MEDICAL RADIOLOGY

Diagnostic Imaging

Henrik S. Thomsen · Judith A. W. Webb (Eds.)

Contrast Media

Safety Issues and ESUR Guidelines

2nd Revised Edition

With Contributions by

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With 10 Figures, 5 in Color and 24 Tables

Springer

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Foreword

Two years only after the publication of the first edition of "Contrast media – Safety issues and ESUR guidelines" in our book series Medical Radiology in 2006, it appeared that a second edition was urgently needed.

The first edition was indeed an exceptional success with our readership and sold out rapidly, but moreover the safety of MR contrast media urgently required a reappraisal after the publication of a new and dramatic adverse reaction to some of the gadolinium-based agents: the so called NSF syndrome.

I am very much indebted to Professor Henrik S. Thomsen and his academic colleagues from the ESUR Contrast Medium Safety Committee for accepting the task to prepare a second edition of their remarkable book. Within a record short period of time they have been able to complete this fully revised new volume.

It offers to the readers a comprehensive overview of all problems related to the use of contrast media in modern radiology and of our latest knowledge and insights in the mechanisms of adverse reactions related to contrast media. It answers all questions that radiologists and referring physicians are confronted with in their daily practice when they consider the administration of these agents to their patients.

I congratulate the editors and all contributing authors for this exceptional work, which should again be considered as the standard text for reference and consultation on the highly important issue of safety of contrast media. I am convinced that this second edition will meet the expectations of the readers and that it will soon be available in many radiological offices.

Leuven

Albert L. Baert

Preface to the 2nd 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 1st 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 Professor 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

Contents

General Issues

Classification and Terminology

1

Peter Aspelin, Marie-France Bellin, Jarl Å. Jakobsen, and Judith A. W. Webb

CONTENTS

1.1 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. 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. 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.

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. The ideal contrast agent would achieve a very high concentration in the tissues without producing any adverse effects. Unfortunately, so far this has not been possible and all contrast agents have adverse effects.

This chapter deals with the classification of contrast agents and the terminology used to describe them.

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1.2 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 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.

1.2.1 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.

Iodine-based contrast agents can be divided into two groups, ionic and nonionic, based on their water solubility. The water in the body is polarised 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. Nonionic 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. Contrast agents may be divided into high-, low- and iso-osmolar agents. 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 nonionic monomers and the ionic dimers have a ratio of 3 (three iodine atoms per particle in solution), and the nonionic dimers have a ratio of 6 (six iodine atoms per particle in solution) (Fig. 1.1). The nonionic dimers are iso-osmolar with blood (300 mosm kg^{-1}) at all concentrations.

Using these properties four different classes of iodine-based contrast agents may be defined:

1. Ionic monomeric contrast agents (high-osmolar contrast media, HOCM), for example amidotrizoate, iothalamate and ioxithalamate

