Contrast Agents for Magnetic Resonance Imaging

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2.1 Introduction

The alteration of signal intensity in diseased tissue forms the basis for magnetic resonance (MR) imaging in diagnostic radiology. The tissue signal intensity observed in MR images is the result of a complex interaction of numerous factors, which can be classified as those that reflect intrinsic properties of biologic tissues, e.g., T1 and T2 relaxation times and proton density, and those that are equipment related, e.g., field strength or pulse sequences. However, due to a wide biologic variation, the relaxation times of normal and abnormal tissues overlap. This limits the ability of plain MR imaging to detect and, even more, to characterize abnormal tissue. By using very specialized pulse sequences, only some of these limitations can be overcome. An alternative solution is provided by MR contrast agents, which alter the tissue relaxation times and can, therefore, be used to manipulate their signal intensity.

It is mainly contrast agents with so-called paramagnetic or superparamagnetic properties that are used to reduce the T1 and T2 relaxation times. Only those agents that are either already on the market and used in clinical practice or those that are late in clinical trials (phase II/III, with a launch to be expected within the next 2–3 years) will be discussed.

2.2 Mechanism of Action

The underlying principle of contrast media action is a chemical alteration of the proton relaxation time. Certain chemical compounds possess unique magnetic properties that arise from the motion of electrically charged electrons, protons, and neutrons. When protons and neutrons exist in pairs, as in nuclei with an
even number of protons and neutrons, their magnetic moments will orient in opposite directions and cancel. However, nuclei with an odd number of protons and neutrons have a nonzero net nuclear magnetic moment, which precesses at the Larmor frequency if placed in an external magnetic field; the surrounding electrons also respond to the applied magnetic field. The resulting magnetic dipole moments arising from the electrons are considerably larger than the nuclear magnetic moments. Thus, if atoms, ions, or molecules with large electronic dipole moments are placed adjacent to protons, their magnetic dipole moments can interact to enhance the relaxation of protons and alter the tissue signal intensity. Therefore, compounds with large electronic magnetic dipole moments may be utilized as contrast agents in MR imaging.

2.2.1 Paramagnetism

Paramagnetism arises in atoms that have unpaired electrons. Placed in an external magnetic field, these atoms show a significant net magnetization because of the preferential orientation of the paramagnetic dipole moments parallel to the applied magnetic field; its magnitude is proportional to the magnitude of the external magnetic field. The most important chemical subgroup of paramagnetic compounds are metal ions (e.g., Mn$^{2+}$ and Fe$^{3+}$) and lanthanide elements, such as gadolinium (Gd) and dysprosium (Dy). Gadolinium is one of the strongest paramagnetic substances because of its seven unpaired electrons. Paramagnetic agents predominantly shorten both the T1-relaxation time and – especially at higher tissue concentrations – the T2-relaxation time.

2.2.2 Superparamagnetism

Superparamagnetism is induced by smaller ferrimagnetic particles that have only a single magnetic domain. In an external magnetic field, these particles show a magnetization curve like that of paramagnetic agents, but with a much stronger response, and saturation effects are readily attained. The increase in magnetization at a field strength of between 0.3 T and 1.5 T is nonlinear. After removal of the magnetic field, no net magnetization is retained. Superparamagnetic contrast agents are basically small and ultrasmall iron oxide particles that shorten mainly the T2-relaxation time. The smaller particles also shorten the T1-relaxation time.

2.2.3 Relaxation Times, Relaxation Rates, and Relaxivity

The T1 and T2 relaxation times are characteristic times describing how long it takes for the signal mechanism of magnetic resonance to return to the original state or to relax. The time taken to return to the original longitudinal magnetization is described by the T1-relaxation time. The T2-relaxation time refers to the component of the bulk magnetization vector which describes how fast the transversal magnetization vanishes. T1- and T2-relaxation times are not exact measures of the time it takes for relaxation; instead, they are time constants that describe the speed of this process and, in this respect, are comparable to time constants that, for example, describe radioactive decay. Both T1- and T2-relaxation times are tissue specific. A short T1 appears as a bright signal, and a short T2 appears as a dark signal on MR images.

