Medical Radiology
Diagnostic Imaging

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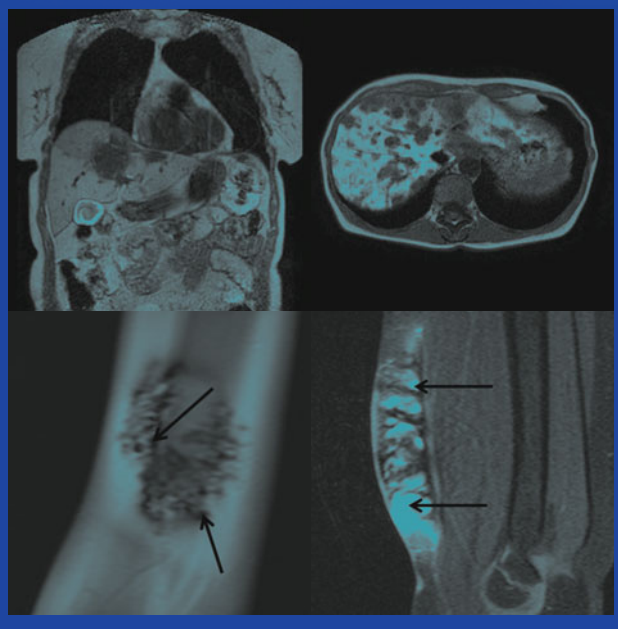
*Editors*

# Contrast Media

## Safety Issues and ESUR Guidelines

*Third Edition*



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Editors

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Third Edition

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# 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 — Henrik S. Thomsen
London, UK — 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 — Henrik S. Thomsen
London, UK — 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.

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# Contents

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# Part I
# General Issues

# Contrast Media Classification and Terminology

Henrik S. Thomsen, Marie-France Bellin, Jarl Å. Jakobsen, and Judith A. W. Webb

## Contents



**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

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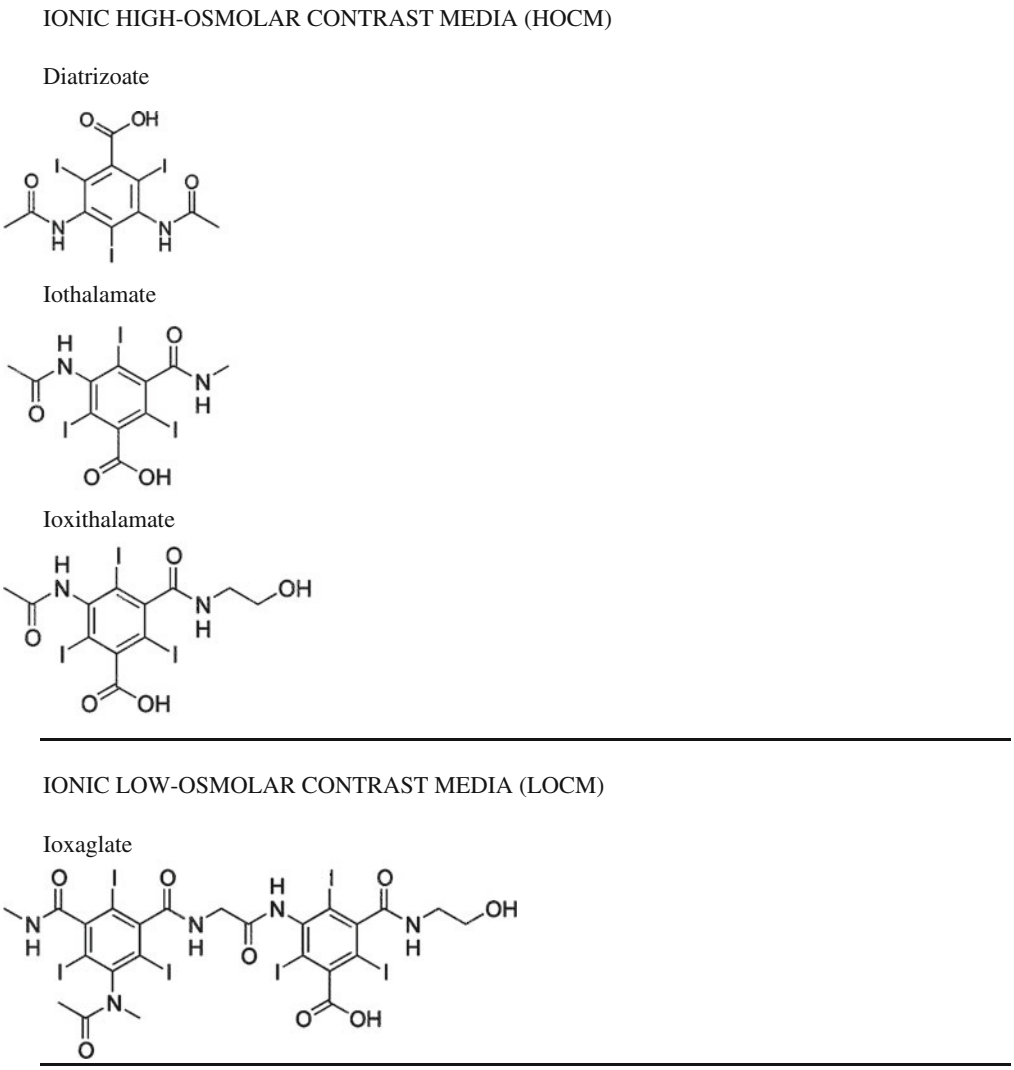