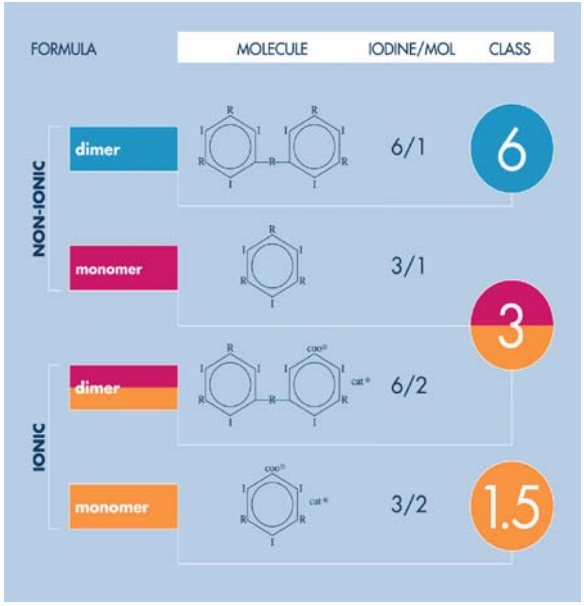


Fig. 1.1. Classification of iodine-based contrast agents

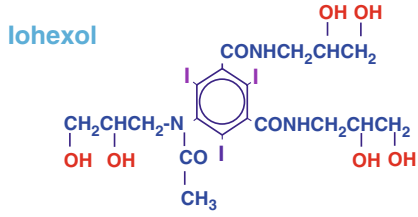
2. Ionic dimeric contrast agents (low-osmolar contrast media, LOCM), for example ioxaglate (Fig. 1.2)
3. Nonionic monomeric contrast agents (low-osmolar contrast media, LOCM), for example iohexol, iopentol, ioxilan, iomeprol, ioversol, iopromide, iobitridol and iopamidol (Fig. 1.2)
4. Nonionic dimeric contrast agents (iso-osmolar contrast media, IOCM), for example iotrolan, iodixanol (Fig. 1.2)

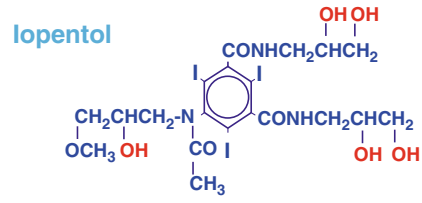
1.2.2 Barium Contrast Agents

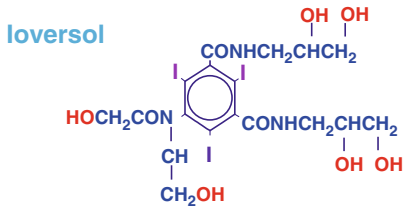
Barium sulphate preparations used to visualise the gastrointestinal tract consist of a suspension of insoluble barium sulphate particles, which is not absorbed from the gut. Differences between the different commercially available agents are very minor and relate to the additives in the different barium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

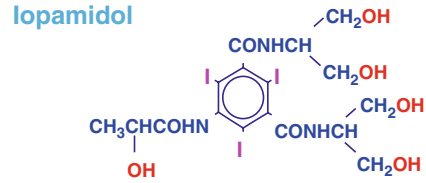
1.3 MR Contrast Agents

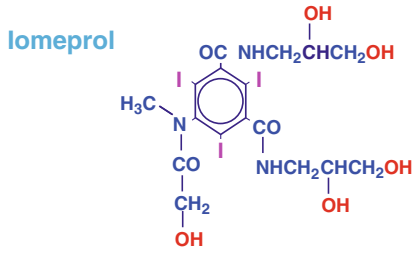
Magnetic resonance (MR) imaging contrast agents contain paramagnetic or superparamagnetic metal ions, which affect the MR signal properties of the

