contrast medium (Eloy et al. 1991). Comparison of assays of fibropeptide A and thrombin-anthrombin complex between ionic agents (both monomeric and dimeric) and non-ionic monomers showed that coagulation times were shorter for non-ionic monomers, but were always longer than in the controls (Parvez and Moncada 1986; Engelhart et al. 1988; Corot et al. 1989; Rasuli et al. 1989; Grabowski et al. 1991a, b; Parvez and Vik. 1991; Idée et al. 2002).

The ionic dimer ioxaglate has anticoagulant activity similar to that of the ionic monomers (Eloy et al. 1991). In one study, the non-ionic dimer iodixanol was found to be significantly less anticoagulant than the non-ionic monomer iohexol (Corot et al. 1996), while in another study it was reported that iodixanol affected the bleeding time similarly to non-ionic monomers (Melton et al. 1995). However, the precise mechanisms responsible for this inhibition are still unclear. It has been suggested that the main factors are inhibition of activation of factor X, which leads to the formation of thrombin from prothrombin (Eloy et al. 1991; Fay and Parker 1998; Idée and Corot 1999) and inhibition of fibrin polymerization (Stormorken et al. 1986; Dawson et al. 1986; Fay and Parker 1998; Dawson 1999). Al Dieri et al. (2001, 2003) showed that ioxaglate blocks feedback activation of factors V and VIII, significantly inhibits platelet-dependent thrombin generation, and boosts the effect of abciximab, whereas iodixanol does not. Interference with the assembly of fibrin monomers by contrast media results in poor fibrin stabilization of clots (Engelhart et al. 1988; Chronos et al. 1993).

Therefore, ionic monomers and dimers have similar anticoagulant activity in vitro, which is more pronounced than that of non-ionic monomers and dimers. Non-ionic monomers probably have more anticoagulant effect than non-ionic dimers.

6.2 Clinical Trials

Clinical data are less easy to evaluate because of patient-related and procedure-related variabilities (state of the hemostatic system, condition of the vessel wall, use of guidewires, catheters, balloons, and stents). Because of the rapid clearance of contrast media, their anticoagulant effect is local rather than systemic and their effect may be not significant if measured in distant peripheral blood vessels.

Following the in vitro observation by Robertson (1987) of more frequent clot formation in blood contaminated syringes with non-ionic monomers than with ionic agents, a few case reports of thrombotic complications in diagnostic angiography with non-ionic monomers have been published (Bashore et al. 1988; Grollman et al. 1988; Millet and Sestier 1989). However, trials have shown no clinical evidence of significant differences in thrombotic complications when ionic agents are compared to non-ionic monomers for coronary angiography (Davidson et al. 1990; Schrader 1998).

Randomized trials comparing ioxaglate to non-ionic monomers during PTCA have produced conflicting results (Piessens et al. 1993; Grines et al. 1996; Esplugas et al. 1991; Malekianpour et al. 1998; Schrader et al. 1999; Fleisch et al. 1999; Danzi et al. 2003). In the two studies with the largest number of patients, one showed no significant difference between ioxaglate and iomeprol in the incidence
of sudden vessel occlusion (Schrader et al. 1999), whereas the other showed a trend toward less thromboembolic complications with ioxaglate compared to ioversol (Fleisch et al. 1999). Scheller et al. (2001) reported that patients undergoing stent placement had fewer acute and subacute stent occlusions when imaged using ioxaglate compared to multiple non-ionic agents. However, Danzi et al. (2003) reported that non-ionic monomers (iopamidol and iopromide) did not adversely affect stent patency when compared to ioxaglate. The considerable periprocedural use of antiplatelet agents may explain their results. A meta-analysis comparing non-ionic monomers to ioxaglate showed a significant reduction of coronary vessel abrupt occlusions with ioxaglate (Cucherat and Leizorovicz 1999). Iodixanol was compared to ioxaglate in three trials. In one, no significant differences with regard to major adverse cardiac events (MACE) were detected (Bertrand et al. 2000). In the second, high-risk patient group, less abrupt vessel occlusions ($p = 0.05$) were found with iodixanol (Davidson et al. 2000). This difference was more significant in patients who did not receive GpIIb/IIIa blockers. In the third, no significant differences between the two contrast media were found and there was no clear advantage with the use of an ionic contrast agent in a large population of patients undergoing percutaneous coronary intervention for both stable and unstable coronary artery disease (Sutton et al. 2002). A recent review showed no important difference in the incidence of clinically significant thrombotic events or MACE between isoosmolar and low-osmolar contrast media (Reiner 2010).

6.3 Contrast Media Interactions with Angiographic Devices

Interactions of contrast media with angiographic devices have been investigated both in vitro and in vivo. The syringe material greatly influenced the possibility of clot formation in syringes containing contrast media and blood. Glass was a more powerful activator of coagulation than plastic, and among the plastic syringes those made of styrene acrylonitrile activated coagulation more than those made of polypropylene. Furthermore, clots formed only in situations where there was very poor angiographic technique (Dawson et al. 1986). Teflon-coated catheters and guidewires are more thrombogenic than polyurethane and much more than polyethylene materials (Dawson 1999). Idée and Corot (1999) comprehensively reviewed the many factors influencing clotting in catheters, including the length of the procedure, blood/catheter contact time, volume of blood in the catheter, size and type of the catheter, type of contrast material, and degree of blood/contrast medium mixture in the catheter. Some of these factors are difficult to control or standardize in clinical studies.

Catheter and guidewire materials probably play a significant role in clinical studies of contrast media and coagulation. The use of equipment with technically improved surfaces will probably largely overcome this problem.

7 Fibrinolysis

Contrast media impede fibrinolysis and delay the onset of lysis by recombinant tissue-type plasminogen activator (rt-PA), urokinase, and streptokinase (Dehmer et al. 1995). This effect is reduced by increasing the concentration of the lysis agent. Contrast media cause fibrin to form in long or thin fibrils, which have a lower mass/length ratio and are more resistant to fibrinolysis (Parvez et al. 1982; Gabriel et al. 1991). In vitro studies have shown that diatrizoate and iohexol delay the onset of lysis induced by all lysis agents. However, ioxaglate delayed the onset of lysis by rt-PA and urokinase but not by streptokinase (Dehmer et al. 1995). Another in vitro study showed that thrombi formed with iodixanol and iohexol are larger and more resistant to thrombolysis compared to thrombi formed with ioxaglate (Jones and Goodal 2003). Bellemain-Appaix et al. (2012) showed that fibrin formed with iodixanol was stiffer and displayed more fibrin fibers than after ioxaglate or in controls. This resulted in a profound reduction in the lysis front velocity. In vivo studies in dogs showed that alteplase-induced thrombolysis could be delayed by iohexol and amidotrizoate, whereas ioxaglate had no significant effect (Pislaru et al. 1998). In a small group of patients undergoing pulmonary angiography, iohexol significantly increased plasma levels of PAI-1, an inhibitor of t-PA and urokinase, while ioxaglate did not (van Beek et al. 1994). A systematic review and meta-analysis investigated the proportion of patients with acute stroke experiencing recanalization after thrombolytic therapy who had received contrast media compared to those who had not. Eighteen studies were considered and recanalization rates were not significantly different between the two groups (Dani and Muir 2010). Other effects on fibrinolysis caused by interactions of contrast media with concomitantly given drugs are described in more detail in “Contrast Media and Interactions with Other Drugs and Clinical Tests”.

8 Conclusion

All contrast agents may alter the morphology and function of red blood cells. However, the overall effect of contrast media on red cells has not been shown to be of clinical...
importance. Similarly, the effect on white blood cells has not been shown to be clinically important. In patients with sickle cell anemia, there does not appear to be an increased risk of adverse events either with low or iso-osmolar iodine-based contrast agents, or with gadolinium-based agents.

In vitro studies have shown that non-ionic monomers cause more activation of platelets than ionic contrast media. Iso-osmolar dimeric contrast media have not been shown to activate platelet function. Clinical studies have not confirmed these in vitro observations.

Contrast media have cytostatic, cytotoxic, and apoptotic effects on endothelial cells. These effects are more evident with ionic contrast media, in particular high-osmolar agents, than with non-ionic media. Contrast media-induced endothelial injury may play a role in the pathophysiology of the effects of contrast media, including hemodynamic effects, thrombosis, and contrast media-induced pulmonary edema.

The risk of thrombosis induced by contrast media relates to the combined effect on platelets, endothelial cells, and coagulation factors. In clinical practice, high-osmolar contrast media can induce thrombosis after intravenous injection, mainly because of endothelial injury produced by the high osmolality. This effect is less with non-ionic low-osmolar and iso-osmolar contrast media.

All contrast media have anticoagulant properties, and ionic media are more anticoagulant than non-ionic compounds. Acute and subacute thrombus formation remains a topic of debate, including the use of low-osmolar ionic contrast media in preference to low-osmolar non-ionic contrast media in coronary interventions. However, the general consensus is that good angiographic technique is the most important factor in reducing thrombotic complications. Drugs and interventional devices that decrease the risk of thromboembolic complications during interventional procedures minimize the importance of the effects of contrast media (Aguirre et al. 1997).

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Effects of Iodine-Based Contrast Media on Thyroid Function

Aart J. van der Molen

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Abstract

Iodine-based contrast media contain free iodide in the solution, which may cause thyrotoxicosis in at-risk patients with Graves’ disease or thyroid autonomy. Systematic evaluation of thyroid function in all patients before iodine-based contrast medium administration is not necessary. It may, however, be appropriate to identify patients with a known nodular goiter, and to recommend follow-up tests of thyroid function for up to 2 years after they receive iodine-based contrast media.

1 Introduction

From time to time contrast medium or iodine-induced hyperthyroidism (IIHT) is brought to the attention of radiologists. Since contrast medium solutions contain some free iodide, contrast media may induce hyperthyroidism or thyrotoxicosis.

The two main reasons for development of thyrotoxicosis are preexisting Graves’ disease and thyroid autonomy. In Graves’ disease thyroid-stimulating autoantibodies enhance iodine uptake and thyroid hormone synthesis. In thyroid autonomy, the autonomous tissue is not under the control of thyroid-stimulating hormone (TSH) and, if subjected to high iodide loads, produces and secretes excessive thyroid hormone with or without a concomitant decrease in TSH. Iodine deficiency is an important factor in the development of thyroid autonomy and goiter. Therefore, iodine-induced thyrotoxicosis is more commonly seen in areas where the iodine intake is low.

2 Terminology

The terms iodine and iodide are often used interchangeably. Iodine is often used in the generic sense as in “iodine deficiency” or in describing diseases like “iodine-induced thyrotoxicosis”. Iodide refers to the metabolically important,
inorganic free form that can be present in excess for a number of reasons. Iodine enters the body in the form of iodide or iodate ions. Iodate is rapidly converted to iodide which can be trapped and organically bound in the thyroid gland.

The term hyperthyroidism is used to describe excessive secretion of thyroid hormone from the thyroid gland which may or may not become clinically symptomatic. Thyrotoxicosis is the preferred term for the clinical syndrome caused by excess thyroid hormone. This excess can be caused by endogenous or exogenous sources of iodide.

3 Iodine Deficient Areas

As iodine deficiency is an important factor in the development of thyroid autonomy and multinodular goiter, in iodine deficient areas the number of patients at risk for iodine-induced thyrotoxicosis is higher. There are still important geographical differences in iodine intake because of differences in national laws, fortification programs (e.g., iodized salt), and awareness (Fig. 1). Global WHO data covering 92% of the world’s population show that prevalence is intimately related to iodized salt intake, which is highest in the Americas. The prevalence of iodine deficiency in the general population has decreased in recent years, but is still lower in the Americas than in Europe, which has the highest prevalence worldwide (de Benoist et al. 2008; Andersson et al. 2012; Zimmermann and Andersson 2012).

The International Council for Control of Iodine Deficiency Disorders (ICCIDD) designated European countries with sufficient, or likely sufficient, and deficient, or likely deficient, iodine nutrition status (Table 1) (www.iccidd.org). More than 60% of nearly 600 million Europeans live in iodine deficient countries, which include countries such as Germany, France, Belgium, Italy, and Spain.

4 Free Iodide

According to the quality control regulations for producing water-soluble contrast media, the content of free iodide per ml is far below the total amount of (organically bound) iodine per ml. In a bottle with a contrast medium concentration of 300 mg l⁻¹, the permitted upper limit of free iodide is generally below 50 μg ml⁻¹ immediately after production and below 90 μg ml⁻¹ after 3–5 years of shelf-life. In most products the actual content of free iodide is less than one-tenth of these upper limits, depending on the time between production and date of use. For instance, a 150-ml dose of a contrast medium containing 10 μg ml⁻¹ provides 1,500 μg free iodide, equivalent to 10 times the recommended daily intake in adults.

In addition, it was shown (Rendl and Saller 2001) that iodine-based contrast media molecules can be de-iodinated in the body. The resulting amount of free iodide depends on the time that the contrast medium is circulating and is
The effects of iodine-based contrast media on thyroid function.

5 Effect of Contrast Media on Thyroid Function in Euthyroid Patients

5.1 Adults

In the mid-1990s (Hehrmann et al. 1996), it was reported that within 21 days of administration of large doses of contrast medium, there is a small decrease, followed by an increase within normal limits, in free thyroxine (T4) and a decrease, followed by a rapid increase (<5 days), within normal limits in TSH. In 102 euthyroid patients that underwent coronary angiography (Fassbinder et al. 2001a), subgroup analyses showed small increases in TSH in small glands but decreases in larger glands. Also a discrete increase in free T4 was seen in patients with large glands and low-normal TSH values. Another study of 22 patients specifically evaluated the early time period after contrast medium administration (Gartner and Weissel 2004). There were increases in TSH 3–5 days after contrast medium administration, with increases outside the normal range (18 %) in patients with basal high-normal TSH values. Thyroid hormone levels were unchanged. This suggests transient subclinical hypothyroidism, a condition more frequently seen in patients with autoimmune (Hashimoto) thyroiditis (Roberts and Ladenson 2004). Thus, in the majority of normal euthyroid patients no changes in thyroid functional parameters are seen, although transient subclinical hypothyroidism or hyperthyroidism may sometimes occur. However, administration of contrast media to a population of geriatric patients may lead to long-lasting subclinical hyperthyroidism with increased free T4 and decreased TSH for as long as 8 weeks after injection (Conn et al. 1996). This is thought to be caused by undiagnosed autonomous nodules in the thyroid glands of these elderly patients.

5.2 Neonates

In two large studies, the newborn infants of women evaluated during pregnancy with CT pulmonary angiography did not show disturbed neonatal TSH levels (Bourjeily et al. 2010; Rajaram et al. 2012). These results were substantiated in another small study (Atwell et al. 2008).

In newborns with immature thyroid glands excess iodine may block thyroid hormone synthesis. A systematic review of 11 studies of neonates who had received iodine-based contrast media found a trend toward increased TSH and decreased free thyroxine (FT4) levels, which was more marked in the premature infants. 8.3 % of term infants and 18.2 % of premature infants required treatment for hypothyroidism (Ahmet et al. 2009). See also “Pregnancy and Lactation: Intravascular Use of Contrast Media”.

6 Contrast Medium-Induced Thyrotoxicosis

6.1 Mechanism of Contrast Medium-Induced Thyrotoxicosis

Iodine is an essential requirement for thyroid hormone synthesis. The recommended daily intake for adults is about 150 μg. The thyroid gland has intrinsic regulatory mechanisms that maintain thyroid function even in the presence of iodide excess. When large amounts of iodide are given to subjects with normal thyroid function, the synthesis of thyroid hormones decreases transiently for about 2 days. This acute inhibition of thyroid hormone synthesis by the increased iodide concentration is called the Wolff-Chaikoff effect. Escape from, or adaptation to, the acute Wolff-Chaikoff effect is produced by blockage of the thyroid iodide trap. This reduces the thyroid iodide concentration because of a decrease in the sodium-iodide symporter (NIS) mRNA and protein expression.

### Table 1

<table>
<thead>
<tr>
<th>Country</th>
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0.01–0.15 % (1 h—1 week circulation time) of the amount of organically bound iodine administered. Biliary contrast media circulate longer and are metabolized at a greater rate resulting in the release of a significant amount of free iodide in the circulation. Therefore, the effects of biliary contrast media on the thyroid may be greater and persist longer than for the other water-soluble media, but since biliary media are no longer used clinically, this is now only of theoretical interest.
Excess iodide ingestion also reduces the release of thyroxine (T₄) and tri-iodothyronine (T₃) from the thyroid. This results in small decreases in serum T₄ and T₃ concentrations with compensatory increases in thyrotropin releasing hormone (TRH) and thyroxine stimulating hormone (TSH) concentrations.

Iodine-induced hyperthyroidism is not a single etiological entity. It may occur in patients with a variety of underlying thyroid diseases, the most important of which are Graves’ disease, and multinodular goiter in patients living in areas of iodine deficiency. Rare causes of hyperthyroidism include the presence of ectopic thyroid tissue (e.g., in the tongue or thorax), or abnormal autoregulation of thyroid tissue, as can occur in patients with well-differentiated papillary, and follicular thyroid carcinoma or its metastases (Roti and Uberti 2001). The exact pathophysiology and epidemiology of the complete spectrum of iodine-induced hyperthyroidism goes beyond the scope of this chapter, and has been reviewed elsewhere (Braverman 1994; Stanbury et al. 1998).

In addition to contrast media, other sources of iodide excess include disinfectants, secretolytic agents, the iodine-containing antiarrhythmic amiodarone, eye drops and ointments, seaweed, multi-vitamin preparations, skin ointments, toothpaste, etc. (Hehrmann et al. 1996).

6.2 Biochemical Diagnosis of Hyperthyroidism

Hyperthyroidism is defined as elevation of plasma free thyroxine (FT₄) or total tri-iodothyronine (T₃) level and suppression of thyroid-stimulating hormone (TSH) level (Martin and Deam 1996).

6.3 Prevalence of Contrast Medium-Induced Thyrotoxicosis

Little is known about the true prevalence of iodine-induced thyrotoxicosis caused by contrast medium. It was calculated (Rendl and Saller 2001) that in an iodine deficient country, 38 cases of thyrotoxic crisis (the most severe form of thyrotoxicosis) caused by contrast medium are seen per year while in the same year about 5 million contrast-enhanced studies are performed (0.0008 %). Two large studies in unselected populations in an iodine deficient area showed a prevalence of 0.25–0.34 % (Nolte et al. 1996; Hintze et al. 1999), while in an iodine sufficient area this figure is tenfold lower at 0.028 % (de Bruin 1994). In an iodine deficient population having CT, the percentages of latent and overt hyperthyroidism are estimated to be 5.8 and 0.8 %, respectively (Saam et al. 2005).

6.4 Clinical Symptoms of Thyrotoxicosis

Hyperthyroidism caused by free iodide in contrast media is usually self-limiting, but in rare cases, and in the presence of risk factors, the free iodide can lead to clinically significant thyrotoxicosis. Hyperthyroidism occurs more frequently in the elderly so the diagnosis may not be apparent, particularly in the presence of cognitive impairment (Martin and Deam 1996). Contrast medium-induced thyrotoxicosis cannot be differentiated clinically from other forms of thyrotoxicosis and, depending on the underlying risk factors, may give rise to symptoms such as weight loss, nervousness, easy fatigability, intolerance to heat, hyperkinesia, periodic paralysis, palpitations, and cardiac arrhythmias.

The most important effects of thyrotoxicosis are cardiovascular. It can aggravate preexisting cardiac disease and can also lead to atrial fibrillation, congestive heart failure, worsening of angina, thromboembolism, and rarely death. In the absence of preexisting cardiac disease, treatment of thyrotoxicosis usually returns cardiac function to normal (Dunn et al. 1998).

Palpitations are probably the most common cardiac symptom. They are caused by either sinus tachycardia or the development of supraventricular tachycardia, usually atrial fibrillation. Atrial fibrillation occurs in 15–20 % of patients with hyperthyroidism, compared with less than 1 % of euthyroid adults. Angina is another common symptom. It usually occurs in patients with known coronary disease, but angina from coronary spasm in previously healthy patients has also been reported. Dyspnea on exertion, pulmonary edema, and other signs of heart failure can also occur, particularly if cardiomyopathy has developed.

Thromboembolic events complicating atrial fibrillation may be the presenting symptom of thyrotoxicosis (Dunn et al. 1998; Roti and Uberti 2001). Tachycardia is the most common sign of thyrotoxicosis on physical examination, occurring in more than 40 % of patients on initial presentation. Other signs of a hyperdynamic circulation, such as systolic hypertension and prominent cardiac pulsations, are frequent.

6.5 Clinical Studies on Contrast Medium-Induced Thyrotoxicosis

There are very few studies dealing with the development of thyrotoxicosis following injection of contrast media. Patient populations and results may differ depending on whether the study was performed in an iodine-deficient or iodine-sufficient area.

A number of studies have been undertaken in areas without iodine deficiency. One study showed no effect on serum T₄, T₃, or FT₄ index up to 56 days after cardiac
catheterization using meglumine ioxaglate (Grainger and Pennington 1981). Seven patients with multinodular goiter, out of a cohort of 24,600 CT scans performed over a 3-year period, needed hospital admission because of clinically severe iodine-induced hyperthyroidism following administration of a total dose of 3–12 mg free iodide in non-ionic contrast media (de Bruin 1994). After CT of the thyroid using 100 ml iohexol, 8 of 22 patients with thyroid disease had a temporary change in thyroid function. Four patients showed increases in TSH levels, while, in a further four, temporary hyperthyroidism developed over a period of 1 month (Nygaard et al. 1998). In geriatric populations, iodine-induced thyrotoxicosis following contrast radiography with iopamidol 370 mgI/ml was the cause of 7 of 28 cases of hyperthyroidism seen over 20 months (Martin et al. 1993). Although the condition appeared self-limiting, it was associated with increased patient morbidity and prolonged hospital stay. In another study from the same group in 60 patients with hyperthyroidism over the age of 70 years, 23 % had been exposed to iodine-based contrast media within the previous 6 months. In 62 % of the patients hyperthyroidism was not suspected at admission (Martin and Deam 1996).

In an iodine-deficient area, the prevalence and pathogenesis of thyrotoxicosis following contrast media administration were evaluated between 1971 and 1979 (Stiedle 1989). In 89 (15 %) of 663 patients with thyrotoxicosis the condition could be related to iodine-based contrast media. The majority (95 %) occurred after 12 weeks. Goiter was present in 63 % of the patients and the majority of them were elderly. In a large study in unselected patients, only 2 of 788 developed hyperthyroidism within 12 weeks of coronary angiography (Hintze et al. 1999). Administration of non-ionic iodine-based contrast medium to 102 euthyroid patients did not lead to hyperthyroidism in any patient, despite the large number of nodularly transformed glands and patients with goiter (Fassbender et al. 2001a). The same study showed that thyroid morphology at ultrasound was not a prognostic indicator for the development of hyperthyroidism.

Marracini et al. (2013) measured free T₃, free thyroxine (T₄), and thyroid-stimulating hormone (TSH) in 1752 consecutive patients before administration of iodine-based contrast medium. Urinary free iodine was measured before and 24 h after contrast medium. In 17 patients with low T₃ syndrome, the thyroid hormone profile was determined 48 h after contrast medium. Patients were divided into 4 groups: euthyroid (60 %), low T₃ syndrome (28 %), hypothyroid (10 %), and hyperthyroid (2 %), and were followed up for an average of 63.5 months. Thyroid dysfunction was frequent in patients who received iodine-based contrast medium and low T₃ syndrome was the predominant abnormality. However, the clinical consequences appear to be limited in most patients, in agreement with the report by Thomsen and Faber (2012).

A large case-controlled study has looked at the relationship between iodine-based contrast media and incident thyroid disturbances. A review of 20 years data from a large US healthcare registry found 178 hyperthyroidism cases in a population of more than 4,500,000 individuals giving an odds ratio (OR) of 1.98 (Rhee et al. 2012). The calculated prevalence is similar to that in a Danish study, probably in the order of 0.0004 % so hyperthyroidism is a very rare adverse reaction, which is treatable. (Thomsen and Faber 2012). Systematic evaluation of thyroid function before iodine-based contrast medium administration in all patients would, therefore, be like looking for a needle in a hay-stack. It might, however, be appropriate to identify patients with a known nodular goiter, and to recommend follow-up thyroid function tests for up to 2 years after iodine-based contrast medium.

Iodine-induced thyrotoxicosis after iodine-based contrast agents does not seem to be a clinically significant problem in unselected patient populations or in euthyroid patients. It appears to be significant only in patients with previous thyroid disease or in patients at risk, especially in areas of iodine deficiency and in geriatric populations. In such patients, information about thyroid status may be of importance to the radiologist before they administer the contrast medium.

7 Prevention and Prophylaxis of Contrast Media-Induced Thyrotoxicosis

Prevention of iodine-induced thyrotoxicosis in patients at high risk is important because treatment with thyrostatic drugs is hindered by the high iodide levels in the blood, and there are more complications associated with treatment than in other forms of thyrotoxicosis.

In patients with risk factors, a strong indication for administering iodine-based contrast medium is essential. If there is manifest hyperthyroidism, administration of contrast medium is contraindicated. In other patients at increased risk, diagnostically equivalent alternative imaging methods not requiring iodine-based contrast media should be considered, e.g., ultrasound, MRI, scintigraphy, or unenhanced CT.

In thyroid autonomy, the amount of autonomous tissue is one of the key determinants of the risk of iodine-induced hyperthyroidism. The results of a previous Technetium scintigram have been used to quantify the amount of autonomous tissue to stratify risk (Emrich et al. 1993; Hehrmann et al. 1996; Fricke et al. 2004). However, this indication for scintigraphy fell into disuse when very sensitive TSH assays became available. To reduce the incidence of iodine-induced thyrotoxicosis further, it has been suggested that prophylactic drugs could be administered,
starting well before the examination. The subject of medical prophylaxis is controversial and recommendations are related to the presence or absence of iodine deficiency.

A number of indications and regimens have been suggested. Prophylaxis by perchlorate only in cardiac patients with a goiter and subnormal levels of TSH has been recommended (van Guldener et al. 1998). In a prospective randomized study in high-risk subjects with autonomy, prophylaxis with either perchlorate or thiamazole only prevented small increases in circulating thyroid hormone levels, but was not able to prevent hyperthyroidism completely and combination therapy was advised (Nolte et al. 1996). Administration of perchlorate and a thioamide class drug to elderly patients with suppressed serum TSH and/or palpable goiter has been suggested (Lawrence et al. 1999). It has been recommended that this combination is started the day before and continued for 2 weeks after contrast medium administration in patients with thyroid autonomy (Hehrmann et al. 1996; Lawrence et al. 1999; Rendl and Saller 2001), but others restrict its use to patients with high Tc-uptake levels (Joseph 1995). A sample combination protocol for prophylaxis is summarized in Table 2.

An alternative strategy is to monitor high-risk patients closely using biochemical tests (Nygaard et al. 1998). In euthyroid, not-at-risk patients, iodine-induced hyperthyroidism after coronary angiography was rare and therefore prophylactic therapy was not considered necessary (Lawrence et al. 1999). It has been recommended that this combination is started the day before and continued for 2 weeks after contrast medium administration in patients with thyroid autonomy (Hehrmann et al. 1996; Lawrence et al. 1999; Rendl and Saller 2001), but others restrict its use to patients with high Tc-uptake levels (Joseph 1995). A sample combination protocol for prophylaxis is summarized in Table 2.

8 Nuclear Medicine Studies and Contrast Media

For a long time, it has been known that giving iodine-based contrast media interferes with both diagnostic scintigraphy and radioiodine treatment. It is believed that the reduced uptake of the radioactive tracer is due to the amount of inorganic free iodide in the contrast medium solution which can range from 1 to 20 μg ml⁻¹ (Coel et al. 1975; Laurie et al. 1992).

8.1 Effect of Contrast Media on Thyroid Scintigraphy

In the nuclear medicine literature, after intravascular (water-soluble) contrast medium administration an interval of 3–6 weeks is advocated before scintigraphy, depending on the indication for the study, and on whether the patient is euthyroid or hyperthyroid (Wilson and O’Mara 1997; Martin and Sandler 2003). To avoid non-diagnostic studies, some hospitals use an interval as long as 3 months. As biliary contrast agents are metabolized and excreted more slowly, a longer interval of 2 months applies. For reasons of consistency and simplicity, a conservative period of 2 months for all types of water-soluble contrast media is recommended (“ESUR Guidelines on Contrast Media Version 8.1”) (van der Molen et al. 2004).

8.2 Effect of Contrast Media on Radio-Iodine Treatment

Before radio-iodine treatment with ¹³¹I, excess iodine should be avoided. Nuclear medicine literature and a European Association of Nuclear Medicine guideline advise that iodine-based water-soluble contrast media should be withheld for 1–2 months before radio-iodine treatment (Tuttle et al. 2003; European Association of Nuclear Medicine 2003), although some hospitals use even longer periods. Also, in preparation of patients iodine-containing antiseptics (e.g. povidone-iodine) should not be used 2 weeks before radioiodine treatment (Tuttle et al. 2003). It seems advisable to wait for 2 months after giving iodine-based water-soluble contrast media before undertaking radio-iodine treatment (“ESUR Guidelines on Contrast Media Version 8.1”) (van der Molen et al. 2004). Because of slower metabolism and excretion, biliary contrast agents should be withheld for a longer period of 3–4 months.

9 Effect of Impaired Renal Function

Water-soluble iodine-based contrast medium molecules are almost completely eliminated from the body within 24 h after injection in patients with normal renal function.
In patients with a decreased glomerular filtration rate (GFR), elimination is delayed and a longer period of interference with nuclear medicine studies can be expected. There is, however, no evidence of an increased risk of contrast medium-induced thyrotoxicosis in patients with severely reduced renal function (GFR < 20 ml/min). There is no evidence in the literature to suggest that deiodination leading to thyrotoxicosis occurs in patients with end-stage renal failure.

10 Nonvascular Routes of Administration

10.1 ERCP

Very little data exists on the administration of iodine-based contrast media by non-vascular routes. Most information is about contrast medium administration during endoscopic retrograde cholangiopancreatography (ERCP). Administration of iodine-based contrast agents into the biliary and pancreatic ducts during ERCP led to significant increases of serum levels of total iodine and free iodide and of urinary iodine excretion which returned to normal in 2–3 weeks in one study (Mann et al. 1994). Levels of TSH, free T₄, and free T₃ remained unchanged and no hyperthyroidism occurred. However, even a small amount of contrast medium given enterally can be associated with thyroid stimulation (Fassbender et al. 2001b). A decrease of TSH and an increase in total T₃, free T₄, and urinary iodine excretion was reported after ERCP, especially in patients with multinodular goiter. However, clinical symptoms of hyperthyroidism did not occur. A third study concluded that routine measurement of TSH and thyroid hormone levels before ERCP is not indicated, given the relatively low iodine load administered during the procedure (Mönig et al. 1999).

10.2 HSG

If hysterosalpingography (HSG) is performed with the oil-soluble contrast medium Lipiodol, there is a risk of clinical hypothyroidism, especially in patients that were subclinically hypothyroid before the procedure (Mekaru et al. 2008). The clinical importance of this is minor since in Europe most HSG for infertility is nowadays performed with iodine-based, water-soluble contrast media.

11 Conclusions

In patients without risk factors, contrast medium-induced thyrotoxicosis is very rare, and it is not necessary routinely to assess thyroid function or morphology before injection of iodine-based contrast media. However, a small group of patients is at increased risk and radiologists should be aware of the potential effects on thyroid function associated with administration of iodine-based contrast media. The history and physical examination are important, and risk factors should always be communicated to the radiologist via the request form.

Patients with Graves’ disease or multinodular goiter with thyroid autonomy are at increased risk of developing thyrotoxicosis after iodine-based contrast medium. In at-risk patients, the prevalence of contrast medium-induced thyrotoxicosis is significantly higher in iodine deficient areas (Rendl and Saller 2001). Also, iodine-induced thyrotoxicosis has been reported to occur more frequently in the elderly (Conn et al. 1996). Clinically, this thyrotoxicosis is most relevant in patients with an associated cardiovascular risk (Dunn et al. 1998). Nowadays, this geriatric population is exposed to diagnostic imaging, including imaging-guided intervention, more frequently than in the past because of major technological advances and increased longevity. Although thyroid stimulation is more common in these patients (even following nonvascular administration of contrast medium), the literature does not unequivocally prove an increased incidence of clinically relevant thyrotoxicosis in the elderly.

Nonetheless, in high-risk patients, knowledge of thyroid function (at least TSH) before a contrast-enhanced study is helpful. All at-risk patients should be monitored closely after the injection of an iodine-based contrast medium, preferably by endocrinologists (Nygaard et al. 1998). Selected patients (e.g., the elderly patient with multinodular goiter and concomitant cardiac disease) may benefit from prophylactic thyrostatic therapy. In patients with established hyperthyroidism, administration of iodine-based contrast media is contra-indicated. It is not advisable to use intravenous cholangiographic media in patients at risk (Rendl and Saller 2001).

A more frequently observed problem in clinical practice is decreased uptake of radioactive technetium and/or iodine in nuclear medicine studies following exposure to iodine-based contrast agents. This has compromised diagnosis of thyroid disorders and treatment of thyroid carcinoma. When urgent treatment is essential, gadolinium-based contrast media up to 0.3 mmol/kg body weight may be used in diagnostic studies (Thomsen et al. 2002; Christensen et al. 2000). However, this seldom results in satisfactory radiographic or CT examinations.

References


## Abstract
Water soluble iodine-based contrast media may increase the airway resistance, the pulmonary vascular resistance (PVR), and also the permeability of the microcirculation. The pathophysiology of these effects and their clinical importance are discussed in this chapter.

## 1 Introduction
The lung is an important target organ for the effects of water-soluble radiographic contrast media. The pulmonary circulation is the first important vascular bed exposed to contrast medium following intravenous injection and during the venous return after arteriographic examinations (Morcos 2003). Several adverse pulmonary effects may follow the intravascular injection of contrast media, including bronchospasm, pulmonary arterial hypertension, and pulmonary edema (Morcos 2000, 2003). In this chapter the effects of contrast media on airways resistance and pulmonary circulation following intravascular administration are discussed.