As mentioned earlier, paramagnetic and superparamagnetic contrast agents shorten the T1- and T2-relaxation times or, in other words, increase the relaxation rates (defined as 1/T1 and 1/T2). The ability of a contrast medium to shorten the relaxation times depends both on the contrast medium concentration in the respective tissue and on the intrinsic relaxation time of the tissue. A concentration of 0.1 mM of a paramagnetic Gd chelate is a powerful relaxation enhancer, sufficient to decrease the relaxation times of biological fluids by 50%. However, to influence tissues of shorter intrinsic relaxation times to the same extent, a higher contrast medium concentration is needed. The power or efficiency of a contrast medium to enhance the relaxation rate is called ‘relaxivity’. For example, the efficiency of Gd-DTPA at enhancing the longitudinal relaxation in water is expressed as relaxivity $R_1 = 4.5$ (mM s)$^{-1}$, whereas the transverse ($T^*$) relaxivity is $R_2 = 6.0$ (mM s)$^{-1}$. The $R_2/R_1$ ratio of 1.3 is typical for paramagnetic contrast media. Because tissue T1-relaxation is inherently slow compared with T2-relaxation, their predominant effect is on T1.
2.3 Extracellular Contrast Agents

The extracellular contrast agents can be divided into low and high molecular-weight agents. The latter will be discussed in Sect. 2.5 due to their blood-pool properties. The low molecular-weight agents belong more or less to the paramagnetic Gd chelates. The prototypical complex of this class of agents is Gd-DTPA (Magnevist, Schering AG, Berlin, Germany), which was the first MR contrast agent introduced into the market in 1988. In the meantime, other agents have been launched or are close to coming to market (Table 2.1).

MultiHance (Gd-BOPTA, Bracco, Milan, Italy) was originally designed as a hepatobiliary contrast agent. However, because about 96% of the compound is excreted renally in humans, it is classified predominantly as an extracellular agent. Another specific feature should be mentioned for Gadovist 1.0 (Gadobutrol, Schering AG, Berlin, Germany): this agent consists of a 1 M concentration instead of the 0.5 M concentration of all other Gd complexes. When compared to other extracellular contrast media, this results in double the concentration and half the injection volume for the same dose, which is advantageous for first-pass imaging examinations, such as perfusion imaging and high-gradient 3D MR angiography.

Apart from these particulars, all Gd complexes basically exhibit the same pharmacodynamic and pharmacokinetic properties, resulting in comparable safety profiles and approvals for nearly the same indications. For detailed information, consult the respective package inserts in the European countries. Therefore, they will be discussed together in the following sections.

2.3.1 Basic Principles and Properties

Because of its strong paramagnetic effect, Gd has been chosen as the metal for all available extracellular MR contrast agents. Due to the high toxicity of free Gd, it has to be firmly bound to ligands, resulting in highly hydrophilic Gd-chelate complexes. The complex stability of all Gd compounds is very high. For example, the in vivo constant for dissociation of Gd-DTPA (Magnevist) is about $10^{23}$. This guarantees that the effect of free Gd is not of any toxicological relevance. The molecules of these contrast agents are designed either as a linear (Magnevist, Omniscan, MultiHance, Optimark) or a macrocyclic structure (Dotarem, Table 2.1. Extracellular contrast agents: overview and registration status

