The mechanisms responsible for image contrast in magnetic resonance imaging (MRI) are many, as are the methods used to produce a clinically useful MRI image. MRI contrast media design requirements, contrast mechanisms, relaxivity theory, and imaging techniques are reviewed first. This is followed by an in-depth discussion of the agents that are currently available and those that will soon come to market, focusing on diagnostic utility and clinical safety. Contrast media add an additional dimension to the manipulation of inherent contrast in MRI. Their application leads to improved sensitivity and specificity in clinical MRI.

BASIC PRINCIPLES

By 1990, just 10 years after its clinical introduction, MRI had become the imaging modality of choice for the study of central nervous system (CNS) disease. Additional broad applications in the abdomen, pelvis, and musculoskeletal system were subsequently established. Concurrent development of contrast media, now in widespread use, aided the rapid expansion of this field. Contrast-enhanced scans offer important additional diagnostic information in many instances. MRI provides high spatial resolution and soft tissue contrast, with sensitivity to contrast media greater than that of x-ray computed tomography (CT). First-pass brain studies now also make possible the assessment of regional cerebral blood volume. New hardware developments, together with advances in contrast media design, continue to drive the expansion of contrast media applications. These build on the large base of current clinical use.

MRI provides excellent soft tissue contrast on unenhanced images. Thus, it was initially speculated that there would be no need for a contrast agent. In the early 1980s, it became apparent that contrast enhancement could substantially improve the sensitivity and specificity of scans. For example, many brain metastases can only be visualized after contrast enhancement. As the benefits of MRI contrast agents became more obvious, their use increased exponentially. Currently, contrast agents are commonly used in clinical practice for a broad range of indications.

Design Requirements

Certain criteria need to be met in the design of an MRI contrast agent. First and foremost is its ability to alter the parameters responsible for image contrast. MRI is unique in that there are multiple parameters responsible for signal intensity. The contrast agent must be efficient in its ability to influence these parameters at low concentrations to minimize dose and potential toxicity.

Second, the contrast agent should possess some tissue specificity in vivo so that it is delivered to a tissue or organ in a higher concentration than to other areas in the body. Once delivered to the desired tissue or organ, it must remain localized for a reasonable period of time so that imaging can be performed.

Third, the contrast agent must be substantially cleared from the targeted tissue or organ in a reasonable period of time, usually several hours after imaging, to minimize potential effects from chronic toxicity. The contrast agent must also be excreted from the body, usually by renal or hepatobiliary routes.

Fourth, the contrast agent must have low toxicity and be stable in vivo while being administered in doses that can affect the MRI relaxation parameters sufficiently to result in visible contrast enhancement. The dose levels of the contrast agent required to meet these criteria must be evaluated for acute and subacute systemic tolerance, potential mutagenicity, teratogenicity, and carcinogenicity. Many other tolerance tests are also required, depending on intended use.

Finally, the contrast agent must possess a suitable shelf life for storage. It must remain stable in vitro for a reasonable period of time while being stored. A shelf life of years is desirable.

Contrast Mechanisms

In conventional radiography and CT, image contrast is generated by differential attenuation of the x-ray beam. The degree of attenuation is directly related to the mass absorption coefficient of the tissue being imaged. The use of a contrast agent with a high mass absorption coefficient (e.g., any of the iodinated agents) results in attenuation of the x-ray beam to a greater degree. This produces contrast enhancement. The mechanisms responsible for contrast enhancement in MRI are multiple, not singular. The large inherent differences in signal intensity between normal tissues also make MRI unique compared with other imaging modalities. To further complicate matters, the appropriate selection of operator-dependent imaging parameters is critical so that these signal intensity differences are exploited to optimize MRI contrast.

The parameters that determine MRI signal intensity
and contrast are many. The first of these, and the easiest
to understand, is spin density. Spin density refers to the
fraction of protons that exists in the voxel of tissue being
imaged and determines the maximum potential MRI
signal intensity that can be realized from that volume of
tissue. Most protons in tissue are water protons. These
far outnumber the protons that are associated with or-
getic compounds in tissue. Because a contrast agent
cannot easily alter the in vivo water content of tissue,
compounds that affect spin density have received little
attention.