## 2 Effects of Contrast Media on Airways Resistance
The adverse respiratory reactions that have been reported with the intravascular use of contrast media include apnea, dyspnea, and bronchospasm (Littner et al. 1977, 1981; Dawson et al. 1983a; Longstaff and Henson 1985; Wilson and Davis 1988; Morcos 2000, 2003). Bronchospasm has been reported to be a contributory factor in 23 % of moderate and 5 % of severe adverse reactions to intravascular administration of radiographic contrast media (Morcos 2003). While symptomatic bronchospasm is rare, occurring in 0.01 % of patients (Morcos 2003), subclinical bronchospasm, detected by a fall in forced expiratory volume in 1 s...
FEV1, is common. It tends to be less pronounced with low-osmolar non-ionic contrast media (Littner et al. 1977, 1981; Dawson et al. 1983a; Longstaff and Henson 1985). However, Wilson and Davis (1988) found that both high-osmolar ionic and low-osmolar non-ionic contrast media produce a comparable fall in FEV and forced vital capacity. Experimental studies in the guinea pig found that the high-osmolar ionic monomer diatrizoate, the low-osmolar non-ionic monomer iopromide, and the iso-osmolar non-ionic dimer iotrolan did not induce a significant increase in airways resistance, and only the low-osmolar ionic dimer ioxaglate caused bronchospasm (Table 1) (Cipolla et al. 1995; Laude et al. 1999). Some retrospective clinical studies have also documented a higher incidence of allergy-like reactions with ioxaglate compared to other types of contrast media (Greenberger and Patterson 1991; Lasser et al. 1997; Laroché et al. 1998). However, there are no prospective clinical studies that have confirmed these observations. In one prospective clinical study, ioxaglate was found to be less likely than conventional high-osmolar agents to produce coughing during pulmonary arteriography (Smith et al. 1987).

The pathophysiology of the changes in airways resistance induced by contrast media remains obscure and could be multifactorial. The underlying mechanism may involve the release of bronchospastic mediators (such as histamine, endothelin (ET), 5-hydroxytryptamine, prostaglandins, thromboxane, and bradykinin), cholinesterase inhibition, vagal reflex, or a direct effect on the bronchi (Lasser et al. 1971; Ring and Sovak 1981; Dawson et al. 1983a; Assem et al. 1991; Szolar et al. 1995a, b; Laude et al. 1999; Peachell and Morcos 1998). Contrast media can cause the release of histamine, a potent bronchoconstrictor, from mast cells and basophils through a direct effect and indirectly by activating the complement system (Assem et al. 1991; Peachell and Morcos 1998). In vitro studies showed dose-dependent histamine release from human lung mast cells and basophils in response to all types of contrast media (Assem et al. 1991; Peachell and Morcos 1998). The high-osmolar diatrizoate induced the largest histamine release from human basophils and human lung mast cells. Ioxaglate and iotrolan caused histamine release from human basophils but not from human lung mast cells. The low-osmolar non-ionic monomer iopromide was a relatively ineffective activator of histamine release from both human lung mast cells and basophils (Table 1) (Peachell and Morcos 1998). The importance of histamine in causing contrast media-induced bronchospasm has not been proved conclusively. Experimental studies have shown that pretreatment with antihistamine H1 receptor antagonist did not prevent contrast media-induced increase in airways resistance (Cipolla et al. 1995; Laude et al. 1999). Pretreatment with prednisolone did not offer any protection against contrast media-induced bronchospasm either, despite the use of the two-dose regime recommended by Lasser et al. (1987) (Lasser 1981, 1998, Lasser et al. 1994; Cipolla et al. 1995; Laude et al. 1999). The use of corticosteroid prophylaxis to prevent contrast media reactions including bronchospasm is controversial. It has been suggested that the use of non-ionic agents alone is better at preventing all categories of reactions than the use of high-osmolar ionic agents with corticosteroid prophylaxis (Wolf et al. 1991; Dawson and Sidhu 1993).

The role of endothelin (ET) in mediating the bronchospastic effects of contrast media has also been investigated (Laude et al. 1999). ET is a potent smooth-muscle

<table>
<thead>
<tr>
<th>Effect</th>
<th>Most marked with following categories of contrast medium</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchospasm (Littner et al. 1981; Longstaff and Henson 1985; Cipolla et al. 1995; Laude et al. 1999)</td>
<td>Low-osmolar ionic dimer</td>
<td>Remains unknown</td>
</tr>
<tr>
<td>Pulmonary edema (Mare et al. 1984; Hauggaard 1996; Sendo et al. 2000; Tomina et al. 2001; Paul and George 2002; Morcos 2003)</td>
<td>Low-osmolar ionic dimer</td>
<td>Endothelial injury</td>
</tr>
<tr>
<td>Increase in pulmonary vascular resistance (Dawson et al. 1983a, b; Liss et al. 1996; Wang et al. 1997; Spitzer et al. 1999; Emery et al. 2001)</td>
<td>High-osmolar ionic monomer</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>Histamine release from lung mast cells (Peachell and Morcos 1998)</td>
<td>High-osmolar ionic monomer</td>
<td>Direct effect on the mast cells</td>
</tr>
<tr>
<td>Histamine release from basophils (Assem et al. 1991; Peachell and Morcos 1998)</td>
<td>High-osmolar ionic monomer</td>
<td>Direct effect on basophils</td>
</tr>
<tr>
<td></td>
<td>Low-osmolar ionic dimer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Iso-osmolar non-ionic dimer</td>
<td>Complement activation</td>
</tr>
</tbody>
</table>
constrictor and produces an increase in the vascular resistance and marked bronchospasm in the lung (Laude et al. 1999; Oldroyd and Morcos 2000). A pharmacologically effective dose of nonselective ET antagonist provided no protection against iodinated contrast media-induced bronchospasm in the guinea pig (Laude et al. 1999).

Leakage of fluids from the microcirculation into the lung tissues and bronchi may also cause an increase in airways resistance. Experimental studies in the guinea pig did not show fluid accumulation in the lungs and the bronchi in association with the contrast medium-induced rise in airways resistance (Laude et al. 1999). Also, aerosolized β2-adrenergic agonist treatment was able to reverse contrast medium-induced increases in airways resistance completely, suggesting that any airway narrowing resulting from edema is minimal (Cipolla et al. 1995; Laude et al. 1999).

A role for cholinesterase inhibition or the vagal reflex in mediating contrast medium-induced bronchospasm has not been confirmed. A direct effect of contrast medium on bronchial smooth muscle cells is possible, and the contribution of other bronchospastic mediators such as leukotrienes and kinins requires further investigation.

### 3 Effects of Contrast Media on Pulmonary Circulation

An increase in pulmonary artery pressure has been reported following the intravascular injection of contrast media (Frisinger et al. 1965; Almen et al. 1980; Mills et al. 1980; Peck et al. 1983; Schrader et al. 1987; Nicod et al. 1987; Rees et al. 1988; Tajima et al. 1994; Pitton et al. 1996; Sunnegardh et al. 1990; Sorenson et al. 1994). This sudden increase in pulmonary artery pressure is thought to contribute to the morbidity and mortality associated with pulmonary angiography, particularly in patients with pulmonary hypertension (Schrader et al. 1987; Nicod et al. 1987; Rees et al. 1988; Tajima et al. 1994; Pitton et al. 1996). There are conflicting reports in the literature about the mechanisms responsible for these effects (Almen et al. 1980; Peck et al. 1983; Schrader et al. 1984, 1987; Rees et al. 1988; Sunnegardh et al. 1990; Sorenson et al. 1994; Kuhtz-Buschbeck et al. 1997; Emery et al. 2001).

Some studies showed that the rise in pulmonary artery pressure is secondary to an increase in pulmonary vascular resistance (PVR) (Schrader et al. 1984; Emery et al. 2001), whereas others indicated that it is due to an increase in cardiac output associated with a decrease in pulmonary vascular resistance (Almen et al. 1980; Sunnegardh et al. 1990; Sorenson et al. 1994; Kuhtz-Buschbeck et al. 1997). In the studies that suggested a fall in the vascular resistance, the PVR was not directly measured and was calculated from the formula $PVR = \frac{(pulmonary \ artery \ pressure - pulmonary \ venous \ pressure)}{cardiac \ output}$. The increase in cardiac output was attributed to reduced peripheral vascular resistance of the systemic circulation caused by contrast medium-induced vasodilatation (Almen et al. 1980; Peck et al. 1983; Schrader et al. 1987; Sunnegardh et al. 1990; Sorenson et al. 1994; Kuhtz-Buschbeck et al. 1997). The fall in PVR could be due to an increase in the capacity of the pulmonary vascular bed by recruitment of closed vessels and active vasodilatation of pulmonary arteries (Emery et al. 2001). Experimental studies have shown that contrast media can induce both dilatation and constriction of pulmonary arteries, but in systemic vascular beds they induce mainly vasodilatation, except in the kidney where vasocostriction predominates (Morcos et al. 1998; Wang et al. 1997; Morcos 1998).

In the isolated blood-perfused lung of the normal rat, iodine-based contrast media (iopromide, ioxaglate, and diatrizoate) and hypertonic solutions of mannitol caused an overall rise in pulmonary artery pressure, reflecting an increase in the PVR. The maximum increase in pulmonary artery pressure was observed with the ionic dimer ioxaglate and the least increase with the non-ionic monomer iopromide (Emery et al. 2001). In isolated lungs from chronically hypoxic rats, where baseline pulmonary artery pressure and resistance are high, a slow rise in pulmonary artery pressure was observed in response to the contrast media (ioxaglate, iotrolan, and iopromide) (Emery et al. 2001). The rise in pulmonary artery pressure with ioxaglate was comparable to that with iotrolan but significantly greater than that with iopromide (Emery et al. 2001).

Surprisingly, the iso-osmolar iotrolan with the lowest vasoactivity induced a significant increase in the PVR in the isolated blood-perfused lung of both the normal and chronically hypoxic rat (Emery et al. 2001). High viscosity and rheological effects on red blood cells of iotrolan could be responsible for the observed increase in the vascular resistance of the isolated lung preparation, which is perfused with blood (Table 1) (Emery et al. 2001). The non-ionic monomer iopromide had the least effect on PVR of both the normotensive and hypertensive rat lung preparation (Emery et al. 2001). This is understandable as iopromide has low vasoactive properties including low viscosity. Its effects on the endothelium are minimal and are unlikely to cause pulmonary edema leading to an increase in PVR (Emery et al. 2001; Zhang et al. 2000). Clinical experience has also shown the absence of major hemodynamic effects with the use of low-osmolar non-ionic monomers in pulmonary angiography, even in patients with pulmonary hypertension (Zuckerman et al. 1996; Nilsson et al. 1998).
The increase in PVR induced by contrast media is most likely caused by a combination of active vasoconstriction of the pulmonary arteries, pulmonary edema, and possibly also by increased blood viscosity (Dawson et al. 1983b; Liss et al. 1996; Wang et al. 1997; Spitzer et al. 1999). The increased blood viscosity could be secondary to cellular effects (increased aggregation of red blood cells with non-ionic contrast media and rigidity with high-osmolar solutions) and the high viscosity of some of the contrast agents (Dawson et al. 1983b; Liss et al. 1996; Spitzer et al. 1999).

Contrast media may also activate adhesion of leucocytes to the endothelium, causing capillary plugging and stasis of red blood cells in the small vessels, and so precipitating an increase in vascular resistance (Emery et al. 2001).

In summary, iodine-based contrast media can induce an increase in PVR and a rise in pulmonary artery pressure through direct effects on the pulmonary circulation.

Non-ionic monomers produce the least increase in pulmonary artery pressure. The mechanisms responsible for the rise in pulmonary artery pressure remain poorly understood.

## 4 Contrast Medium-Induced Pulmonary Edema

Contrast medium-induced pulmonary edema is often secondary to endothelial injury, leading to an increase in the permeability of the microcirculation and accumulation of fluid in the lung (Morcos 2003).

Pulmonary edema produced by contrast media could also be responsible for the increase in the PVR and rise in pulmonary artery pressure caused by these agents. Experimental studies have shown that ioxaglate, which induced the largest increase in the PVR of the isolated rat lung preparation, is more cytotoxic to the vascular endothelium than diatrizoate and non-ionic contrast media (Table 1) (Benyon et al. 1994; Zhang et al. 2000; Emery et al. 2001). Ioxaglate induced greater pulmonary edema in the rat than non-ionic monomeric contrast media (Mare et al. 1984; Sendo et al. 2000; Tominaga et al. 2001). Interestingly, in the rat nitric oxide (Sendo et al. 2000) and estrogen (Tominaga et al. 2001) offered some protection against ioxaglate-induced pulmonary edema.

Pulmonary edema may also occur in patients with incipient cardiac failure, when large doses of contrast medium, particularly of high-osmolar agents, are used (Frisinger et al. 1965; Morcos 2003). Pulmonary edema has been reported in 10–20 % of cases of fatal reaction to intravenous infusion of contrast media (Hauggaard 1996; Paul and George 2002). Subclinical pulmonary edema without obvious signs or symptoms of respiratory distress is thought to be common after intra-vascular contrast media administration but its true incidence is difficult to establish (Morcos 2003).

### References


Gadolinium Chelates and Stability

Sameh K. Morcos

Abstract

The gadolinium ions which enhance the signals in MR images are very toxic, so in the contrast medium molecule they have to be strongly attached to a chelate to avoid adverse effects. The linear chelate molecules are open chains which can fold and unfold off the gadolinium ion with ease. In contrast, the macrocyclic chelate molecules are rigid rings of almost optimal size to cage the gadolinium ion. Experimental data, both in vitro and in vivo, and clinical observations, have confirmed the lower stability of the linear gadolinium-based molecules compared to the more stable macrocyclic agents.

1 Introduction

Extracellular gadolinium-based MRI contrast media are all chelates containing gadolinium ions (Gd\(^{3+}\)). Free gadolinium is highly toxic and can cause splenic degeneration, central lobular necrosis of the liver, enzyme inhibition, calcium channel blocking, and a variety of hematological abnormalities (Dawson 1999; Desreux and Gilsoul 1999). Therefore, it is crucially important that Gd\(^{3+}\) should be strongly attached to a chelate to avoid these toxic effects. There are six extracellular gadolinium-based contrast agents currently available for clinical use; there is another one which can be used both as organ specific and as an extracellular agent (Table 1) (Idee et al. 2006; Morcos 2007). The configuration of the molecule is either linear or cyclic and they are available as ionic or non-ionic preparations. There are differences in the chemical stability of these agents and in their liability to release free gadolinium ions. There is increasing evidence that the instability of gadolinium-based contrast agents could be an important factor in the pathogenesis of the serious complication of nephrogenic systemic fibrosis (NSF) (Morcos 2007, 2011). (“Nephrogenic Systemic Fibrosis and Gadolinium-Based Contrast Media”).
In this chapter, the chemical structure of gadolinium-based contrast agents is discussed, highlighting the important features that determine the stability of the molecules. The methods used to assess the stability of these agents are presented and the relevance of the stability of gadolinium-based contrast agents to the development of NSF is discussed.

## 2 Chemistry

The chemical principles involved in the production of Gd-chelates are presented in a simplified manner but with the intention of not compromising scientific accuracy. The gadolinium ion has nine coordination sites. **Coordination sites** represent the number of atoms or ligands directly bonded to the metal center such as Gd$^{3+}$. A **ligand** is a molecule or atom that is bonded directly to a metal center. The bonding between the metal center (Gd$^{3+}$) and the ligands is through **valent bonds** in which shared electron pairs are donated to the metal ion by the ligand. In an ionic linear molecule such as Gd-DTPA, Gd$^{3+}$ is coordinated with five carboxyl groups and three amino nitrogen atoms. The remaining vacant site is coordinated with a water molecule which is important for signal enhancement by the contrast agent in T1-weighted MR imaging (Dawson 1999; Desreux and Gilsoul 1999; Morcos 2007).

In contrast, the linear structure, which is a flexible open chain, provides weaker protection of the Gd ion (Idee et al. 2006; Morcos 2007). For the Gd$^{3+}$ to break free from a macrocyclic chelate, it must simultaneously break 5–6 coordination sites, while Gd$^{3+}$ can break free easily from the linear chelate because the separation occurs sequentially (Gibby et al. 2004).

All the macrocyclic agents available for clinical use, whether ionic or non-ionic, are derived from a 12-membered macrocyclic polyaminocarboxylate ring (Brücher and Sherry 2001). The number and identity of the side chains affect the stability of these agents and a minimum of three carboxylate side groups is necessary to form reasonably stable Gd-complexes (Fig. 1).

Because of charge neutralization in the complexation process, lanthanides prefer carboxylate donor atoms rather than etherial or alcoholic oxygens (Tweedle 1992; Kumar 1997). The negatively charged carboxylate oxygens are more powerful donor atoms than are uncharged hydroxy oxygen atoms (Tweedle 1992). Using the ionic macrocyclic complex Gd-DOTA, which has four carboxylate side groups, as a reference, when one carboxylate group is replaced with a hydroxy-propyl group [Gd-DOTA to Gd-HP-DO3A], the stability and binding constants decrease (Tweedle 1992; Brücher and Sherry 2001).

### Table 1

<table>
<thead>
<tr>
<th>Gadolinium-based contrast agent</th>
<th>Type</th>
<th>Thermodynamic stability constant</th>
<th>Conditional stability</th>
<th>Amount of excess (mmol l$^{-1}$)</th>
<th>Kinetic stability (dissociation half-life at pH 1.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadoversetamide, Gd-DTPA-BMEA</td>
<td>Non-ionic linear</td>
<td>16.6</td>
<td>15</td>
<td>28.4</td>
<td>Not available</td>
</tr>
<tr>
<td>Gadodiamide, Gd-DTPA-BMA</td>
<td>Non-ionic linear</td>
<td>16.9</td>
<td>14.9</td>
<td>12</td>
<td>35 s</td>
</tr>
<tr>
<td>Gadobutrol, Gd-BT-DO3A</td>
<td>Non-ionic cyclic</td>
<td>21.8</td>
<td>Not available</td>
<td>Not available</td>
<td>24 h</td>
</tr>
<tr>
<td>Gadoteridol, Gd-HP-DO3A</td>
<td>Non-ionic cyclic</td>
<td>23.8</td>
<td>17.1</td>
<td>0.23</td>
<td>3 h</td>
</tr>
<tr>
<td>Gadopentetate, Gd-DTPA</td>
<td>Ionic linear</td>
<td>22.1</td>
<td>18.1</td>
<td>0.4</td>
<td>10 min</td>
</tr>
<tr>
<td>Gadobenate, Gd-DTPA</td>
<td>Ionic linear</td>
<td>22.6</td>
<td>18.4</td>
<td>None</td>
<td>Not available</td>
</tr>
<tr>
<td>Gadoterate, Gd-DOTA</td>
<td>Ionic cyclic</td>
<td>25.8</td>
<td>18.8</td>
<td>None</td>
<td>&gt;1 month</td>
</tr>
</tbody>
</table>

In this chapter, the chemical structure of gadolinium-based contrast agents is discussed, highlighting the important features that determine the stability of the molecules. The methods used to assess the stability of these agents are presented and the relevance of the stability of gadolinium-based contrast agents to the development of NSF is discussed.
of the sterically uncrowded hydroxypropyl group of Gd-HP-DO3A with the bulky 2,3-dihydroxy-(1-hydroxymethyl)-propyl group to form Gd-BT-DO3A results in further destabilization of the complex. The bulky side chain destabilizes binding interaction between Gd$^{3+}$ and each of the three carboxylate side arms (Kumar 1997). The bulky chain is also more acidic than the hydroxypropyl group and weakens the binding with Gd$^{3+}$. Lanthanides such as Gd$^{3+}$ behave like typical “hard” acids and interact preferentially with hard bases rather than with softer bases (Kumar 1997; Brücher and Sherry 2001). Therefore, increasing the acidity of the side chain decreases the stability of the Gd-chelate (Kumar 1997; Brücher and Sherry 2001). Based on these chemical principles, the stability of the three available macrocyclic agents follows the order of DOTA $>$ HP-DO3A $>$ BT-DO3A (Morcos 2007). However, it is fair to state that all macrocyclic agents available for clinical use are quite stable in comparison to the linear gadolinium chelates.

3 In Vitro Measurements to Assess Stability

The measurements used to assess the stability of the chelate molecules are: the thermodynamic stability constant (measured under very alkaline conditions (pH $\sim$ 11), because at this pH there are no competing hydrogen ions for the chelate and a theoretical maximum stability for the chelate is obtained), the conditional stability constant (measured at physiological pH of 7.4), and the kinetic stability (dissociation half-life under very acidic conditions (pH 1)) (Gibby et al. 2004; Rofsky et al. 2008). The details of how to obtain these measurements are beyond the scope of this chapter. The higher the value of these measurements, the higher is the stability of the molecule (Idee et al. 2006; Morcos 2007).

![Fig. 1](image.png)

Table 2 Dissociation half-life ($T_{1/2}$) of gadolinium-based contrast agents under the same laboratory conditions (Port et al. 2008)

<table>
<thead>
<tr>
<th>Gadolinium-based contrast agents</th>
<th>T$\frac{1}{2}$ pH 1.2</th>
<th>T$\frac{1}{2}$ pH 1</th>
<th>T$\frac{1}{2}$ pH 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temp</td>
<td>37$^\circ$</td>
<td>37$^\circ$</td>
<td>25$^\circ$</td>
</tr>
<tr>
<td>Gadoterate meglumine</td>
<td>85 h</td>
<td>23 h</td>
<td>338 h</td>
</tr>
<tr>
<td>Gadobutrol</td>
<td>18 h</td>
<td>7 h</td>
<td>43 h</td>
</tr>
<tr>
<td>Gadoteridol</td>
<td>4 h</td>
<td>1.6 h</td>
<td>3.9 h</td>
</tr>
<tr>
<td>All linear chelates</td>
<td>ND</td>
<td>ND</td>
<td>&lt;5 s</td>
</tr>
</tbody>
</table>

The amount of excess chelate in the gadolinium-based contrast agent preparations is another marker of the stability of these agents. A large amount of excess chelate is present in agents of low stability (Green and Krestin 2006). The excess chelate is included in the preparation to ensure the absence of free Gd$^{3+}$ in solution. The addition of excess chelate to gadodiamide (non-ionic linear chelate) dramatically reduces the acute toxicity of non-formulated preparations (no excess chelate) by a factor of 2.5 as shown by acute toxicity studies (intravenous LD$_{50}$) (Idee et al. 2006).

As expected from the chemical structure, the stability measurements confirm the superior stability of the ionic macrocyclic chelate and the low stability of the non-ionic linear chelates (Morcos 2007). The ionic macrocyclic chelate has the highest stability values and the longest dissociation half-life and no excess chelate is required in the commercial preparation (Table 1). In contrast, the non-ionic linear chelates have a short dissociation half-life, the lowest stability values, and the highest amount of excess chelate (Table 1) (Morcos 2007). A study evaluating the dissociation half-life of gadolinium-based contrast agents under the same laboratory conditions confirmed that the ionic macrocyclic chelate had the highest kinetic stability followed by the non-ionic macrocyclic chelates, with the linear chelates having the lowest kinetic stability (Port et al. 2008) (Table 2).

The dissociation of gadolinium-based contrast agents incubated in human serum at 37 $^\circ$C is another suitable method for predicting the stability of these agents in vivo. The highest release of gadolinium (Gd$^{3+}$) was observed with the non-ionic linear chelates gadodiamide and gadoversetamide. The addition of phosphate to serum markedly increased the release of Gd$^{3+}$ and the total amount of Gd$^{3+}$ released at day 15 increased from 20 % to around 35 % of the total dose of these agents. With the ionic linear chelate gadopentetate dimeglumine, phosphate did not increase the total amount of Gd$^{3+}$ released, which remained at 2 %, but the speed of the release was increased in day 1 to 2 % and remained at this level up to day 15. The smaller release of free Gd$^{3+}$ from the ionic linear chelates compared to the non-ionic chelates is due to a higher thermodynamic stability of the former. No release of Gd$^{3+}$ was observed with...
the macrocyclic gadolinium-based contrast agents even after phosphate was added to the serum. This study again confirmed the high stability of the macrocyclic gadolinium-based contrast agents and showed that the non-ionic linear chelates have the lowest stability (Frenzel et al. 2008).

4 In Vivo Measurements to Assess Stability

There are several factors in vivo, such as endogenous ions, enzymes, and other biological elements that may work simultaneously to dissociate the Gd-chelate with unpredictable effects. Therefore, it has been suggested that ex vivo data are not reliable to predict the behavior of gadolinium-based contrast agents in vivo as the conditions under which measurements are obtained differ from those in vivo (Tweedle 2007). However, dissociation half-life under acidic conditions has been accepted as a reliable ex vivo measurement that can predict the stability of these agents in vivo (Wedekin et al. 1992).

Retention of Gd in tissues has been used to assess the stability of Gd-CM in vivo. Once the Gd cation dissociates from the chelate, it is immediately carried away by endogenous anions such as citrates and phosphates and is deposited in the body tissues, where it can persist for long periods of time. In the chelated form, virtually all the injected Gd is eliminated from the body by 5 days after administration. Therefore, most of the Gd detected in the body 3–8 days after administration of a gadolinium-based contrast agent is likely to have been released from the chelate (Gibby et al. 2004). Thus, the higher the retention of Gd in tissues, the lower is the stability of the gadolinium-based contrast agent.

In rats and mice with normal renal function, Gd retention in the tissues 2 weeks after injection of the non-ionic linear chelate gadodiamide was three times greater than that observed with the ionic linear chelate Gd-DTPA. Gd retention in tissues was minimal with two of the macrocyclic agents tested, Gd-DOTA and Gd-HP-DO3A, and the least retention was observed with the non-ionic macrocyclic agent Gd-HP-DO3A (Wedekin et al. 1992; Tweedle et al. 1995). Rats with normal renal function were given repeated injections of gadolinium-based contrast agents for 4 weeks to simulate the gadolinium exposure of patients with severe renal impairment. Gadolinium retention in the skin, liver, and femur was 30 times greater with a non-ionic linear chelate than with the macrocyclic compounds (Sieber et al. 2008). When rats with normal renal function were given gadolinium-based contrast media on five consecutive days, small amounts of gadolinium were retained in the skin at 1 year. The greatest amounts were retained with the non-ionic linear agents, while, 24 days after injection, the amounts retained with the macrocyclic agents were similar to the animals which were not given contrast medium. (Pietsch et al. 2009). In rats with subtotal nephrectomy which received intravenous gadolinium-based contrast agents for five consecutive days, tissue relaxometry measurements indicated in vivo dissociation of the non-ionic linear gadolinium-based contrast agent gadodiamide while the ionic macrocyclic agent gadoterate remained stable (Fretellier et al. 2011). In a recent study in rats with subtotal nephrectomy, gadodiamide caused a 40 times greater increase in skin gadolinium than the macrocyclic agent gadoterate (Haylor et al. 2012).

Clinical studies have also showed that gadodiamide leaves 2–4 times more Gd$^{3+}$ in the bone than Gd-HP-DO3A in patients with normal renal function (White et al. 2006).

In summary, animal studies and clinical data have confirmed the ex vivo measurements, which indicate that the least stable agents are the non-ionic linear chelates.

5 Transmetallation

Transmetallation of gadolinium-based contrast media leads to release of free gadolinium by replacement of the Gd$^{3+}$ within the chelate molecule by body cations such as iron, copper, zinc, and calcium (Tweedle et al. 1988; Laurent et al. 2001). Only zinc can displace a significant amount of Gd$^{3+}$, because its concentration in the blood is relatively high (55–125 µmol l$^{-1}$) whereas copper is present in very small amounts (1–10 µmol l$^{-1}$) and calcium ions have low affinity to organic ligands (Laurent et al. 2001). Iron ions are tightly bound by the storage proteins ferritin and hemosiderin and are not available for transmetallation with Gd$^{3+}$ (Cacheris et al. 1990). Transmetallation between Gd$^{3+}$

![Fig. 2](image-url)
and zinc results in the formation of zinc chelate, which is excreted in urine. The released Gd$^{3+}$ becomes attached to endogenous anions, such as phosphate, citrate, hydroxide, or carbonate, which deposit in the tissues as insoluble compounds (Fig. 2) (Gibby et al. 2004). In vivo (Corot et al. 1998), in vitro (Laurent et al. 2001, 2006), and human studies (Kimura et al. 2005; Puttagunta et al. 1996) have shown that linear chelates, particularly the non-ionic ones, cause a large increase in zinc excretion in urine. The non-ionic linear chelate gadodiamide induced a decrease of 32% of plasma zinc after a single injection in healthy volunteers (Puttagunta et al. 1996). This is thought to be secondary to transmetallation and the presence of excess chelate in the gadodiamide preparation. In patients undergoing contrast-enhanced MRI examination, gadodiamide caused a large increase in zinc excretion in the urine, which was almost three times greater than that induced by the ionic linear molecule Gd-DTPA (Kimura et al. 2005). In comparison, the ionic macrocyclic Gd-DOTA had no effect on zinc excretion (Kimura et al. 2005). Ex vivo studies have also confirmed that all macrocyclic gadolinium-based contrast agents are insensitive to transmetallation by zinc ions compared to the open-chain complexes (Laurent et al. 2001, 2006).

6 Stability and Nephrogenic Systemic Fibrosis

Gadolinium-based contrast agents are eliminated from the body through the kidneys and their biological half-life in patients with normal renal function is 1.5 h. In patients with advanced renal impairment, half-life can be prolonged to 30 h or more (Thomsen et al. 2006). Patients on hemodialysis advanced renal impairment, half-life can be prolonged to patients with normal renal function is 1.5 h. In patients with body through the kidneys and their biological half-life in Gadolinium-based contrast agents are eliminated from the urine. The released Gd$^{3+}$ becomes attached to compounds (Fig. 2) (Gibby et al. 2004). In vivo (Corot et al. 1998), in vitro (Laurent et al. 2001, 2006), and human studies (Kimura et al. 2005; Puttagunta et al. 1996) have shown that linear chelates, particularly the non-ionic ones, cause a large increase in zinc excretion in urine. The non-ionic linear chelate gadodiamide induced a decrease of 32% of plasma zinc after a single injection in healthy volunteers (Puttagunta et al. 1996). This is thought to be secondary to transmetallation and the presence of excess chelate in the gadodiamide preparation. In patients undergoing contrast-enhanced MRI examination, gadodiamide caused a large increase in zinc excretion in the urine, which was almost three times greater than that induced by the ionic linear molecule Gd-DTPA (Kimura et al. 2005). In comparison, the ionic macrocyclic Gd-DOTA had no effect on zinc excretion (Kimura et al. 2005). Ex vivo studies have also confirmed that all macrocyclic gadolinium-based contrast agents are insensitive to transmetallation by zinc ions compared to the open-chain complexes (Laurent et al. 2001, 2006).

7 Conclusion

The chemical structure of gadolinium-based contrast agents determines their stability. The least stable gadolinium-based contrast agents are the non-ionic linear chelates and the most stable are the macrocyclic chelates. The stability of the Gd chelate used is an important factor in the pathogenesis of NSF.

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# Diagnostic Efficacy of Gadolinium-Based Contrast Media

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## Abstract

Since the introduction of gadolinium-based contrast agents, multiple studies have shown that they improve the diagnostic efficacy of MRI significantly. Compared to unenhanced MRI, all agents help to improve the detection and delineation of lesions and so alter the diagnosis in up to 40% of patients. Doubling or tripling the standard dose of 0.1 mmol kg$^{-1}$ body weight may be beneficial for particular indications, such as brain perfusion, equivalent single dose MRI study for brain metastasis or small vessel MR angiography. Comparative studies do not show clinically significant differences in diagnostic efficacy between the various extracellular gadolinium-based contrast media. Agents at a higher concentration, or which bind protein, may be relatively more suitable for particular applications, such as dynamic contrast MRI. Gadoxetate disodium provides improved liver diagnosis. It has a primary role in the characterization of benign liver lesions and is an important problem-solving or presurgical tool in the diagnosis and management of liver metastases and hepatocellular carcinoma.

## 1 Introduction

After the invention of MRI in the early 1970s, it was believed that the multiple variable image acquisition parameters would produce sufficient intrinsic image contrast to make contrast agents unnecessary. However, in the late 1970s and early 1980s, experiments with a number of paramagnetic compounds led to the first MR images using gadopentetate dimeglumine by Schering AG (now Bayer Healthcare) and the University of California at San Francisco, which were shown at the Society for Magnetic Resonance in Medicine meeting in 1983. It was not until the beginning of 1988 that gadopentetate dimeglumine was introduced to the market, and within a short time contrast-enhanced MRI as a routine procedure became a clinical reality (de Haen 2001).
Since the introduction of gadopentetate dimeglumine, a number of other extracellular Gd-based contrast agents have been introduced. These agents together with their most important physicochemical data are summarized in “Contrast Media Classification and Terminology”.

## 2 Terminology and Populations

In the era of evidence-based medicine, it is important to understand the terminology used. The terms efficacy, effectiveness, and efficiency all have different meanings (Haynes 1999).

Efficacy (“Can it work?”) refers to the extent that contrast media do more good than harm under ideal conditions. With optimized clinical trial conditions, the effects are usually studied in selected populations in which confounding factors such as concomitant medications, interventions, etc. are limited as much as possible.

Effectiveness (“Does it work in practice?”) refers to the extent that contrast media do more good than harm under everyday conditions in routine clinical practice. The criteria for trials studying effectiveness are much more relaxed, and concomitant medications and interventions, etc. are permitted. While efficacy trials are designed to study causal relationships, effectiveness trials study management of disease. Ineffectiveness of a specific intervention, such as the use of contrast media, may therefore not only relate to its efficacy, but also to other factors such as the particular clinical setting, provider compliance, patient adherence, reimbursement, etc.

Finally, efficiency (“Is it worth it?”) measures the effect of an intervention in relation to the resources it consumes. Trials of efficiency are commonly referred to as cost-effectiveness trials.