<table>
<thead>
<tr>
<th>Trademark and generic name</th>
<th>Manufacturer</th>
<th>Chelate structure</th>
<th>Registration status (EU) and dose (mmol/kg)</th>
<th>CBS</th>
<th>Body</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnevist® gadopentetate (Gd-DTPA/dimegl.)</td>
<td>Schering AG</td>
<td>Open chain</td>
<td>0.3</td>
<td>0.3</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Dotarem® gadoterate (Gd-DOTA/megl.)</td>
<td>Guerbet</td>
<td>Macrocyclic ionic</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>MultiHance® gadobenate (Gd-BOPTA)</td>
<td>Bracco</td>
<td>Open chain ionic</td>
<td>Liver 0.1</td>
<td>Liver 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omniscan® gadodiamide (Gd-DTP-BMA)</td>
<td>Amersham</td>
<td>Open chain neutral</td>
<td>0.3</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>ProHance® gadoteridol (Gd-HP-DO3A)</td>
<td>Bracco</td>
<td>Macrocyclic neutral</td>
<td>0.3</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Optimark® gadoversetamide (Gd-DTPA-BMEA)</td>
<td>Mallinckrodt</td>
<td>Open chain neutral</td>
<td>Submitted</td>
<td>Submitted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadovist® 1.0 and 0.5 gadobutrol</td>
<td>Schering AG</td>
<td>Macrocyclic neutral</td>
<td>0.3</td>
<td>MRA-submitted</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ProHance, Gadovist), which is of minor relevance for their pharmacodynamic and pharmacokinetic properties. The osmolality of these compounds varies from 590 mosmol/kg H₂O (Gadovist 0.5 M) up to 1980 mosmol/kg H₂O (Magnevist). However, due to the low doses of 0.1–0.3 mmol/kg body weight (BW) (0.2–0.6 ml/kg), the amount of osmotically active 'particles' (total osmotic load) is, at the higher doses, even lower than low osmolar nonionic X-ray contrast agents. Consequently, the osmolality of the available contrast agents does not have any effect on the safety or tolerability profile of any of those agents.

While Gd is responsible for the paramagnetic effect of these complexes, the ligand determines the pharmacokinetic behavior. Due to the high hydrophilicity of the Gd chelates and their low molecular weight, they rapidly diffuse into the interstitial space after intravenous injection and a short intravascular phase. The protein binding is negligible. The elimination of the unmetabolized Gd complexes from the body occurs via renal excretion with a plasma half-life of about 90 min. The compounds are completely eliminated after a maximum of 24 h if the glomerular filtration is not diminished. The half-life is prolonged in patients with impaired renal function, but this does not change the safety profile (Sect. 2.3.3.1).

2.3.2
Efficacy

2.3.2.1
Clinical Indications

The extracellular contrast agents have a broad indication spectrum, which will be discussed in more detail in the respective chapters. Mainly for two reasons, about 60%–70% of the contrast-enhanced MRI examinations are performed in CNS indications. The first reason is that, historically, MRI first became clinical routine in those areas for which motion or flow artifacts, due to long-lasting imaging sequences, either did not exist or were of only minor importance. Those areas are predominantly the CNS and the musculoskeletal system, with the latter being the second important indication area in MR imaging.

The second – and probably even more important – reason for CNS being the biggest indication for the use of contrast agents in MR imaging is the existence of a blood-brain barrier (BBB). Therefore, the extracellular agents behave in the normal brain as an intravascular contrast agent that only diffuses into the interstitial space, leading to an enhancement in the case of a BBB-leakage caused by a tumor, trauma, infarction, or inflammatory/demyelinating disease. Metastases do not have a BBB and enhance after the injection of contrast media as well.

As mentioned before, musculoskeletal diseases such as bone tumors or inflammatory diseases are important indications, as are tumors of the kidneys, glands, pelvic organs, breast, and liver. In imaging of the liver, extracellular agents provide important information for the detection of hypervascularized lesions and for lesion characterization in general (using dynamic sequences). Breast imaging has also become a more important indication. However, it should be noted that only for very specific questions, e.g., dense tissue or silicon implants, has MR imaging been accepted as the imaging technique of choice; currently, not enough data from representative populations have been published to justify the use of MR imaging as a routine or even as a screening examination.

A relatively new and very promising indication is 3D MR angiography. This technique requires the use of contrast agents due to the very fast imaging sequences. Most of the examinations can be performed as first-pass imaging using Gd chelates, which provide good image quality. Only a few vessel areas, such as the coronary arteries, venous vessels, or interventional procedures, require an intravascular contrast agent.