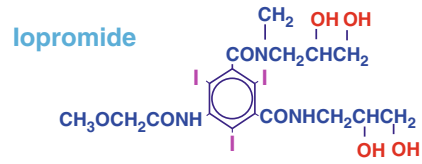


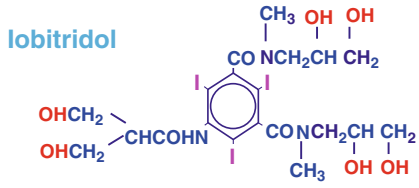


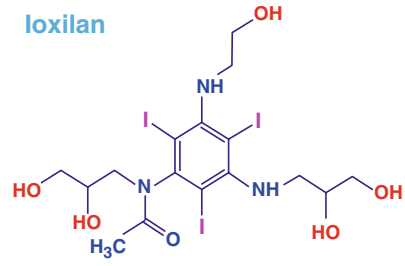


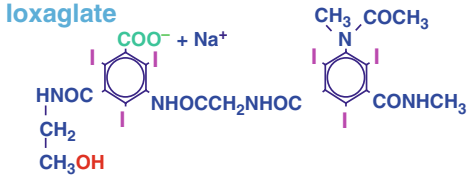


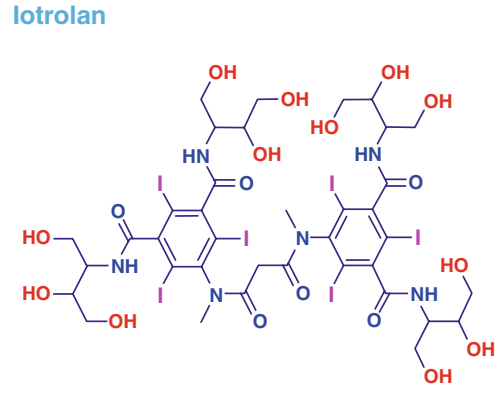












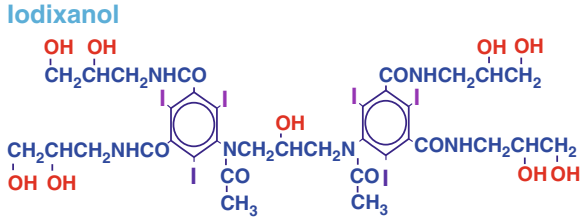


Fig. 1.2. Iodine-based contrast agents (nonionic monomers, ionic and nonionic dimers)

surrounding tissues. They are used to enhance contrast, to characterise lesions and to evaluate perfusion and flow-related abnormalities. They can also provide functional and morphological information.

1.3.1 Paramagnetic Contrast Agents

Paramagnetic contrast agents are mainly positive enhancers that reduce T1 and T2 relaxation times and increase signal intensity on T1 weighted MR images. 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. In two other paramagnetic agents, the active constituent is manganese, which has similar relaxivity properties to gadolinium, but in contrast to gadolinium is an ion that occurs naturally in the body. In all paramagnetic agents, which are used intravascularly, the active gadolinium or manganese is bound to a ligand in a chelate to minimise its toxicity.

1.3.1.1 Gadolinium Contrast Agents

Gadolinium contrast agents may be considered in two categories: non-specific extracellular gadolinium chelates and high relaxivity agents. The non-specific extracellular 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.

Gadolinium agents are also classified by the chemical structure of the ligand to which the gadolinium is bound. The ligands are either linear or cyclic, and may be ionic, which have a charge in solution, or nonionic. The stability of gadolinium contrast agents depends on their kinetic, thermodynamic and conditional 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.

Currently available gadolinium contrast agents may be classified as follows (Figs. 1.3 , 1.4):

A. Non-specific extracellular gadolinium chelates
   1. Ionic, linear ligand, e.g. gadopentetate dimeglumine
   2. Nonionic, linear ligand, e.g. gadodiamide, gadoversetamide
   3. Ionic, cyclic ligand, e.g. gadoterate dimeglumine
   4. Nonionic, cyclic ligand, e.g. gadobutrol, gadoteridol

B. High relaxivity agents
   Ionic, linear ligand, e.g. gadobenate dimeglumine, gadofosveset trisodium and gadoxetate disodium.

Extracellular non-specific gadolinium 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 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.

1.3.1.2 Liver Specific Agents

As well as the high relaxivity gadolinium contrast agents described in Sect. 1.3.1.1, liver specific agents include two manganese compounds, the manganese chelate mangafodipir trisodium and manganese-chloride together with promoters for oral intake (CMC–001) (Fig. 1.5).

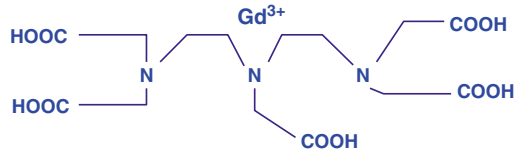
The gadolinium based agents and manganese are taken up to a varying degree by hepatocytes and excreted in the bile. Mangafodipir trisodium releases manganese ions by transmetallation with zinc, and these are bound by alpha 2 macroglobulin and transported to the liver. The manganese chloride preparation is given orally and reaches the liver via the portal system. Manganese has five unpaired electrons and is a powerful T1 relaxation agent. It has greater intracellular uptake than gadolinium and has three times greater T1 relaxivity in liver tissue.