## 3 Efficacy in Single Dose Administration

The value of using extracellular gadolinium-based contrast agents in neurological, spinal, cardiac, abdominal, and vascular imaging has been described in many clinical studies in the literature. Most of the specific quantitative efficacy data reviewed in this chapter come from the clinical trials necessary for registration of these agents. In the first section, only studies that deal with a particular agent are described.

### 3.1 Standard (0.5 M) Concentration Agents

Specific efficacy data were published for gadopentetate dimeglumine in the late 1980s and early 1990s, especially for brain and spinal applications. First results using T1-weighted (T1w) spin echo sequences showed enhancement that made small posterior fossa tumors more conspicuous (Stack et al. 1988). In the brain, gadopentetate revealed many lesions not shown by unenhanced imaging (Hesselink et al. 1988; Russell et al. 1989), and the diagnosis was changed in up to 37% of patients (Runge et al. 1988; Russell et al. 1989). In the spine, gadopentetate was especially helpful for intradural tumors (Stimac et al. 1988), providing additional information in almost all cases and changing the diagnosis in 30% of patients (Sze et al. 1990). Gadopentetate administration in infants and children also led to improved tumor detection and lesion conspicuity (Bird et al. 1988; Elster and Rieser 1989; Eldevik and Brunberg 1994). As a result of the immature renal function in infants, the imaging time window is significantly prolonged (Elster 1990). In infants and children, gadolinium-based contrast agents should be used selectively, based on the findings of the clinical examination and unenhanced imaging (Elster and Rieser 1989; Eldevik and Brunberg 1994). In MR angiography (MRA), a review of more than 4,000 patients across a variety of vascular territories showed good efficacy of gadopentetate in doses of 0.1–0.3 mmol kg\(^{-1}\) (Goyen and Debatin 2004).

For the renal arteries, a dose of 0.1 mmol kg\(^{-1}\) is sufficient (Heverhagen et al. 2009), while for the peripheral arteries, the contrast medium dose can be reduced to 0.1 mmol kg\(^{-1}\) when scanned at 3T (Habibi et al. 2008).

In the abdomen, gadopentetate can be used effectively for multiple indications and it can also be used as an oral contrast agent for bowel imaging. When combined with pineapple juice, it is an effective agent to lower signal intensity in the duodenum during MR cholangiopancreatography (MRCP) (Duarte et al. 2012). The macrocyclic agent gadoterate meglumine can be used for multiple indications, and has a good safety profile, including in small children (Emond and Brunelle 2011), and patients with chronic kidney disease (Deray et al. 2013). In brain imaging, its use improved the definition of pathological lesions and so improved sensitivity and specificity (Parizel et al. 1989). In vascular imaging, it produced better definition between mural thrombus and slow flow in time-of-flight MRA (Laissy et al. 1995). In children, gadoterate was helpful for diagnosing tumors in the brain and spine (Lipski et al. 1990). In MRA, multiple studies in non-coronary vascular territories have shown the superiority of contrast-enhanced MRA over time-of-flight MRA at 1.5T and 3T (Kang et al. 2010).

After administration of gadoteridol (the first non-ionic agent on the market), additional diagnostic information was obtained in the majority of patients, making a change in diagnosis possible in 29.4% of cranial, 33.5% of spinal, and 35.1% of head and neck studies (Runge et al. 1990, 1991a, b, 1992; Zoarski et al. 1993). In children, the benefit...
was even greater in the brain than in the spine, with brain diagnosis modified in 48 % and spinal diagnosis modified in 20 % (Ball et al. 1993). Efficacy was not reduced by using higher doses (Carvlin et al. 1992). Early studies using enhanced time-of-flight intracranial MRA showed a more limited benefit, with additional findings only changing the diagnosis in 8 % of patients (McLachlan et al. 1994).

Use of the non-ionic, linear agent gadodiamide improved lesion detection and delineation, which facilitated diagnosis in the brain or head and neck in the majority of patients (Kaplan et al. 1991; Sze et al. 1991, Aslanian et al. 1996; Ekholm et al. 1996, 2001). In large, multicenter studies it was shown that its use could change the diagnosis in 17.0–28.6 % of patients (Sze et al. 1991, Aslanian et al. 1996). In children, efficacy was similar, and in infants efficacy was good (Marti-Bonmati et al. 2000). In older children, imaging after gadodiamide gave additional diagnostic information in 65–82 % of cases (Lundby et al. 1996; Hanquinet et al. 1996). Phase-3 studies of MRA of the renal and peripheral arteries showed good results with 0.1 mmol/kg doses of gadodiamide compared to noncontrast MRA, and equivalent to intra-arterial digital subtraction angiography (IA-DSA) (Bui et al. 2010; Garovic et al. 2010). For renal arteries, double dose MRA at 1.5T outperformed single dose studies at 3T (Herborn et al. 2008).

Experience with gadoversetamide is limited. Like the other agents, administration in adults and children resulted in increased diagnostic confidence and better delineation of brain pathology (Grossmann et al. 1998; Lowe et al. 2006). Diagnosis of acute and chronic myocardial infarction can be done safely and well with doses of 0.2 mmol kg⁻¹ (Kim et al. 2008; Huber et al. 2008).

### 3.2 High (1.0 M) Concentration and Protein-Binding Agents

While all the agents already discussed are available in a 0.5 M concentration, gadobutrol was introduced to the market in a 1.0 M concentration to improve the gadolinium flux during contrast agent injection for newer applications such as MR perfusion imaging and contrast-enhanced MR angiography.

In routine brain imaging, it was found that a 0.1 mmol kg⁻¹ dose (i.e., half the volume of the other agents) was sufficient (Lemke et al. 1997), but in brain perfusion studies better results could be achieved with a 0.3 mmol kg⁻¹ dose (Benner et al. 2000). Compared to gadobutrol in a 0.5 M formulation, the 1.0 M concentration produced a sharper contrast peak and improved quality and superior contrast in the relative Cerebral Blood Flow and Mean Transit Time parameter maps (Tombach et al. 2003). In multiple studies, the use of gadobutrol for contrast-enhanced aortoiliac or total body MRA had high sensitivity (92–96 %) and high specificity (89–97 %). There was excellent interobserver agreement and comparable performance for therapy planning using intra-arterial DSA (Schäfer 2003, 2007; Hentsch et al. 2003; Herborn et al. 2004; Mohrs et al. 2004).

**Gadobenate dimeglumine** was initially developed for liver imaging and the results were better than dynamic MRI (Marin et al. 2009; Morana et al. 2011). It has a slightly higher R1- and R2-relaxivity in vitro, but because of protein binding its relaxivity in blood is almost 50 % higher than gadopentetate (“Contrast Media Classification and Terminology”). The beneficial effect of this increased relaxivity was soon investigated in other applications, such as brain imaging, perfusion MR, and MRA. Using gadobenate in brain studies improved the detection and delineation of lesions and increased diagnostic confidence (Schneider et al. 2001; Baleriaux et al. 2002). In brain perfusion, the increased R2-relaxivity allowed good T2⁎ perfusion MRI and post-processed maps, even with a dose of 0.1 mmol kg⁻¹ (Cotton 2006).

Contrast-enhanced MRA significantly increases diagnostic quality compared to unenhanced MRA. Diagnostic quality in many vascular beds is better at 0.1 mmol kg⁻¹ than at lower doses (Schneider et al. 2007). A further dose increase has no clinically relevant benefit (Kroencke et al. 2002; Wikstrom et al. 2003). In the runoff vessels, MRA enhanced with gadobenate led to improved sensitivity and specificity for clinically relevant (>50 %) stenoses compared to time-of-flight MRA (Thurnher et al. 2007). In the renal arteries, single dose gadobenate gave good sensitivity for clinically significant renal artery stenosis (Soulez et al. 2008). For the diagnosis of internal carotid artery stenosis, 3D contrast-enhanced MRA correlated better with 3D rotational angiography than did intra-arterial (2D) DSA (Anzalone et al. 2005).

### 4 Efficacy in Triple versus Single Dose Administration

For a number of agents, higher dose or dose accumulation studies have been performed to improve efficacy. Doses up to 0.3 mmol kg⁻¹ have been studied in the brain for diagnosing metastases and for MR angiography.

In the brain, gadopentetate in 0.3 mmol kg⁻¹ doses was associated with an improved contrast-to-noise ratio (CNR) and better visual assessment ratings (Haustein et al. 1993). The number of metastases detected increased significantly by 15 and 43 %, when 0.2 and 0.3 mmol kg⁻¹, respectively, were administered (van Dijk et al. 1997). However, triple doses gave no additional benefit when the single dose study was negative, but were helpful where MRI findings were...
equivocal or when a single dose study showed a solitary lesion (Sze et al. 1998). More recent studies of MRA showed no benefit of higher doses for vessel enhancement, but vessel contrast improved. In large vessels like the abdominal arteries (Heverhagen et al. 2007) or the carotids (Jourdan et al. 2007), a dose of 0.1 mmol kg\(^{-1}\) is considered sufficient.

A high dose of gadodiamide resulted in better delineation of pathologic structures and tumor size in the brain with increasing contrast agent dose (Demaerel et al. 1994). In peripheral MRA, high doses improved sensitivity and specificity, and the depiction of collateral circulation was similar to intra-arterial DSA (Krause et al. 2005).

With gadoteridol, brain lesions were also shown better at higher dose with improved lesion detection (Runge et al. 1992; Yuh et al. 1992, 1994, 1995). In a preliminary study, additional information from high dose gadoteridol led to a potential modification in the treatment of 35 % of patients, which was likely to be cost-effective (Yuh et al. 1992; Mayr et al. 1994).

High doses of gadobutrol can be administered with relatively smaller volumes or lower injection rates. The added benefit from triple dose imaging was less than that between standard dose imaging and unenhanced MRI. Nevertheless, the added information from triple dose examinations could change treatment in up to 20 % of patients (Lemke et al. 1997; Vogl et al. 1995). Application of Magnetization Transfer combined with a single dose may be equivalent to triple dose imaging (Knauth et al. 1996).

Because of its improved T1-relaxivity, gadobenate improved reader confidence and lesion conspicuity. There was only improvement in the number of detected lesions up to a dose of 0.2 mmol kg\(^{-1}\), but not beyond that (Schneider et al. 2001). Results were similar if the first dose of 0.1 mmol kg\(^{-1}\) was split into two lower doses of 0.05 mmol kg\(^{-1}\) each (Baleriaux et al. 2002).

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5 Comparative Efficacy of Agents

5.1 Standard (0.5 M) Concentration Agents

Most of the newer agents have been compared with the older ones, especially with gadopentetate and to a lesser extent with gadoterate.

Gadoterate was compared to gadopentetate in two studies. No differences in efficacy were found by Brugeries et al. (1994). Interestingly, the authors concluded that “the greater stability of gadoterate theoretically might reduce biological interactions in man.” Similar results were obtained in a large central nervous system study by Oudkerk et al. (1995), who found that additional findings changed treatment in 17.0 % of gadoterate and 17.3 % of gadopentetate patients, respectively.

Multiple studies have compared the efficacy of gadodiamide to gadopentetate and/or gadoterate in CNS applications and none showed any significant difference in efficacy (Myhr et al. 1992, Baleriaux et al. 1993; Valk et al. 1993; Akeson et al. 1995). In a double-blind randomized MRA study with intra-arterial DSA as reference standard, Schäfer et al. (2006) found no substantial differences between gadodiamide and gadopentetate in sensitivity and specificity for detecting stenosis.

Gadoteridol and gadoversetamide have been compared with gadopentetate in liver and brain imaging. Multiple readers found no significant difference between the agents at either site (Greco et al. 2001; Rubin et al. 1999; Grossman et al. 2000).

5.2 High (1.0 M) Concentration and Protein-Binding Agents

Agents with special characteristics may have a special role. In particular, gadobenate with its higher relaxivity in plasma due to protein binding has been extensively tested.

Gadobutrol for contrast-enhanced pulmonary perfusion MRI performed best at 0.1 mmol kg\(^{-1}\), but did not lead to increased signal-to-noise ratio (SNR) compared to gadopentetate in the low-dose range (0.025–0.1 mmol kg\(^{-1}\)) (Fink et al. 2004). For the diagnosis of brain metastases, an equimolar dose of gadobutrol showed improved conspicuity of lesions compared to gadopentetate (Anzalone et al. 2009). As expected, double dose gadobutrol outperformed double dose gadopentetate in the diagnosis of brain metastases, both in detection and conspicuity (Kim et al. 2010). However, compared to gadoteridol, no superiority for single or double dose MRI was seen for brain metastasis detection (Katakami et al. 2011).

In multiple MRA studies in volunteers and patients, improved signal-to-noise and contrast-to-noise of gadobutrol 1 M compared to equimolar doses of gadopentetate 0.5 M was shown, with a high sensitivity and specificity for diagnosing aortoiliac stenosis (Goyen et al. 2001, 2003). In a recent large multicenter study of focal renal lesions, 0.1 mmol kg\(^{-1}\) gadobutrol 1 M was diagnostically equivalent to an equimolar dose of gadopentetate 0.5 M (Tombach et al. 2008).

A single dose of gadobutrol is as efficacious as double dose gadopentetate for diagnosing myocardial infarction on delayed enhanced MRI (De Cobelli et al. 2012).

In the liver, gadobutrol was not inferior to gadopentetate in equimolar doses in a large Phase 3 trial (Hammerstingl et al. 2009), but showed superiority in double dose...
administration for hypervascular hepatocellular carcinoma (HCC) (Kim et al. 2008).

More recently, gadobutrol has also been compared to gadoterate. For brain metastases, gadobutrol was qualitatively and quantitatively superior (Anzalone et al. 2013). Both agents were comparable for evaluating bone osteomyelitis (Pennekamp et al. 2011). Gadobutrol was better than gadoterate for analyzing delayed enhancement in chronic myocardial infarction. It showed the size of the infarct well and gave good discrimination between infarcted myocardium and the ventricular lumen (Wagner et al. 2013).

MRI of the brain with normal dose gadobenate may be a valid alternative to using high doses of the other agents. Comparative cross-over studies with equal doses of gadopentetate or gadoterate have repeatedly shown improved percentage contrast enhancement, higher sensitivity for lesion detection, increased lesion-to-brain contrast, and reader preference for gadobenate in both intra-axial and extra-axial CNS tumors (Colosimo et al. 2001, 2004; Essig et al. 2001, 2006b; Knopp et al. 2004; Maravilla et al. 2006; Kuhn et al. 2007). This has also been shown at 3T (Rumboldt et al. 2009). In a multicenter study comparing multiple doses of gadobenate and gadodiamide, both agents had similar efficacy, but at a slightly lower dose for gadobenate (Runge et al. 2001, 2002).

Another application in which the higher relaxivity may be beneficial is MRA of the aortoiliac and runoff vessels. Higher signal-to-noise and contrast-to-noise ratios with higher diagnostic image quality in the smaller femoro-tibial or pedal vessels was demonstrated with gadobenate compared to gadopentetate (von Tengg-Kobligk et al. 2003; Knopp et al. 2003; Kreitner et al. 2008; Gerretsen et al. 2010). However, when gadoterate was the comparator agent, sensitivity and specificity was equal between agents. Most benefit is probably in showing vessels below the knee, where the number of non-assessable vessel segments was lower for gadobenate (Wyntenbach et al. 2003; Rasmus et al. 2008).

For the renal arteries and lower aorta, efficacy was not reduced when single dose (0.1 mmol kg$^{-1}$) gadobenate was compared to double dose (0.2 mmol kg$^{-1}$) gadopentetate (Prokop et al. 2005; Soulez et al. 2008). A newer indication where a higher relaxivity is beneficial for tumor diagnosis is MRI of the breast. In a large multicenter study, an equimolar dose of gadobenate gave superior results to gadopentetate (Martincich et al. 2011).

5.3 High (1.0 M) Concentration versus Protein-Binding Agents

Some studies have directly compared the two methods of achieving higher signal intensity, namely higher concentration agents (gadobutrol) and protein-binding agents (gadobenate). In brain perfusion MRI, susceptibility effects for a single dose were not significantly different between the agents, for quantitative parameters and parametric maps, either at 1.5 T (Essig et al. 2002) or at 3 T (Thilmann et al 2005). Double doses of the two agents produced better overall image quality but no clinical benefit over single dose examinations. (Thilmann et al. 2005; Essig et al. 2006a). In the MERIT-study, 0.1 mmol/kg gadobenate performed better than gadobutrol for the diagnosis of brain metastases (Seidl et al. 2012).

In MRA, both diluted and undiluted gadobutrol and gadobenate resulted in significantly higher signal-to-noise than gadopentetate, but there was no difference between the higher signal-to-noise ratio agents (Herborn et al. 2003). Single dose gadobenate at 3T is similar in efficacy to double dose gadobutrol at 1.5T (Attenberger et al. 2010).

In recent comparisons of body applications, gadobutrol and gadobenate showed similar efficacy in breast lesion detection and characterization (Pediconi et al. 2013).

6 Liver-Specific Agents

Gadobenate dimeglumine, with its higher R1- and R2-relaxivity and limited (2–4 %) hepatobiliary excretion, was initially developed for liver imaging (Marin et al. 2009; Morana et al. 2011, Frydrychowicz et al. 2012a), but nowadays is used mainly as an extracellular agent. A hepatobiliary phase of 60–120 min is impractically long. Currently, the most widely used liver-specific gadolinium-based agent is gadoxetate disodium. Because it has 10 % protein binding, its R1- and R2-relaxivity in plasma is high. Hepatobiliary uptake is mediated via organic anion-transporting polypeptide 8 (OATP8) transporters and excretion via multi-drug resistance proteins (MRP), predominantly MRP-3, and is of the order of 50 %, allowing for a short, practical delay of the hepatobiliary phase (HBP) of 15–20 min, preferably slightly longer if MR cholangiography (ce-MRC) is the main purpose of the study.

6.1 Protocol Optimization

A time-efficient MRI protocol includes T1 weighted (T1w) in and out of phase gradient echo, T2 weighted (T2w) turbo spin echo, and diffusion weighted imaging (DWI) sequences. During contrast medium administration, a dynamic, multiphase 3D T1w gradient echo sequence in the arterial, portal venous and early delayed or equilibrium phases (3 min) is done. The enhancement in the dynamic phase with gadoxetate may be less conspicuous than with other agents, including gadobenate (Gupta et al. 2012). The protocol is completed by the delayed hepatobiliary...
phase (15–20 min), and, if needed, a separate ce-MRC sequence can be added. In these latter phases the signal-to-noise can be increased by increasing the flip angle to 25–40° (Kim et al. 2013). As there is no adverse effect of the contrast media on T2w or DWI imaging, these sequences may be acquired in the interval between the dynamic T1w gradient echo sequence and the hepatobiliary phase (Frydrychowicz et al. 2012a).

6.2 Efficacy in the Management of Incidental Liver Lesions

One of the best documented indications for gadoxetic acid MRI is the differentiation of focal nodular hyperplasia (FNH) from hepatocellular adenoma (HCA). FNH and HCA can be diagnosed with very high accuracy (92–100 %) by a combination of T2w, dynamic and HBP images. FNH usually enhances more than HCA in the arterial phase (Purysko et al. 2012, Grazioli et al. 2012). In hemangioma the signal intensity matches the signal in the portal vein, while most lesions are hypointense in the equilibrium and hepatobiliary phases (Tamada et al. 2011).

6.3 Efficacy in the Evaluation of Hepatocarcinogenesis and HCC

Multistep hepatocarcinogenesis, the process by which a dysplastic nodule develops into a hepatocellular carcinoma (HCC), is often more likely in lesions smaller than 1.5 cm. Nodules suspect for HCC classically show hyperintensity on T2w images and DWI with strong enhancement in the arterial phase and wash-out in portal venous and equilibrium phases. The enhancement of HCC correlates positively with uptake transporter OATP-8 and excretion transporter MRP-3, but is not necessarily correlated with histologic grade. If there is cirrhosis, enhancement of the fibrotic parenchyma will be decreased and the study may even be non-diagnostic. This can be reduced to some extent by double dose techniques. Hypointensity in the HBP is the most important marker of malignancy, but 5–10 % of hypervascular HCC may show iso- to hyperintensity on HBP, which is associated with lower aggressiveness. Hyperintensity on T1w before contrast agent administration may occur, especially in moderately or well differentiated HCC. Gadoxetate MRI with dynamic and hepatobiliary imaging is superior to 64-slice MDCT for diagnosing hypervascular HCC in patients with cirrhosis, especially for smaller lesions (Di Martino et al. 2010, Baek et al. 2012, Hwang et al. 2012).

When gadoxetate MRI is added to multidetector CT in patients with Barcelona Clinic Liver Cancer (BCLC) grade 0-A cirrhosis, more HCC lesions can be found, and this alters clinical management and prognosis (Jin et al. 2013). DWI is complementary, since hyperintensity can help to diagnose small lesions and to predict which hypovascular HCC lesions will later progress to hypervascular HCC (Kim et al. 2012a). Gadoxetate MRI is also an optimal technique for diagnosing early HCC, a recently defined well-differentiated subtype with slower growth which is hypointense on HBP images and fat-containing with signal drop on out-phase T1w gradient echo images, but may not enhance in the arterial phase (Sano et al. 2011). In the growing number of patients with HCC nodules after minimal invasive therapies such as radio-frequency ablation, gadoxetate MRI may prove to be a very sensitive technique to evaluate residual disease or recurrence.

6.4 Efficacy in Liver Metastases

The MRI protocol has best results if gadoxetic acid for optimal detection is combined with DWI for improved characterization, especially for small metastases (Chung et al. 2011, Koh et al. 2012). Usually, both hypervascular and hypovascular metastases become relatively hypointense on HBP images. Breast cancer metastases may show a target appearance with peripheral hypointensity and central enhancement (Ha et al. 2012). Patterns in the dynamic phase are crucial for differentiating metastases (ring enhancement) from hemangiomas (peripheral nodular or homogeneous enhancement and bright on T2w images) (Goshima et al. 2010, Motosugi et al. 2011). Multiple studies have shown better results with gadoxetate MRI for diagnosing liver metastases than with multidetector CT (Motosugi et al. 2011, Kim et al. 2012b) or contrast-enhanced PET-CT (Seo et al. 2011). In patients scheduled for liver resection, gadoxetate-enhanced MRI helps to define vascular and biliary variations and can give an estimate of liver function of the remnant liver.

6.5 Efficacy in MR Cholangiography and Other Indications

Contrast-enhanced T1w-MR cholangiography (MRC) as an addition to T2w-MRC has been shown to be helpful by providing functional as well as morphological information in a variety of bile duct pathologies (Gupta 2013), such as primary sclerosing cholangitis (Frydrychowicz et al. 2012b), sphincter of Oddi dyskinesia, and post-surgical bile duct stenosis or leaks (Allegre Castellanos et al. 2012). Chronic liver disease will decrease the signal intensity of the bile ducts on T1w-MRC, and images can often become non-diagnostic.
Promising new applications of gadoxetate MRI include the evaluation of liver fibrosis using quantification of contrast medium uptake or MR Elastography (Noren et al. 2013), and its increasing role in the evaluation of mass-forming intrahepatic cholangiocarcinoma (Kang et al. 2012).

7 Summary and Conclusions

Since the introduction of the first gadolinium-based contrast agent in 1988, it has become clear that these agents significantly improve the diagnostic efficacy of MRI. Studies on single agents have shown that, when compared to un-enhanced sequences, all agents help to improve the detection and delineation of lesions and this can alter diagnosis in up to 40 % of patients.

Doubling or tripling the standard dose of 0.1 mmol kg\(^{-1}\) body weight may be beneficial for selected indications, such as brain perfusion, equivocal single dose MRI study for brain metastasis, and small vessel MRA. A more limited number of studies has compared the various agents. These studies do not show clinically significant differences in diagnostic efficacy between the various extracellular gadolinium-based contrast agents. Agents with higher concentration or protein binding may be relatively more suitable for particular applications, such as perfusion MRI. The higher relaxivity agents may be used in somewhat lower doses than the extracellular agents. For the liver, the number of specific agents has been reduced in recent years. Gadoxetate disodium provides improved diagnosis, based on the combination of dynamic and hepatobiliary phases. It has a primary role in the characterisation of benign liver lesions and is an important problem-solving or presurgical tool in the diagnosis and management of liver metastases and hepatocellular carcinoma (Zech et al. 2013).

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Abstract

The atomic weight of gadolinium renders it radio-opaque at the KeVs used for radiography. Based on the incorrect assumption that gadolinium-based contrast media were not nephrotoxic, several investigators started using gadolinium-based contrast media for radiography, including CT, in patients with reduced renal function instead of using iodine-based contrast media. Nephrotoxicity of gadolinium-based contrast agents when used for radiographic studies, CT and MRI has now been described in both man and animals with renal impairment. Nephrogenic systemic fibrosis is another important adverse reaction after some gadolinium-based contrast media in patients with renal impairment. Gadolinium-based contrast media should not be used as contrast agents for radiography, including CT, in patients with reduced renal function. Gadolinium-based contrast media may be helpful for radiography in patients with normal renal function who have had multiple severe adverse reactions to iodine-based contrast media.

1 Introduction

At the kV (~70) used for digital angiography, the attenuation of X-rays by gadolinium is approximately the same as for iodine and at the kV (~120) used for CT, the attenuation of X-rays by gadolinium is approximately double that of iodine, therefore theoretically gadolinium could replace iodine as a radiographic contrast agent.

The first reported use of gadolinium for its radio-opacity was in 1989, when a CT scan showed urinary hyperattenuation (Janon 1989). Subsequently, it was suggested that patients with significant renal impairment and/or previous severe reactions to iodine-based contrast media should receive gadolinium-based MRI contrast agents instead of the traditional iodine-based radiographic contrast agents (Engelbrecht et al. 1996; Bittner et al. 1997; Albrecht and...
Dawson 2000). Prince et al. (1996) compared nephrotoxicity of high doses (0.2–0.4 mmol/kg) of a gadolinium-based agent with iodine-based contrast medium and found the gadolinium-based agent was less harmful for the kidney. Although this study did not investigate the use of gadolinium-based contrast medium as a radiographic agent, it was nonetheless cited as indicating the lower nephrotoxicity of gadolinium-based agents by many authors who proposed the use of gadolinium agents in radiography. Another possible indication suggested for using gadolinium-based contrast agents rather than iodine-based agents is before thyroid treatment with radioactive iodine to avoid interference by iodine-based agents with the therapeutic iodine uptake.

Gadolinium-based contrast agents are in general known to be safe and not nephrotoxic in the usual MRI doses of up to 0.3 mmol kg\(^{-1}\) body weight (BW). However, the dose requirement for a satisfactory diagnostic study differs between MR and X-ray examination because different properties of the gadolinium are being used in the two modalities. The use of gadolinium-based contrast agents in radiographic examinations is contentious and the risks are poorly understood (Thomsen et al. 2002; Thomsen 2003).

2 Molar Concentrations of Gadolinium- and Iodine-Based Contrast Agents

The first four marketed gadolinium contrast media (gadopentetate dimeglumine, gadoterate, gadodiamide, gadoteridol) are available in a concentration of 0.5 mmol ml\(^{-1}\). Gadobenate dimeglumine is also available in this concentration but, unlike the other four agents, is also excreted via the liver (4 %) (“Contrast Media Classification and Terminology”). Gadobutrol has been introduced in a concentration of 1 mmol ml\(^{-1}\). All six agents have one Gd-atom per molecule, so the molar concentration of the agent and of the gadolinium is the same. Traditionally, iodine-based radiographic contrast media are marketed based on the mg of iodine per ml, with a concentration of 300 mg I ml\(^{-1}\) being equal to 2.38 mmol I ml\(^{-1}\). Since there are three iodine atoms per molecule, the molar concentration of the agent is only 0.8 mmol ml\(^{-1}\).

The commonly used dose for body CT is 150 ml of a 300 mg I ml\(^{-1}\) (2.38 mmol I ml\(^{-1}\)) solution. For body CT, a patient weighing 70 kg would receive 120 mmol of the iodine-based agent molecule (0.8 mmol ml\(^{-1}\) × 150 ml) and approximately 360 mmol of iodine (2.38 mmol ml\(^{-1}\) × 150 ml). The standard dose for contrast-enhanced MR examination is 0.1 mmol kg\(^{-1}\) resulting in 0.2 ml kg\(^{-1}\) BW of a 0.5 mmol ml\(^{-1}\) gadolinium-based contrast agent. For MR examination, the same 70 kg patient would receive 7 mmol of the gadolinium-based agent molecule and 7 mmol of gadolinium [0.5 mmol ml\(^{-1}\) × 14 ml (0.2 ml kg\(^{-1}\) BW × 70 kg BW)]. Thus, the number of iodine-based contrast agent molecules administered for CT would be approximately 17 times that of gadolinium containing molecules for MR, and the number of iodine atoms administered would be 51 times that of gadolinium. For smaller and larger patients, the dose may differ depending on whether CT-protocols have fixed contrast medium doses or take BW into consideration.

3 Attenuation of X-Rays by Iodine and Gadolinium

Iodine has the atomic number 53 and an atomic weight of 127, whereas gadolinium has the atomic number 64 and an atomic weight of 157. Attenuation increases with the atomic number of the atom but decreases with the energy (keV) of the X-ray photons, except at the K-edges. At photon energies between the K-edge of iodine [33 kilo electron Volt (keV)] and that of gadolinium (52 keV), iodine attenuates approximately twice as many X-ray photons as gadolinium does. At all other photon energies, the opposite prevails (Nyman et al. 2002). For CT, the maximal X-ray photon energy is between 120 and 140 keV and the most common photon energies in the spectrum are between 60 and 70 keV. This is above the K-edge of gadolinium, so the attenuation by gadolinium in this situation is about twice that of iodine; but since there are three iodine atoms per contrast medium molecule, the iodine-based contrast agent molecule attenuates 1.5 times more radiation than the gadolinium-based contrast molecule does. For common radiographic examinations, the maximal X-ray photon energy is between 70 and 90 keV and the most common photon energies in the spectrum are above and below the K-edge of gadolinium (50 keV). Because of the range of photon energies, attenuation is approximately the same for iodine and gadolinium atoms. Hence, the attenuation by the iodine-based contrast agent molecule is three times that of the gadolinium-based contrast molecule (Nyman et al. 2002).

It should theoretically be possible to obtain radiographic images of diagnostic quality with gadolinium-based contrast agents, but the image quality will generally be inferior to that achieved with iodine-based contrast agents. This can be explained by the difference in molar concentrations between gadolinium- and iodine-based contrast agents. A 0.5 mmol ml\(^{-1}\) concentration of iodine-based contrast agent contains 63 mg I ml\(^{-1}\). Assuming that a 0.5 mmol ml\(^{-1}\) concentration of gadolinium-based contrast agent attenuates to the same extent as a 0.5 mmol ml\(^{-1}\) concentration of the iodine-based agent, a patient receiving these equi-attenuating concentrations receives only 1/3 of the contrast medium
molecules with the iodine-based agent that would be necessary with the gadolinium-based agent. Considering the molar concentration of an iodine-based contrast agent at 300 mg I ml\(^{-1}\), the attenuation of this preparation is almost five times that of gadolinium preparations of the same volume. Thus, the volume of gadolinium preparation required to obtain “comparable” attenuation is five times that of the iodine preparation.

4 Pharmacokinetics

The gadolinium chelates have pharmacokinetics similar to those of iodine-based radiographic contrast agents with the exception of gadobenate dimeglumine which is also excreted by the liver in small amounts (“Contrast Media Classification and Terminology”, “Diagnostic Efficacy of Gadolinium-Based Contrast Media”, “Organ-specific Gadolinium-Based Contrast Media”). Gadobenate dimeglumine is, however, mainly used for non-liver-specific indications similar to the six other “extracellular” gadolinium chelates (“Contrast Media Classification and Terminology”, “Diagnostic Efficacy of Gadolinium-Based Contrast Media”). Both gadolinium- and iodine-based agents are distributed in the extracellular space and excreted by glomerular filtration. Thus, the T\(_{1/2}\) is almost the same, and both types of agents can be used to measure the glomerular filtration rate. In patients with normal kidney function about 98 % of these agents are excreted within 24 h of injection. However, in patients with severe renal impairment, excretion of gadolinium- and iodine-based agents differs and it may take weeks before the agents are eliminated from the body. Nearly no gadolinium is found in the feces in patients with renal insufficiency, whereas up to 6 % of the injected iodine has been recovered in the feces of such patients (Joffe et al. 1998). No free gadolinium is found in the blood several days after injection of gadolinium chelates in patients with end-stage renal failure despite the slow excretion (Joffe et al. 1998; Normann et al. 2000), but this does not mean that it cannot be found in other parts of the body such as bone and liver.

5 Toxicity (LD\(_{50}\))

Acute intravenous LD\(_{50}\) of contrast media in mice is expressed as mmol iodine or gadolinium per kg BW. For the five gadolinium-based contrast agents, dimeglumine gadopentetate, gadobenate dimeglumine, gadoterate, gadoteridol and gadodiamide, the figures are 6, 8, 8, 18, and 20 mmol gadolinium kg\(^{-1}\), respectively. According to Idée et al. (2006) the determination for gadodiamide is based on two subsequent injections 30 min. apart. The LD\(_{50}\) for the conventional high osmolality iodine-based contrast agent diatrizoate is about 50 mmol iodine kg\(^{-1}\). The LD\(_{50}\) of low osmolality non-ionic monomers, e.g., iopromide, is much higher, about 150 mmol iodine per kg (Weinmann et al. 1990; Weinmann 1999). When amounts of contrast medium producing equal attenuation of X-rays are compared, these LD\(_{50}\) values suggest that the acute intravenous toxicity of the gadolinium-based contrast media is 7.5–25 times that of the non-ionic iodine-based monomers.

6 Incidence of General Reactions to Gadolinium-Based Contrast Agents

General adverse reactions similar to those observed with iodine-based contrast media may be seen following injection of gadolinium-based contrast agents, but the frequency is lower, with the incidence of moderate and severe reactions well below 1 % (Niendorf et al. 1991; Thomsen 1997). However, the number of patients exposed to unapproved dosages (above 0.3 mmol kg\(^{-1}\) BW) is still too small to draw any conclusion about the safety of these higher doses. In the few published studies, varying doses of gadolinium-based agents (20–440 ml) have been used and the number of patients has been small.