2.3.2.2
Dose

The dose which was first established for the use of Magnevist in CNS indications is 0.1 mmol/kg BW or 0.2 ml/kg BW. Although the available pulse sequences and the technology in general have changed significantly during the last decade, the recommended dose for Gd chelates has been widely confirmed and further extended for most of the so-called whole-body indications. Thus, the dose of 0.1 mmol/kg (0.2 ml/kg) can be considered as the accepted standard dose for MR imaging. A few exceptions have to be mentioned: a dose reduction to 0.05 mmol/kg BW (0.1 ml/kg) was discussed for the early detection of hypophyseal microadenomas during a dynamic imaging sequence, and an increase of the dose should be considered for the following:
1. High-gradient 3D MR angiography. This angiography technique was introduced in 1995. At the very beginning, doses of up to 0.5 mmol/kg BW (1 ml/kg) were administered. In the meantime, due to faster sequences and better bolus tracking techniques in particular, the maximum doses are in the range 0.1–0.3 mmol/kg BW (0.2–0.6 ml/kg). A dose of 0.1–0.15 mmol/kg BW (0.2–0.3 ml/kg) seems to be a robust dose providing sufficient and reproducible image quality.

2. Detection and characterization of focal CNS lesions. Several clinical studies have demonstrated that using Gd doses of 0.2 mmol/kg or 0.3 mmol/kg BW (0.4–0.6 ml/kg), additional brain metastases can be detected in about 20% of this patient population compared with the standard dose. A double or triple dose may also allow better characterization of low-grade gliomas, better detection of tumor recurrence, and a more reliable selection of representative biopsy sites in those tumors. However, in most of the patients, the additional information does not have any therapeutic consequences. Therefore, the general dosing recommendation is to administer 0.1 mmol/kg BW (0.2 ml/kg) of any Gd chelate and to increase the dose by a further injection of 0.1–0.2 mmol/kg BW (0.2–0.4 ml/kg) only in those patients for whom any additional information would have direct impact on the further therapy.

Another area which is still under discussion with regard to the necessary Gd dose concerns patients with multiple sclerosis. Many reports suggest that, at a double or triple dose, more enhancing lesions can also be detected. However, the clinical relevance of these findings is not yet fully understood. Consequently, the general dose recommendation is still the standard dose of 0.1 mmol/kg BW (0.2 ml/kg).

3. Brain perfusion. Brain perfusion imaging is normally performed using T2*-W sequences (instead of T1-W sequences) and susceptibility imaging. The optimal dose for this technique depends very much on the sequence used. If brain perfusion imaging is performed with a fast GRE sequence, the optimal dose is in the range of about 0.3 mmol/kg BW (0.6 ml/kg), as shown in a double-blind dose-comparative study with Gadovist 1.0. A lower dose can also be used, but the reproducibility is significantly worse. If the examination is carried out using EPI sequences, the optimal dose is probably slightly lower than 0.3 mmol/kg, due to the higher sensitivity of these sequences for susceptibility effects. As there has been no controlled dose comparison so far, a final recommendation is not yet possible.

2.3.3 Safety

Most of the safety data are based on the published experience with Magnevist, which has been administered intravenously to more than 37 million patients over the last decade. However, on the basis of several comparative clinical trials and the growing experience with the other extracellular Gd compounds, it can be assumed that they all have a comparable safety profile. Overall, this class of contrast agents is by far the safest compared with other contrast agents.

Data from controlled clinical trials and from a pre- and post-marketing surveillance in several million patients show an overall incidence of adverse reactions of 1%–2%. This incidence is about two to three times higher in patients with a history of allergies or in patients with asthma. The most frequent adverse reactions are listed in Table 2.2.

The most relevant adverse reaction which may occur after intravenous (IV) injection of Gd compounds is an anaphylactoid reaction that also occurs with other contrast agents. The incidence of anaphylactoid reactions is about six times lower than with nonionic X-ray contrast agents. Nevertheless, IV injection of Gd complexes should be only performed if emergency equipment is available. As far as is known, there is no relationship between adverse reactions and doses of up to at least 0.3 mmol/kg BW. Based on limited experience, patients given doses of up to 0.5 mmol/kg BW also do not show any further increase in the incidence of adverse reactions.

<table>
<thead>
<tr>
<th>Type of adverse event</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>0.42</td>
</tr>
<tr>
<td>Local warmth/pain</td>
<td>0.42</td>
</tr>
<tr>
<td>Headache</td>
<td>0.26</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0.13</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0.10</td>
</tr>
<tr>
<td>Urticaria/allergy-like shir reaction</td>
<td>0.10</td>
</tr>
<tr>
<td>Focal convulsia</td>
<td>0.03</td>
</tr>
</tbody>
</table>
2.3.3.1
Use in Patients with Impaired Renal Function

In a number of patients, the administration of X-ray contrast agents leads to an impairment of renal function. This is mostly a transient effect, which can be minimized by sufficient hydration of the patient. However, for patients with already impaired renal function, this became a relevant clinical problem that was carefully studied for MR contrast agents as well.