1.3.2 Superparamagnetic Contrast Agents

Superparamagnetic contrast agents include superparamagnetic iron oxides (SPIOs) and ultra small

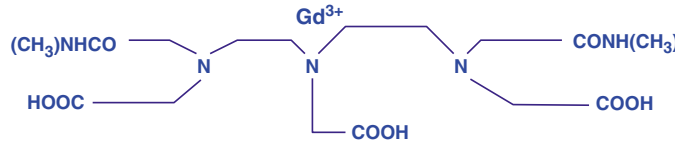
Ionic, linear

Gd-DTPA (gadopentetate dimeglumine)

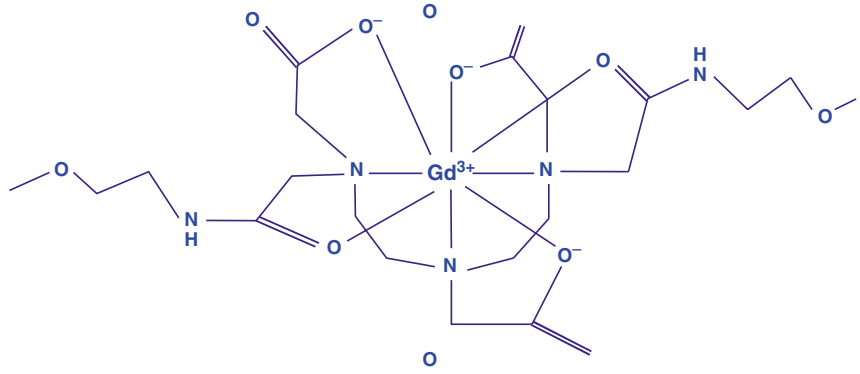


Nonionic, linear

Gd-DTPA-BMA (gadodiamide)

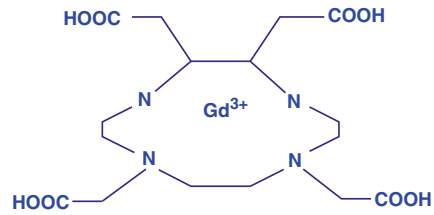


Gd-DTPA-BMEA (gadoversetamide)



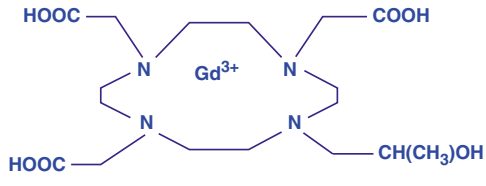
Ionic, cyclic

Gd-DOTA (gadoterate meglumine)



Nonionic, cyclic

Gd-HP-DO3A (gadoteridol)



Gd-BT-DO3A (gadobutrol)