7 Clinical and Experimental Studies

Prince et al. (1996) studied 64 patients undergoing MR examination with a gadolinium-based contrast medium and a radiographic examination with an iodine-based contrast medium. They concluded that high-dose gadolinium chelates are significantly less nephrotoxic than iodine-based agents, since eleven of the 64 patients had a significant increase in serum creatinine after intravenous or intra-arterial administration of iodine-based contrast media, whereas none had increased serum creatinine levels after intravenous administration of a gadolinium-based contrast agent. However, the molar doses and concentrations of the iodine and gadolinium atoms were not comparable. Although the exact dose of the iodine-based contrast agent used for each patient could not be verified, between 30 and 60 g I was administered. For the MR examinations between 0.2 and 0.4 mmol kg\(^{-1}\) BW were used. Assuming that all patients were of standard BW (~ 70 kg), the dose of iodine atoms was approximately 17 times greater than that of gadolinium atoms. Had equi-attenuating doses been used, the results might have been different.

Over recent years, gadolinium-based contrast agents have been used for examinations such as CT, intravenous urography, and digital subtraction angiography of various parts of the body (e.g., liver, renal, and peripheral arteries).
Albrecht and Dawson (2000) studied 15 patients receiving 0.3 mmol kg\(^{-1}\) BW gadopentetate dimeglumine; five had abdominal CT, five had abdominal DSA and five had intravenous urography. No side effects were reported, but generally the image quality was inferior to that obtained subsequently with standard doses of iodine-based contrast media (50–150 ml of a 300 or 350 mg I ml\(^{-1}\) solution). The authors suggested that higher doses including more concentrated solutions of gadolinium-based contrast media might be useful (Albrecht and Dawson 2000). To optimize visualization of gadolinium-based contrast media, Hui et al. (2011) recommended the use of a flat panel detector as it improves the conspicuity of the agents during digital subtraction angiography.

Gadolinium-based contrast media have also been used for endoscopic retrograde cholangiography, cystography, urethrocystography, and retrograde pyelography and during percutaneous nephrostomy and biliary tract drainage giving adequate image quality with no side effects (Velmas and Markkola 1998). Coche et al. (2001) reported successful detection of pulmonary embolism using gadolinium-enhanced helical CT (0.4 mmol kg\(^{-1}\) gadodiamide), without any problems, in a 77-year-old woman with previous allergy-like reaction to iodine-based contrast medium and renal insufficiency (serum creatinine of 200 \(\mu\)mol ml\(^{-1}\)). Henes et al. (2011) evaluated the diagnostic accuracy of gadolinium- and iodine-enhanced CT of the pulmonary arteries for the detection of pulmonary embolism in pigs. Down to segmental level the diagnostic accuracy in detection of pulmonary embolism was identical.

A total of 14 patients with abnormal S-creatinine levels underwent digital subtraction vena cavaography with a gadolinium-based contrast agent (maximum 0.4 mmol kg\(^{-1}\) BW) for filter placement, thrombolysis, or diagnosis. Three of the 14 patients had a significant increase in serum creatinine (>44 \(\mu\)mol ml\(^{-1}\)), but there were other concurrent causes, which might account for the deterioration of renal function (Kaufmann et al. 1999). It was concluded that gadolinium-based contrast agents were suitable for digital subtraction venography in patients with renal insufficiency.

In an azotemic patient with suspected renal artery stenosis, a total of 40 ml (0.5 mmol ml\(^{-1}\)) undiluted dimeglumine gadopentetate was injected arterially (Matchett et al. 1996). The serum creatinine increased from 290 to 390 \(\mu\)mol l\(^{-1}\), but this might have been attributable to a myocardial infarction which the patient developed 3 days after the procedure. Acute renal failure was described following lower extremity arteriography with 80 ml of 0.5 mmol ml\(^{-1}\) (0.44 mmol kg\(^{-1}\) BW) of gadoteridol in an insulin-dependent diabetic patient with nephropathy (Gemery et al. 1998). Serum creatinine transiently increased from 350 to 820 \(\mu\)mol ml\(^{-1}\) and the deterioration was considered most likely due to the contrast agent.

A total of 31 patients with azotemia or previous severe adverse reaction to iodine-based contrast media underwent digital subtraction angiography with between 20 and 60 ml of 0.5 mmol ml\(^{-1}\) gadopentetate (Hammer et al. 1999). In nine cases, CO\(_2\) was also used and in eight cases between 6 and 40 ml of iohexol 350 mgI ml\(^{-1}\) (mean 17.8 ml) were used. In no patient did S-creatinine increase more than 44 \(\mu\)mol l\(^{-1}\) within 48 h. Spinosa et al. (1998) studied 13 renal transplant patients with suspected vascular causes of renal insufficiency and/or accelerated hypertension with both CO\(_2\) and a gadolinium-based contrast agent (16–60 ml gadodiamide). Digital subtraction angiography was considered adequate in all patients. In two patients renal failure progressed (>44 \(\mu\)mol l\(^{-1}\) within 48 h), but concurrent causes of the renal dysfunction were also present; one had received 20 ml and the other had received 60 ml of gadodiamide. During peripheral arteriography Spinosa et al. (1999) found that gadodiamide with an osmolality of 789 mOsm per kilogram of water was less painful than gadopentetate dimeglumine with an osmolality of greater than 1,800 mOsm per kilogram of water. No effects on renal function were found. Later Spinosa et al. (2000) reported one of 18 azotemic patients (6 %) whose renal function deteriorated after undergoing CO\(_2\) angiography supplemented with 0.5 mmol ml\(^{-1}\) gadodiamide (20–100 ml; mean volume 55 ml; 0.13–0.4 mmol kg\(^{-1}\)). The affected patient received 70 ml gadodiamide (0.3 mmol kg\(^{-1}\) BW).

Injections of 80–440 ml of gadodiamide during arteriography have also been reported (Gemmete et al. 2001). A serum creatinine increase of 53 \(\mu\)mol ml\(^{-1}\) or more occurred in 8 of 20 patients (40 %) with a pre-procedural serum creatinine of 115–548 \(\mu\)mol ml\(^{-1}\). In three of the eight patients, the creatinine values did not return to baseline value. Following peripheral arteriography with a gadolinium-based agent, angioplasty and stent placement, a patient with renal insufficiency (340 \(\mu\)mol l\(^{-1}\)) developed acute renal failure and acute pancreatitis (Schenker et al. 2001). Acute pancreatitis has been seen both after intra-arterial (Gemery et al. 1998) and intravenous (Terzi and Sokmen 1999) injection of a gadolinium-based contrast agent.

Based on a literature review, Saleh et al. (2011) concluded that gadolinium-based contrast agents are a potential alternative for radiography in patients with severe allergy to iodine-based contrast media. However, they should only be used in doses up to 0.4 mmol/kg\(^{-1}\) BW, which may limit their use in complex interventional peripheral and coronary procedures. Also, there is a higher risk of ventricular arrhythmias with intracoronary gadolinium-based contrast media than with iodine-based contrast media (Saleh et al. 2011).
8 Experimental Nephrotoxicity

Intravenous injection (9 ml kg$^{-1}$) of gadopentetate (0.1 mol ml$^{-1}$), iohexol (300 mg I ml$^{-1}$), metrizoate (300 mg I ml$^{-1}$), and normal saline in rabbits produced nephrotoxicity of the same order for all three contrast agents (Leander et al. 1992). The molar concentration and dose of iodine atoms was 24 times higher than the molar concentration and dose of gadolinium atoms. Thus, the iodine-based agents might have had a lower nephrotoxic effect than the gadolinium-based agents if the two agents had been compared in equi-attenuating doses and concentrations. Rat studies where high equimolar doses (4.59 mmol kg$^{-1}$ BW) of gadolinium-based agents (gadopentetate and gadodiamide) and iodine-based agents (diatrizoate and iohexol) were injected intravenously showed no significant deterioration in the function of normal and diseased kidneys (Thomsen et al. 1994, 1995). There was a significant correlation between albuminuria and the osmolality of the contrast medium, with gadopentetate causing the highest excretion of albumin and gadodiamide and iohexol the least, but the degree of albuminuria does not correlate with the nephrotoxic potential of a contrast medium. In these studies, the dose of iodine atoms was three times the dose of gadolinium atoms.

In an ischemic rat model, intra-aortic injections of 1.5 ml (0.5 mmol ml$^{-1}$) gadopentetate (0.75 mmol Gd atoms) and 2.6 ml 370 mg I ml$^{-1}$ diatrizoate (7.6 mmol iodine atoms) caused a significant decrease in creatinine clearance of similar magnitude, 50 and 67 %, respectively (Deray et al. 1990; Brillet et al. 1994). Gadoterate [1.5 ml (0.5 mmol l$^{-1}$)] alone caused no decrease in renal function in this model. The dose of iodine was ten times higher than the dose of gadolinium and the two different doses produced a similar significant decrease in creatinine clearance. Whether the iodine-based contrast medium would produce less decrease in creatinine clearance than the gadolinium-based medium if equimolar doses had been given remains speculative.

In an experimental model of renal ischemia in pigs, 0.5 molar gadopentetate dimeglumine (3 ml kg$^{-1}$ BW) caused severe impairment of renal function, while the low-osmolar gadodiamide caused less deterioration in renal function, and the low-osmolar iohexol (3 ml of 190 mg I ml$^{-1}$ per kg BW) caused even less (Elmstahl et al. 2004). Three ml per kg BW of iohexol (70 mg I ml$^{-1}$), which for angiography is equi-attenuating with 0.5 M gadopentetate dimeglumine, caused no change in renal function. Iodine-based contrast agents had better renal tolerance and radiodensity than did gadolinium-based contrast agents during arteriography in ischemic porcine kidneys (Elmstahl et al. 2008). An in vitro study using the isolated perfused rat kidney showed that a large dose of gadopentetate dimeglumine (0.3 mmol kg$^{-1}$ BW) did not cause significant reduction in renal function (Brown et al. 1993). However, an equimolar dose per kg BW of iodine atoms in a 70 kg man would be 10 ml at concentration of 265 mg I ml$^{-1}$.

9 Gadolinium-based Contrast Media and Nephrotoxicity in Patients

Sam et al. (2003) reported that in 3.5 % of 195 patients with abnormal pre-examination creatinine clearance levels, acute renal failure (anuria) developed after gadolinium-based contrast medium administration. For MR angiography the incidence was 1.9 % and for digital subtraction angiography 9.5 %. Dialysis was required in three of the seven patients who developed acute renal failure. The average baseline creatinine clearance in the whole group was 38.2 ± 1.6 ml min$^{-1}$ 1.73 m$^{-2}$ and in the seven patients who developed contrast medium induced nephropathy (CIN) was 32.5 ± 7.8 ml min$^{-1}$ 1.73 m$^{-2}$. The doses of dimer constant gadopentetate ranged from 0.31 to 0.41 mmol kg$^{-1}$ for MR angiography and 0.27–0.42 mmol kg$^{-1}$ for digital subtraction angiography. CIN occurred after a moderate, approved dose (0.14 mmol kg$^{-1}$) of a gadolinium-based contrast medium in a patient with moderate to severe diabetic nephropathy and chronic heart failure (Thomsen 2004). Akgun et al. (2006) reported acute tubular necrosis in a renal biopsy following exposure to a gadolinium-based contrast agent. In diabetic patients with multiple risk factors it may be appropriate to take the same precautions before enhanced MR examinations as before enhanced radiographic examinations. After having a gadolinium-based contrast agent 3 times within 3 weeks an 80-year-old patient developed rapid deterioration of pre-existing renal insufficiency and uremic symptoms and pulmonary edema; temporary hemodialysis (three times) was performed and renal function improved (Fujisaki et al. 2011). In a patient with impaired renal function the possibility remains that, for CT arteriography, using a low concentration iodine-based contrast medium of equal attenuation to a gadolinium-based contrast agent may have less risk of causing CIN (Nyman et al. 2008).

Bridges et al. (2009) retrospectively studied 33 patients with impaired renal function, but not on dialysis, in whom estimated glomerular filtration rate had been measured within 48 h before and within 5 days after injection of 40–200 ml gadodiamide for radiography. The change in estimated glomerular filtration rate ranged from $-8.8$ to $+42.9$ ml min$^{-1}$ 1.73 m$^{-2}$, with a statistically significant median improvement of 2.4 ml min$^{-1}$ 1.73 m$^{-2}$. In contrast, Sambol et al. (2011) found a prevalence of acute renal failure of 11.2 % (20 patients) on a retrospective review of 153 patients undergoing 179 intra-arterial...
exposures to gadodiamide either alone (33 %) or in combination with iodine-based contrast medium (67 %). Four patients needed dialysis for irreversible renal failure, another four experienced irreversible renal deterioration, and in the remainder renal function returned to baseline. They concluded that patients with serum creatinine levels above 266 μmol l\(^{-1}\) before the examination and who received more than 0.4 mmol kg\(^{-1}\) of gadodiamide were at higher risk of acute renal failure (Sambol et al. 2011).

10 Risk of Nephrogenic Systemic Fibrosis

Two studies of nephrogenic systemic fibrosis (NSF) have included patients who had received gadolinium-based contrast media during conventional angiography or CT. Bridges et al. (2009) retrospectively identified 61 patients who had received gadolinium-based contrast media during conventional angiography or CT. Bridges included patients who had received gadolinium-based contrast media either alone (33 %) or in combination (67 %) with iodine-based contrast media. The patient records (not visual inspection) stated that one patient developed NSF, a prevalence of 1.6 %. Hoppe et al. (2010) retrospectively reviewed the records of 27 patients (10 females and 17 males) with renal insufficiency (eGFR < 60 ml min\(^{-1}\) 1.73 m\(^{-2}\)), who underwent conventional angiography. 25 of the 27 received gadodiamide in a dose of 44 ± 15.5 ml (range 15–60 ml) or 0.24 ± 0.12 mmol kg\(^{-1}\) (range 0.1–0.53 mmol kg\(^{-1}\)). Mean estimated glomerular filtration rate before angiography was 26 ml min\(^{-1}\) 1.73m\(^{-2}\) and after angiography 33 ml min\(^{-1}\) 1.73 m\(^{-2}\). Additional MRI studies with gadolinium contrast medium were performed in 15 patients, one of whom developed biopsy-confirmed NSF. Thus, NSF certainly can occur after exposure to gadolinium contrast media used for angiography and CT. However, at least half of the patients in the above-mentioned studies had only a moderately reduced glomerular filtration rate and were not at the same risk of NSF as patients with a glomerular filtration rate below 15 ml min\(^{-1}\) 1.73 m\(^{-2}\) or on dialysis.

Sambol et al. (2011) retrospectively reviewed 153 patients who had undergone 179 intra-arterial exposures to gadolinium-based contrast media either alone (33 %) or in combination (67 %) with iodine-based contrast media. The average pre-procedure serum creatinine was 172 μmol l\(^{-1}\) and the average dose of gadodiamide was 0.45 mmol kg\(^{-1}\). NSF was not diagnosed in any of the patients, but 12.4 % of the patients had died before the follow-up took place.

11 Conclusion

The atomic weight of gadolinium renders it radio-opaque at the KeVs used for radiography, and several reports have shown that gadolinium-based agents can give diagnostic images in radiographic examinations, including CT, when iodine-based contrast agents are contraindicated for a variety of reasons. However, radiographic image quality with gadolinium-based agents is generally inferior to that with iodine-based agents. The five commercially available gadolinium-based agents (dimeglumine gadopentetate, gadobenate dimeglumine, gadoteridol, gadodiamide, gadobenate) only have one gadolinium atom per molecule and have a molar concentration of gadolinium five times less than the molar concentration of iodine in the iodine-based monomers, which have three iodine atoms per molecule. These chemical differences mean that gadolinium-based contrast media are more nephrotoxic than iodine-based contrast media in doses which produce equivalent X-ray attenuation.

Nephrotoxicity of gadolinium-based contrast agents used for radiographic studies, CT and MRI has now been described in both man and animals. High doses (>0.3 mmol kg\(^{-1}\) BW) of gadolinium-based agents are contraindicated in patients with impaired renal function. Patients with reduced renal function are also at risk of developing NSF after the less stable gadolinium agents (‘‘Nephrogenic Systemic Fibrosis and Gadolinium-Based Contrast Media’’).

Gadolinium-based contrast media should not be used for radiographic examinations in patients with impaired renal function, but they may be useful for radiographic examinations in patients with normal renal function who have had multiple severe adverse reactions to iodine-based contrast media.

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Acute Adverse Reactions to Gadolinium-Based Contrast Media

Henrik S. Thomsen and Georg M. Bongartz

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Abstract

Acute non-renal and renal adverse reactions occur after administration of gadolinium-based contrast media just as after iodine-based contrast media. However, the rate of acute non-renal adverse reactions is much lower after gadolinium-based contrast media than after iodine-based contrast media. Acute renal adverse reactions (contrast medium-induced nephropathy, CIN) do occur after gadolinium-based contrast media but are extremely infrequent after administration of the low doses (0.1–0.3 mmol l⁻¹ kg⁻¹) used for MRI. Knowledge about higher doses is limited, but the frequency of renal adverse reactions is predicted to be closer to that seen after iodine-based contrast media.

1 Introduction

For many years, gadolinium-based contrast agents have been considered extremely safe, without or with only minimal risk. However, gadolinium-based contrast agents are not inert drugs. They may cause acute non-renal adverse reactions (e.g., anaphylactoid reactions), acute renal adverse reactions (e.g., contrast-induced nephropathy), delayed adverse reactions (nephrogenic systemic fibrosis), problems at the site of injection (e.g., local necrosis), and laboratory abnormalities. The use of contrast enhanced MRI has increased over the past decade, as a variety of new applications have been described and put into clinical practice, and so the number of administrations of gadolinium-based contrast agents has also increased considerably. This increase has, to some extent, been countered by the fear of nephrogenic systemic fibrosis (Thomsen et al. 2007) and by the financial crisis, which has reduced the number of examinations, at least in the US (Sharpe et al. 2013). A contrast agent is given in only about one-third of MR examinations, compared to the figure of two-thirds for CT and the average amount of contrast molecules in mmol used per examination for enhanced MRI is about eight...
2 Acute Non-Renal Adverse Reactions

2.1 Incidence

Because of differences in study design and definitions of adverse reactions used, it is difficult to draw definite conclusions about the incidence of adverse effects following gadolinium-based contrast media. In European and Japanese studies, gadopentetate dimeglumine had low adverse incidence rates (0.63 %), while in the USA, where different rules for registration and documentation of adverse events are legally imposed, the incidence was 7.6 % (Niendorf et al. 1991a). Early studies suggested that the safety profiles of gadopentetate dimeglumine, gadoterate meglumine, gadoteridol, gadodiamide, gabodenate dimeglumine, and gadoversetamide were comparable (Shellock and Kanal 1999; Kirchin and Runge 2003). In general, the total incidence rate of adverse events appears to be less than 5 % and the incidence of a single adverse event is below 1 % (Niendorf et al. 1991a, b; Oudkerk et al. 1995; Thomsen 1997).

Murphy et al. (1996) described a 0.1 % frequency of allergic-like reactions to gadolinium-based contrast agents among 21,000 patients over an almost 5-year period. A retrospective survey involving 53 institutions showed that 241 allergy-like reactions (0.03 %) occurred after 825,535 injections (Murphy et al. 1999). Dillman et al. (2007) reported that there were 54 (0.07 %) acute allergy-like reactions in 78,353 intravenous administrations of gadolinium-based contrast agents in a retrospective study over 6 years. Seventy-four percent of the reactions were considered mild. One patient experienced three acute allergy-like reactions during the period.

A European post marketing surveillance study of 24,308 patients who received gadoterate meglumine intravenously for a variety of diagnostic examinations reported that the incidence of adverse events was 0.4 % (Heborn et al. 2007). Most reactions were rated as minor, such as a feeling of warmth or altered taste. In a Japanese post-marketing surveillance study of the same agent over 4 years, which included 1,300 inpatients and 2,144 outpatients, 40 adverse reactions were recorded in 32 patients, giving an overall incidence of adverse reactions of 0.93 % (Ishiguchi and Takahashi 2010). Gastrointestinal disorders (nausea, vomiting) were the most commonly reported adverse reactions in both the European (0.56 %) and the Japanese study (0.49 %). Li et al. (2006) reported a reaction frequency of 0.48 % in 9,528 patients, based on prospective recording in an incidence log book over 5 years in a single center in Hong Kong. Different rates of reaction are unlikely to be due to geographical or genetic differences.

Prince et al. (2011) reported 40 deaths after administration of gadolinium-based contrast agents between 2004 and 2009 which were reported to the FDA; the incidence of reactions varied between 0.15 and 0.7 per million injections, and none of these cases were related to NSF.

The number of published studies is too small to draw any conclusions about safety of higher unapproved dosages.

2.2 Types of Reaction

The most common reported adverse events with gadolinium-based contrast agents are headache, nausea, vomiting, hives, and altered taste (Kirchin and Runge 2003; Runge 2000; Shellock and Kanal 1999; Heborn et al. 2007; Ishiguchi and Takahashi 2010). Symptoms such as headache may not be related to the contrast agent. For example, headache might be caused by the patient’s disease, or might relate to the noise in the MR scanner. Interestingly, patients undergoing MR examination in an almost silent scanner (0.1 T) do not report headache after enhanced MRI (Thomsen 1997).

Anaphylactoid reactions to gadolinium-based contrast agents do occur, but their incidence is very low. The first documented anaphylactoid reaction to gadopentetate dimeglumine was not seen in clinical trials but some time after approval (Runge 2000). The true incidence of anaphylactoid reactions for gadolinium chelates is not known, but appears to be between 1:100,000 and 1:500,000 (Shellock and Kanal 1999).

2.3 Predisposing Factors

Possible factors that may increase an individual’s risk of an acute allergy-like reaction include a history of previous allergy-like reaction to intravenous contrast media (either gadolinium- or iodine-containing) and previous allergic reaction to a substance other than contrast media. The risk of adverse reactions to gadopentetate dimeglumine was 3.7 times higher in patients with a previous history of reaction to iodine-based contrast media (Niendorf et al. 1991b). However, this finding has not been confirmed in other studies. It is now generally accepted that there is no cross-reaction between gadolinium- and iodine-based agents.
Although acute allergy-like reactions occurred more frequently in adults than in children, and in females than male patients in one study, these differences were not statistically significant (Dillman et al. 2007).

### 2.4 Treatment and Premedication

Treatment of adverse reactions to gadolinium-based contrast agents is the same as for iodine-based agents ("Management of Acute Adverse Reactions to Contrast Media"). Prompt recognition and treatment are crucial and invaluable in blunting an adverse response of a patient to gadolinium-based contrast agents and may prevent a reaction from becoming severe or even life-threatening.

Dillman et al. (2008) recently reported that allergy-like reactions to gadolinium-based contrast agents could occur despite premedication with corticosteroids and antihistamines. Two-thirds of the reactions were mild. All patients had a history of allergy-like reactions to either a gadolinium- or iodine-based contrast agent. Currently, there is no evidence of any advantage of premedication before administration of gadolinium-based contrast agents, even in patients who have reacted earlier to contrast agents.

### 2.5 Reaction Rates with Different Agents

As has already been noted, the majority of early studies and reviews did not show significant differences in reaction rates among the different gadolinium-based agents (Shellock and Kanal 1999; Kirchin and Runge 2003; Greenen and Krestin 2006). However, there have been recent suggestions that there may be different adverse event rates among different agents.

Abujudeh et al. (2010) reported that the rates of acute non-renal adverse reactions to gadopentetate dimeglumine and gadobenate dimeglumine were 0.14 and 0.28 % based on 32,659 administrations (gadopentetate 27,956 administrations and gadobenate 4,703 administrations). However, direct comparison of adverse reactions rates of the two agents was not possible because of the prospective uncontrolled study design.

Prince et al. (2011) raised the possibility, based on data from the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) collected from 2004 to 2009, that there might be different incidences of severe reactions among gadolinium agents. However, retrospective studies of adverse events may be influenced by the over-reporting of acute adverse events when a new drug is first marketed, described by Weber (Weber 1984), and known as the Weber effect. Many radiologists switched from a non-ionic linear gadolinium-based agent to an ionic linear agent or a macrocyclic agent when there was uncertainty about what to do after the link between some gadolinium-based contrast agents and the development of nephrogenic systemic fibrosis became apparent. This change may have led to increased reports of adverse events with the new contrast agent (Thomsen and Webb 2012). In support of this suggestion, Davenport et al. (2013) showed a significant transient increase in the frequency of reported allergic-like reactions after gadobenate dimeglumine was substituted for gadopentetate dimeglumine. After 2 years, the rate returned to the previous level.

Retrospective studies may underestimate the true rate of adverse reactions. In particular, mild reactions may be underestimated whereas the rate of severe reactions is more likely to be correct.

Also, retrospective studies do not take into account the so-called Lalli effect, when minor symptoms after contrast medium may be caused by anxiety. Prospective randomized studies are the only way to obtain reliable data (Thomsen and Webb 2012).

### 2.6 Further Safety Data for Individual Gadolinium-Based Agents

In a descriptive study of moderate to severe reactions after either gadopentetate dimeglumine or gadoterate meglumine in approximately 30,000 patients over a 10-year time period, three moderate to severe reactions occurred, all after gadoterate meglumine (de Ridder et al. 2001).

In 56 patients with multiple sclerosis, who had monthly MRI examinations with gadopentetate dimeglumine 0.1 mmol kg\(^{-1}\) for research purposes, no significant effects on routine hematology, serum chemistry, renal and liver function, and serum iron profiles were found. Patients had received between 3 and 53 doses of gadopentetate dimeglumine. It was concluded that repeated monthly administration of gadopentetate dimeglumine at the standard dose is safe (Tresley et al. 1997). However, the long-term effects have not yet been studied. In a phase III study in 199 patients with suspected CNS pathology, patients either received 0.1 or 0.3 mmol kg\(^{-1}\) gadopentetate dimeglumine (Haustein et al. 1993). A total of 15 adverse events in 12 patients were encountered, 8 in the 0.1 mmol kg\(^{-1}\) group and 7 in the 0.3 mmol kg\(^{-1}\) group.

During phase I–III studies with gadoversetamide, no significant differences in adverse event rates for doses between 0.1 and 0.4 mmol kg\(^{-1}\) were noted (Brown et al. 2002). In another study with gadoversetamide, patients received 0.1, 0.3, or 0.5 mmol kg\(^{-1}\) and the incidence of adverse events increased significantly with increasing dose (Swan et al. 1999a).

In a phase III clinical trial, 38 patients received the standard gadodiamide dose and 40 received a triple dose.
Five patients from the standard dose group and two from the triple dose group reported adverse events, none of which were judged to be related to the contrast medium (Demaeerel et al. 1994). In a double blind multicenter study of single versus triple dose gadodiamide, no adverse events possibly related to gadodiamide administration were recorded (Thurnher et al. 2001).

Over 13 months, 23,553 doses of gadobenate dimeglumine were administered (Bleicher and Kanal 2008). 178 reactions (0.76 %) were recorded, of which 13 % required treatment.

Morgan et al. (2011) prospectively assessed the adverse reaction rates during gadoteridol-enhanced MR in 28,078 patients. The overall reaction rate was 0.66 %, including 177 mild (95 %), 6 moderate, and 4 severe reactions. The most frequent reaction was nausea, which occurred in 149 patients (79.7 %) of the patients who had an adverse reaction and in 0.53 % of the overall population. There was no difference in type or severity of reactions between patients receiving a half dose versus patients receiving the standard dose.

**Gadobutrol** produced adverse reactions are considered to be possibly drug-related in 4.6 % of patients (Balzer et al. 2003). Gadobutrol is contra-indicated in patients with uncorrected hypokalemia. Also, special care is needed in patients with a family history of congenital long QT syndrome, who have a history of arrhythmias after taking drugs that prolong cardiac repolarization or who are taking class III antiarrhythmic drugs. Recommendations are based on the assumption that gadobutrol in a high dose (>4 times maximal dose) can block potassium channels, resulting in prolonged QT interval and accelerated ventricular rhythm.

### 2.7 Comparison of Gadolinium- and Iodine-Based Agents

Hunt et al. (2009) studied retrospectively the frequency and characteristics of adverse reactions to low-osmolar iodine- and gadolinium-based contrast agents at a single center. Adverse reactions were identified using recording by radiologists and nurses. A total of 456,930 contrast medium doses (298,491 low-osmolar iodine-based, 158,439 gadolinium-based) were administered over the study period. The frequency of adverse reactions was 0.15 % after iodine-based contrast media and 0.04 % after gadolinium-based agents. The most common adverse effects were hives (274, 52.5 %) and nausea (92, 17.6 %). Seventy-two of the adverse events after low-osmolar iodine-based contrast agents and 15 of the events after gadolinium-based contrast agents required treatment. Only 16 patients with adverse effects needed transfer to the emergency department for further observation or treatment. One possible reason for the lower prevalence of adverse reactions to gadolinium-based than to iodine-based contrast agents may be the much lower doses of the agents used for MRI than for radiography. For example, the molar dose of contrast medium for enhanced MRI of the brain is on average eight times lower than that for CT of the brain.

### 3 Acute Renal Adverse Reactions (Contrast-Induced Nephropathy)

In most patients with moderate to severe impaired renal function, gadopentetate dimeglumine, gadoterate meglumine, gadodiamide, gadobenate dimeglumine, gadoteridol, gadobutrol, and gadoversetamide do not significantly affect serum creatinine levels when administered in standard doses (Bellin et al. 1992; Haustein et al. 1992; Joffe et al. 1998; Swan et al. 1999a, b; Tombach et al. 2001; Yoshi- kawa and Davies 1997). However, CIN may occur after gadolinium-based contrast media, just as after iodine-based contrast media (“Contrast Medium-Induced Nephropathy”, “Radiography with Gadolinium-Based Contrast Media”). CIN is more likely to occur after larger doses of gadolinium-based contrast media, as with iodine-based contrast media.

Nephrotoxicity of gadolinium-based contrast agents has been documented in both man and animals. Use of high doses (>0.3 mmol kg$^{-1}$ BW) of gadolinium-based contrast agents in patients with impaired renal function is clearly contra-indicated (Thomsen et al. 2002). In 2003, Sam et al. reported that after gadolinium-based contrast agents acute renal failure developed in 3.5 % of 195 patients with an abnormal creatinine clearance. After MR angiography the incidence was 1.9 % and after digital subtraction angiography 9.5 %. Doses of gadopentetate dimeglumine ranged from 0.31 to 0.41 mmol kg$^{-1}$ for MR angiography and from 0.27 to 0.42 mmol kg$^{-1}$ for digital subtraction angiography. Dialysis was required in 40 % of the patients who developed acute renal failure. CIN has even been reported after an intravenous injection of 0.14 mmol l$^{-1}$ of a gadolinium-based contrast agent (Thomsen 2004).

A study of X-ray arteriography in pig kidneys, made temporarily ischemic by arterial balloon occlusion, found that 0.5 M gadolinium-based contrast agents were more nephrotoxic than both equal-attenuating (70 mg I ml$^{-1}$) and equimolar (190 mg I ml$^{-1}$) concentrations of iodine-based agents (Elmstahl et al. 2004). Using the same ischemic porcine model, Elmstahl et al. found that the histomorphological changes caused by gadolinium-based contrast agents were similar to those caused by iodine-based agents (Elmstahl et al. 2007). Vacuolization appeared to be independent of osmolality and viscosity of the contrast medium, and did not seem to be an indicator of renal impairment. Briguori et al. (2006) showed in a prospective study that using gadolinium-based contrast agents in patients with
chronic renal insufficiency did not appear to reduce the rate of CIN, as compared to iodine-based contrast agents.

In a retrospective study, which included 473 patients with stages 3 and 4 renal failure who received 0.2 ml kg\(^{-1}\) of gadolinium-based contrast medium, Ergun et al. (2006) found that the risk factors for acute renal failure after gadolinium-based contrast agents included diabetic nephropathy and low glomerular filtration rate.

The risk of CIN is very low when doses of gadolinium-based contrast agents approved for MR (<0.3 mmol kg\(^{-1}\)) are used. When approved doses are used, the risk of CIN is much lower than the risk of NSF when less stable gadolinium-based agents are used (“Radiography with Gadolinium-Based Contrast Media”, “Nephrogenic Systemic Fibrosis and Gadolinium-Based Contrast Media”). When stable agents are used in approved doses, the risk of CIN may be slightly higher than the risk of NSF, which is close to zero.

4 Conclusion

Clinical trials and experience have shown that in general, gadolinium-based contrast agents produce relatively few acute reactions. However, acute reactions are possible and may occur in any patient. Allergy-like reactions occur after less than 1 % of gadolinium-based contrast agent administrations. There is no difference in rate between the various approved extracellular gadolinium-based agents. Reactions are the same as those seen after iodine-based contrast agents. In most cases they are mild, but a few severe anaphylactoid reactions have been reported. Allergy-like reactions may occur despite pretreatment with corticosteroid and antihistamine. Therefore, one must always be prepared to treat an adverse reaction after administration of a gadolinium-based contrast agent. Management is similar to that of reactions to iodine-based contrast agents. Appropriate knowledge, training, and preparation are essential to ensure prompt effective treatment. Premedication before administering gadolinium-based contrast agents is not generally indicated.

Acute renal adverse reactions may occur after administration of gadolinium-based contrast agents in approved doses (<0.3 mmol kg\(^{-1}\) BW), but these occur very infrequently. Above 0.3 mmol kg\(^{-1}\) BW, the risk is much higher in patients with reduced renal function, and gadolinium-based contrast agents should not be used in these patients at doses greater than 0.3 mmol kg\(^{-1}\) BW.

Prospective randomized studies are the only way to obtain reliable data about adverse events. Comparative studies of acute non-renal adverse reactions to contrast media must ensure that the different agents are given under identical conditions. This does not occur in retrospective studies, where the Lalli and Weber effects are not controlled.

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Nephrogenic Systemic Fibrosis
and Gadolinium-Based Contrast Media

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Abstract
Nephrogenic systemic fibrosis (NSF) is an adverse reaction to gadolinium, which is toxic in its free, unchelated form. NSF is seen after the least stable gadolinium-based contrast agents in patients with reduced renal kidney function or on dialysis. The introduction of guidelines has led to a reduction in the incidence of NSF, but it is too soon to state that it has been totally eliminated. The long-term effects of retention of gadolinium in the body require further investigation.