In a study including patients with various degrees of impaired renal function, the short-term effect (24 h) and the long-term effect (up to 120 h) of a single IV injection of 0.1 mmol/kg BW Magnevist on the creatinine clearance was investigated. At no time and in no patient was there an effect on renal function that was attributable to the Gd injection. These results could be confirmed by further retrospective analyses of bigger patient populations, e.g., a meta-analysis of all Magnevist phase-III data. Another result of the above-mentioned study was that the Gd complexes can be removed from the body by hemodialysis in case of acute renal failure. An almost complete elimination is achieved after three hemodialyses. These results were confirmed recently by another controlled clinical study using Gadobutrol 1.0 at doses of 0.1 and 0.3 mmol/kg in patients with different degrees of renal impairment.

2.3.3.2
Use in Pediatrics

From a regulatory point of view, there are two age groups within the category of pediatrics. One group is aged from 2 to 18 years, the other consists of newborns and infants up to 2 years. The four extracellular Gd chelates on the market (Magnevist, Dotarem, Omniscan, and ProHance) are approved for CNS indications in children from 2 to 18 years of age; some are approved for newborns and for whole-body indications as well.

In a clinical study involving 72 children under 2 years of age, a single or repeated injection of 0.1 mmol/kg BW Magnevist was given. Two of the 72 patients experienced an adverse event (2.7%). One adverse event was diarrhea, the other a facial edema, most likely related to a concomitant medication. In a big post-marketing surveillance study of more than 15,000 patients reported by Nelson, more than 900 pediatric patients under the age of 18 years were included. The data confirm a low incidence of adverse reactions in this patient population that was comparable to the incidence in adults. Thus, there is no known age-related specific risk of injecting Gd chelates.

2.4
Tissue-Specific Contrast Agents

The rapid extravasation of the extracellular contrast media leads to a transient but unspecific signal increase in parenchymal organs, e.g., in the liver and spleen. Whereas the characterization of focal lesions can be improved by extracellular agents during the early perfusion phase, the lesion detection of small lesions in particular is not improved significantly. Sometimes lesions are obscured due to the diffuse enhancement (as in CT). Consequently, much effort in contrast-media research went into more specific contrast agents. The most advanced area is the development of liver-specific contrast agents. Another area of interest is improved imaging of lymph nodes – in particular, the question of whether enlarged lymph nodes are metastatic or not. Both areas will be discussed in detail below.

2.4.1
Liver-Specific Contrast Agents

In general, two different approaches or classes of contrast media exist to target the liver: (1) paramagnetic, hepatobiliary T1 contrast media, taken up by the hepatocytes of the liver, and (2) superparamagnetic particles phagocytosed by cells of the reticulo-endothelium system (RES) and acting as T2 contrast agents. The basic idea of both the hepatobiliary and the RES-specific contrast media is that they can only be taken up by liver tissue containing the respective cells. Tissue of nonhepatic origin, such as metastases, does not show any uptake and remains as a bright or dark spot within the liver (Fig. 2.1). In lesions of hepatic origin, the uptake depends on the number and the functional integrity of the hepatocytes or RES cells. The variation between several lesion types and the resulting differential uptake of contrast media provide useful information for lesion characterization.

In general, all liver-specific contrast media that are already on the market or that are currently in late phases of clinical development improve the detection of liver lesions by up to 20%, depending on the patient popula-
tion and how the findings were confirmed by independent procedures. As there are no comparative trials so far, it is not known whether a certain contrast medium or one of the two classes (RES-specific and hepatobiliary CA) is superior with regard to lesion detection.

The ability to characterize lesions depends very much on the capability of a contrast medium to allow dynamic imaging, as important information can be obtained from this early perfusion phase. However, by the principal mechanism of uptake into RES cells and hepatocytes, important information about the integrity of the respective system can be gained.