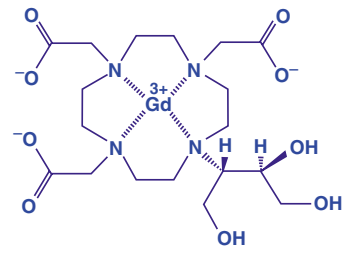


Fig. 1.3. Extracellular gadolinium-based contrast agents

Ionic, linear

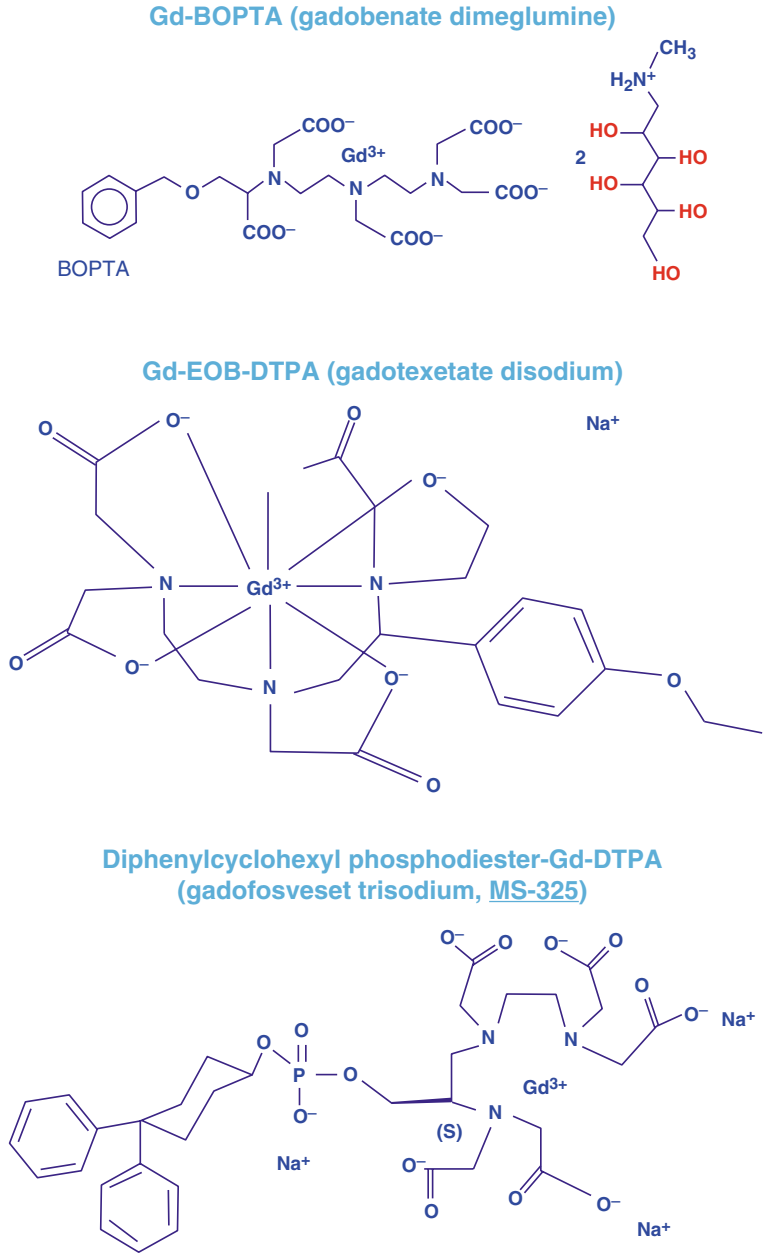


Fig. 1.4. High relaxivity gadolinium-based contrast agents

superparamagnetic iron oxides (USPIOs). Two preparations of SPIOs are available: ferumoxides and ferucarbotran. These particulate agents are composed of an iron oxide core, 3–5 nm in diameter, covered by low molecular weight dextran for ferumoxides and by carbodextran for ferucarbotran, which prevent uncontrolled aggregation of the magnetic crystals.

SPIOs and USPIOs 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.

In principle, smaller particles circulate longer in the blood space and may accumulate in the macrophages of the lymph nodes, liver and spleen, while large particles have a shorter half life and target the liver more specifically.

Ferumoxides amd ferucarbotran are approved for adult patients and liver imaging while USPIOs

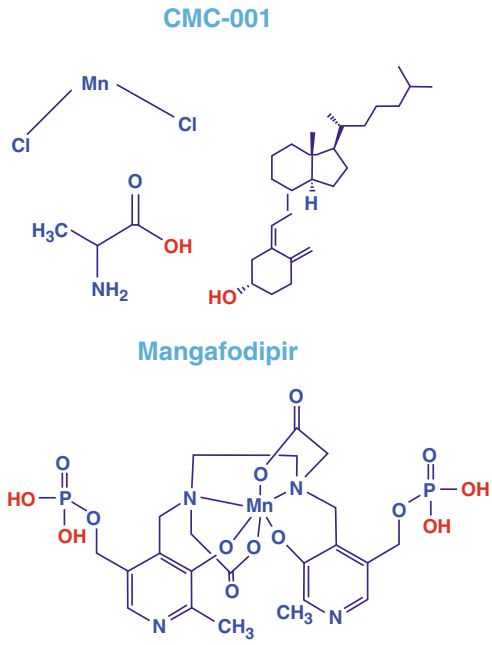


Fig. 1.5. Manganese-based contrast agents

are under investigation for MR lymphography. The surface structure of USPIOs gives them an extended circulation time and they also have the potential to be used as positive blood pool contrast agents.

