MEDICAL RADIOLOGY

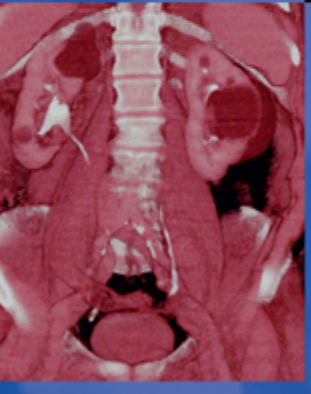
Diagnostic Imaging

A. L. Baert
M. Knauth

Contrast Media

Safety Issues and ESUR Guidelines

2nd Revised Edition



H.S. Thomsen
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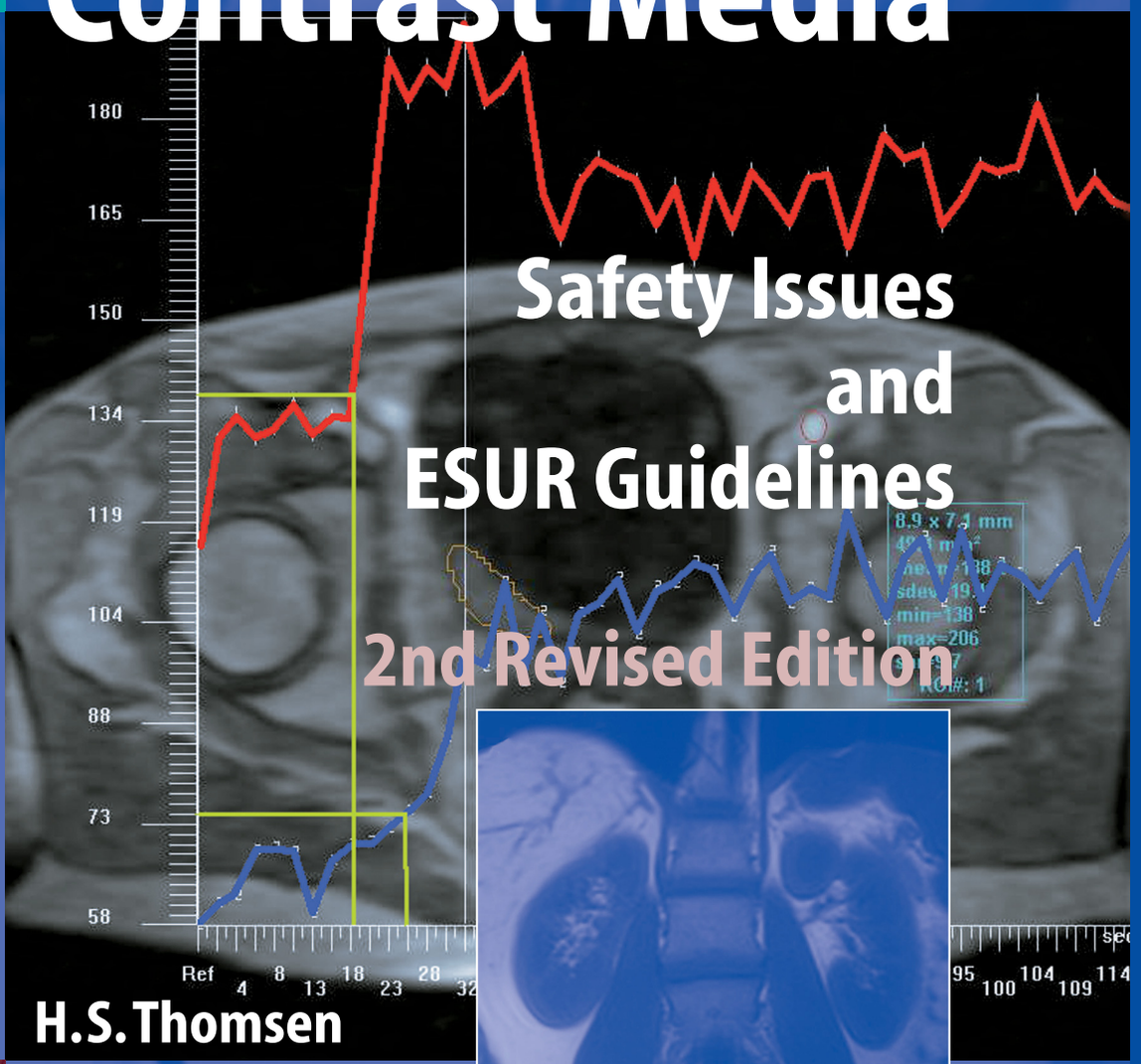

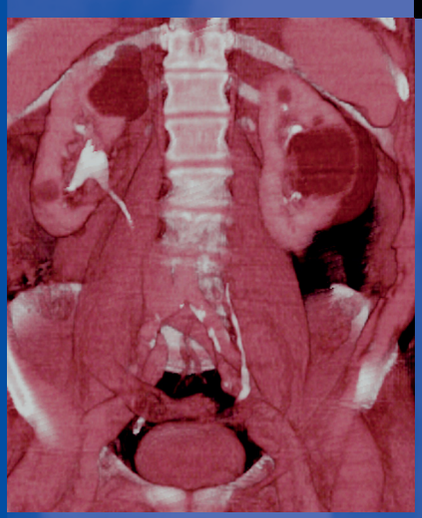

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MEDICAL RADIOLOGY

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

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2nd Revised Edition

With Contributions by

P. Aspelin · M.-F. Bellin · G. Biondi-Zoccai · G. Heinz-Peer · J. Å. Jakobsen · M. Lotrionte
S. K. Morcos · R. Oyen · J. M. Raine · F. Stacul · D. I. Stenver · H. S. Thomsen
A. J. van der Molen · J. A. W. Webb

Foreword by

A. L. Baert

With 10 Figures, 5 in Color and 24 Tables

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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

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General Issues

Classification and Terminology

1

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

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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

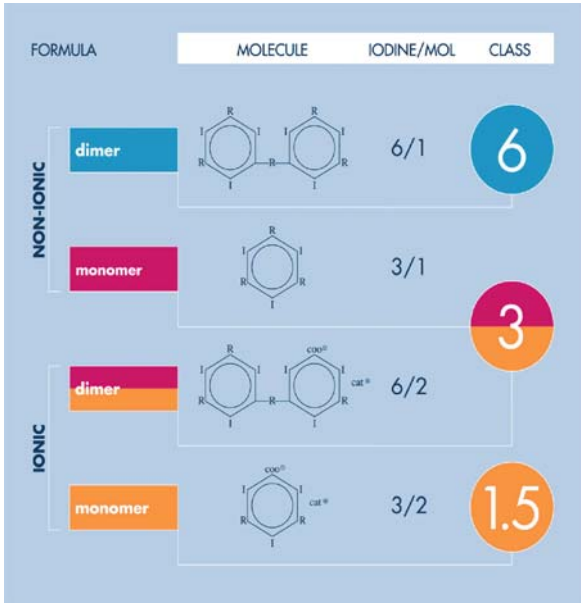

Fig. 1.1. Classification of iodine-based contrast agents

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