**Fig. 1** Chemical structure of commercially available iodine-based contrast agents

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

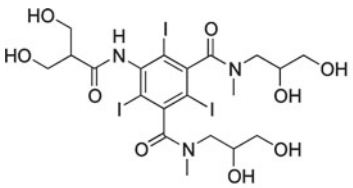
Water-soluble iodine-based contrast agents that diffuse throughout the extracellular space are principally used during computed tomography (CT), angiography and other conventional radiography. They can also be administered directly into the body cavities, for example the gastrointestinal tract and the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

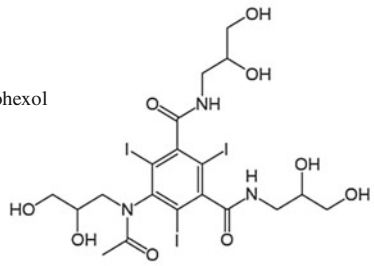
Iodine-based contrast agents can be divided into two groups, ionic and non-ionic, based on their water solubility (Dawson et al. 1999; Thomsen et al. 1999). The water in the body is polarized unevenly with positive poles around the

NON-IONIC LOW-OSMOLAR CONTRAST MEDIA (IOCM)

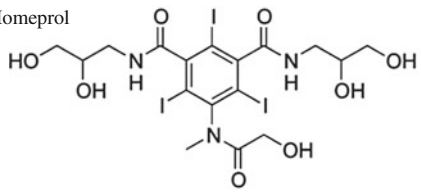
Iobiditrol



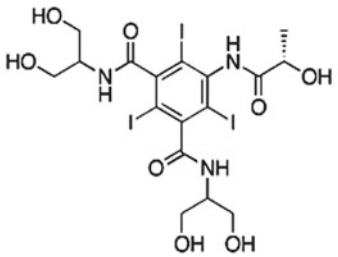
Iohexol



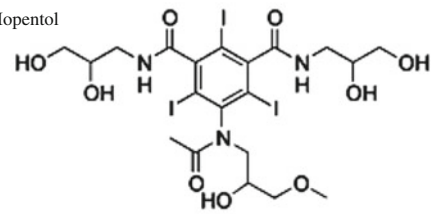
Iomeprol



Iopamidol



Iopentol



Iopromide

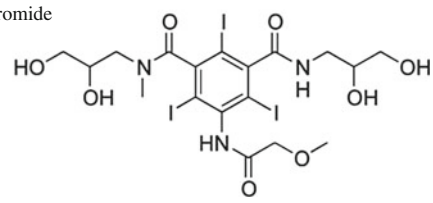
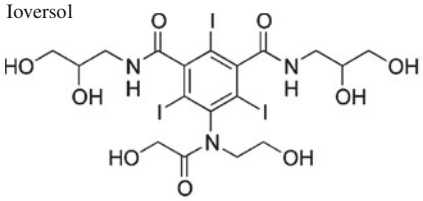
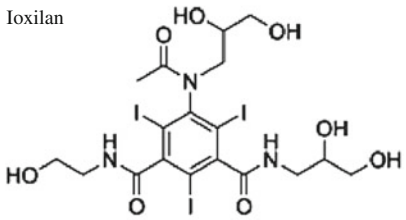