After injection, SPIO and USPIO particles are metabolised into a soluble, non-superparamagnetic form of iron. Iron is incorporated into the body pool of iron (e.g. ferritin, hemosiderin and hemoglobin) within a few days.

1.4 Ultrasound Contrast Agents

Ultrasound contrast agents 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 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. They 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.

1.4.1 Classification

Ultrasound contrast agents can be divided into five different classes: (1) Nonencapsulated gas microbubbles (e.g. agitated or sonicated), (2) stabilised 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 (USCA) can also be classified based on their pharmacokinetic properties and efficacy: (1) Non-transpulmonary USCAs, 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 USCAs 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 USCAs 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 USCAs 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.

Agents that are currently available commercially or are close to being available commercially are listed in Table 1.1.

Table 1.1. Some ultrasound contrast agents

Product name	Constituents
Definity™ (DMP 115)	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
Levovist® (SHU 508A)	Galactose-based, palmitic acid stabilised air-bubbles

Requests for Imaging Using Contrast Agents: What Information Must be Provided

2

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CONTENTS

2.1 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 (Thomsen 2006; Morcos 2005a, b; Morcos and Thomsen 2001, Morcos et al. 2001, 2005). 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 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 administration to ensure that all necessary measures to reduce the risk are taken.

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2.2 Iodine-Based Contrast Media

2.2.1 Risk Factors for Acute Non-Renal Adverse Reactions

There is a sixfold increase in incidence of severe reactions to both ionic and nonionic contrast agents in patients with a history of previous severe adverse reaction to contrast agents. Asthma is also an important risk factor with reported six- to tenfold 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).

2.2.2 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 (Chap. 16). There is an increased incidence of delayed skin reactions to contrast agents in patients who have received nonionic dimers or interleukin-2 (IL-2) (Morcos et al. 2005; Webb et al. 2003).

2.2.3 Risk Factors for Contrast-Induced Nephropathy

Pre-existing renal impairment [serum creatinine > 130 µmol l^{-1} or preferably eGFR < 60 ml min^{-1} 1.73 m^{-2}] calculated according to the Modification of Diet in Renal Disease (MDRD) study equation (Bostom et al. 2002) is an important risk factor particularly if it is associated with diabetes mellitus. The degree of renal insufficiency is a major determinant of the severity of contrast-induced nephropathy (CIN) (Thomsen 2006). An eGFR of 30 ml min^{-1} 1.73 m^{-2} or less markedly increases the incidence and severity of CIN (Morcos et al. 1999; McCullough et al. 1997). 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 (Morcos et al. 1999; McCullough et al. 1997; Morcos 2004, 2005b).

Since pre-existing renal impairment is a crucial 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 used in many centers for this purpose, but has several limitations for accurate assessment of renal function (Morcos 2005b; Thomsen et al. 2005) and eGFR is a better test, when serum creatinine is abnormal, but it is not perfect as all equations overestimate renal function to various degrees.

2.2.4 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 (see Chaps. 11, 14). This is an important issue to be included in a questionnaire.

2.2.5 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 (see Chap. 18).

2.3 MRI Contrast Agents

MR contrast agents include extracellular and liver-specific agents. Patients at risk of adverse reactions to these agents are briefly discussed further.

2.3.1 Extracellular Gadolinium-Based 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 $weight^{-1}$ (Ergün et al. 2006; Thomsen 2004; Zhang et al. 2006; Briguori et al. 2006; Sam et al. 2003). However, patients with preexisting 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 recently 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 (Chap. 24).