### 2.4.1.1 Hepatobiliary Contrast Agents

Three paramagnetic hepatobiliary contrast agents have recently been approved in the USA and Europe or are currently in phase-III clinical development. The three contrast media are given in Table 2.3.

The latter two Gd-based contrast media are chemical derivates of Magnevist in which a carboxyl group is replaced by a lipophilic moiety. This leads to an uptake into hepatocytes by an anionic carrier system, an intracellular binding to transport proteins, and finally, secretion into the biliary system. The degree of specific uptake by the hepatocytes is drug and species dependent. Whereas both Gd-based contrast agents, Eovist and MultiHance, show a distinct uptake in various animal species, in humans only 2%–4% of MultiHance, but about 50% of Eovist are specifically taken up by the liver and excreted into the biliary system. Nevertheless, both agents improve the detection of liver lesions. The contrast media portion not eliminated via the biliary route is excreted via the kidneys, similar to the extracellular contrast agents.

**Fig. 2.1A,B.** Multiple metastatic lesions at pre- and 20 post-injection of Gd-EOB-DTPA. Distinct signal increase of the normal liver parenchyma but no enhancement within the lesions on T1-GRE sequences (Reimer, Münster, Germany)

**Table 2.3**

<table>
<thead>
<tr>
<th>No.</th>
<th>Product Name</th>
<th>Description and Approval Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Teslascan (Mn DPDP, Mangafodipir, Nycomed Imaging AS, Oslo, Norway), which obtained market approval in 1997</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>MultiHance® (Gadolinium BOPTA, Gadobenat, Bracco, Milan, Italy), which has been approved for liver imaging and has also been developed as extracellular contrast agent</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Eovist® (Gd-DTPA, Schering AG, Berlin, Germany), which completed phase-III development</td>
<td></td>
</tr>
</tbody>
</table>

|
intracellular dissociation. Whereas DPDP and the still-complete Mn-DPDP complex (15%–20%) are renally eliminated within 24 h, free Mn\(^{2+}\) remains in the body for several days and accumulates not only in the liver but to a lesser extent in the pancreas, gastric mucosa, adrenal glands, and some intracerebral structures before it is biliarly or renally eliminated. The half-life therefore is not clearly determined.

2.4.1.1.1  
**Dose and Mode of Administration**

Teslascan is approved for a dose of 5 \(\mu\)mol/kg BW. Whereas this dose is infused in a 10 mM concentration over a period of about 15–20 min, a higher concentration (50 mM) is used for a slow bolus injection (1–2 min) in the USA. However, in both cases, the injection speed does not allow any dynamic imaging. The optimal imaging time point is at 15–30 min after the end of infusion/injection. In some cases, later images at 4 h provide additional information for lesion characterization.

MultiHance is injected as a fast bolus at a dose of 0.05 mmol/kg BW, which provides the opportunity of dynamic imaging. Due to the relatively low uptake of MultiHance (about 2%–4% by hepatocytes), the accumulation of a sufficient amount of contrast medium in the liver lasts longer, and the best imaging time point is therefore about 60–120 min after injection. It could be shown that the signal increase in the liver at that time is comparable to the enhancement after injection of Teslascan.

For Eovist, which can also be injected as a fast bolus for dynamic imaging, doses between 3 \(\mu\)mol/kg and 50 \(\mu\)mol/kg BW have been tested in clinical phase-II studies. The recommended dose currently used in phase-III studies is 25 \(\mu\)mol/kg BW, which is sufficient for the combination of dynamic imaging and hepatobiliary phase imaging, as well as for imaging in patients with liver cirrhosis or impaired liver function. The optimal imaging time point for the hepatobiliary phase is about 15–20 min after injection, but the imaging window is at least up to 120 min.

2.4.1.1.2  
**Safety and Tolerability**

All available data indicate a good safety profile for all three agents. It seems that the two Gd-based agents (MultiHance and Eovist) exhibit a comparable pattern and incidence of adverse reactions, as do extracellular Gd compounds. For Teslascan, the rate of adverse reactions depends very much on the dose and injection speed. After a dose reduction from 10 to 5 \(\mu\)mol/kg BW and a slow infusion, the adverse event rate went down to about 7%–10%, without any of the flush symptoms that had been reported in the phase-II studies and in the US studies for which, even in phase III, a slow bolus injection was used. After bolus injection, flush symptoms are reported by more than 70% of the patients. However, these symptoms are transient and of mild intensity and affect the patient’s comfort but do not raise a safety concern. For none of the three compounds is any relevant change of laboratory parameters reported.