1 Introduction
Since early 2006, evidence has accumulated that some gadolinium-based contrast agents, particularly gadodiamide, may cause a potentially devastating or even fatal scleroderma-like, fibrosing condition called nephrogenic systemic fibrosis (NSF) in patients with renal failure (Thomsen 2006; Thomsen et al. 2007a; Thomsen and Bennett 2012). Some months later it was shown that gadopentetate dimeglumine may also trigger NSF, but not with the same frequency as gadodiamide (Wertman et al. 2008). This development shocked the radiological community because for many years it was believed that gadolinium-based contrast agents were very safe. However, since gadolinium-based agents were introduced, there have been rapid developments in MR techniques and in the use of these agents, which could not have been foreseen when most of the agents were developed and underwent early testing (phase I–III trials).

2 Was Nephrogenic Systemic Fibrosis a Surprise?
NSF was a great surprise for the overwhelming majority of physicians, but not for a small minority. In 1983, changes in collagen structure were reported after exposure to
lanthanides (Evans and Drouven 1983). “Biochemistry of Lanthanides”, a comprehensive text about these ions, was published in 1990 (Evans 1990). The abstracts and discussions of the 1991 workshop on contrast-enhanced magnetic resonance organized by the Society of Magnetic Resonance in Medicine were published in Magnetic Resonance in Medicine (SMRM workshop on contrast enhanced magnetic resonance 1991), but were not widely read. At this meeting, the stability of non-ionic linear-chelated gadolinium agents was heavily debated. It was noted that pathological changes which occurred after exposure to a non-ionic linear chelate gadolinium agent were not seen after exposure to an ionic linear agent. Preclinical findings with a new non-ionic linear chelate, gadopendiamide, were reported in 1992. Because of concerns about the safety findings, which were similar to those seen after other non-ionic linear chelates, clinical trials of gadopendiamide were not undertaken (Müller et al. 1992). In 1995, a Belgian group showed that, over time, gadodiamide releases gadolinium in serum (Maton et al. 1995). Unfortunately, the report of this observation was not released until 2012 when it was made public by the Danish Ministry of Health. Frenzel et al. (2008) made similar observations and noted that in serum non-ionic linear agents released the toxic gadolinium ion, differing significantly from other agents. The first paper discussing transmetallation was published in 1988 and actually included a warning about the use of less stable gadolinium-based contrast media in patients with renal impairment (Tweedle et al. 1988). It will never be known why these safety concerns did not receive attention outside a small group of experts, but the sequence of events illustrates the importance of disseminating all information to physicians and to the regulatory authorities.

### 3 Clinical Features of NSF

NSF was first described in San Diego, California, USA in 1997 as an idiopathic skin condition characterized by thickening and hardening of the skin of the extremities and sometimes the trunk, with an increase in the number of dermal fibroblast-like cells associated with collagen remodeling and mucin deposition. However, it took another 3 years before the observation was reported in the peer-reviewed literature (Cowper et al. 2000). Observations from four medical centers were included in the report. The diagnosis of NSF is not easy. It requires systematic examination of the skin as well as careful light-microscopy of a deep skin biopsy. The diagnostic scoring system proposed by the NSF registry in New Haven (Connecticut) should be followed (Girardi et al. 2011).

NSF affects all ages and races. The typical patient has end-stage renal disease (ESRD) (Thomsen et al. 2007a; Cowper et al. 2008). Most reported patients are on regular hemodialysis treatment, but there are centers where most patients were not on hemodialysis.

The first signs of NSF may be seen within hours of exposure to gadolinium-based contrast agents, but may occur as late as 3 months after exposure (Marckmann et al. 2008). It has even been claimed that NSF may occur several years after exposure to a gadolinium-based contrast agent. During the latent period, gadolinium may have accumulated in a tissue other than skin, for example, bone. Tweedle et al. (1995) studied $^{155}$Gd release from four different gadolinium-based contrast agents in mice and rats and found that gadolinium was retained in liver and bone, with greater amounts with the linear than with the macrocyclic agents. These findings were confirmed by Wadas et al. (2010) in mice, and they also showed that retention of gadolinium in bone was greater in renally impaired mice. Transmetallation, in which gadolinium exchanges with cations that occur naturally in the body, starts immediately after the agent has entered the blood (“Gadolinium Chelates and Stability”), particularly when there is increased phosphate in the blood (Frenzel et al. 2008).

In most patients NSF begins with subacute swelling of the distal extremities, followed in subsequent weeks by severe skin induration, which may extend to involve the thighs, forearms, and lower abdomen (Cowper et al. 2008; Marckmann et al. 2008). The skin induration may be aggressive and associated with constant pain, muscle restlessness, and loss of skin flexibility. In some cases, NSF leads to serious physical disability, including becoming wheelchair bound. For many patients, the skin thickening inhibits flexion and extension of joints, resulting in contractures. Severely affected patients may be unable to walk or fully extend the upper and lower limb joints. Complaints of muscle weakness are common, and deep bone pain in the hips and ribs has been described. Radiography may show soft tissue calcification. There is great variability. NSF severity may be graded from 0 to 4: 0 no symptoms, 1 mild physical, cosmetic, or neuropathic symptoms not causing any kind of disability, 2 moderate physical and/or neuropathic symptoms limiting physical performance to some extent, 3 severe symptoms limiting daily physical activities (walking, bathing, shopping, etc.), and 4 severely disabling symptoms causing dependence on aid or devices for common, daily activities (Marckmann et al. 2008). Marckmann et al. (2008) reported that approximately 50 % of their patients had developed severe or “disabling” stage 3 and 4 NSF.

NSF was initially observed in and thought to affect the skin only, so it was called nephrogenic fibrosing dermopathy (NFD) but it is now known that it may involve organs such as the liver, lungs, muscles, and heart. Involvement of internal organs may explain the suspected increased mortality of NSF patients. In up to 50 % of patients the disease is progressive and severe. NSF may contribute to death by causing scarring
of organs (which impairs normal function), by restricting effective ventilation, or by restricting movement leading to falls, which may cause fractures or hemorrhage. Other patients have died as a result of renal disease or transplant surgery. In one study it was shown that 18-month mortality was increased significantly compared to patients without NSF (40 vs. 16 %, respectively), with an adjusted hazard ratio of 2:9 (95 % CI (1.3–6.5), p = 0.008) (Todd et al. 2007). Swaminathan et al. (2008) found that of 32 patients with nephrogenic systemic fibrosis, 10 died at a median of 112 days after diagnosis. At autopsy (3 patients) there were appreciable amounts of gadolinium, iron, and aluminum, as measured by indirectly coupled plasma-mass spectrometry and confirmed by X-ray fluorescence, in the heart, blood vessels, and skin. In this high-risk group, it is difficult to differentiate deaths caused by complications of the underlying disease and its treatment from those due to NSF.

Since the first 2–3 years after the link between gadolinium and the development of NSF was recognized, very little has been added to the typical clinical picture: (1) use of a non-ionic linear gadolinium-based contrast agent (not necessarily in high doses as it has occurred after 0.1 mmol kg⁻¹), (2) renal insufficiency including treatment with dialysis, (3) great variability in involvement from a small skin plaque to generalized involvement of the skin and internal organs. There is very likely to be a further unknown factor, or factors, as all patients with renal insufficiency exposed to a non-ionic linear chelate do not develop NSF, at least within the current follow-up period.

### 3.1 Pathophysiology

In patients with advanced chronic kidney disease, the elimination half-life of gadolinium-based contrast agents can be prolonged to 30 h or more (Morcos et al. 2002). Release of free Gd³⁺ from gadolinium-based contrast agents by transmetallation and spontaneous dissociation is likely to occur if the contrast agent remains in the body for a long time, as, for example, in patients with end-stage renal disease, including those on dialysis (Morcos 2007). Three consecutive hemodialysis sessions over 6 days would be required to clear 97 % of the dose of gadolinium-based contrast agents from the body. Only 69 % of the dose would be removed after 20 days of continuous ambulatory peritoneal dialysis (Morcos et al. 2002). It seems reasonable to suggest that free Gd³⁺ ions become attached to endogenous anions particularly phosphate and form insoluble salts that deposit in tissues. These insoluble molecules will then be engulfed by local macrophages, which in turn will release a range of cytokines, including TGF β, which attract circulating fibrocytes and initiate the process of fibrosis (Morcos 2007; Parazella 2007). There is evidence that tissue fibrosis in NSF is caused by circulating fibrocytes recruited from the circulation, rather than by proliferation of resident dendritic cells. In addition, hybridization studies have showed a marked increase in TGF β mRNA levels in the skin and fascia of patients with NSF (Cowper 2007; Cowper et al. 2008).

Sieber et al. (2008a) gave rats with normal renal function repeated injections of 2.5 mmol kg⁻¹ of six different gadolinium-based contrast agents over a 20-day period. 2.5 mmol kg⁻¹ is a high dose for humans but not for rats because of the much more rapid clearance of these agents from the blood in rats. Skin lesions consistent with human NSF were seen as early as 8 days after starting nonformulated gadodiamide exposure and 20 days after starting formulated gadodiamide [gadodiamide plus the excess ligand caclidiamide, (the commercial solution)] solution, but not when gadopentetate was given. The highest Gd³⁺ concentrations in the skin and the most advanced skin lesions were found in animals that received the low stability agents. Skin changes occurred despite the rats’ normal renal function and the fact that the biological half-life of gadolinium-based agents in rats is approximately one-sixth of that in man. In a further study of rats given 2.5 mmol kg⁻¹ of six gadolinium-based agents, the highest concentrations of gadolinium in skin, liver, and bone occurred with gadodiamide. With gadopentetate, skin gadolinium concentration was 10 times less and with gadoterate and gadobutrol 30 times less (Sieber et al. 2008b). A previous study in humans showed that Gd³⁺ deposition in bone occurs in patients with normal renal function: Gd³⁺ retention in bone with gadodiamide was 2–4 times more than with the macrocyclic agent gadoteridol (White et al. 2006). These studies suggest that multiple large doses of low stability gadolinium-based contrast agents may cause heavy metal intoxication even in patients with normal renal function.

Serum from NSF patients has recently been shown to stimulate fibroblast hyaluron synthesis by up to sevenfold and collagen by up to 2.4-fold compared to control fibroblast cultures incubated with serum derived from healthy volunteers and dialysis patients not suffering from NSF. Fibroblasts exposed to gadodiamide (1.0 mM) for up to 7 days showed significant stimulation of proliferation (Edward et al. 2008). Gadodiamide has also induced the expression of α-smooth muscle actin staining, suggesting induction of a myofibroblast phenotype (Edward et al. 2008). Further studies comparing various gadolinium-based contrast agents are required to show whether they have different effects on fibroblasts. In vitro studies on human fibroblasts in culture showed that gadodiamide stimulates fibroblast proliferation and collagen production but has no significant effect on keratinocytes. The stable macrocyclic agent meglumine gadoterate had no effects except at very high (10 mM) concentrations (MacNeil et al. 2011).
3.2 Validation of NSF Cases

Because NSF may mimic other skin lesions that occur in patients with end-stage renal failure (Tables 1 and 2), the diagnosis of NSF should never be made without histological evaluation by an experienced dermatopathologist as well as a careful inspection of the skin by an experienced dermatologist or nephrologist (Girardi et al. 2011). The diagnostic scoring system proposed by the NSF registry in New Haven (Connecticut) should always be used (Girardi et al. 2011); it allows more objective assessment of cases. Use of the Yale scoring system should be an essential criterion used by editors when they accept papers. Some cases reported as NSF, for example, to the health authorities, after investigation turned out not to be NSF.

Correlation of the disease with exposure to drugs or contrast media requires adequate documentation of patient exposure. Not all radiology departments had adequate registration systems for the dose and name of the contrast medium used. Sometimes nicknames were used independent of the product administered or a brand-name continued to be used even though a new product had been introduced. Also the patient’s weight was not recorded. Incomplete records caused problems in retrospective studies looking for unsuspected NSF cases. In the future it is very important that a record is always kept of the type and amount of each injection of gadolinium-based contrast agent given and that all new cases of NSF are reported to the appropriate National Regulatory Authority. Interestingly, no National Medicines Agency had any record of NSF before the first 20 cases of gadodiamide-induced NSF were submitted to them on March 30th 2006 (Stenver 2008) or almost 1 year after the first thoughts about a correlation were submitted for publication (Grobner 2006). In Denmark, one case was reported in 2003 and another in 2004 under another diagnosis; review of the histopathologic specimen in 2006 showed that the correct diagnosis was NSF and this probably was the cause of the second patient’s death (Marckmann 2008; Bennett et al. 2012a, b). Sadly neither the Medicines Agency nor the manufacturer started a major review of these cases.

The authorities only need four simple facts: (1) initials, birth date, and sex of the patient, (2) the adverse event, (3) name of the drug, and (4) name of the reporting person, including occupation. However, this limited information requires validation before the case can be confirmed as being NSF associated with use of a gadolinium-based contrast agent. Validation becomes even more difficult when several gadolinium products have been used in a short period of time. Thus, if two different gadolinium-based contrast agents have been injected, for example, within 8 weeks of each other or longer, it may be impossible to determine with certainty which agent triggered the development of NSF and the situation is described as “confounded.” In this situation, the agent that is most likely to be responsible is the one that has triggered NSF in other unconfounded situations.

3.3 Cofactors in the Development of NSF

Time has shown that two factors are important for the development of NSF: (1) reduced renal function and (2) exposure to one of the less stable gadolinium-based contrast agents. However, NSF does not develop in all at-risk patients after exposure to the less stable gadolinium-based contrast agents (Thomsen et al. 2007a) and many investigators have sought cofactors that may destabilize these agents.

Many cofactors have been suggested: High doses of erythropoietin (EPO), metabolic acidosis, iron and ferritin, chronic inflammation, hypercoagulability, thrombotic events, recent vascular surgery, recent renal transplant failure, recent surgery, anion gap, or increased phosphate. However, no universal cofactor apart from renal failure has been identified. Marckmann et al. (2007) could not identify any exposure/event other than gadodiamide common to more than a minority of the patients who developed NSF. The Center for Disease Control and Prevention found that only exposure to gadolinium-based contrast agents during the preceding 6 months or preceding year remained statistically significant in their case–control study of 19 NSF cases (Center For Disease and Prevention 2007). Over 36% of the patients in the Four American University Study were outpatients (Wertman et al. 2008) and the authors concluded that NSF is also seen in patients who have renal compromise but whose medical condition is relatively stable. The majority of 19 patients in the study by Marckmann et al. (2007) belonged to this group.

Current knowledge suggests that there may be several cofactors that increase the risk of NSF after some
gadolinium-based contrast agents. However, some of the factors may have been listed just by chance because enhanced MRI was performed when the particular factors were present. For example, in some departments enhanced MRI is done as part of the evaluation of thromboembolic symptoms, post surgical complications, etc., whereas in other departments MRI is not used in these situations. Therefore, one institution may report that NSF occurs more frequently in patients with particular conditions but others cannot confirm it because they use enhanced MRI differently. Although NSF has not been totally eradicated, the number of patients is so small, at least in Western Europe, North America, and Japan, that it is unlikely that the missing factor or factors will ever be identified in man. The high-risk agents are now little used in the above-mentioned countries.

### 3.4 Prevalence

In several studies, based on pathologic or nephrologic registers, the prevalence of NSF after exposure to gadodiamide has been reported to be between 3 and 7% in patients with reduced renal function (Thomsen and Marckmann 2008). In patients with CKD 5 (GFR less than 15 ml min⁻¹ 1.73 m⁻²), who have been contacted and examined, it may be as much as 18% (Rydahl et al. 2008); all those with suspicious lesions had a skin biopsy. The prevalence was higher after two injections (or more) (36%) than after a single injection (12%), indicating a cumulative effect (Rydahl et al. 2008). Todd et al. (2007) reported that 30% of patients on dialysis had developed NSF based on a systematic examination of the patients in five dialysis centers; biopsies were only taken in a few patients. In the peer-reviewed literature only one center has reported a large number (>10) of NSF cases after gadopentetate dimeglumine (Todd et al. 2007), whereas many centers have reported more than 10 cases after gadodiamide (Thomsen and Marckmann 2008). This difference is not just a reflection of the market share of the two products, because gadopentetate dimeglumine has been administered to as many as 4–5 times the number of patients who have had gadodiamide. In the Four American University Study, the overall incidence was 0.039 % after gadodiamide and 0.003 % after gadopentetate dimeglumine (Wertman et al. 2008). The benchmark incidence of NSF was one in 2,913 patients who underwent gadodiamide-enhanced MRI and one in 44,224 patients who underwent gadopentetate dimeglumine-enhanced MRI (p < 0.001). The study was based on patient records from databases of dermatology, pathology, internal medicine, nephrology, transplant surgery, and radiology departments and not systematic examination of patients with reduced renal function exposed to a gadolinium-based contrast agent.

About 6 years after the first paper (Grobner 2006) indicating a link between gadolinium-based contrast agents and development of NSF, only a few questionable cases of NSF after exposure to a macrocyclic agent or to a high-relaxivity agent (i.e., the protein-binding agents gadobenate dimeglumine, gadofosveset trisodium, gadoxetate disodium) have been published in the peer-reviewed literature. A few unconfounded cases have been reported after gadobutrol, but there is uncertainty about the histopathologic changes (Wollanka et al. 2009; Elmholdt et al. 2010; Collidge et al. 2010). Reilly (2008) found no NSF cases in 141 patients on long-term dialysis who had received gadoteridol and Janus et al. (2010) found no cases of NSF in 135 patients with advanced renal impairment (GFR ≤ 30 ml/min) who had received gadoterate. Nearly the same number of patients have received a macrocyclic agent as a non-ionic linear agent, when the three macrocyclic agents are taken together.

Up to 2012, a total of 711 NSF cases have been published (Pirovano et al. 2012). It is likely that they constitute only a small percentage of all cases. It is not known how many patients developed NSF because only two studies include systematic inspection of the skin in patients with reduced renal failure or on dialysis, and patients may have died with or of undiagnosed NSF between 1996 and 2006.

### 3.5 Registries

Many registries have collected data about NSF cases and this leads to confusion. The International Center for Nephrogenic Fibrosing Dermopathy Research (ICNFDR, http://www.icnfdr.org) has collected cases of NSF submitted to them since 2000. A case can only be registered if the head of the registry, Dr. Shawn Cowper, has evaluated the histologic specimen and agrees with the diagnosis of NSF. Since 8 June 2006, the FDA has encouraged reporting of American cases through Med-Watch. The cases are not validated and many do not fulfill the aforementioned criteria or the criteria for being included in the International Registry. Nonetheless, the figures are quoted frequently. The same applies to the reports submitted to National Regulatory Authorities in the various European countries, all of which rely on the vendor to collect the validating data. Both the Contrast Media Committees of the American College of Radiology and the European Society of Urogenital Radiology have asked their members to report cases, but these again are not validated. Also the vendors have a registry, which should be identical to that of the National Regulatory Authorities, but is not, because vendors do not use the same criteria. Finally, there is the peer-reviewed literature, which provides the most reliable information, but suffers from delays in the collection of data and the publication process. By 1 February 2008, 190 cases (confirmed by biopsy and...
clinical reviewed literature: 157 had gadodiamide, 8 had gadopentetate, 3 had gadoversetamide, and in 5 no exposure could be verified. In 18, the agent could not be identified and 4 received several agents (Broome 2008). During the following 4 years the figure for published cases increased to 711 (Pirovano et al. 2012), and gadodiamide is still the agent in most cases.

4 Patients at Risk for NSF

Patients at higher risk are those with CKD 4 and 5 (GFR < 30 ml min⁻¹), those on hemo- or peritoneal dialysis and patients with reduced renal function who have had or are awaiting liver transplantation (Thomsen et al. 2007a; Thomsen 2007). Patients at lower risk are those with CKD 3 (GFR 30-59 ml min⁻¹) and children under 1 year, because of their immature renal function. To date, no cases where the patient had normal renal function, CKD 1 and 2 (GFR > 60 ml min⁻¹ 1.73 m⁻²), have been reported in the literature. Patients with acute renal failure are at particular risk as the reduced renal function may be overlooked by a single determination of their estimated glomerular filtration rate (eGFR). If they receive a less stable gadolinium agent when they have low renal function and then develop NSF, NSF does not disappear when the renal function improves (Kalb et al. 2008).

4.1 Determination of Glomerular Filtration Rate

Accurate determination of the glomerular filtration rate is not easy. The most precise method measures inulin clearance and isotope methods give similar results (Blaufox et al. 1996). However, both methods are cumbersome and impractical for daily use (Thomsen et al. 2005). Measurement of serum creatinine is not satisfactory because more than 25 % of older patients have normal serum creatinine levels but reduced glomerular filtration rates. A single determination of the glomerular filtration rate does not exclude acute renal insufficiency.

Renal function can also be estimated using specially derived predictive equations that use not only serum creatinine but also characteristics such as weight, height, race, and gender (“Chronic Kidney Disease, Serum Creatinine and Estimated Glomerular Filtration Rate (eGFR)”).

The Cockcroft-Gault equation was published in 1976 and was widely adopted for estimation of creatinine clearance from serum creatinine levels (Cockroft and Gault 1976). The equation was developed using two steps: First, urinary creatinine excretion per body weight (UV/kg) was estimated from age in hospitalized patients; creatinine clearance was then calculated by multiplying by weight and dividing by serum creatinine (P) using the standard “UV/P” clearance formula. Not surprisingly, the high-risk patients who were used to develop the Cockcroft-Gault equation had lower muscle mass (creatinine excretion) than healthier individuals in the general population.

The Modification of Diet in Renal Disease (MDRD) equation was published in 1999 and later simplified (Levey et al. 1999, 2000, 2007). This equation automatically estimates GFR from serum creatinine for most laboratories. The equation was developed using patients who had CKD identified by elevated serum creatinine levels and who had a fourfold higher risk for progressing to ESRD. Despite the selective nature of the equation population, it has been widely advocated that estimated GFR (eGFR) be reported when <60 ml min⁻¹ 1.73 m⁻² instead of reporting serum creatinine levels.

The most accurate results are obtained with the Cockcroft-Gault equation, whereas the most precise formula is the Modification of Diet in Renal Disease (MDRD) study equation. Unfortunately, the predictive capabilities of these formulae are suboptimal (Bostom et al. 2002). In addition, they are not useful for patients with a glomerular filtration rate above 60 ml min⁻¹ (Stevens et al. 2006). Different methods also can result in very different values for glomerular filtration rate (Stevens et al. 2006; Band et al. 2007; Eken and Kilicaslan 2007). For example, a 43-year-old 70 kg male patient with a creatinine level of 264 μmol l⁻¹ has a glomerular filtration level of 32 ml min⁻¹ if it is calculated by the Cockcroft-Gault equation. The same patient will have a glomerular filtration level calculated by the MDRD equation of 33 ml min⁻¹ if he is Afro-American and 27 ml min⁻¹ if he is Caucasian. Thus, it would have been illegal to use one of the less stable agents in a Caucasian if the glomerular filtration rate had been estimated by the MDRD equation, but not if it had been estimated by the Cockcroft-Gault equation.

In 2009, a third equation CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) was published (Levey et al. 2009). It was developed in an effort to create a formula more accurate than the MDRD formula, especially when actual GFR is greater than 60 ml min⁻¹ 1.73 m⁻². Pooled data from 10 studies including 8,254 patients were used to validate the new equation. Around 16 additional studies, which included 3,896 participants, were used for external validation. The CKD-EPI equation performed better than the MDRD (Modification of Diet in Renal Disease Study) equation, especially at higher GFR, with less bias, and greater accuracy. Michels et al. (2010) concluded that the absolute bias of all formulae is influenced by age. The
CKD-EPI and MDRD formulas are also influenced by GFR, and the Cockcroft-Gault equation is additionally influenced by body weight and BMI. In general, CKD-EPI gives the best estimation of GFR, although the performance is close to that of MDRD (“Chronic Kidney Disease, Serum Creatinine and Estimated Glomerular Filtration Rate (eGFR)”).

4.2 What to Do?

In practice, it is easier to use one of the more stable gadolinium agents, for which eGFR measurement before administration may not be mandatory. No differences in diagnostic efficacy have been demonstrated among the six extracellular agents (“Diagnostic Efficacy of Gadolinium-Based Contrast Media”).

If departments continue to use two agents, other problems arise (Wertman et al. 2008):

- A suitable agent must be chosen for each individual patient.
- Patients with reduced renal function must be identified. Serum creatinine should be measured within 7 days of contrast medium administration in patients with previously elevated serum creatinine or who have a history suggesting the possibility of elevated serum creatinine, namely (1) renal disease, (2) renal surgery, (3) proteinuria, (4) diabetes mellitus, (5) hypertension, (6) gout, and/or (7) recent nephrotoxic drugs (Thomsen et al. 2005). Alternatively, serum creatinine should be measured and eGFR calculated in all patients referred for enhanced imaging.
- Some at-risk patients may be missed because of operator or laboratory error.
- The possibility that NSF is only one of potentially several diseases related to the presence of gadolinium in the body is not accounted for.
- The possibility remains that there will be greater retention of gadolinium in the body with potential late sequelae if the less stable agents are used.

There are several conditions where alternative imaging is diagnostically inferior and cannot replace enhanced MRI. The risk of the NSF is low if the non-ionic linear chelates are avoided, and if the most stable agents are used in the smallest dose consistent with a diagnostic result in at-risk patients. Despite the American College of Radiology recommendation that hemodialysis should be used in at-risk patients (Kanal et al. 2007), initiating dialysis should be considered with care, since the morbidity of hemodialysis in a patient not already adjusted to hemodialysis is higher than the risk of NSF after exposure to a macrocyclic gadolinium agent. The risk of complications (procedural, allergy-like reactions, contrast-induced nephropathy, radiation) following conventional or CT arteriography with iodine-based contrast medium must also be weighed carefully against performing MR using a stable gadolinium agent. In most cases there is no better alternative to enhanced MRI (Thomson et al. 2007b; Diego 2008).

5 Why did it Take so Long?

It took nearly 9 years from the diagnosis of the first NSF case to the recognition that the disease was associated with exposure to the less stable gadolinium-based contrast agents. There are many good reasons for this. Uremic patients are exposed to many drugs and the drugs change during the progress of their disease. Also, a variety of factors could produce a severe dermopathy in these patients (Table 1). Generally contrast agents, in particular MR agents, have been considered safe inert drugs. NSF is a delayed reaction that mainly occurs weeks (or years) after the patient has received the contrast medium. It does not occur in all CKD 5 patients (GFR less than 15 ml min\(^{-1}\) 1.73 m\(^2\) and/or dialysis) and to date has only been reported in the peer-reviewed literature after administration of the less stable gadolinium-based contrast agents. Most patients have not been exposed to non-ionic linear agents, which are the least stable (“Gadolinium Chelates and Stability”). Mild changes of NSF, for example, on the legs, may have gone

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<th>Table 1 Skin lesions that may mimic nephrogenic systemic fibrosis on clinical examination [adapted from Cowper (2007)]</th>
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undiaugmed and only severe changes that have led to sig-
nificant disability have been noticed. Access to MRI has
increased considerably since 2000 and new techniques such
as step-wise angiography based on a single contrast medium
injection are now available. Until recently, most radiolo-
gists and clinicians did not know about NSF. Since this
adverse effect was unknown, it was not included in the
approved summary of product characteristics, and would
not have been linked to the contrast medium by physicians,
even if an adverse drug effect was considered (Thomsen and
Bennett 2012). There must be sufficient cases of a new
syndrome to evaluate before clinicians can recognize its
association with a particular drug (Bennett et al. 2012a, b).
In view of all these circumstances, it is not surprising that it
took time for the connection to be recognized.

6 Has NSF Been Eliminated?

The FDA has received more than 1600 reports of NSF, all
of patients who had an injection of gadolinium-based
contrast medium before 2010 (Bennett et al. 2012a, b). A
total of 711 NSF cases have been published (Pirovano
et al. 2012). These cases probably represent the tip of
the iceberg. Many patients with NSF may have died from
1996 through 2006 without having their diagnosis recog-
nized. In a French study of more than 500 patients
undergoing dialysis, 56% received a gadolinium-based
contrast agent after 2009 (Amet et al. 2012), and they did
not find any cases of NSF. The overwhelming majority
received gadoterate, but six received a gadolinium-based
contrast agent that was contraindicated according to the
Summary of Product Characteristics. Possible explanations
are that information about dialysis treatment was not
included on the request for the examination, that the
 technician administered the wrong vial by mistake, or that
kidney function tests were not recorded or were incorrectly
recorded. While agents which are contraindicated in some
patients are available in a department, mistakes will hap-
pen. Such mistakes may not be recognized, but, if they
are, will any skin changes which occur be reported to the
health authorities? Because administration of gadodiamide,
gadopentetate, and gadoversetamide in patients with
reduced renal function has been contraindicated in Europe
since 2007, the responsible radiologist will be in a difficult
legal situation if the patient mistakenly receives this
product and develops NSF. Thus, it is premature to con-
clude that NSF has been totally eliminated. As part of the
process of eliminating NSF, the introduction of guidelines
(Thomsen 2007) for the use of gadolinium-based contrast
agents has been beneficial.

7 Legal Aspects

In May 2006, the FDA issued their first warning based on the
reports from Austria and Denmark. In February 2007 the
European Medicines Agency (EMA) stated that the use of
gadodiamide in patients with poor renal function was con-
traindicated and in June 2007, the contraindication was
extended to gadopentetate dimeglumine. In July 2007 gad-
oversetamide was approved for the European market with
the same contraindication as had already been issued for
gadodiamide and gadopentetate dimeglumine. In November
2008 Denmark requested a European review of gadolinium
contrast media. In July 2010 the European Commission
endorsed changes to the product summaries of the different
gadolinium-based contrast agents proposed by the EMA; in
general the review confirmed the decisions taken by the
EMA in 2007 (Commission Decision of 1.7.2010). In their
reports, the EMA classify agents as being at high, interme-
diate, or low risk of inducing NSF, based on their chemical
properties. They recommended that intermediate risk agents
are avoided in patients with poor renal function and that low
risk agents can be used with caution. There are no clinical
studies to support the differentiation of intermediate from
low risk agents and the FDA does not make this distinction.
In September 2010, the FDA finally followed the EMA and
stated that gadoversetamide, gadodiamide, and gadopente-
tate dimeglumine were contraindicated in patients with poor
renal function (Food and Drug Administration. Press
Release September 9th 2010). The marketing authorization
holder of gadoversetamide had already voluntarily stated
that its use was contraindicated in patients with poor renal
function in November 2009. Since the fall of 2010, the drug
regulatory authorities in Europe and the US have agreed
about the precautions necessary for the use of gadolinium-
based contrast agents (Thomsen 2010).

Recently, the American College of Radiology (ACR
Committee on Drugs and Contrast Media 2012) changed
their recommendations. The Committee stated that NSF
developing after gadolinium-based contrast medium
administration to patients with eGFR > 30 ml min$^{-1}$1.73 m$^{-2}$ is exceedingly rare but eGFR determinations may
fluctuate from one day to the next (with an eGFR level just
above 30 on one day changing to an eGFR below 30 on
another day). Therefore, they concluded that the precautions
described above for CKD4 and CKD5 patients should also
be recommended for patients with an eGFR < 40 ml min$^{-1}$1.73 m$^{-2}$, whereas no special precautions are required in
patients with an eGFR of 40–59 ml min$^{-1}$1.73 m$^{-2}$. In
Europe the recommendations still follow the Summary of
Product Characteristics of gadodiamide, gadoversetamide,
and gadopentetate, and these agents may only be used with
special caution in patients with an eGFR of 30–59 ml min\(^{-1}\) 1.73\(^{-2}\) (Thomsen et al. 2013; ‘‘ESUR Guidelines on Contrast Media Version 8.1’’).

### 8 Gadolinium and Patients with Normal Renal Function

Gadolinium has been demonstrated in the skin of patients with NSF (High et al. 2007; Abraham et al. 2008) and in the bone of patients who had received a gadolinium-based contrast agent but did not develop NSF (White et al. 2006). The bone accumulation was about four times greater after a linear chelate agent than after a non-ionic cyclic agent in patients with normal renal function (White et al. 2006). The rates of dissociation of gadolinium from macrocyclic ligands are several orders of magnitude slower than their dissociation from linear systems (Rosky et al. 2008). The amount of gadolinium in the skin of patients with NSF seems to increase up to 3 years after the last exposure to a gadolinium-based contrast agent (Abraham et al. 2008). Where does it come from? Bone has a slow turnover. The long-term implications of gadolinium deposition in bone, which is likely to occur more commonly in pediatric patients because of the more active bone creation in this population, have yet to be determined (Wertman et al. 2008). Another risk group could be patients who undergo multiple-enhanced MRI examinations, for example, women with an increased risk of breast cancer who may follow recommendations to undergo annual enhanced MRI. After each examination some gadolinium will accumulate in the bone and it will stay there for many years (Abraham and Thakral 2008). What will happen when the gadolinium is released from bone, for example, when osteoporosis increases bone turnover? The release of an overload of gadolinium might cause classic toxicity symptoms, not NSF. Free gadolinium may produce liver necrosis, obstruct calcium ion passage through muscle cells, and interfere with intracellular enzymes and cell membranes by the process of transmetallation, a phenomenon whereby Gd\(^{3+}\) replaces endogenous metals such as zinc and copper. The safety of multiple injections of gadolinium-based contrast agents has never been studied; the phase I-III studies that led to approval by the health authorities included only a single injection in man and in most cases at a dose of 0.1 mmol kg\(^{-1}\) body weight. Since then there has been a major revolution in the use of enhanced MRI. The chance of having several enhanced MRI examinations within a shorter period is much higher now than 15 years ago when there were only 1,000–2,000 MRI units worldwide and each had a lower throughput. The phase I-III studies did not foresee these changes and can therefore not be used to document safety of these products as they are now used. One product could easily be safe in the 1993 environment, but not 15 years later.