2.3.2 Liver-Specific MR Contrast Agents

MR liver-specific contrast agents include superparamagnetic oxides, manganese contrast agents and hepatobiliary gadolinium chelates. The risk factors with these agents are summarized below.

Superparamagnetic iron oxides (SPIO). Back pain and flushing are the most frequently reported adverse reactions to these agents, but no risk factors have been identified (Ros et al. 1995). However, the administration of these agents in patients with known allergy or hypersensitivity to parenteral iron or dextran should be avoided and they should be used with caution in patients with hemosiderosis or hemochromatosis (Bellin et al. 2005).

Manganese-based contrast agents. Nausea, headache and pruritus may develop after infusion of the intravascular formulation, but no predisposing factors have been identified (Bellin et al. 2005).

Hepatobiliary gadolinium chelates. The most common adverse reactions include headache, nausea, and flushing (Bellin et al. 2005). Serious adverse reactions are rare. No risk factors have been identified for these reactions.

2.4 Discussion

It is vital that all the relevant information about the patient is readily available before contrast agent administration to minimize the potential risks and to take the necessary measures to prevent an adverse reaction. Of all the potential adverse reactions to contrast agents, those which are most likely to have serious sequelae are severe anaphylactoid reactions and CIN. It is proposed that the request for an imaging test requiring contrast agent administration should provide information about important risk factors for these complications. An awareness of the drug history is also important as there is the possibility of interaction between contrast agents and other drugs. In addition, patients with thyroid disease, particularly elderly patients living in regions with iodine deficiency, can be adversely affected by contrast media. Information about risk factors should be available before the appointment for a contrast agent enhanced examination to plan prophylactic measures or to advise an alternative imaging technique not requiring contrast agent administration. 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 many of the questionnaire answers as possible before contrast agent administration and make a judgment of benefit against risk depending on the clinical problem under investigation.

Demanding an extensive list of information with the request is not practical and may not receive the cooperation of referring clinicians. Thus, it is important to focus the questionnaire on important risk factors for serious complications that are most likely to be encountered in clinical practice. The ESUR contrast agent questionnaire should be considered as a supplement to the standard referral for imaging examinations. It 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. The completed contrast agent questionnaire should be sent with the request to the Imaging Department for further action. The ESUR questionnaire can be found in Chap. 29.

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Off-Label Use of Medicines: Legal Aspects

3

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CONTENTS

3.1 Introduction

In Europe, subject to certain exemptions explained later, no medicine can be marketed for human use without a Marketing Authorisation 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 authorised indications, commonly known as off-label use, and use of unlicensed medicines (i.e. medicines without a marketing authorisation) 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.

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

European medicine 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 authorised manufacturer
- Any radionuclides in the form of sealed sources

3.3 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 authorisation, 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 centralised authorisations valid in all member states.

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

The terms in which a marketing authorisation 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 authorisation holder, from the European Medicines Agency, from some Member State competent authorities and via the Electronic Medicines Compendium on www.medicines.org.uk. The SPC also forms the basis for the Patient Information Leaflet (PIL), which accompanies the medicine and is written in terms that are understandable by patients. Clearly, a medicine that is unlicensed will not have an SPC or PIL. Marketing authorisation holders are required to keep their authorisations 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.

3.4 Definition of Off-Label Use

The term "off-label use" applies to prescribing or administration outside any of the terms of the marketing authorisation, generally in relation to indications, dosage, or contra-indications. The expression relates to a term used in the US authorisation process: the Food and Drug Administration (FDA) approves product labelling. A medicine that is prescribed off-label will be accompanied by information that 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 authorisation application or variation has yet to be made. These include drugs in development and undergoing clinical trials.
- Medicines for which a marketing authorisation application or variation has been refused.
- Medicines that no longer have a relevant marketing authorisation because it has been suspended, revoked, not renewed or compulsorily varied.
- Products prepared in formulations specially adapted to special populations such as lower