**Fig. 1** continued

Ioversol

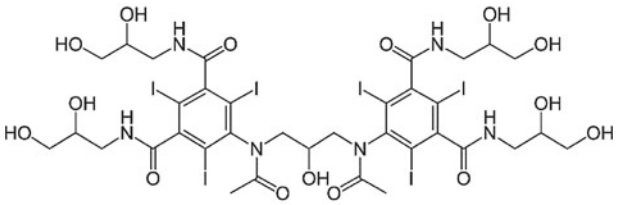


Ioxilan



NON-IONIC ISO-OSMOLAR CONTRAST MEDIA (LOCM)

Iodixanol



Iotrolan

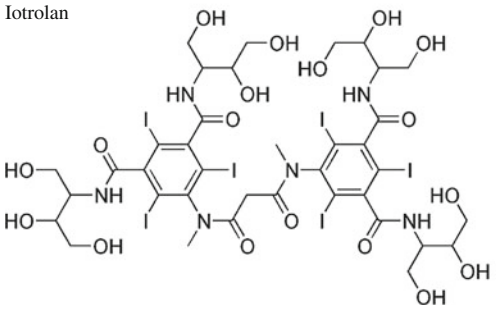


**Fig. 1** continued

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

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

| Contrast agent | Trade name | Structure | Charge | Class | Maximum g–Iodine/ml |
|---|---|---|---|---|---|
| Diatrizoate | Renografin, Hypaque | Monomer | Ionic | HOCM | 358–370 |
| Amidotrizoate | Urografin | Monomer | Ionic | HOCM | 300 |
| Iothalamate | Conray | Monomer | Ionic | HOCM | 370 |
| Ioxithalamate | Telebrix | Monomer | Ionic | HOCM | 350 |
| Ioxaglate | Hexabrix | Dimer | Ionic | LOCM | 320 |
| Iopamidol | Iopamiro, Isovue | Monomer | Non–Ionic | LOCM | 370 |
| Iohexol | Omnipaque | Monomer | Non–Ionic | LOCM | 350 |
| Iomeprol | Iomeron, Imeron | Monomer | Non–Ionic | LOCM | 400 |
| Iopentol | Imagopaque | Monomer | Non–Ionic | LOCM | 300 |
| Ioxilan | Oxilan | Monomer | Non–Ionic | LOCM | 350 |
| Ioversol | Optiray | Monomer | Non–Ionic | LOCM | 350 |
| Iopromide | Ultravist | Monomer | Non–Ionic | LOCM | 370 |
| Iotrolan | Isovist | Dimer | Non–Ionic | IOCM | 320 |
| Iodixanol | Visipaque | Dimer | Non–Ionic | IOCM | 320 |

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

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.