Another risk group could be patients with diabetes mellitus; after approximately 10 years, 50% may develop diabetic nephropathy, but these patients cannot be identified when they have normal renal function. If some gadolinium remains in the body from a MR-examination when the patient had normal function, it is possible that this patient will develop more severe NSF after enhanced MRI with a less stable agent when their GFR becomes severely reduced (CKD 5). Marckmann et al. (2007) showed that, independent of renal function, patients with severe NSF had a higher life-time dose of the gadolinium-based agent than those developing non-severe NSF.

A lot of detailed and careful research is vital before we can be sure that there will not be new problems in 10–20 years because of retention of the heavy metal gadolinium in the body for long periods of time.

### 9 Conclusion

NSF is an important delayed adverse reaction to some gadolinium-based contrast agents, which occurs in patients with impaired renal function (Thomsen 2006). The recognition of this reaction to agents previously considered to be very safe emphasizes the need to have a good clinical indication for all enhanced MRI examinations, to choose an agent that leaves the smallest amount of gadolinium in the body (stable agents and high relaxivity agents), and to keep complete records of the type and dose of agent given.

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**Table 2** Histopathologic differential diagnosis for nephrogenic systemic fibrosis [adapted from Cowper (2007)]

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<td>Dermatofibrosarcoma protuberans</td>
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<td>Melanoma (spindle-cell variant)</td>
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<td>Granuloma annulare</td>
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Research into the etiology of NSF has drawn attention to the retention of gadolinium in the body tissues long after an enhanced MR examination even in patients with normal renal function. The safety implications of this are as yet unclear and further research is necessary.

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Organ-Specific Gadolinium-Based Contrast Media

Marie-France Bellin and Peter Leander

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Abstract

Organ-specific contrast agents were developed after conventional extracellular gadolinium chelates and there are fewer data about their safety. They belong to different classes of agent and therefore exhibit different physico-chemical properties, modes of action, and metabolic pathways. Currently, agents for both hepatobiliary imaging and blood pool imaging are available commercially. Based on laboratory data, all these agents are considered to be in the ‘intermediate risk’ category for inducing NSF. NSF has not been reported after any of these agents, but clinical experience is extremely limited for two of them.

1 Introduction

Although nonspecific extracellular gadolinium (Gd) chelates dominate the MR contrast agent market, some gadolinium-based organ-specific contrast agents have tissuespecific properties that permit targeted MRI of organs such as the liver or MR angiography. Gadolinium-based organ-specific contrast agents (Table 1) are increasingly used to detect and characterize liver lesions better (Bellin et al. 1994, 2003; Ros et al. 1995; Kopp et al. 1997; Spinazzi et al. 1999; Kirrchin and Runge 2003; Marti-Bonmati et al. 2003; Bluemke et al. 2005; 2010; Brismar et al. 2012) and to improve the efficacy of MR angiography (Goyen et al. Ichikawa et al. 2005; Rapp et al. 2005; Nikolaou et al. 2006; Schneider et al. 2010; Iezzi et al. 2011). Although there are theoretical safety concerns, these MR contrast agents have been shown to be safe and well-tolerated in clinical use.

2 Organ-Specific Gadolinium Chelates

Hepatobiliary gadolinium chelates include gadobenate dimeglumine (Gd-BOPTA), which is currently approved in Europe and the United States of America for MRI of the
central nervous system (CNS), hepatic MRI and MR angiography, and gadoxetic acid disodium (Gd-EOB-DTPA), which is approved for hepatic MRI in some European countries, Japan and the US. They are paramagnetic compounds that are taken up by functioning hepatocytes and excreted in bile. Gadobenate dimeglumine and gadoxetic acid disodium are eliminated by both the renal and hepatobiliary routes. Hepatic uptake accounts for 2–4 % of the injected dose of gadobenate (kidney pathway: 96–98 %) and 50 % of the injected dose of gadoxetic acid disodium (kidney pathway: 50 %) in patients with normal hepatic and renal function.

### 2.1 Gadobenate Dimeglumine

The ionic, linear agent *gadobenate dimeglumine* (Gd-BOPTA) was initially developed for liver imaging. It has only slightly greater R1- and R2-relaxivity than gadopentetate in vitro, but its relaxivity in plasma is almost twice that of gadopentetate because of weak protein binding. The beneficial effect of this increased relaxivity was soon explored in other routine applications such as brain imaging, perfusion MR, and MR angiography. Unlike other available gadolinium-based agents that are excreted exclusively by glomerular filtration in the kidneys, Gd-BOPTA is eliminated by both the renal and hepatobiliary pathways (Kirchin et al. 1998, 2001; Spinazzi et al. 1999). Hepatic uptake accounts for 2–4 % of the injected dose in man.

In addition, this agent has a capacity for weak and transient protein binding (Cavagna et al. 1997), making it suitable for MR angiography (Schneider et al. 2010) with an in vivo T₁ relaxivity approaching twice that of the conventional gadolinium chelates. The approved dose for hepatic imaging is 0.05 mmol kg⁻¹ (0.1 ml kg⁻¹ of a 0.5 M solution) and for CNS imaging and MR angiography 0.1 mmol kg⁻¹ (0.2 ml kg⁻¹ of a 0.5 M solution). Gadobenate dimeglumine should be administered undiluted followed by a bolus of 0.9 % sodium chloride solution. It is currently approved in the US, Canada, Europe, Asia, and Australasia for MR imaging of the central nervous system (CNS) and related tissues, liver, and MRA of the renal and aorto-ilio-femoral vessels in adults and children over 2 years of age.

Gadobenate dimeglumine behaves as a conventional extracellular contrast agent in the first minutes following administration and can be used for dynamic bolus imaging. It then behaves as a liver-specific agent in a later, delayed phase, 40–120 min after administration. As it is taken up specifically by normally functioning hepatocytes through a complex interplay of various carrier systems, it produces a marked and long-lasting enhancement of the normal liver parenchyma. As most tumor nodules are devoid of functional hepatocytes, they do not take up the agent and thus appear hypointense on enhanced MR images (Hamma et al. 1999; Kirchin et al. 2001). Numerous clinical trials have shown that Gd-BOPTA increases sensitivity and specificity and thus increases detection and characterization of liver tumors (Rosati et al. 1994; Caudana et al. 1996; Vogl et al. 1997; Kirchin et al. 1998; Manfredi et al. 1998, 1999; Hamm et al. 1999; Grazioli et al. 2000; Peterstein et al. 2000).

Four exhaustive reviews have been published (Rosati et al. 1994; Hamm et al. 1999; Kirchin et al. 2001; Shellock et al. 2006), including extended clinical experience from phase I studies to post-marketing surveillance. They reported a low incidence of serious events and confirmed the excellent safety profile of Gd-BOPTA. Between July 1990 and September 2000, 2,891 subjects participated in 65 clinical trials, including 2,540 subjects (2,430 adults and 110 children) who received Gd-BOPTA. One thousand nine hundred and eighty-six (78.2 %) subjects received a single injection and 554 subjects received two or more injections. For adult patients and volunteers, the overall incidence of adverse events was 19.8 % and events potentially related to Gd-BOPTA administration were reported in 15.1 % of adult patients. Headache, injection site reaction, nausea, abnormal taste, and flushing were the most common adverse

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* Also extracellular agent
events, with a reported frequency of between 1.0 and 2.6%. Serious adverse events potentially related to Gd-BOPTA were reported in five (0.2%) patients. An apparent tendency toward a greater incidence of both total and study agent-related events was noted in patients younger than 65 years and in studies conducted in the US compared to Europe.

A study comparing gadobenate dimeglumine and gadopentetate dimeglumine for MR imaging of liver tumors reported an incidence of adverse events of 4.7% (6/128) for gadobenate versus 1.6% (2/127) for gadopentetate, but the difference was not significant (Küwatsürü et al. 2001). Results of controlled studies were available in 410 patients and revealed no differences between Gd-BOPTA and Gd-DTPA or placebo in the incidence and type of adverse events. For the controlled liver study and for patients with renal impairment, end-stage renal disease, or hepatic impairment, the incidence of adverse events following Gd-BOPTA administration was similar to that following placebo administration. There were no clinically important changes in vital signs, clinical laboratory data, or ECG findings. The most frequently reported adverse event among the hematology parameters was hypochromic anemia (0.6%). In the pediatric population (n = 110 subjects), the incidence of adverse events was 12.7%; one event was classified as severe but not related to the study agent, and two events were classified as serious (one report of worsening of vomiting that was considered to be possibly related, and one report of hypoxia that was considered to be not related). In a review evaluating the safety and tolerability of gadobenate dimeglumine relative to that of gadopentetate dimeglumine in 924 subjects (including 174 pediatric subjects) enrolled in ten clinical trials, Shellock et al. (2006) showed that the safety profile of gadobenate dimeglumine was similar to gadopentetate dimeglumine in patients and volunteers. In a retrospective analysis of the occurrence of adverse events which included 38,568 patients (Herborn et al. 2009), adverse events totaled 1.2%, and 11 patients (0.03%) experienced serious adverse events. The most frequent findings were nausea, vomiting, and a feeling of warmth (Herborn et al. 2009). No safety concerns were noted in a phase III study comparing gadobenate dimeglumine and gadopentetate dimeglumine (Martincich et al. 2010). The excellent safety profile of gadobenate dimeglumine was confirmed in the pediatric population in a retrospective study which included 200 pediatric inpatients (Schneider et al. 2013). No clinically adverse events were reported among children and there were no changes in creatinine or bilirubin levels even in very young children.

No unconfounded case of nephrogenic systemic fibrosis (NSF) that could be related to the administration of gadobenate dimeglumine has been reported in adults or in children. Gadobenate dimeglumine has a very high conditional stability constant and no excess chelate. It is not known whether biliary excretion conveys a decreased risk for developing NSF. Because of the increased relaxivity of gadobenate dimeglumine, it may be possible to inject a half dose (0.05 mmol kg\(^{-1}\)) without losing efficacious contrast enhancement. This possible advantage should be evaluated by further research (Lin and Brown 2007).

The package insert indicates that patients should be observed during the 15 min following injection as the majority of severe adverse events occur within 15 min after injection. Gadobenate dimeglumine is contraindicated in patients with known allergy or hypersensitivity reactions to gadolinium.

### 2.2 Gadoxetic Acid

Gadoxetic acid disodium (Gd-EOB-DTPA) is a paramagnetic hepatobiliary contrast medium with hepatocellular uptake via the anionic-transporter protein and a molecular weight of 726 Da. In human plasma, it has a higher T1-relaxivity than Gd-DTPA (R1 8.2 mM\(^{-1}\) s\(^{-1}\)) because of a greater degree of protein binding (~10%). At body temperature, the aqueous formulation of 0.25 mol l\(^{-1}\) has an osmolality of 890 mOsmol kg\(^{-1}\) water, a viscosity of 1.22 mPa, and a thermodynamic stability constant of log \(K_{\text{Gd}}=23.46\). Biodistribution studies revealed dose-dependent renal (40.9 ± 2.35%) and biliary (57.0 ± 2.49%) excretion without signs of metabolism and an enterohepatic recirculation of approximately 2.1 ± 0.56% (Schümann-Giampieri et al. 1992; Weinmann et al. 1992; Hamm et al. 1995).

Like other gadolinium agents, gadoxetic acid disodium behaves as a conventional extracellular contrast agent in the first minutes following administration and can be administered as a fast intravenous bolus. The liver-specific, delayed phase starts earlier than Gd-BOPTA and delayed imaging can be started as early as 15–20 min after administration, giving it a logistic advantage over the other liver-specific media (Giovagnoni and Paci 1996; Reimer et al. 2004). Since it is given as a bolus, dynamic imaging is possible. The uptake of Gd-EOB-DTPA by the hepatocytes allows imaging to be performed in parenchymal phases as well. Therefore, twofold lesion information is obtained: lesion vascularity during the dynamic phase and lesion cell composition during the late phase of imaging (Halavaara et al. 2006; Raman et al. 2010; Ichikawa et al. 2010), leading to improved detection and characterization of focal hepatic lesions compared with unenhanced MR imaging (Raman et al. 2010; Ichikawa et al. 2010). The excretion by the biliary system is significantly greater than with Gd-BOPTA (2–4%), making contrast-enhanced MR cholangiography also feasible (Bollow et al. 1997).
A preclinical safety evaluation study of gadoxetic acid disodium concluded that it was well tolerated with high safety margins between the single diagnostic dose and the doses showing adverse effects in animal studies (Dohr et al. 2007). No indications of reproductive or developmental toxicity, potential contact allergenic, or genotoxic effects were observed. No organ toxicity was observed.

For gadoxetic acid disodium, premarking safety data in humans are available from registration clinical trials. In phase I trials with tested doses between 0.01 and 0.1 mmol kg$^{-1}$ body weight, no serious side effects or changes in laboratory values were seen in 44 healthy volunteers (Hamm et al. 1995). The phase II trials were conducted in two parts. As a result of these trials, 0.025 mmol kg$^{-1}$ body weight (or 7 ml for a 70 kg adult) was considered to be the optimum dose for clinical use. While no adverse events were reported in any of 33 patients in the first part (Reimer et al. 1996), eight minor adverse events were reported in the second part in six of 171 patients. No adverse effects were graded as serious and there were no significant changes in vital parameters or laboratory values (Stern et al. 2000). In the phase III multicenter trial reported by Huppertz et al. (2004), 162 patients received Gd-EOB-DTPA and showed improved liver lesion detection. A total of 21 adverse events were recorded in 11 patients (6.8%). Of these, 13 were definitely, possibly, or probably related to the contrast medium, and most frequent symptoms included nausea, headache, altered taste, vaso-dilatation, and injection site pain (Bollow et al. 1997; Huppertz et al. 2004). In a review summarizing the safety data on Gd-EOB-DTPA from phase II and phase III clinical studies conducted in Europe, Japan, and the US (Breuer et al. 2003), a total of 120 (8.5%) of the 1,404 patients experienced one or more adverse effects, which in 3.4% of the patients were considered by the investigator to be definitely, possibly, or probably related to the drug. None of the eight serious adverse events that occurred in five patients were considered to be drug related. The excellent clinical tolerance of Gd-EOB-DTPA was confirmed by the results of the phase III study conducted by Bluemke et al. (2005), which enrolled adult patients who had liver lesions and were scheduled to undergo liver surgery. They received 25 μmol kg$^{-1}$ (0.1 ml kg$^{-1}$) Gd-EOB-DTPA as an intravenous bolus injection at a rate of 2 ml s$^{-1}$. Fifteen events in 10 patients were classified as definitely, probably, or possibly contrast material-related and were all mild or moderate in intensity. The authors concluded that compared with pre-contrast imaging, post-contrast MR imaging with Gd-EOB-DTPA gave improved sensitivity for lesion detection in two of three blinded readers, with no substantial adverse events (Bluemke et al. 2005). In a multicenter prospective study which included 178 patients with suspected focal hepatic lesions, 9.6% of patients who received Gd-EOB-DTPA reported 21 drug-related adverse events (Ichikawa et al. 2010). In another single-center study, it has also been shown that the total clearance of Gd-EOB-DTPA did not significantly change in patients with mild and moderate hepatic impairment, while the pharmacokinetics profile significantly changed in patients with end-stage renal failure, with an increased T1/2 (Geshwend et al. 2011). In addition, no unconfounded case of NSF has been reported in the literature that could be related to the administration of Gd-EOB-DTPA. However, the number of patients with reduced renal function who have received this contrast agent is not known.

Recently, Davenport et al. (2013) reported that intravenous gadoxetate disodium can result in acute self-limiting dyspnea which can reduce the quality of arterial phase MR images. Dyspnea was observed in 14 out of 99 patients, and was significantly more frequent than in the gadobenate group, in which it occurred in 5 out of 99. This effect was not seen in the registration studies and needs further investigation.

Interactions of Gd-EOB-DTPA with commercially available drugs have only been tested in animal models. In a rat model, only rifampicin significantly decreased hepatic enhancement, while prednisolone, doxorubicin, cisplatin, and propanolol led to a slight increase in enhancement (Kato et al. 2002).

### 3 MR Angiography Blood Pool Agent: Gadofosveset Trisodium

Gadofosveset (MS-325) was the first intravascular contrast agent approved in 2005 in the European Union for magnetic resonance angiography (MRA) in adults. Its indications were peripheral arterial disease, aortoiliac occlusive disease, critical limb ischemia, and renal artery stenosis. In 2008, the FDA approved its use for the evaluation of aortoiliac occlusive disease in adults. On 18 October 2011, the European Commission issued a decision to withdraw the marketing authorization for gadofosveset, following a decision of the marketing authorization holder to voluntarily withdraw the marketing authorization for commercial reasons. Today, the product is still in use in the US and Canada.

This gadolinium-based blood-pool contrast agent non-covalently binds to albumin in the blood. This reversible binding to albumin enhances the paramagnetic effectiveness of gadolinium and allows the administration of lower contrast agent doses compared with the doses needed for conventional MR angiography (Nikolaou et al. 2006). Gadofosveset is 2–3 times more stable than Gd-DTPA at pH 7.4 and is 10–100 times more kinetically inert (Caravan et al. 2001). In addition, the albumin-binding characteristic extends the vascular lifetime of the agent and thus allows...
longer vascular imaging time, potentially higher spatial resolution, and larger anatomic coverage. T½ of the agent is about 18 h in patients with normal renal function or 12 times longer than that of the traditional extracellular gadolinium-based contrast agents. The recommended dose is only 1/3–1/4 of the standard dose recommended for the extracellular agents. Hepatic uptake accounts for 9% of the injected dose of gadofosveset with 91% excreted by the kidney. This contrast agent has been reported to provide significant improvement in effectiveness (increase in accuracy, sensitivity, and specificity) over unenhanced MRA for the assessment of aortoiliac occlusive disease (Goyen et al. 2005; Rapp et al. 2005) and arterial disease of the foot (Bosch et al. 2008). However, recent comparative studies with gadobenate dimeglumine for MR angiography of the renal or aorto-iliac-femoral arteries reported either similar (Iezzi et al. 2011) or better (Schneider et al. 2010) diagnostic performance for gadobenate dimeglumine than gadofosveset trisodium.

Results of previous dose-range studies have shown that 0.03 mmol kg⁻¹ was the most clinically appropriate dose for MR angiography of aortoiliac occlusive disease (Perreault et al. 2003). Steger-Hartmann et al. investigated the toxicity of gadofosveset (Steger-Hartmann et al. 2006), including studies of acute, repeated-dose, reproductive, and developmental toxicity as well as local tolerance, immunotoxicity, and mutagenic potential. They concluded that gadofosveset was well tolerated with reasonable safety margins between the single diagnostic dose of 0.03 mmol kg⁻¹ in humans and the doses resulting in adverse effects in animal studies. In 2006, Shamshi et al. published a summary of safety of gadofosveset at 0.03 mmol kg⁻¹ body weight dose in phase II and phase III clinical trials. No severe adverse events were reported in the phase II trial. Overall safety data were pooled from eight studies that included subjects with known or suspected vascular disease who were administered 0.03 mmol kg⁻¹ gadofosveset (767 subjects) or placebo (49 subjects). Pooled data revealed no clinically significant trends in adverse events, laboratory assays, vital signs, oxygen saturation, physical examination, and electrocardiography. Contrast agent-related adverse events were reported by 176 (22.9%) patients receiving gadofosveset and by 16 (32.7%) patients receiving placebo (Shamshi et al. 2006).

The most common adverse events were nonspecific and were: feeling hot, nausea, headache, burning sensation, feeling cold, paresthesia, vasodilatation, and dry mouth (Rapp et al. 2005; Bosch et al. 2008). Most of the treatment-related adverse events occurred within 5 min after gadofosveset administration, and most of them resolved spontaneously within 15 min (Bosch et al. 2008). In a study comparing gadobenate dimeglumine with gadofosveset trisodium (Iezzi et al. 2011), the rate of adverse events appeared higher with gadofosveset trisodium (9.2% of patients in the renal studies and 7.7% in the peripheral studies after gadobenate dimeglumine compared with 30.3–22.1% of patients after gadofosveset trisodium). It is not known how many patients with end-stage renal failure have been examined with gadofosveset and as yet no unconfounded cases of NSF following its administration have been reported (Chryschochou et al. 2010).

Other possible applications of blood-pool agents are now being considered. They include the assessment of venous thromboembolism, coronary artery disease, sinus venous thrombosis, and also perfusion MR studies, and monitoring of inflammatory changes.

4 Conclusion

Organ-specific contrast agents were developed later than conventional extracellular gadolinium chelates and fewer data exist about their safety. They belong to different classes of agent and therefore exhibit different physicochemical properties, modes of action, and metabolic pathways. In each category, at least one agent has been approved for clinical use to improve lesion detection and characterization on MR examinations. Despite the inherent toxicity of the Gd ion and the relatively newness of Gd-based organ-specific contrast agents, these contrast agents are simple to use and appear in general to be safe and well tolerated (Chryschochou 2010). Guidelines on the safety aspects are presented in Appendix A. The European Regulatory Authorities and the European Contrast Safety Committee of the European Society of Urogenital Radiology classify all three agents as having “intermediate risk of NSF” (Stenver 2008).

References


Abstract

Different microbubble ultrasound contrast agents have been approved for abdominal and cardiac applications, and their use has increased over recent years. Experimental studies with high power ultrasound beams have shown that microbubbles produce bioeffects in the cells of nearby tissues as a result of cavitation. To prevent these effects, the power of the ultrasound beam should be kept below the cavitation threshold. Clinically, most adverse reactions result in minor, self-resolving events such as headache, nausea, altered taste, and a sensation of heat. Anaphylactoid reactions, however, may rarely occur and usually resolve spontaneously or with symptomatic treatment. In a few cases anaphylactoid reactions may be severe, or even fatal. Despite this, microbubble contrast agents are safe by any reasonable standard, and certainly are safe compared to iodine- and gadolinium-based contrast agents.

1 Introduction

Contrast-enhanced ultrasound (CEUS) is increasingly used in clinical practice for both cardiac and abdominal applications (Claudon et al. 2013; Mulvagh et al. 2008; Piscaglia et al. 2012). Contrast agents approved for clinical use are well tolerated. Their use does not involve ionizing radiation, and, unlike iodine-based contrast agents, they are not nephrotoxic. Use of microbubble contrast agents, however, raises potential safety concerns. As with all drugs, rare adverse events may occur, in spite of extensive previous studies on safety (Geleijnse et al. 2009; Ionescu 2009; Jakobsen et al. 2005; Kaul and Wei 2009; Miller et al. 2008; ter Haar 2009).

The most common adverse reactions reported in large clinical trials are headache and altered sensation at the injection site, both of which occur in approximately 2 % of

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patients. Other relatively frequent adverse reactions are nausea, flushing, paresthesiae, and altered taste. A limited number of severe reactions have been documented, including, rarely, death.

Besides reactions that are apparent clinically, a number of biological effects secondary to cavitation have been shown experimentally. Cavitation may be responsible for subclinical tissue damage or physiological changes, including premature ventricular contractions and microvascular damage. These effects can be avoided by keeping the power of the ultrasound beam (i.e., the mechanical index) below the cavitation threshold.

### 2 The Acoustic Properties of Microbubble-Based Ultrasound Contrast Media

Ultrasound contrast agents are gas-filled microbubbles with a mean diameter less than that of a red blood cell (i.e., 2–6 μm). They are composed of a shell of biocompatible materials, including proteins, lipids, or biopolymers, which contains gases of low solubility and diffusibility, such as perfluorocarbon or sulfur hexafluoride. There are only a few products currently approved for clinical use (Table 1). Some microbubble agents previously licensed have been withdrawn for purely commercial reasons (Table 2). Other microbubble agents have been tested experimentally and had a good safety profile, but have not been introduced in the market.

Microbubbles behave as an active source of sound and modify the characteristic signature of the echo from blood. They are excellent enhancers because the acoustic impedance of gas is very different from that of blood. When properly insonated with a high power ultrasound beam, microbubbles collapse, producing a transient high intensity broadband signal. With a lower power ultrasound beam, the microbubbles undergo complex oscillation in the beam and work by resonating, rapidly contracting and expanding in response to the pressure changes of the sound wave. A variety of contrast-specific ultrasound modes have been developed to detect the nonlinear behavior of microbubbles.

Microbubble contrast agents are eliminated through the lungs, by respiration, and through the liver. They are not filtered by the kidney, nor are they able to enter the interstitial space. They act as blood pool agents until they are metabolized. The absence of renal excretion explains why they are not nephrotoxic. Some microbubble agents, however, have a postvascular hepatoo- and/or spleno-specific phase from 2 to 5 min after intravenous administration. This phenomenon is probably produced by adherence of the microbubbles to the hepatic sinusoids or by selective uptake of the microbubbles into the reticuloendothelial system by phagocytosis (Harvey et al. 2001).

### 3 Experimental Findings with Microbubble-Based Ultrasound Contrast Media

The cavitation phenomenon refers to the activity, growth, and disruption of microbubbles. It has long been recognized as the most likely potential mechanism for the nonthermal bioeffects of diagnostic ultrasound (Fowlkes 2008; Ultrasound 1998b). Cavitation does not occur unless the tissues are insonated by sufficient energy. The cavitation threshold depends on the number of microbubbles, on their physical properties, and on the characteristics of the ultrasound beam. Microbubble disruption causes large changes in pressure and temperature in the neighboring structures,
Cavitation effects are unlikely to occur during a baseline ultrasound examination because suitable gases are normally practically nonexistent in the body (Church et al. 2008; Miller et al. 2008; Stratmeyer et al. 2008). The cavitation hazard increases when microbubble contrast agents are given. This has caused some concern about the safety of ultrasound contrast agents and may be a potential safety issue in specific situations where vascular damage would be harmful and therefore clinically important, such as the eye and brain (Piscaglia et al. 2012).

During therapeutic ultrasound, excessive heating of tissue has been documented (Fujishiro et al. 1998; Sokka et al. 2003; Wu 1998). It is therefore recommended that therapeutic ultrasound and lithotripsy are avoided in the day after the use of ultrasound contrast agents (Brayman and Miller 1997; Dalecki et al. 1997; Delius et al. 1994).

Pulmonary effects have been studied. Animal studies showed no significant influence of ultrasound contrast media on left ventricular function or myocardial blood flow (Main et al. 1997; Meza et al. 1996). Dramatic cardiopulmonary compromise may occur when microbubble contrast agents are given intravenously to animals which have abundant pulmonary macrophages, such as pigs (Ostensen et al. 1992). During their pulmonary transit, microbubbles are recognized as foreign bodies and pulmonary macrophages try to engulf them. They also release toxic chemicals, including thromboxane A2, which raise pulmonary vascular resistance and can lead to a decrease in cardiac output and resulting hypotension. This effect can be prevented by pretreatment with indomethacin or aspirin, or with a specific thromboxane A2 receptor blocker. The reaction of the lungs to ultrasound contrast media differs between species (Kaul and Wei 2009). Pigs are far more prone to pulmonary uptake than species which normally have fewer pulmonary macrophages such as rats (Walday et al. 1994), monkeys (Ostensen et al. 1992), dogs (Yamaya et al. 2002), rabbits, and humans (Wei et al. 2012). There is concern that some diseases may be associated with increased pulmonary macrophage number or activity, but the importance of this in increasing the risks of using microbubble contrast agents in humans is yet to be proved.

4 Clinical Safety of Ultrasound Contrast Media

Despite extensive investigations (Borges et al. 2002; Myreng et al. 1999; Morel et al. 2000; Robbin and Eisenfeld 1998), the side effects documented in animal studies have not been observed in clinical practice. The most common general adverse events reported, which occur in approximately 2% of patients, are the same as those seen with...
other types of contrast media, namely, headache, warm sensation, and flushing. More unusual events, occurring in <1 % of patients, are nausea and vomiting, dizziness, chills and fever, altered taste, abdominal pain, respiratory disorders, pharyngitis, pruritus, rash, abnormal vision, dry mouth, dizziness, personality disorder, insomnia, nervousness, hyperglycemia, peripheral edema, ecchymosis, and sensory-motor paresis (Jakobsen et al. 2005; Herzog 2008; Myrgren et al. 1999; Rott 1999; ter Haar 2002; Weiss et al. 2012). Such effects are usually transient and mild, are similar for many contrast agents, and were also seen in placebo groups.

Very rarely, features suggestive of hypersensitivity, such as skin erythema, bradycardia, hypotension, or anaphylactic shock, have been reported associated with the use of microbubble contrast agents. Few of these had a fatal outcome (EMEA 2004; Wei et al. 2008).

In a postmarketing analysis of 157,838 patients who had SonoVue injection (Dijkmans et al. 2005) there were 19 severe adverse events (0.012 %), three (0.002 %) with a fatal outcome (EMEA 2004). The patients who died had a high underlying risk of major cardiac complications (severe coronary artery disease, bradycardia, and hypotension accompanied by myocardial ischemia and/or infarctions) which could have been fatal independent of microbubble use. There was no clear evidence of direct cardiac toxicity in any of these serious events. Also in the US, a postmarketing survey reported four deaths within 30 min of contrast agent administration (Definity) for cardiac imaging, but the deaths were not clearly attributable to the contrast agent injection (ter Haar 2009; Wei et al. 2008).

Although they are very rare, the possibility of severe adverse events following microbubble injection raised concerns about the safety of ultrasonographic contrast agents and led to restriction of their approved indications both in Europe and in the US. In May 2004, the European Medicines Agency (EMA) took precautionary measures which restricted the use of SonoVue to non-cardiac imaging procedures. This restriction was later removed, and a precautionary statement was issued stating that extra caution should be exercised in patients with conditions such as severe hypotension, bradycardia, cardiac arrest, and myocardial infarction. At present, SonoVue may be used 7 days after an acute coronary syndrome. Intracoronary administration is not approved and is considered contraindicated, although it has been used without complications in thousands of patients with hypertrophic cardiomyopathy undergoing septal ablation (Senior et al. 2009). Similarly, in October 2007, the United States Food and Drug Administration (FDA) emphasized the risks of serious cardiopulmonary reactions following microbubble contrast media administration, and issued new warnings and contraindications for their use. In May 2008, the FDA revised their changes in labeling, and relaxed their previous warnings.

As data on large series of patients have accumulated, evidence has mounted that microbubble contrast agents are safe by any reasonable standard. Symptomatic premature ventricular contractions have been observed during triggered imaging with ultrasound contrast medium (van Der Wouw et al. 2000), but other investigations did not confirm these data (Kudo et al. 2002). In a retrospective analysis of 78,383 echocardiographic contrast examinations (66,164 with Definity, 12,219 with Optison), more than 10,000 injections were given to critically ill patients or to patients with acute chest pain of suspected cardiac origin. Severe reactions considered to be “probably” related to the ultrasound contrast agent occurred in eight outpatients (0.01 %), and all recovered (Wei et al. 2008). In a retrospective series of 42,408 patients receiving microbubble contrast agents (Optison and Definity) during myocardial perfusion imaging, matched with a cohort of 15,989 patients not receiving ultrasound contrast agents, no significant differences in death or myocardial infarction rates were observed (Dolan et al. 2009). In a retrospective series of 58,254 patients with contrast-enhanced echocardiography, there was a 24 % decreased risk of short-term (1-day) mortality compared to the noncontrast study (Main et al. 2008). In a retrospective study on 10,792 patients who underwent contrast-enhanced (Optison and Definity) stress echocardiography, no statistical difference in the incidence of short-term events within 72 h was observed, compared to the noncontrast study (Abdelmoneim et al. 2009). In a retrospective analysis of the safety of SonoVue in more than 23,000 patients, the overall reported rate of serious adverse events was 0.0086 % (two serious adverse events and no deaths) (Piscaglia and Bolondi 2006). Several other investigations have confirmed these data (Aggeli et al. 2008, 2012; Dijkmans et al. 2009; Gabriel et al. 2008).

Safety of microbubble contrast agents has also been extensively tested in critically ill patients and in those with acute coronary disease. In 3,704 consecutive patients with stable chest pain and with suspected acute coronary syndrome stress, contrast-enhanced echocardiography was not associated with excess adverse events compared with patients undergoing the unenhanced study, despite the greater comorbidities, ischemic burden, and worse left ventricular function of the group which received contrast agents (Anantharam et al. 2009). In 115 consecutive patients with acute (<24 h) myocardial infarction, contrast agent administration did not induce any significant change in vital signs, physical examination, and ECG (Nucifora et al. 2008).
5 Nonvascular Use of Ultrasound Contrast Media

In addition to intravascular use, microbubble contrast agents are suitable for intracavitary administration (Piscaglia et al. 2012). Voiding urosonography is a clinically established procedure for the diagnosis of vesicoureteric reflux. While Levovist was licensed for intravascular use, currently available microbubble contrast agents are not. However, many institutions perform voiding urosonography with SonoVue since the withdrawal of Levovist.

Several investigations have shown that intravascular use of currently available microbubble contrast agents is safe. In particular, no adverse events were observed in a total of 798 examinations with SonoVue reported in four different studies (Ascenti et al. 2004; Duran et al. 2012; Kis et al. 2010; Papadopoulou et al. 2009), nor in a large retrospective study of 4,131 patients who received either Levovist or SonoVue (Riccabona 2012).

Microbubble contrast agents have also been used extravascularly to image Fallopian tubal patency, to detect peritoneo-pleural communication, to evaluate fistulas, and to solve other clinical problems (Piscaglia et al. 2012). In these cases also, no contrast agent related complications were observed.

6 Recommendations for the Use of Ultrasound Contrast Media

The European Committee for Medical Ultrasound Safety (ECMUS) recommends that ultrasound examinations should only be performed by competent personnel trained and updated in safety matters. Ultrasound contrast media should only be used if there is a good clinical indication, and the risk/benefit ratio must be carefully assessed (ECMUS (ECMUS) 2011). As in all diagnostic ultrasound procedures, the MI and TI values should be continually checked and kept as low as possible. In patients with recent acute coronary syndrome or clinically unstable ischemic heart disease, cardiac examinations with ultrasound contrast agents should be avoided. The use of ultrasound contrast agents should be avoided in the 24 h before extracorporeal shock wave therapy.