2.4.1.2  
**RES-Specific Contrast Agents**

One superparamagnetic RES-specific agent or contrast medium has been on the market under the trademark Endorem (AMI 25, Guerbet, France) in Europe since 1996. Another contrast medium, Resovist (Schering AG, Berlin, Germany) has recently received approval in the EU and will be available in most European countries in 2001/2002. Both agents belong to the so-called SPIOs (small iron oxide particles), with hydrodynamic diameters of about 150 nm (Endorem) and 60 nm (Resovist). To avoid in vivo aggregation of the particles and to increase the cardiovascular tolerability in particular, SPIOs have to be coated. This is done with dextran in the case of Endorem and small molecular-weight carboxy-dextran in the case of Resovist.

The two agents are taken up by RES cells (Fig. 2.2) and mainly phagocytosed by Kupffer cells in the liver and to a lesser extent also in the spleen, bone marrow, and lymph nodes. The half-life in plasma before phagocytosis is biphasic. There is a rapid uptake of the bigger particles with a half-life of about 5 min and a slower uptake of smaller particles with a half-life of about 2–3 h. After phagocytosis, the iron goes into the physiological iron pool and the respective physiological iron metabolism.

2.4.1.2.1  
**Dose and Mode of Administration**

The recommended dose range for Endorem in Europe is 15 \(\mu\)mol Fe/kg BW. Endorem has to be prepared
Fig. 2.2A–C. Unenhanced T1 GRE (A) and T2 TSE (B) MR images of a cystic lesion and an adenoma. Signal decrease of the normal liver and of the adenoma on T2 TSE (C) images after intravenous injection of Resovist due to uptake of the iron oxide particles by functioning RES cells. No uptake and no signal decrease in the cystic lesion (Stiskal, Vienna, Austria)
immediately before administration by dissolution in a volume of about 100 ml of 5% glucose. It must be infused over a period of 20–30 min due to some hypertonic reactions in early clinical trials. Imaging can be started after a further 15 min.

Resovist is a ready-for-use suspension that is injected I.V. as a fast bolus, allowing dynamic imaging. The clinical dose is a fixed volume of 0.9 ml per patient with a body weight of 35 kg, but less than 60 kg and 1.4 ml for patients with a body weight of 60 kg and above. These volumes correspond to doses of 6–11 µmol Fe/kg BW.

2.4.1.2.2 Safety and Tolerability

Safety data from more than 800 patients were reported from the phase-III clinical trials with Endorem. The reported incidents of adverse events are between 10.3% in Europe and 15% in the USA. One of the most frequently reported adverse effects is lumbar back pain in more than 4% of the patients. The etiology of this symptom is unknown. In most of the patients, the symptoms disappeared after reduction of the infusion speed; however, in several patients, active treatment was necessary. The remaining adverse reactions are all well-known from other contrast agents and are not of any concern. The reported cardiovascular side effects after rapid injection during the early phase-I studies are not observed when the compound is infused slowly.

Resovist has been administered to more than 1200 patients during clinical phase-II and phase-III trials worldwide so far. No effects on heart rate or blood pressure have been reported after fast bolus injection. The overall incidence of adverse events is about 9%; 5.5% of these were assessed relative to the study drug used by the clinical investigators. Back pain is reported in less than 0.5% of cases and is of mild intensity.

With regard to laboratory parameters, a transient decrease within the normal range of the activity of clotting factor XI has been observed. This does not result in any changes in the overall bleeding time or coagulation tests such as PTT and Quick. As with all other contrast agents, allergoid or anaphylactic reactions can, in principle, occur with both contrast agents.