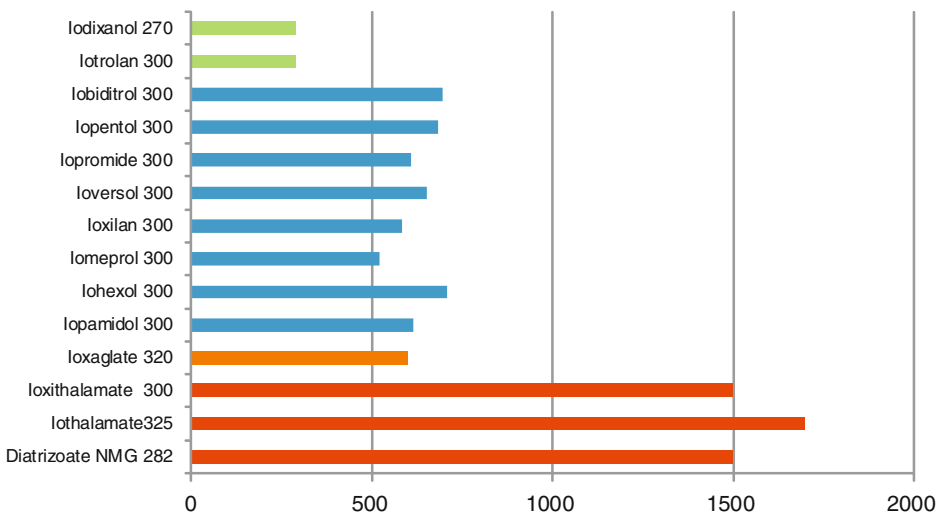



**Fig. 2** Osmolality (mOsmol/kg) of iodine-based contrast media at a concentration around 300 mgI/ml

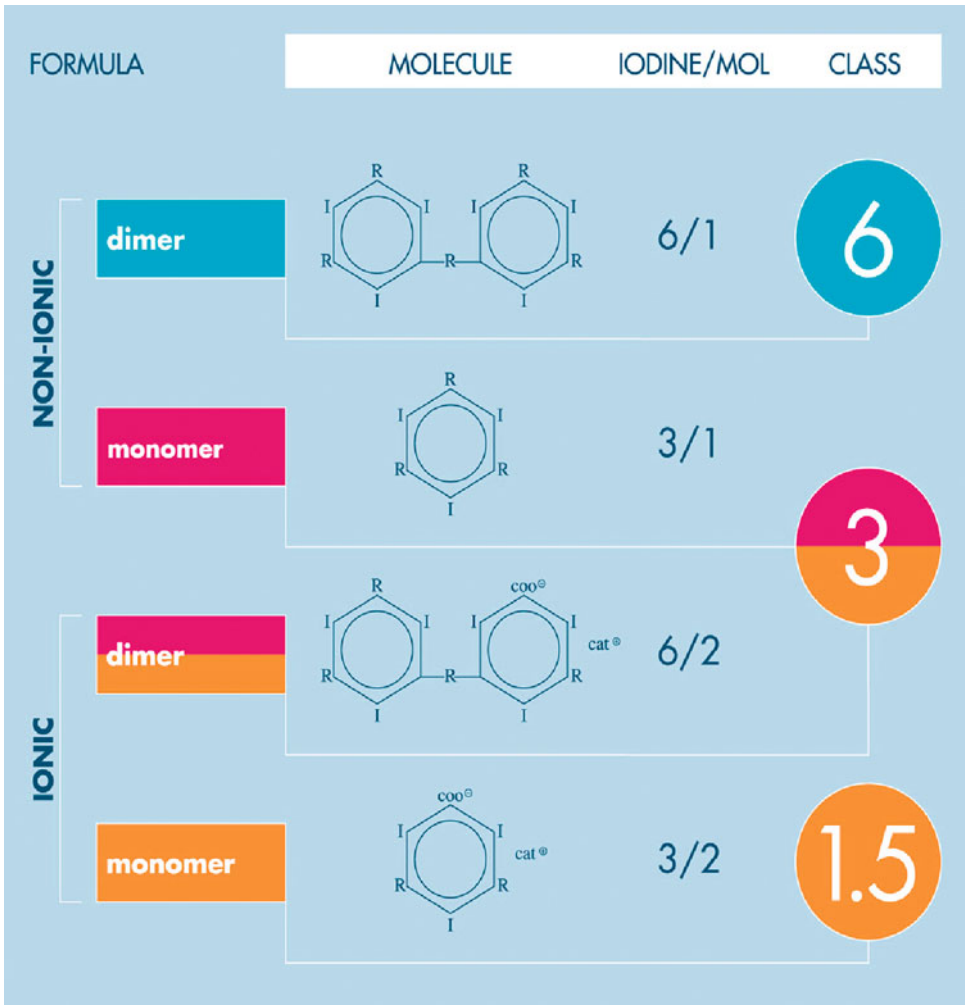



**Fig. 3** Classification of iodine-based contrast agents

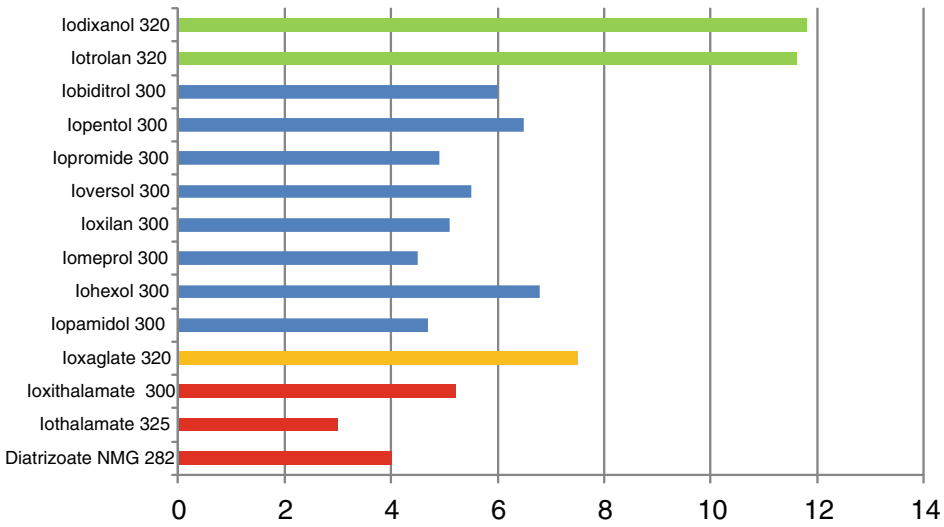



**Fig. 4** Viscosity (mPa.s) of iodine-based contrast media at a concentration around 300 mgl $ml^{-1}$ and at 37 °C

### 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 gadoxetate, which has the greatest biliary excretion, is mainly used for liver imaging.

**Fig. 5** Extracellular gadolinium-based contrast agents

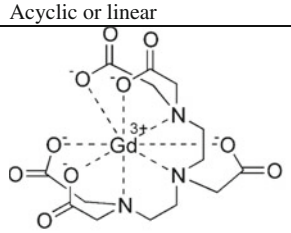
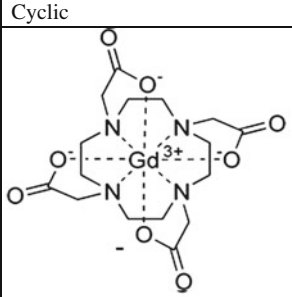
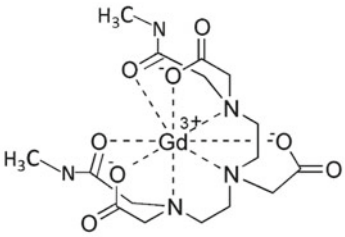