7 Conclusion

As with any other drug, ultrasound contrast agents have been submitted to extensive clinical investigation of both safety and efficacy before and after approval by national health authorities. Experimental and clinical studies have shown that there are potential hazards in the use of microbubble contrast agents. However, experience accumulated in large clinical trials has shown that the overall risk of serious adverse reactions during CEUS is small (Hayat and Senior 2005). Also, microbubble contrast agents are not nephrotoxic (Piscaglia et al. 2012) and the incidence of adverse events associated with them appears to be much lower than that of current iodine-based or MR contrast agents. The use of ultrasound contrast media must always be clinically justified. In order to reduce the hazard of cavitation, the acoustic output should be kept at the lowest level consistent with obtaining diagnostic information.

Today, many investigators consider ultrasound contrast agents also to be safe in unstable patients, even though neither the FDA nor the EMEA have yet withdrawn their warnings. As with any drug or contrast agent, the risk of an anaphylactic reaction remains and the use of these products in unstable patients should be restricted to centers with full resuscitation capability (“Management of Acute Adverse Reactions to Contrast Media”).

References

Part VIII

Barium Preparations
Barium Preparations: Safety Issues

Sameh K. Morcos

Abstract
Barium preparations are generally safe and adverse effects are uncommon. This chapter describes these adverse effects which include colonic retention of barium, leakage of barium from the gastrointestinal tract, aspiration of barium into the bronchial tree, and intravasation of barium. Allergic reactions to the additives in the barium preparations may also occur.

1 Introduction

The use of barium sulphate to image the gastrointestinal tract (GIT) was first proposed in 1910 by Bechem and Gunther. Since those early days barium sulphate preparations have improved markedly and are now used routinely in radiology departments worldwide. Adverse effects directly related to the oral or rectal administration of barium preparations are discussed in this chapter (Table 1). Technique related complications of barium examinations are beyond the scope of this account.

2 Barium Sulphate

All barium preparations are based on barium sulphate, which is a heavy insoluble material produced from barite. Pure barium sulphate suspension is not suitable for imaging the GIT as it flocculates easily and produces very poor mucosal coating. Therefore, additives (e.g., pectin, sorbitol, agar–agar, carboxymethyl-cellulose) are used in commercial barium preparations to enhance the mucosal coating properties of the suspension, prevent flocculation, and improve the taste for oral use (Almen and Aspelin 1995). More than 90 different additives have been described in the literature. However, the manufacturers of the barium suspensions very often keep the exact type and proportions of additives in each barium preparation secret for commercial reasons.
Barium sulphate is insoluble in water and theoretically nontoxic (Morcos 2000). The particles of barium sulphate suspension remain in the intestinal lumen and are not absorbed. Barium ions are toxic, but the extremely small amounts of barium ions that are present in the suspension and available for intestinal absorption are regarded as being of no practical importance (Almen and Aspelin 1995).

The adverse effects of barium preparations are summarized in Table 1.

Oral or rectal administration of barium sulphate is usually safe but constipation and abdominal pain may occur after barium meals or enemas (Smith et al. 1988). The main risk is that barium may remain in the colon for 6 weeks or longer in elderly patients or patients with partial colonic obstruction. Prolonged stasis of barium may occur following a barium enema into the distal loop of a colostomy (Morcos 2000). Baroliths (barium fecoliths) are rare complications of barium contrast examinations and usually seen in colonic diverticula. Baroliths are often asymptomatic but may be associated with abdominal pain, appendicitis, bowel obstruction, or perforation. They may even have to be removed surgically (Smith et al. 1988; Morcos and Brown 2001). Baroliths of the small bowel are rare. A case of small bowel obstruction secondary to a barolith which developed at the site of narrowing of a loop of ileum caused by a carcinoid tumor has been reported (Regan et al. 1999).

### Table 1 Adverse effects of barium preparations

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retention of barium in colon</td>
<td>Abdominal discomfort</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td>Formation of barolith</td>
<td>Bowel obstruction</td>
</tr>
<tr>
<td></td>
<td>Appendicitis</td>
</tr>
<tr>
<td>Aggravation of toxic dilatation of the colon</td>
<td>Colonic perforation may be precipitated</td>
</tr>
<tr>
<td>Leakage of barium into peritoneal cavity</td>
<td>Peritonitis</td>
</tr>
<tr>
<td></td>
<td>Peritoneal adhesions and bowel obstruction</td>
</tr>
<tr>
<td>Extraperitoneal leakage of barium</td>
<td>Granulomatous inflammatory reaction</td>
</tr>
<tr>
<td></td>
<td>Fibrosis</td>
</tr>
<tr>
<td>Aspiration of barium into bronchial tree</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td></td>
<td>Chemical pneumonia</td>
</tr>
<tr>
<td>Intravasation of barium suspension</td>
<td>Barium pulmonary emboli</td>
</tr>
<tr>
<td></td>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td></td>
<td>Septicaemia</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
</tr>
<tr>
<td>Allergic reactions to barium preparations</td>
<td>Severe anaphylactic reactions may develop to the additives of the barium preparations</td>
</tr>
<tr>
<td></td>
<td>Bronchospasm</td>
</tr>
<tr>
<td></td>
<td>Angioedema</td>
</tr>
<tr>
<td></td>
<td>Urticaria</td>
</tr>
</tbody>
</table>

Toxic dilatation of the colon may be aggravated by barium enema (Morcos 2000; Williams and Harned 1991).

Barium sulphate, even when sterile, can cause marked peritoneal irritation with considerable fluid loss into the peritoneal cavity (Morcos 2000). Perforation into the peritoneal cavity following barium enema occurs rarely. Those at risk are children, debilitated adults, or patients in whom the colon is already weakened by inflammatory, malignant, or parasitic disease. The perforation may be triggered by manipulations involved in giving the barium enema or may result from hydrostatic pressure (Morcos 2000). Perforation of the colon by barium enema may result in death (Morcos 2000). The incidence of perforation is approximately one in 6,000 examinations. The mixture of barium and feces produces severe peritonitis and dense adhesions. The mortality has been reported to be 58% with conservative treatment, and still as high as 47% with surgical intervention (Zheutlin et al. 1952). Early surgery is indicated and large volumes of intravenous fluids improve the prognosis. Patients who recover may develop fibrogranulomatous reactions and adhesions, which can lead to bowel obstruction or ureteric occlusion (Morcos 2000). Perforation of the duodenum and barium leakage into the peritoneal cavity may also occur rarely in patients with duodenal ulcer (Morcos 2000).

Extraperitoneal perforation and leakage of barium into the retroperitoneum or mediastinum may cause few immediate symptoms, but delayed endotoxic shock can develop 12 h later and is frequently fatal. Inflammatory reaction leading to formation of barium granulomata and fibrosis may occur. Painful masses, rectal strictures, and ulcers have
been described following extraperitoneal leakage (Morcos 2000).

Intravenous barium intravasation after enema examination has also been reported and may be associated with mortality of up to 55%. Barium emboli in the lungs, disseminated intravascular coagulation, septicemia, and severe hypotension have been documented following barium intravasation. Most cases have been attributed to trauma from the tip of the enema tube or retention balloon, mucosal inflammation, or misplacement of the tube in the vagina. The amount and speed of intravasation of the barium, as well as the site of the intravasation and the general health of the patient determine the outcome of this complication (Morcos 2000; Williams and Harned 1991). Accidental administration of a barium enema into the vagina instead of the rectum may occur and can be very hazardous: in a number of these patients there has been rupture of the vagina with fatal venous intravasation of barium (Morcos 2000). Barium leaking into a sigmoid abscess during a barium enema examination and intravasating into the portal venous system has been reported (Wheatley and Eckhauser 1991).

Disseminated intravascular coagulation, septicemia, and severe hypotension have also been documented following venous intravasation of Gastrografin, a high osmolar watersoluble contrast medium preparation containing sodium and meglumine diatrizoate used for imaging of the GIT and suitable only for oral or rectal administration. (Glauser et al. 1999). Low osmolar water-soluble contrast media should be used in preference to Gastrografin or barium preparations in patients with suspected compromise of bowel wall integrity.

Aspiration of barium sulphate preparation into the lungs during barium meal examination can cause significant respiratory embarrassment particularly in patients with poor respiratory function and general condition. If thick barium paste is inhaled, it occludes small bronchi and may cause fatal asphyxiation. Aspiration of barium may also cause fatal pneumonia (Lareau and Berta 1976; Gray et al. 1980; Tamm and Kortsik 1999; Morcos and Brown 2001). Persistent alveolar deposition of barium sulphate is seen on the chest radiograph, and only decreases slightly over time (Tamm and Kortsik 1999). Bronchoscopy has been recommended early after barium aspiration to extract barium from the bronchial tree, and prophylactic antibiotic therapy is important to prevent lung infection (Tamm and Kortsik 1999). Water-soluble low osmolar contrast media, which are better tolerated, should be used instead of barium preparations if there is a possibility of aspiration during an upper GIT examination (Ginai et al. 1994).

Hypersensitivity reactions to products used during barium meal examinations are extremely rare (Morcos 2000). Barium sulphate is generally regarded as an inert and insoluble compound that is neither absorbed nor metabolized and is eliminated unchanged from the body. However, some studies have demonstrated that very small amounts of barium ions can be absorbed from the GIT. Isolated cases of barium encephalopathy have been attributed to absorption of barium following the use of barium sulphate (Morcos 2000). Plasma and urine barium levels can be elevated after oral barium sulphate administration. In addition, many additives are present in commercial barium products and are essentially the same as the additives used in food products. Some of these agents can induce an immune response. A patient with a history of a severe reaction to barium agents should not receive barium products again (Morcos and Brown 1999; Seymour and Kesack 1997; Stringer et al. 1993).

Reactions to other aspects of the barium enema procedure are now being recognized with increasing frequency and could be as common as one in 1,000 (Morcos 2000). They vary from urticarial rashes to severe anaphylactic collapse, and can be particularly severe in patients with asthma (Morcos 2000). Hypersensitivity to the latex balloon catheter used in double contrast barium enemas appears to be a common mechanism (Owenby et al. 1991), but hypersensitivity to glucagon, to the preservative methylparaben, or to other additives seems to be responsible in some cases (Morcos 2000).

A fatal case of poisoning resulted from the use of barium sulphide that had been mistaken for barium sulphate has been reported (Morcos 2000). A guideline on the safe use of barium preparations can be found in “ESUR Guidelines on Contrast Media Version 8.1”.

References

Zheutlin N, Lasser EC, Rigler LG (1952) Clinical studies on the effect of barium in the peritoneal cavity following rupture of the colon. Surgery 32:96
Abstract
Contrast media appear to be just as safe in children as they are in adults. The risk factors are the same and the same precautions should be taken. The main differences relate to differences in technique necessitated by differences in size, differences in relative body compartment size, growth, immature renal function, etc., as well as to limited published evidence on their use and safety. Not all agents are approved for use in children, but most of the nonapproved agents can be used off-label with the informed consent of the parents.

1 Introduction
Throughout childhood the same contrast media are used as in adults. However, in children, a variety of factors specific to size and age must be taken into account:
1. The physiology of children, particularly neonates, differs from adults. In early life, factors such as a relatively higher circulating blood volume, faster heart rate, shorter circulation time, shorter distances, smaller structures, different body composition, and immature renal function all affect the dose and timing of contrast agent administration.
2. There is very limited evidence available about the handling of contrast media by the neonatal kidney in the first weeks of life. Recommendations have therefore to be based on consensus developed using information from older subjects, rather on direct scientific evidence.
3. Children generally have a lower incidence of adverse reactions, particularly severe reactions, to contrast media.
4. In children, the smaller blood vessels necessitate smaller needles, and these reduce the speed of contrast medium injection, increase the effect of contrast medium viscosity, and lead to altered delay times.
5. In children, there is a greater risk of fluid imbalance between different compartments, which is particularly important for gastrointestinal, oral, and rectal contrast medium administration. This is very important when using hyperosmolar contrast media, especially in premature infants and in young and sick children and infants with labile circulatory systems.

6. Not all contrast media are approved for pediatric use. For some specific applications, such as liver-specific MR contrast media and ultrasound contrast media, no registered agents are available for neonates and children. If such agents are used in neonates, infants or children their use is off-label, which necessitates more detailed informed consent from the parents (“Off-Label Use of Contrast Media: Practical Aspects”). Also, licensing of contrast media and the approval process, as well as legal requirements, vary significantly throughout Europe and the rest of the world, making general statements difficult. The Summary of Product Characteristics must be consulted for the agent in question.

Some other general considerations apply to all contrast agent use in infants and children. First, a higher level justification is needed for invasive investigations, and use of contrast medium is a first step of invasiveness. Second, all imaging using ionizing radiation must be based on a valid indication because neonates, infants and young children are significantly more sensitive to radiation than adults and have a longer expected life span in which to experience possible long-term adverse effects (Hammer et al. 2011; Krille et al. 2012; Pearce et al. 2012). Third, the different physiology and anatomy of children suggest that contrast agent dynamics and long-term effects may be different from those in adults. For example, it has been suggested that gadolinium may accumulate in the bone marrow under certain circumstances, and may be particularly toxic to bone marrow in young children, in whom there is active hemopoiesis occurring in the peripheral red bone marrow (Hocine et al. 1995; Idee et al. 2006). Currently, there is no evidence that this occurs but it has not been fully investigated. It therefore seems prudent to recommend that macrocyclic gadolinium-based contrast media, which are likely to leave the smallest amount of gadolinium in the bone marrow and the body, should be used in children.

Finally, other methods of achieving contrast between the tissues should be used whenever possible to reduce the need for contrast media. Examples are using air to fill the gastrointestinal tract on plain films or at fluoroscopy, using saline or water to fill and distend bowel and body cavities for CT, MRI, or ultrasound, and using cranberry or blueberry juice or similar manganese containing drinks as bowel contrast media in MRI. These methods will not be discussed further in this chapter, the remainder of which focuses on contrast media.

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2 Oral/Gastrointestinal Radiopaque Contrast Media

Oral radiopaque contrast media are used to image the gastrointestinal tract, with typical pediatric indications being gastrointestinal and anorectal malformations (e.g., atresia, duplication, fistula, stenosis, Hirschsprung’s disease, etc.), and anatomical and functional assessment of persistent gastro-esophageal reflux and neonatal stool transport and passage problems. In general, particularly in older children, the use of radiopaque contrast media is similar to that in adults, although less frequent. However, in the very young, because of the immature mucosal barrier and the greater risk of fluid and electrolyte imbalance, there are some differences in the ways contrast media are used.

Most commonly barium-based contrast media are used because they give good opacification of the gastrointestinal tract and outline the mucosal lining well. However, in large amounts and higher concentrations, barium agents can cause constipation and, to reduce this, emulsifiers have been added in modern formulations. Also, if perforation with barium spill into the peritoneum occurs, it may cause peritoneal granulomatous inflammation, barium-based contrast media should be avoided and water soluble low- or iso-osmolar non-ionic iodine-based contrast media should be used (Zerin 1992; Hiorns 2011).

Hyperosmolar barium-based contrast media, most commonly containing amidotrizoate, have traditionally been used for upper gastrointestinal tract studies as well as for diagnosing and/or treating meconium transport problems in newborns, especially those born preterm (Kao and Franken 1995). With these contrast media, there is a high risk of fluid and electrolyte imbalance and mucositis, with resultant potentially disastrous and even life-threatening consequences (Leonidas et al. 1976). High osmolar iodine-based agents are, therefore, usually contraindicated in neonates and infants and in many departments are banned, with non-ionic low- or iso-osmolar iodine-based contrast media used instead. The only acceptable exception is if high osmolar agents are diluted at least 3:1 and used to treat preterm babies with meconium transport problems under proper monitoring and with appropriate fluid and electrolyte replacement.
Non-ionic low- and iso-osmolar iodine-based contrast media are the agents of choice, particularly in neonates and infants with possible fistula or at risk of aspiration or perforation, although they provide less good contrast and poorer outlining of the bowel contour. Very rarely, it may be necessary to use other agents where high mucosal detail is required provided there are no specific contraindications (Table 1). In older children, low-osmolar iodine-based agents can be used as an alternative when barium-based suspensions are contraindicated (McAlister and Siegel 1984; Basu et al. 2009).

For oral bowel contrast during pediatric CT, diluted low-osmolar iodine-based contrast media (e.g., iopamidol) in a 2 % solution are usually used, with the volume given based on the patient’s age (Table 2) (Sorantin et al. 2002; Sorantin 2013).

For some indications, air may serve as an ideal negative contrast agent, for example, to diagnose and reduce intussusception or to diagnose deep and high bowel obstruction, and this may help to reduce the use of iodine-based contrast media. Air may also be used for double contrast studies to improve radiopaque contrast medium demonstration of the detail of the gastric wall and bowel.

### 3 Iodine-Based Contrast Media for Other Intraluminal Applications

Iodine-based contrast media are used in children to opacify the bladder for voiding cystourography, and also rarely for bronchography, fistulography, arthrography, or sialography, or for interventional procedures which require body cavities to be outlined. These studies, especially filling body cavities to guide intervention, should be done with the same contrast media as are used intravascularly, i.e., low- or iso-osmolar iodine-based agents. Hyperosmolar ionic iodine-based contrast media should only be used in intact systems where there is no risk of extravasation or accidental intravascular administration, for example, for voiding cystourethrography, commonly using a low-iodine concentration such as 100–150 mgI ml⁻¹. The subtle antimicrobial effect of the hyperosmolar agents may be advantageous for cystography (Dawson et al. 1983; Speck 1999).

### 4 Intravascular Iodine-Based Contrast Media

Iodine-based contrast media are mainly used intravascularly for CT and interventional procedures, and are also used for diagnostic angiography. Occasionally, they are used for intravenous urography, but this is increasingly being avoided due to the risk of contrast-induced nephropathy.
Table 3  Recommended weight- and age-dependent dose and concentration for pediatric intravenous iodine-based contrast agent use when using age adapted KV settings

<table>
<thead>
<tr>
<th>Age</th>
<th>Iodine concentration (mg/ml)</th>
<th>Dose (ml/kg b.w.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 year</td>
<td>150–200</td>
<td>2.5</td>
</tr>
<tr>
<td>Between 1 and 2 years</td>
<td>200–250</td>
<td>2.0</td>
</tr>
<tr>
<td>Older than 2 years</td>
<td>250–300</td>
<td>1.5</td>
</tr>
<tr>
<td>Older than 6 years</td>
<td>300–350</td>
<td>1–1.5</td>
</tr>
</tbody>
</table>

Note 1. Use a higher iodine concentration for smaller and more peripheral vessels, and with higher KV. 2. Do not administer more than 100 ml of contrast agent

Adapted from Sorantin 2013

replaced by MR-urography or ultrasonography. Beyond infancy, the indications and contraindications for these agents and their renal excretion are similar to those in adults and will not be discussed further as they are considered in other chapters. The risk of acute and delayed reactions after intravascular iodine-based agents was evaluated by Mikkonen et al. (1995).

In neonates and infants, however, there is very little evidence-based data on renal contrast agent excretion. The neonatal kidney is immature and its function is less than 20 % of that in an adult. Also, in neonates, especially those that are premature, and in young infants, fluid volume and osmolar balance are less stable and circulating relative blood volume is larger than in older children and adults. This means that particular care is necessary when contrast-enhanced studies in neonates, infants, and in preterm babies are being considered.

The recognized complications of iodine-based contrast media, such as contrast-induced nephropathy, ‘allergic’ reactions, and thyrotoxicosis in patients at risk, also occur in children. Appropriate precautions, similar to those in adults, have to be taken, such as checking for renal disease or renal functional impairment, and assuring adequate hydration (Brasch 2008; Riccabona et al. 2010). Serum creatinine levels in children are much lower than in adults because they have less muscle mass, and the appropriate normal range for age must be used (Schwartz et al. 1976). GFR calculation should be done with equations adapted to be suitable for young pediatric patients (Filler et al. 2013, Langlois 2008; Ring et al. 2008, Schwartz and Work 2008; Schwartz et al. 2009).

For premedication before contrast medium and treatment of adverse reactions, different strategies dependent on age are recommended. These are usually developed as a standard in a given institution, in cooperation with the pediatricians and anesthesiologists, and are similar to the recommended measures in adults. There are also some guidelines for more general use. An example is the corticosteroid and antihistamine premedication regimen for children with known allergy to iodine-based contrast media recommended by the American College of Radiologists (ACR) of oral Prednisone 0.5–0.7 mg/kg (up to 50 mg) at 13, 7, and 1 h before contrast medium injection, and Diphenhydramine 1.25 mg/kg (up to 50 mg) 1 h before contrast medium injection (ACR 2012, 2012a, 2012b).

A particular point of discussion is whether low- or iso-osmolar iodine-based contrast media are preferable. It is possible that low-osmolar low-viscosity contrast media may protect the immature kidney in particular, compared to iso-osmolar contrast media, by keeping sufficient fluid within the vascular bed to prevent sluggish flow and secondary complications (Persson 2011). This phenomenon may also affect contrast medium flow through the renal tubules, and low-osmolar agents may prevent stasis there also.

Contrast agent concentration and iodine load have not been studied in infants, so there is insufficient evidence to produce general guidelines on the optimal contrast medium iodine concentration to use. It has been suggested that a concentration of 150–350 mg I ml⁻¹ concentration is sufficient in neonates, infants, and young children, with the lower concentration chosen for younger patients, especially, since lower KV settings of 80 or 100 kV are used. However, higher iodine concentrations and higher KV settings may be necessary to assess small peripheral vessels on CT-angiography (Frush 2008; Zoo et al. 2011; Sorantin et al. 2013a, b).

The dose of a contrast agent depends on its concentration and on the iodine load; the higher the iodine load, the lower the dose and the greater the contrast achieved. However, since neonates and infants have a relatively higher circulating blood volume, a higher dose of contrast agent may be necessary. In general, 2 ml kg⁻¹ (to a maximum of 3 ml kg⁻¹) is suggested for neonates, 2 ml kg⁻¹ for infants, and thereafter 1–1.5 ml kg⁻¹ (Pärtan 2013; Sorantin et al. 2002, 2013a, b) (Table 3). Higher doses and higher iodine concentrations have been used for CT-angiography or interventional procedures, particularly cardiography and angiography, but this was associated with an increased incidence of contrast-induced nephropathy (Frush 2008; Kurian et al. 2013; Heran et al. 2010). Higher contrast agent doses therefore must be considered when risk versus benefit is being assessed for a particular patient and should be
discussed with the clinicians involved, including the pediatric nephrologist, as well as with the parents or carers.

5 Gadolinium-Based Contrast Media

There is little safety data available about the use of gadolinium-based agents in children, particularly neonates and infants aged less than 1 year. As in adults, the important factors are gadolinium elimination, the risk of transmetallation, the effect of renal function, acidosis and dehydration, and the possibility of nephrogenic systemic fibrosis (NSF) (“Nephrogenic Systemic Fibrosis and Gadolinium-Based Contrast Media”).

There are very few, partially verified reports of NSF in infants and children (Eldevik and Brunberg 1994; Karacaaltincaba et al. 2009; Riccabona et al. 2008a). NSF has been reported in one 6-year-old patient and in older children after administration of the least stable linear agents to children with renal impairment (Dharnidharka et al. 2007; Foss et al. 2009; Jain et al. 2004). Recent research on the prevalence of NSF in children identified 20 pediatric cases, 12 of which had documented gadolinium exposure (K. Darge, Personal communication). To date, no case has been reported after macrocyclic agents or in children with normal renal function. There is insufficient data to know whether NSF is less likely to occur in children than in adults with a similarly degree of renal impairment. In children, the guidelines recommended by the American College of Radiologists, the ESUR Contrast Medium Safety Committee, the ESPR Uroradiology task force and the ESUR Pediatric working group (ACR 2012; Mendichovszky et al. 2008; Riccabona et al. 2009; Thomsen et al. 2013) should be followed (“Nephrogenic Systemic Fibrosis and Gadolinium-Based Contrast Media”, “ESUR Guidelines on Contrast Media Version 8.1”). It should be noted, however, that estimated GFR (eGFR) values in premature infants and neonates may be <30 ml min$^{-1}$ 1.73 m$^{-2}$ because of immature renal function, not renal impairment. Age adapted normal creatinine values, which are much lower than in adults because of the smaller muscle mass (Schwartz et al. 1976) and specific pediatric GFR calculations which take the lower GFR values into account should be used (Langlois 2008; Ring et al. 2008; Schwartz and Work 2008; Schwartz et al. 2009). In premature babies and neonates, although an eGFR value <30 ml min$^{-1}$ 1.73 m$^{-2}$ should not be considered to be an absolute contraindication to the most stable agents, caution should still be exercised when administering gadolinium-based contrast media, since the potentially fatal disease of NSF and the long-term effects of gadolinium retention in the body are not yet fully understood.

Problems have also occurred because of poor hydration and temporarily impaired renal function, with increases in serum creatinine after administration of gadolinium-based agents, in school children and adolescents as well as younger children. There is no good data available yet on the handling of gadolinium-based agents by the neonatal kidney, and therefore recommendations are based on extrapolation from adult physiology. In general, administration of gadolinium-based agents should, if possible, be avoided in the first months of life.

Recommendations for using gadolinium-based contrast media in children are given below:

1. Gadolinium-based contrast media should only be used in children when the clinical problem cannot be solved using other imaging methods, such as ultrasonography, or unenhanced MRI techniques, such as MR angiography or perfusion imaging based on Time-of-Flight or arterial spin labeling techniques (Mannelli et al. 2012; Penfield and Reilly 2008).

2. The most stable macrocyclic gadolinium-based agents should be used, and the less stable linear compounds, which are more likely to induce NSF, should be avoided (Penfield and Reilly 2008; Morcos 2007).

3. Assessment of renal function by measuring creatinine and glomerular filtration rate is essential, using normal ranges suitable for age, particularly in those at risk of renal disease or with a recent disease that might have affected renal function. In children with a GFR lower than 30 ml min$^{-1}$ 1.73 m$^{-2}$, gadolinium-based contrast media should be avoided unless there is a compelling indication and no alternative substitute of less risk in children.

4. If the GFR is between 30 and 60 ml min$^{-1}$ 1.73 m$^{-2}$, a pediatric nephrologist should be consulted before the gadolinium-based agent is given and there should be appropriate preparation with hydration, correction of acidosis, and similar measures. Also, informed consent should be obtained from the parents and the patient (if legally applicable).

5. Double dose administration should be avoided in children on general principles, although there is no direct evidence that this is harmful. However, the dose may be corrected to allow for the relatively higher circulating blood volume which, in ml kg$^{-1}$ body weight, is effectively about one and a half times higher than in older patients for the first months of life.

6. In general, administration of gadolinium-based contrast media should be avoided in the first months of life, unless for serious indications, and after careful consideration.

7. As repeated administration potentially leads to a higher cumulative systemic dose and is a possible risk factor, repeated investigations should be avoided and single dose techniques are advised. The patient’s cumulative dose should be recorded and in the patient’s file or in a register. Careful documentation of an individual patient’s dose for follow-up, particularly in at-risk
patients, over a longer period of time is important, but it is also important to keep a register of all patients to obtain data for future analysis which will provide evidence for neonatal and pediatric administration of these agents in the future.

In some countries no cyclic gadolinium-based contrast media are registered for use in neonates and in the first years of life. The safety and imaging potential of some agents, however, have been specifically studied for children aged over 1 year (Baker et al. 2004; Hahn et al. 2009; Forsting and Palkowitch 2010). If a contrast-enhanced study is necessary in neonates and young infants, the risk to benefit relation has to be properly considered, particularly taking into account the risk of alternative iodine-based contrast medium and radiation when a contrast-enhanced CT would be the only alternative. The summary of Product Characteristics (the ‘insert’) should always be checked to find to what extent the contrast agent has been approved for children. If the agent is not approved, provided it is not contraindicated, it can be used with the informed consent of the parents. Lack of approval is usually because phase 3 studies are rarely done in very young children.

6 Ultrasound Contrast Media

Currently, no ultrasound contrast media are approved for pediatric use and the only compound which was registered for use in children has been taken off the market. However, because of the higher radiation sensitivity of children, particularly the very young, there is an increasing demand to use imaging methods not involving ionizing radiation. This has led to an increased number of off-label administrations of some ultrasound contrast media in neonates, infants, and children (Esposito et al. 2012; Piskunowicz et al. 2011; Riccabona 2012; Schreiber-Dietrich and Dietrich 2012).

The same indications and contraindications apply as in adults (Ter Haar 2009; Torzilli 2005). Since ultrasound contrast media are not excreted by the kidney, renal function, and renal immaturity do not affect the use of these agents (Calliada et al. 1998). Possible impairment of the metabolic pathways of the carrier molecule, which may, for example, be a lipid, protein, or sugar, must be considered and may be a contraindication. Thus, galactosemia was a contraindication for the galactose-based ultrasound contrast medium, which has been taken off the market.

There are a few studies and meta-analyses which have evaluated current knowledge about ultrasound contrast media administration during childhood, most of them focusing only on the intra-vesical use (i.e., contrast-enhanced voiding urosonography- ce-VUS) (Mccarville 2011; Piskunowicz et al. 2012; Papadopoulou et al. 2012; Riccabona et al. 2008b; Riccabona 2012; Taylor 2000; Valentini et al. 2002; Zimbaro et al. 2007). Most studies looked at diagnostic reliability and details of the procedure, and safety aspects in children have rarely been addressed (Darge 2010; Ntoulia et al. 2013; Papadopoulou et al. 2012). However, all the available data, even if it is mostly from adults, indicate a good safety profile for ultrasound contrast media. They have an extremely low incidence of side effects, which are usually mild and far less frequent than with iodine-and gadolinium-based contrast media and also less frequent than in adults (Correas et al. 2001; Morel et al. 2000; Nolsoe et al. 2011; Piscaglia and Bolondi 2006). As with all other contrast media, ultrasound contrast media can be used in any body cavity as well as intravascularly, most commonly intravenously in adults, whereas in children the most common application is intravesically.

The indications for and findings on intravenous administration are similar to those in adults. However, in children, the incidence of malignancy is lower so there is less need for malignancy-related liver imaging. Pediatric intravenous use of ultrasound contrast media is most often for trauma imaging, differential diagnosis, and post-transplant assessment.

Table 4 Dose suggestions for pediatric ultrasound contrast agent use (SonoVue®, Bracco, Milano, Italy), based on clinical experience

<table>
<thead>
<tr>
<th>Application</th>
<th>Dose Suggestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast-enhanced voiding urosonography (ce-VUS)</td>
<td>0.5–1% of actual bladder filling volume</td>
</tr>
<tr>
<td>Note</td>
<td>For Optison, 0.5% of bladder volume appears sufficient (Darge et al. 2013)</td>
</tr>
<tr>
<td>Intravenous contrast-enhanced ultrasonography (iv. CEUS)</td>
<td></td>
</tr>
<tr>
<td>Neonates:</td>
<td>0.1–0.25 ml/kg b.w.</td>
</tr>
<tr>
<td>Infants:</td>
<td>0.1 ml/kg b.w.</td>
</tr>
<tr>
<td>Older children (&gt;20 kg body weight):</td>
<td>0.05 ml/kg b.w.</td>
</tr>
<tr>
<td>Adolescents: adult doses</td>
<td>2.4–4.8 ml</td>
</tr>
</tbody>
</table>

No studies of appropriate dose are available, but some dose-finding studies have been done for ce-VUS

NB No ultrasound contrast agent has been approved for use in children; its use is off-label ("Off-Label Use of Medicines: Legal Aspects", "Off-Label Use of Contrast Media: Practical Aspects")
The dose should be adapted to the child’s size. Currently, there are no proper pediatric studies of appropriate dose for all the available ultrasound contrast media, so the dose is usually extrapolated from the adult dose in relation to the child’s body weight, and the higher relative circulating blood volume in children should also be taken into account (Table 4).

The most common use of ultrasound contrast media in children, which is specific to children, is intravesical administration for contrast-enhanced voiding urosonography (ce-VUS) for assessment of vesicoureteral reflux. This may be complemented by perineal ultrasonography during voiding for assessment of the urethra. (Ascenti et al. 2004; Berrocal et al. 2001, 2005; Darge and Troeger 2002; Darge 2008; Darge et al. 2013; Duran et al. 2009; Kenda et al. 2000; Riccabona et al. 2008b). To date, no adverse events have been reported with this use of ultrasound contrast media, which in addition has good sensitivity and specificity (Darge 2011; Papadopoulou et al. 2012; Riccabona 2012).

In conclusion, the use of ultrasound contrast media in neonates, infants, and children has been recommended not only by various local groups, but also by the European Federation of Ultrasound in Medicine and Biology, for well-defined clinical indications, in spite the fact that administration is off-label (Claudon et al. 2008; Piscaglia et al. 2012; Nolsoe et al. 2011; Riccabona 2012). The use of ultrasound contrast media should always be considered as an alternative to other studies that use radiation, and parents should be provided with appropriate information to enable them to decide whether to give informed consent.

7 Conclusion

The safety considerations when using contrast media in neonates, infants, and children are similar, but not the same as, in adults. The dose of contrast agent must be adjusted to the individual patient, and age specific normal values of serum creatinine, etc. must be used. In children, for radiography, including CT, non-ionic iodine-based contrast media should be used and, for MRI, macrocyclic gadolinium-based agents should be chosen. The Summary of Product Characteristics should be consulted, particularly since not all contrast media are tested in children in accordance with the rules of the various Medicine Agencies. This does not mean that untested and officially unapproved contrast media may not be used in children, but that informed consent must be obtained from the parents. However, if a contrast agent is absolutely contraindicated, it may not be used, even with informed consent.

References


Appendix A: ESUR Guidelines on Contrast Media
Version 8.1

Version 8.1 differs from version 8.0 because section A.3.4 has been updated.
Academic Members of the Contrast Media Safety Committee of the European Society of Urogenital Radiology

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A.3.5 Pregnancy and Lactation
A.3.6 Interaction with Other Drugs and Clinical Tests
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A.3.8 Safety of Barium Contrast Media
A.4 Questionnaires to be completed by clinicians referring patients for examinations
using iodine- or gadolinium-based contrast media
A.1 Non-renal Adverse Reactions

A.1.1 Acute Adverse Reactions

Definition: An adverse reaction which occurs within 1 h of contrast medium injection.