2.4.2 Lymphographic Contrast Agents

Whereas the bigger iron-oxide particles are mainly phagocytosed in the liver, smaller particles exhibit a blood half-life and are able to penetrate the vascular endothelium. From the interstitial space, they reach the lymphatic system and are taken up by macrophages. One such compound, with the expected trade name Sinerem (AMI 227, Guerbet, Paris, France/Combidex, Advanced Magnetics, USA), is currently under development. The uptake of the iron particles leads to a homogeneous signal decrease in normal lymph nodes, whereas metastatic lymph nodes remain bright and inhomogeneous on T1-W sequences. Sinerem is – comparable to Endorem – infused over about 20 min, at doses of 1.7 mg Fe/kg and 2.6 mg Fe/kg BW. So far, it has been tested in patients with head and neck primaries as well as pelvic tumors. The preliminary first results are promising; however, it has also been reported that there is either no or minimal uptake in inflammatory lymph nodes. This will be a problem in a referential diagnosis of those nodes.

2.5 Blood-Pool Agents

Blood-pool contrast agents are defined by a longer intravascular half-life and are mainly designed for MR angiographic examinations. In principle, the prolongation of blood half-life can be achieved by three different approaches:

- the use of superparamagnetic iron-oxide particles which exhibit an increasing blood half-life the smaller they are.
- the use of paramagnetic Gd compounds which form reversible larger molecules by in vivo protein binding
- the synthesis of paramagnetic Gd-based polymeric macromolecules.

The latter two approaches have in common that the contrast agents cannot diffuse into the interstitial space due to their macromolecular size.

For all approaches, contrast agents are currently under clinical development. Three of these contrast agents belong to the group of superparamagnetic USPIOs. NC100150 (Clariscan, Amersham) completed phase II in conventional MRA indications. Further trials are ongoing
in cardiac as well as in oncologic indications. The safety data known so far do not indicate any relevant problems.

SH U 555 C (Schering AG Berlin, Germany) is about to enter phase-III development in the field of MRA, whereas AMI 7228 (Advanced Magnetics, USA) just started first clinical studies.

MS 325 (Epix Medical, Boston, USA) and B-22956/1 (Bracco, Milan, Italy) are representative of the group of paramagnetic T1 agents with in vivo albumin-binding properties.

Whereas the latter agent is in an early stage of development for which no clinical data have been published, phase-III studies using MS 325 are ongoing. According to published results, the image quality of MR angiograms is excellent, and imaging can be continued for at least 90 min. The safety data indicate a good safety profile of this contrast agent.

For the paramagnetic polymeric T1 agents like Gado-mer 17 (Schering AG, Berlin, Germany) and P 792 (Guerbet, Paris, France), also only limited information is available, as both agents are in phase I and phase II of clinical development. Both agents were tested in cardiac indications and seem to provide promising imaging features.

The perspective of all the blood-pool agents is to enable imaging of vessel structures. These agents compete for the standard MR angiography indication with the extracellular Gd compounds. For high resolution MRA, however, a larger imaging window might be advantageous. Furthermore, imaging of the coronary vessels which has not been technically possible with MR imaging so far will most likely require a contrast agent which resides longer in the intravascular space.

Beyond macrovascular imaging, the evaluation of microvascular imaging mainly in tumors might become a promising indication for blood-pool agents in the future.

### 2.6 Gastrointestinal Contrast Agents

Again, as with the group of IV contrast media, the gastrointestinal compounds can be classified into positive and negative enhancers. Table 2.4 gives an overview of the existing agents.

<table>
<thead>
<tr>
<th>Table 2.4</th>
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<tbody>
<tr>
<td><strong>Trademark</strong></td>
</tr>
<tr>
<td>Magnevist enteral® gadopentetate (Gd-DPTP/dimegl)</td>
</tr>
<tr>
<td>FerriSeltz® OMR (Fe-III-Ammoniumcitrate)</td>
</tr>
<tr>
<td>Abdoscan® OMP Ferristene)</td>
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<tr>
<td>Lumirem® AMI 121 (Ferumoxsilum)</td>
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<tr>
<td>LumenHance® MnCl2</td>
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</table>

With regard to clinical efficacy, safety, and tolerability, there is no clear advantage of either positive or negative enhancers. Only a few relative clinical indications exist, such as pancreatic tumors, pelvic tumors, and inflammatory bowel disease. The reported adverse reactions are mainly diarrhea, abdominal pain, and meteorism.

### Further Reading