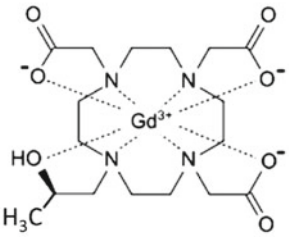
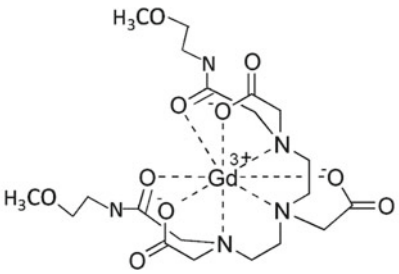
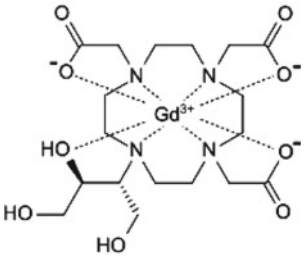
| Chelate | Acyclic or linear | Cyclic |
|---|---|---|
| Ionic |  Gadopentetate dimeglumine |  Gadoterate |
| Non-ionic |  Gadodiamide |  Gadoteridol |
| |  Gadoversetamide |  Gadobutrol |

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

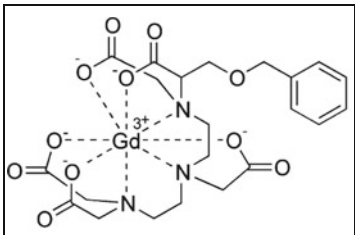
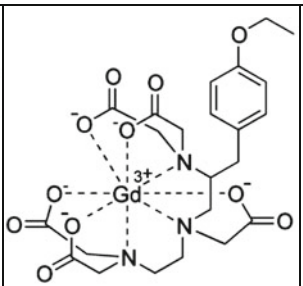
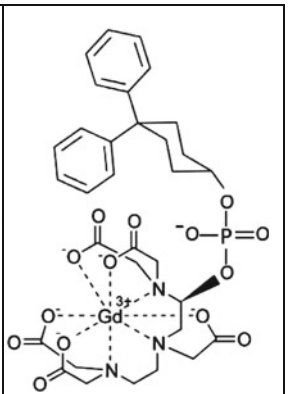
| | | |
|---|---|---|
|  Gadobenate dimeglumine |  Gadoxetate disodium |  Gadofosveset |

**Table 2** Gadolinium-based agents: brand names and characteristics (organ specific or extracellular, protein binding, biliary excretion)