<table>
<thead>
<tr>
<th>Classification</th>
</tr>
</thead>
</table>
| Mild           | Nausea, mild vomiting  
|                | Urticaria  
|                | Itching  
| Moderate       | Severe vomiting  
|                | Marked urticaria  
|                | Bronchospasm  
|                | Facial/laryngeal edema  
| Severe         | Hypotensive shock  
|                | Respiratory arrest  
|                | Cardiac arrest  
|                | Convulsion  

A.1.1.1 Acute Adverse Reactions to Iodine-Based Contrast Media

<table>
<thead>
<tr>
<th>Risk factors for acute reactions</th>
</tr>
</thead>
</table>
| Patient-related                  | Patient with a history of:  
|                                  | • Previous moderate or severe acute reaction (see classification above) to an iodine-based contrast agent  
|                                  | • Asthma  
|                                  | • Allergy requiring medical treatment  
| Contrast medium-related          | High osmolality ionic contrast media  

To reduce the risk of an acute reaction

For all patients

- Use a non-ionic contrast medium  
- Keep the patient in the Radiology Department for 30 min after contrast medium injection  
- Have the drugs and equipment for resuscitation readily available (see Sect. A.1.1.3)

For patients at increased risk of reaction (see risk factors above)

- Consider an alternative test not requiring an iodine-based contrast agent  
- Use a different iodine-based agent for previous reactors to contrast medium  
- Consider the use of premedication. Clinical evidence of the effectiveness of premedication is limited. If used, a suitable premedication regime is prednisolone 30 mg (or methylprednisolone 32 mg) orally given 12 and 2 h before contrast medium injection

Extravascular administration of iodine-based contrast media

- When absorption or leakage into the circulation is possible, take the same precautions as for intravascular administration
A.1.1.2 Acute Adverse Reactions to Gadolinium-Based Contrast Media

### Risk factors for acute reactions

<table>
<thead>
<tr>
<th>Patient-related</th>
<th>Patients with a history of</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Previous acute reaction to gadolinium-based contrast agent</td>
</tr>
<tr>
<td></td>
<td>• Asthma</td>
</tr>
<tr>
<td></td>
<td>• Allergy requiring medical treatment</td>
</tr>
</tbody>
</table>

| Contrast medium-related         | The risk of reaction is not related to the osmolality of the contrast agent: the low doses used make the osmolar load very small |

#### To reduce the risk of an acute reaction

<table>
<thead>
<tr>
<th>For all patients</th>
<th>Keep the patient in the Radiology Department for 30 min after contrast medium injection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Have the drugs and equipment for resuscitation readily available (see Sect. A.1.1.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>For patients at increased risk of reaction (see risk factors above)</th>
<th>Consider an alternative test not requiring a gadolinium-based contrast agent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Use a different gadolinium-based agent for previous reactors to contrast medium</td>
</tr>
<tr>
<td></td>
<td>Consider the use of premedication. There is no clinical evidence of the effectiveness of premedication. If used, a suitable premedication regime is prednisolone 30 mg (or methylprednisolone 32 mg) orally given 12 and 2 h before contrast medium</td>
</tr>
</tbody>
</table>

Note: The risk of an acute reaction to a gadolinium-based contrast agent is lower than the risk with an iodine-based contrast agent, but severe reactions to gadolinium-based contrast media may occur.

### A.1.1.3 Management

#### First line emergency drugs and instruments which should be in the examination room.

- Oxygen
- Adrenaline 1:1,000
- Antihistamine H1—suitable for injection
- Atropine
- β2-agonist metered dose inhaler
- I.V. Fluids—normal saline or Ringer’s solution
- Anti-convulsive drugs (diazepam)
- Sphygmomanometer
- One-way mouth “breather” apparatus

#### Simple guidelines for first line treatment of acute reactions to all contrast media

*The same reactions are seen after iodine- and gadolinium-based contrast agents and after ultrasound contrast agents. The incidence is highest after iodine-based contrast agents and lowest after ultrasound agents.*

**Nausea/Vomiting**
- **Transient:** Supportive treatment
- **Severe, protracted:** Appropriate antiemetic drugs should be considered.

**Urticaria**
- **Scattered, transient:** Supportive treatment including observation.
- **Scattered, protracted:** Appropriate H1-antihistamine intramuscularly or intravenously should be considered. Drowsiness and/or hypotension may occur.
- **Generalized:** Appropriate H1-antihistamine intramuscularly or intravenously should be given. Drowsiness and/or hypotension may occur. Consider Adrenaline 1:1,000, 0.1–0.3 ml (0.1–0.3 mg) intramuscularly in adults, 50 % of adult dose to pediatric patients between 6 and 12 years old and 25 % of adult dose to pediatric patients below 6 years old. Repeat as needed.
Bronchospasm

1. Oxygen by mask (6–10 l/min)
2. β-2-agonist metered dose inhaler (2–3 deep inhalations)
3. Adrenaline.

*Normal blood pressure*

Intramuscular: 1:1,000, 0.1–0.3 ml (0.1–0.3 mg) [use smaller dose in a patient with coronary artery disease or elderly patient]

In pediatric patients: 50% of adult dose to pediatric patients between 6 and 12 years old and 25% of adult dose to pediatric patients below 6 years old. Repeat as needed.

*Decreased blood pressure*

Intramuscular: 1:1,000, 0.5 ml (0.5 mg).

In pediatric patients: 6–12 years: 0.3 ml (0.3 mg) intramuscularly, <6 years: 0.15 ml (0.15 mg) intramuscularly.

Laryngeal Edema

1. Oxygen by mask (6–10 l/min)
2. Intramuscular adrenaline (1:1,000), 0.5 ml (0.5 mg) for adults, repeat as needed.

   *In pediatric patients: 6–12 years: 0.3 ml (0.3 mg) intramuscularly, <6 years: 0.15 ml (0.15 mg) intramuscularly.*

Hypotension

*Isolated hypotension*

1. Elevate patient’s legs
2. Oxygen by mask (6–10 l/min)
3. Intravenous fluid: rapidly, normal saline or Ringer’s solution
4. If unresponsive: adrenaline: 1:1,000, 0.5 ml (0.5 mg) intramuscularly, repeat as needed

   *In pediatric patients: 6–12 years: 0.3 ml (0.3 mg) intramuscularly, <6 years: 0.15 ml (0.15 mg) intramuscularly.*

*Vagal reaction (hypotension and bradycardia)*

1. Elevate patient’s legs
2. Oxygen by mask (6–10 l/min)
3. Atropine 0.6–1.0 mg intravenously, repeat if necessary after 3–5 min, to 3 mg total (0.04 mg/kg) in adults. In pediatric patients, give 0.02 mg/kg intravenously (max. 0.6 mg per dose), repeat if necessary to 2 mg total.
4. Intravenous fluids: rapidly, normal saline or Ringer’s solution.

Generalized Anaphylactoid Reaction

1. Call for resuscitation team
2. Suction airway as needed
3. Elevate patient’s legs if hypotensive
4. Oxygen by mask (6–10 l/min)
5. Intramuscular adrenaline (1:1,000), 0.5 ml (0.5 mg) in adults. Repeat as needed.

   *In pediatric patients: 6–12 years: 0.3 ml (0.3 mg) intramuscularly, <6 years: 0.15 ml (0.15 mg) intramuscularly.*

6. Intravenous fluids (e.g. normal saline, Ringer’s solution)
7. H1-blocker e.g. diphenhydramine 25–50 mg intravenously.
A.1.2 Late Adverse Reactions

<table>
<thead>
<tr>
<th>Definition:</th>
<th>A late adverse reaction to intravascular iodine-based contrast medium is defined as a reaction which occurs 1 h to 1 week after contrast medium injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactions:</td>
<td>Skin reactions similar in type to other drug-induced eruptions. Maculopapular rashes, erythema, swelling, and pruritus are most common. Most skin reactions are mild to moderate and self-limiting</td>
</tr>
<tr>
<td>A variety of late symptoms (e.g., nausea, vomiting, headache, musculoskeletal pains, fever) have been described following contrast medium, but many are not related to contrast medium</td>
<td></td>
</tr>
<tr>
<td>Risk factors for skin reactions:</td>
<td>Previous late contrast medium reaction</td>
</tr>
<tr>
<td></td>
<td>Interleukin-2 treatment</td>
</tr>
<tr>
<td></td>
<td>Use of non-ionic dimers</td>
</tr>
<tr>
<td>Management:</td>
<td>Symptomatic and similar to the management of other drug-induced skin reactions e.g. antihistamines, topical steroids and emollients</td>
</tr>
<tr>
<td>Recommendations:</td>
<td>Patients who have had a previous contrast medium reaction, or who are on interleukin-2 treatment should be advised that a late skin reaction is possible and that they should contact a doctor if they have a problem</td>
</tr>
<tr>
<td></td>
<td>Patch and delayed reading intradermal tests may be useful to confirm a late skin reaction to contrast medium and to study cross-reactivity patterns with other agents</td>
</tr>
<tr>
<td></td>
<td>To reduce the risk of repeat reaction, use another contrast agent than the agent precipitating the first reaction.</td>
</tr>
<tr>
<td></td>
<td>Avoid agents which have shown cross-reactivity on skin testing</td>
</tr>
<tr>
<td></td>
<td>Drug prophylaxis is generally not recommended</td>
</tr>
</tbody>
</table>

Note: Late skin reactions of the type which occur after iodine-based contrast media have not been described after gadolinium-based and ultrasound contrast media

A.1.3 Very Late Adverse Reactions

Definition: An adverse reaction which usually occurs more than 1 week after contrast medium injection.

<table>
<thead>
<tr>
<th>Type of reaction</th>
<th>Iodine-based contrast media</th>
<th>Thyrotoxicosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadolinium-based contrast media</td>
<td>Nephrogenic systemic fibrosis</td>
<td></td>
</tr>
</tbody>
</table>

A.1.3.1 Thyrotoxicosis

<table>
<thead>
<tr>
<th>At risk</th>
<th>Patients with untreated Graves’ disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with multinodular goiter and thyroid autonomy, especially if they are elderly and/or live in area of dietary iodine deficiency</td>
</tr>
<tr>
<td>Not at risk</td>
<td>Patients with normal thyroid function</td>
</tr>
<tr>
<td>Recommendations</td>
<td>Iodine-based contrast media should not be given to patients with manifest hyperthyroidism</td>
</tr>
<tr>
<td></td>
<td>Prophylaxis is generally not necessary</td>
</tr>
<tr>
<td></td>
<td>In selected high-risk patients, prophylactic treatment may be given by an endocrinologist; this is more relevant in areas of dietary iodine deficiency</td>
</tr>
<tr>
<td></td>
<td>Patients at risk should be closely monitored by endocrinologists after iodine-based contrast medium injection</td>
</tr>
<tr>
<td></td>
<td>Intravenous cholangiographic contrast media should not be given to patients at risk</td>
</tr>
</tbody>
</table>
A.1.3.2 Nephrogenic Systemic Fibrosis

A diagnosis of nephrogenic systemic fibrosis (NSF) should only be made if the Yale NSF Registry clinical and histopathological criteria are met (J Am Acad Dermatol 2011; 65:1095–1106). The link between nephrogenic systemic fibrosis (NSF) and gadolinium-based contrast agents was recognized in 2006.

**Clinical features of NSF**

<table>
<thead>
<tr>
<th>Onset</th>
<th>From the day of exposure for up to 2–3 months, sometimes up to years after exposure</th>
</tr>
</thead>
</table>
| Initially | • Pain  
  • Pruritus  
  • Swelling  
  • Erythema  
  • Usually starts in the legs |
| Later | • Thickened skin and subcutaneous tissues—‘woody’ texture and brawny plaques  
  • Fibrosis of internal organs, e.g. muscle, diaphragm, heart, liver, lungs |
| Result | • Contractures  
  • Cachexia  
  • Death, in a proportion of patients |

**Patients**

- **At higher risk**:  
  - Patients with CKD 4 and 5 (GFR <30 ml/min)  
  - Patients on dialysis  
  - Patients with acute kidney insufficiency

- **At lower risk**:  
  - Patients with CKD 3 (GFR 30–59 ml/min)

- **Not at risk of NSF**:  
  - Patients with stable GFR >60 ml/min

**Contrast agents: Risk classification (based on laboratory data) and Recommendations**

**Highest risk of NSF**

| Contrast agents | Gadodiamide (Omniscan<sup>®</sup>)  
  | Ligand: Non ionic linear chelate (DTPA-BMA)  
  | **Incidence of NSF**: Estimated to be 3–18 % in at-risk subjects  
  | Gadopentetate dimeglumine (Magnevist<sup>®</sup> plus generic products)  
  | Ligand: Ionic linear chelate (DTPA)  
  | **Incidence of NSF**: Estimated to be 0.1–1 % in at-risk subjects  
  | Gadoversetamide (Optimark<sup>®</sup>)  
  | Ligand: Non ionic linear chelate (DTPA-BMEA)  
  | **Incidence of NSF**: Unknown |

(continued)
**Recommendation**

These agents are CONTRAINDICATED in

- patients with CKD 4 and 5 (GFR <30 ml/min), including those on dialysis
- acute renal insufficiency
- pregnant women
- neonates

These agents should be used with CAUTION in

- patients with CKD 3 (GFR 30–60 ml/min)
  - There should be at least 7 days between two injections
- children less than 1 year old

Lactating women: Stop breastfeeding for 24 h and discard the milk

Serum creatinine (eGFR) measurement and clinical assessment of patient before administration: **Mandatory**

These agents should never be given in higher doses than 0.1 mmol/kg per examination in any patient

---

**Intermediate risk of NSF**

**Contrast agents**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Ligand</th>
<th>Incidence of NSF</th>
<th>Special feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadobenate dimeglumine (Multihance®)</td>
<td>Ionic linear chelate (BOPTA)</td>
<td>No unconfounded cases have been reported</td>
<td>It is a combined extracellular and liver specific agent with 2–3 % albumin binding. Diagnostic results can be achieved with 50 % lower doses than with usual extracellular agents. In man ~4 % is excreted via the liver</td>
</tr>
<tr>
<td>Gadofosveset trisodium (Vasovist®, Ablavar®)</td>
<td>Ionic linear chelate (DTPA-DPCP)</td>
<td>No unconfounded cases reported, but experience is limited</td>
<td>It is a blood pool agent with affinity to albumin (&gt;90 %). Diagnostic results can be achieved with 50 % lower doses than extracellular Gd-CM. Biological half-life is 12 times longer than for extracellular agents (18 h compared to 1½ h, respectively); 5 % is excreted via the bile</td>
</tr>
<tr>
<td>Gadoxetate disodium (Primovist®, Eovist®)</td>
<td>Ionic linear chelate (EOB-DTPA)</td>
<td>No unconfounded cases have been reported but experience is limited</td>
<td>It is an organ specific gadolinium contrast agent with 10 % protein binding and 50 % excretion by hepatocytes. Diagnostic results can be achieved with lower doses than extracellular Gd-CM</td>
</tr>
</tbody>
</table>

---

**Lowest risk of NSF**

**Contrast agents**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Ligand</th>
<th>Incidence of NSF</th>
<th>Special feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadobutrol (Gadovist®, Gadavist®)</td>
<td>Non-ionic cyclic chelate (BT-DO3A)</td>
<td>A few unconfounded cases have been reported, but there is uncertainty about the histopathologic changes</td>
<td></td>
</tr>
<tr>
<td>Gadoterate meglumine (Dotarem®, Magnescope®)</td>
<td>Ionic cyclic chelate (DOTA)</td>
<td>No unconfounded cases have been reported</td>
<td></td>
</tr>
<tr>
<td>Gadoteridol (Prohance®)</td>
<td>Non-ionic cyclic chelate (HP-DO3A)</td>
<td>No unconfounded cases have been reported</td>
<td></td>
</tr>
</tbody>
</table>
Recommendation

These agents should be used with CAUTION in

- patients with CKD 4 and 5 (GFR <30 ml/min)
  - There should be at least 7 days between two injections

Pregnant women: Can be used to give essential diagnostic information

Lactating women: The patient should discuss with the doctor whether the breast milk should be discarded in the 24 h after contrast medium

Laboratory testing of renal function (eGFR) is not mandatory. Renal function assessment by questionnaire should be used if serum creatinine is not measured

Recommendation for all patients

Never deny a patient a clinically well-indicated enhanced MRI examination

In all patients use the smallest amount of contrast medium necessary for a diagnostic result

Always record the name and dose of the contrast agent used in the patient records

*Confounded cases:* If two different Gd-CM have been injected, it is impossible to determine with certainty which agent triggered the development of NSF and the situation is described as ‘confounded’. *Unconfounded cases:* The patient has never been exposed to more than one agent.

## A.2 Renal Adverse Reactions

Definition: Contrast-induced nephropathy (CIN) is a condition in which a decrease in renal function occurs within 3 days of the intravascular administration of a CM in the absence of an alternative aetiology. An increase in serum creatinine by more than 25% or 44 umol/l (0.5 mg/dl) indicates CIN.

### A.2.1 Renal Adverse Reactions to Iodine-Based Contrast Media

**Risk factors for contrast medium-induced nephropathy**

<table>
<thead>
<tr>
<th>Patient-related</th>
<th>Procedure-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>• eGFR less than 60 ml/min/1.73 m² before intra-arterial administration</td>
<td>• Intra-arterial administration of contrast medium</td>
</tr>
<tr>
<td>• eGFR less than 45 ml/min/1.73 m² before intravenous administration</td>
<td>• High osmolality agents</td>
</tr>
<tr>
<td>• In particular in combination with</td>
<td>• Large doses of contrast medium</td>
</tr>
<tr>
<td>• Diabetic nephropathy</td>
<td>• Multiple contrast medium administrations within a few days</td>
</tr>
<tr>
<td>• Dehydration</td>
<td></td>
</tr>
<tr>
<td>• Congestive heart failure (NYHA grade 3–4) and low LVEF</td>
<td></td>
</tr>
<tr>
<td>• Recent myocardial infarction (&lt;24 h)</td>
<td></td>
</tr>
<tr>
<td>• Intra-aortic balloon pump</td>
<td></td>
</tr>
<tr>
<td>• Peri procedural hypotension</td>
<td></td>
</tr>
<tr>
<td>• Low hematocrit level</td>
<td></td>
</tr>
<tr>
<td>• Age over 70</td>
<td></td>
</tr>
<tr>
<td>• Concurrent administration of nephrotoxic drugs</td>
<td></td>
</tr>
<tr>
<td>• Known or suspected acute renal failure</td>
<td></td>
</tr>
</tbody>
</table>

- Known or suspected acute renal failure
A.2.1.1 Time of Referral

Elective Examination

Identify patients who require measurement of renal function

- Patients with known eGFR less than 60 ml/min/1.73 m²
- Patients who will receive intra-arterial contrast medium
- Age over 70
- Patients with a history of:
  - Renal disease
  - Renal surgery
  - Proteinuria
  - Diabetes mellitus
  - Hypertension
  - Gout
  - Recent nephrotoxic drugs

Determine eGFR (or SCr) within 7 days of contrast medium administration

Emergency Examination

Identify at-risk patients (see above) if possible:

- Determine eGFR if the procedure can be deferred until the result is available without harm to the patient.
- If eGFR cannot be obtained, follow the protocols for patients with eGFR less than 60 ml/min/1.73 m² for intra-arterial administration and eGFR less than 45 ml/min/1.73 m² for intravenous administration as closely as clinical circumstances permit.

A.2.1.2 Before the Examination

Elective examination

At-risk patients (see above)

- Consider an alternative imaging method not using iodine-based contrast media
- Discuss the need to stop nephrotoxic drugs with the referring physician
- Start volume expansion. A suitable protocol is intravenous normal saline, 1.0–1.5 ml/kg/h, for at least 6 h before and after contrast medium. An alternative protocol is intravenous sodium bicarbonate (154 mEq/l in dextrose 5 % water), 3 ml/kg/h for 1 h before contrast medium, and 1 ml/kg/h for 6 h after contrast medium

Emergency examination

At risk patients (see above)

- Consider an alternative imaging method not using iodine-based contrast media
- Start volume expansion as early as possible before contrast medium administration (See elective examination)

A.2.1.3 Time of Examination

At-risk patients (see above)

- Use low or iso-osmolar contrast media
- Use the lowest dose of contrast medium consistent with a diagnostic result

Patients not at increased risk

- Use the lowest dose of contrast medium consistent with a diagnostic result

A.2.1.4 After the Examination

At-risk patients

Continue volume expansion

Determine eGFR 48–72 h after contrast medium

Note: No pharmacological prophylaxis (with renal vasodilators, receptor antagonists or endogenous vasoactive mediators or cytoprotective drugs) has yet been shown to offer consistent protection against contrast-induced nephropathy.
A.2.2 Renal Adverse Reactions to Gadolinium-Based Contrast Media

A.2.2.1 MR Examinations
- The risk of nephrotoxicity is very low when gadolinium-based contrast media are used in approved doses.
- In patients with reduced renal function refer to ESUR guidelines on NSF, Sect. A.1.3.2.

A.2.2.2 Radiographic Examinations
- Gadolinium-based contrast media should not be used for radiographic examinations in patients with renal impairment.
- Gadolinium-based contrast media are more nephrotoxic than iodine-based contrast media in equivalent X-ray attenuating doses.

A.2.3 Patients Taking Metformin

A.2.3.1 Iodine-Based Contrast Media

1. Patients with eGFR equal to or greater than 60 ml/min/1.73 m² (CKD 1 and 2) can continue to take metformin normally.
2. Patients with eGFR 30–59 ml/min/1.73 m² (CKD 3)
   a. Patients receiving intravenous contrast medium with eGFR equal to or greater than 45 ml/min/1.73 m² can continue to take metformin normally.
   b. Patients receiving intra-arterial contrast medium, and those receiving intravenous contrast medium with an eGFR between 30 and 44 ml/min/1.73 m², should stop metformin 48 h before contrast medium and should only restart metformin 48 h after contrast medium if renal function has not deteriorated.
3. Patients with eGFR less than 30 ml/min/1.73 m² (CKD 4 and 5), or with an intercurrent illness causing reduced liver function or hypoxia. Metformin is contraindicated and iodine-based contrast media should be avoided.
4. Emergency patients. Metformin should be stopped from the time of contrast medium administration. After the procedure, the patient should be monitored for signs of lactic acidosis. Metformin should be restarted 48 h after contrast medium if serum creatinine/eGFR is unchanged from the pre-imaging level.

A.2.3.2 Gadolinium-Based Contrast Media

No special precautions are necessary when diabetic patients on metformin are given gadolinium-based contrast medium.

A.2.4 Dialysis and Contrast Medium Administration

All iodine- and gadolinium-based contrast media can be removed by hemodialysis or peritoneal dialysis. However, there is no evidence that hemodialysis protects patients with impaired renal function from contrast medium-induced nephropathy or nephrogenic systemic fibrosis. In all patients, avoid osmotic and fluid overload. To avoid the risk of NSF refer to Sect. A.1.3.2.

<table>
<thead>
<tr>
<th>Patients on dialysis</th>
<th>Iodine-based contrast medium</th>
<th>Gadolinium-based contrast medium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodialysis</td>
<td>• Correlation of time of the contrast medium injection with the hemodialysis session is unnecessary</td>
<td>• Correlation of time of the contrast medium injection with the hemodialysis session is recommended</td>
</tr>
<tr>
<td></td>
<td>• Extra hemodialysis session to remove contrast medium is unnecessary</td>
<td>• Extra hemodialysis session to remove contrast medium as soon as possible after it has been administered is recommended</td>
</tr>
<tr>
<td>Continuous ambulatory peritoneal dialysis</td>
<td>• Hemodialysis to remove the contrast medium is unnecessary for iodine-based contrast medium, but for gadolinium-based contrast medium it should be discussed with referring physician</td>
<td></td>
</tr>
</tbody>
</table>
A.3 Miscellaneous

A.3.1 Contrast Medium Extravasation

| Type of injuries | • Most injuries are minor |
|                 | • Severe injuries include skin ulceration, soft tissue necrosis, and compartment syndrome |

| Risk factors | • Use of a power injector |
|             | • Less optimal injection sites including lower limb and small distal veins |
|             | • Large volume of contrast medium |
|             | • High osmolar contrast media |

| Technique-related | • Inability to communicate |
|                  | • Fragile or damaged veins |
|                  | • Arterial insufficiency |
|                  | • Compromised lymphatic and/or venous drainage |
|                  | • Obesity |

| Patient-related | • Intravenous technique should always be meticulous using appropriate sized plastic cannula placed in a suitable vein to handle the flow rate used during the injection |
|                | • Test injection with normal saline |
|                | • Use non-ionic iodine-based contrast medium |

| To reduce the risk | • Conservative management is adequate in most cases |
|                    | – limb elevation |
|                    | – apply ice packs |
|                    | – careful monitoring |
|                    | • If a serious injury is suspected, seek the advice of a surgeon |

A.3.2 Pulmonary Effects of Iodine-Based Contrast Media

| Pulmonary adverse effects | • Bronchospasm |
|                         | • Increased pulmonary vascular resistance |
|                         | • Pulmonary edema |

| Patients at high risk | • History of asthma |
|                       | • History of pulmonary hypertension |
|                       | • Incipient cardiac failure |

| To reduce the risk of pulmonary adverse effects | • Use low or iso-osmolar contrast media |
|                                               | • Avoid large doses of contrast media |

A.3.3 Effects of Iodine-Based Contrast Media on Blood and Endothelium

The clinically important adverse effect of iodine-based contrast media on blood and endothelium is thrombosis. It is recognized that:
• All contrast media have anticoagulant properties, especially ionic agents.
• High osmolar ionic contrast media may induce thrombosis due to endothelial damage, particularly in phlebographic procedures.
• Drugs and interventional devices that decrease the risk of thromboembolic complications during interventional procedures minimize the importance of the effects of contrast media.
Guidelines

- Meticulous angiographic technique is mandatory and is the most important factor in reducing thromboembolic complications.
- Low- or iso-osmolar contrast media should be used for diagnostic and interventional angiographic procedures including phlebography.

A.3.4 Contrast Media and Catecholamine-Producing Tumors (Pheochromocytoma and Paraganglioma)

Preparation

(a) Before intravenous iodine- or gadolinium-based contrast medium: No special preparation is required.
(b) Before intra-arterial iodine-based contrast medium: α- and β-adrenergic blockade with orally administered drugs under the supervision of the referring physician is recommended.

Type of contrast medium which should be used

<table>
<thead>
<tr>
<th>Iodine-based agents</th>
<th>Gadolinium-based agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pregnancy</strong></td>
<td></td>
</tr>
<tr>
<td>(a) In exceptional circumstances, when radiographic examination is essential, iodine-based contrast media may be given to the pregnant female. (b) Following administration of iodine-based agents to the mother during pregnancy, thyroid function should be checked in the neonate during the first week</td>
<td>(a) When there is a very strong indication for enhanced MR, the smallest possible dose of one of the most stable gadolinium-based contrast agents (see Contrast agents: Intermediate and low risk of NSF, Sect. A.1.3.2) may be given to the pregnant female. (b) Following administration of gadolinium-based agents to the mother during pregnancy, no neonatal tests are necessary</td>
</tr>
<tr>
<td><strong>Lactation</strong></td>
<td></td>
</tr>
<tr>
<td>Breast feeding may be continued normally when iodine-based agents are given to the mother</td>
<td>Breast feeding should be avoided for 24 h after contrast medium if high risk agents are used</td>
</tr>
<tr>
<td><strong>Pregnant or lactating mother with renal impairment</strong></td>
<td>See renal adverse reactions (see Sect. A.2.1). No additional precautions are necessary for the fetus or neonate</td>
</tr>
</tbody>
</table>

A.3.5 Pregnancy and Lactation

<table>
<thead>
<tr>
<th>Iodine-based agents</th>
<th>Gadolinium-based agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pregnancy</strong></td>
<td></td>
</tr>
<tr>
<td>(a) In exceptional circumstances, when radiographic examination is essential, iodine-based contrast media may be given to the pregnant female. (b) Following administration of iodine-based agents to the mother during pregnancy, thyroid function should be checked in the neonate during the first week</td>
<td>(a) When there is a very strong indication for enhanced MR, the smallest possible dose of one of the most stable gadolinium-based contrast agents (see Contrast agents: Intermediate and low risk of NSF, Sect. A.1.3.2) may be given to the pregnant female. (b) Following administration of gadolinium-based agents to the mother during pregnancy, no neonatal tests are necessary</td>
</tr>
<tr>
<td><strong>Lactation</strong></td>
<td></td>
</tr>
<tr>
<td>Breast feeding may be continued normally when iodine-based agents are given to the mother</td>
<td>Breast feeding should be avoided for 24 h after contrast medium if high risk agents are used</td>
</tr>
<tr>
<td><strong>Pregnant or lactating mother with renal impairment</strong></td>
<td>See renal adverse reactions (see Sect. A.2.1). No additional precautions are necessary for the fetus or neonate</td>
</tr>
</tbody>
</table>

A.3.6 Interaction with Other Drugs and Clinical Tests

<table>
<thead>
<tr>
<th>General recommendation</th>
<th>Be aware of the patients drug history. Keep a proper record of the contrast medium injection (time, dose, name). Do not mix contrast media with other drugs in tubes and syringes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs needing special attention</td>
<td></td>
</tr>
<tr>
<td>• Metformin</td>
<td>Refer to renal adverse reactions section (Sect. A.2.1)</td>
</tr>
<tr>
<td>• Nephrotoxic drugs</td>
<td>Refer to renal adverse reactions section (Sect. A.2.1)</td>
</tr>
<tr>
<td>• Cyclosporine</td>
<td>Refer to renal adverse reactions section (Sect. A.2.1)</td>
</tr>
<tr>
<td>• Cisplatin</td>
<td>Refer to renal adverse reactions section (Sect. A.2.1)</td>
</tr>
<tr>
<td>• Aminoglycosides</td>
<td>Refer to renal adverse reactions section (Sect. A.2.1)</td>
</tr>
<tr>
<td>• Non steroid anti-inflammatory drugs</td>
<td>Refer to renal adverse reactions section (Sect. A.2.1)</td>
</tr>
<tr>
<td>• β-blockers</td>
<td>β-blockers may impair the management of bronchospasm and the response to adrenaline</td>
</tr>
<tr>
<td>• Interleukin-2</td>
<td>Refer to late adverse reactions section (Sect. A.1.2)</td>
</tr>
</tbody>
</table>
A.3.7 Safety of Ultrasound Contrast Media

**Statement:** Ultrasound contrast media are generally safe

**Contraindication:** Severe heart disease (e.g. New York class III/IV)

**Type and severity of reactions:** The majority of reactions are minor (e.g. headache, nausea, sensation of heat, altered taste) and self-resolving. More severe acute reactions are rare and are similar to those after iodine- and gadolinium-based agents (see Sect. A.1.1).

**To reduce the risk:** Check for intolerance to any of the components of the contrast agent. Use the lowest level of acoustic output and shortest scanning time to allow a diagnostic examination.

**Treatment:** If a serious event occurs—see non-renal adverse reaction section (Sect. A.1.1.3)

---

A.3.8 Safety of Barium Contrast Media

<table>
<thead>
<tr>
<th><strong>Recommended action</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Contraindications</strong></td>
</tr>
<tr>
<td>Integrity of gut wall compromised</td>
</tr>
<tr>
<td>Use iodine-based water-soluble contrast media</td>
</tr>
<tr>
<td>In neonates and patients at risk of leakage into mediastinum and/or lungs use low-</td>
</tr>
<tr>
<td>or isoosmolar contrast media</td>
</tr>
<tr>
<td>Previous allergic reactions to barium products</td>
</tr>
<tr>
<td>Use iodine-based water-soluble contrast media and be prepared to treat a reaction</td>
</tr>
<tr>
<td><strong>Cautions</strong></td>
</tr>
<tr>
<td>Bowel strictures</td>
</tr>
<tr>
<td>Use only small amounts</td>
</tr>
<tr>
<td>Extensive colitis</td>
</tr>
<tr>
<td>Avoid barium enemas</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
</tr>
<tr>
<td>Reduced bowel motility</td>
</tr>
<tr>
<td>Encourage fluid intake</td>
</tr>
<tr>
<td>Venous intravasation</td>
</tr>
<tr>
<td>Early identification and careful observation</td>
</tr>
<tr>
<td>Antibiotics and intravenous fluids</td>
</tr>
<tr>
<td>Emergency treatment may be needed</td>
</tr>
<tr>
<td>Aspiration</td>
</tr>
<tr>
<td>Bronchoscopic removal for large amounts</td>
</tr>
<tr>
<td>Chest physiotherapy</td>
</tr>
<tr>
<td>Antibiotics</td>
</tr>
</tbody>
</table>
A.4 Questionnaires to be completed by clinicians referring patients for examinations using iodine- or gadolinium-based contrast media

Questionnaire for iodine-based contrast media administration to be completed by the referring clinician.

1. History of moderate or severe reaction to an iodine-based contrast medium
   - Yes
   - No

2. History of allergy requiring treatment
   - Yes
   - No

3. History of asthma
   - Yes
   - No

4. Hyperthyroidism
   - Yes
   - No

5. Heart Failure
   - Yes
   - No

6. Diabetes Mellitus
   - Yes
   - No

7. History of renal disease
   - Yes
   - No

8. Previous renal surgery
   - Yes
   - No

9. History of proteinuria
   - Yes
   - No

10. Hypertension
    - Yes
    - No
<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gout</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most recent measurement of serum creatinine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Value:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Date:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the patient currently taking any of the following drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Metformin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Interleukin 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• NSAIDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Aminoglycosides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• β-blockers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Completed by _______________________________  Date ___________________________
<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. History of moderate or severe reaction to a MRI contrast medium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. History of allergy requiring treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. History of asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Has the patient end-stage renal failure (eGFR &lt; 30 ml/min/1.73 m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Has the patient reduced renal function* (eGFR between 30 and 60 ml/min/1.73 m²)?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Only if high risk agents are used.

Completed by ________________________________ Date _____________________
Appendix B: Publications from the ESUR Contrast Media Safety Committee


Thomsen HS, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR) (2005) In which patients should serum-creatinine be measured before contrast medium administration? Eur Radiol 15: 749–754


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