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

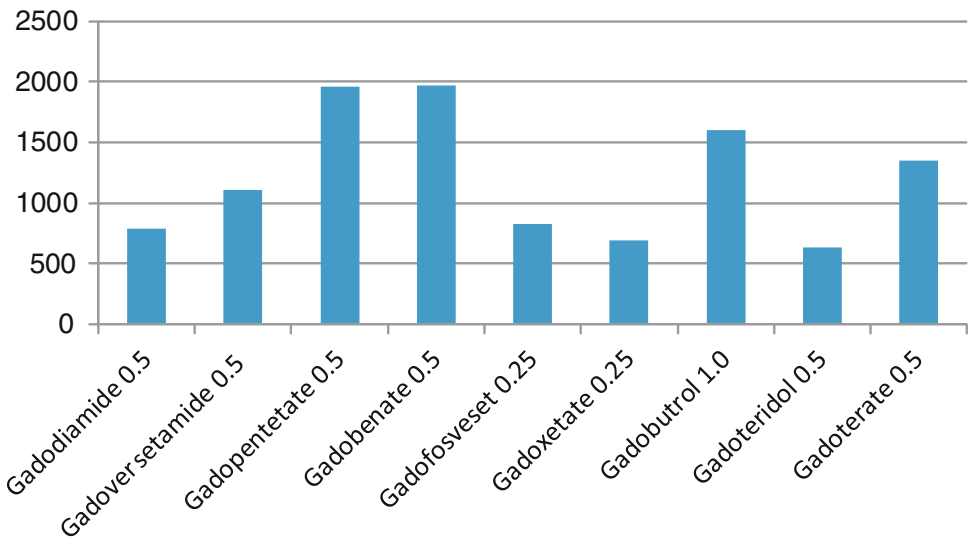



**Fig. 7** Osmolality (mOsmol/kg) of the gadolinium-based contrast media at their marketed concentrations (mmol/ml)

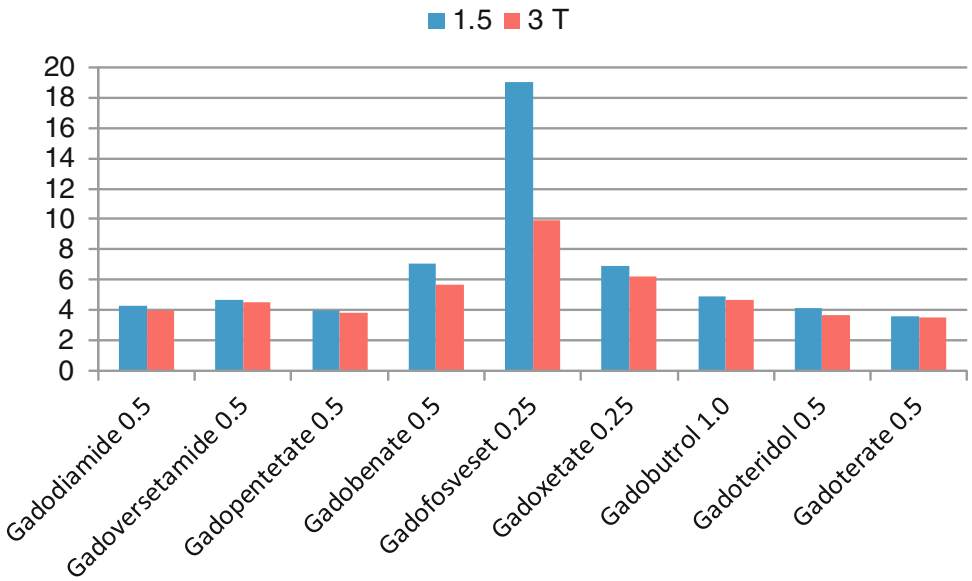



**Fig. 8** Relaxivity ($r_1$, $mM^{-1}s^{-1}$) of gadolinium-based contrast media in plasma in 1.5 and 3*T* (37 °C)

## 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 reticuloendothelial 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

| Product name | Constituents |
|---|---|
| Definity™ (Luminity®) | Fluorocarbon gas in liposomes |
| SonoVue® (BR1) | Sulphur hexafluoride gas in polymer with phospholipid |
| Optison™ (FS069) | Octafluoropropane-filled albumin microspheres |
| Sonazoid™ (NC100100) | Perfluorinated gas-containing microbubbles |

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# Requests for Imaging Using Contrast Media: What Information Must be Provided

Sameh K. Morcos and Marie-France Bellin

## Contents




**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.


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## 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 nonorgan-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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