Another common parameter exploited in the genera-
tion of MRI contrast is relaxivity. There are two relaxivi-
ity parameters that are unique to each tissue: T1 and T2.
Longitudinal or spin-lattice relaxation time, known as
T1, refers to the amount of time it takes for the tissue
magnetization to return to its equilibrium state in the
longitudinal direction of the main magnetic field after
excitation with a radiofrequency (RF) pulse. The excess
energy that is absorbed by the magnetic spins from the
RF pulse is transferred back to the environment during
the relaxation process. The second relaxivity property
of tissue is transverse or spin-spin relaxation, referred to as
T2 relaxation. In this relaxation process, the excess en-
ergy deposited in the tissue by the RF pulse is subse-
quently transferred between magnetic spins. This trans-
ferred energy results in loss of spin phase coherency in
the transverse plane and spin dephasing.

Contrast agent enhancement that is based on alter-
ation of these two relaxivity parameters can be catego-
rized according to the relative change it imparts on
either T1 or T2. A contrast agent that predominantly
affects T1 relaxation is referred to as a positive relaxation
agent. This is because reducing T1 results in increased
signal intensity on a T1-weighted image. By comparison,
a contrast agent that predominantly affects T2 relaxation
is considered a negative relaxation agent. This is because
reducing T2 results in decreased signal intensity on a
T2-weighted image.

Another determinant of signal intensity in MRI is
magnetic susceptibility. Susceptibility describes the abil-
ity of a substance to become magnetized in an external
magnetic field. There are four categories of magnetic
susceptibility. Most organic compounds are diamagnetic
substances and have a small, negative magnetic suscep-tibility when placed in an external magnetic field. Para-
agnetic substances have a net positive magnetic suscep-
tibility, whereas superparamagnetic and ferromagnetic
materials have very large net positive susceptibilities.
Diamagnetic susceptibility has a negligible effect in clin-
ical MRI; therefore, diamagnetic substances are of little
interest as contrast agents.

Paramagnetic substances afford the greatest flexibility
in contrast agent design and have, therefore, received
the greatest attention in contrast media development.
The presence of a paramagnetic ion, such as gadolinium,
can strongly influence the relaxation properties of
nearby protons, leading to changes in tissue contrast.
Paramagnetic contrast agents are predominantly used as
positive T1 relaxation contrast agents, with little effect
seen on T2 relaxation, and then only at high concen-
trations. The positive net magnetic susceptibility of a para-
magnetic ion actually has little influence as an actual
enhancement mechanism in conventional MRI studies.
This effect is important in one application: the assess-
ment of cerebral perfusion. Here the contrast is injected
as a bolus and observed during its first pass through the
tissue. The concentration of the agent is then sufficiently
high to permit observation of the susceptibility effect.

By comparison, the large net magnetic susceptibility
of superparamagnetic and ferromagnetic compounds
more directly influences tissue contrast, with little effect
on relaxation per se. Superparamagnetic substances
are individual particles that are large enough to be a domain.
When these particles are exposed to an external mag-
netic field, they align with the field, resulting in a large
net positive magnetization. When removed from the
magnetic field, they return to random orientations and
lose their magnetization. By comparison, ferromagnetic
compounds are large collections of interacting domains
in a crystalline matrix. They exhibit an extremely large
net positive magnetization in an external magnetic field
and maintain this when removed from the field. Both
superparamagnetic and ferromagnetic compounds have
received substantial attention in regard to their applica-
tion as MRI contrast agents. These agents function as
negative contrast agents, because the large positive mag-
netic moment induces spin dephasing in tissue, with
resulting signal loss.

The final two parameters that provide image contrast
in MRI are diffusion and perfusion. The intensity of the
MRI signal is based on the magnitude of the bulk
magnetization lying in the transverse plane. It is maximal
when all the transverse spins are in phase coherence.
Movement or diffusion of water on a microscopic level
leads to spin dephasing and loss of phase coherence in
the transverse plane. This subsequently results in the
loss of MRI signal intensity. Similarly, perfusion of blood
in the microcirculation of the tissue being imaged also
contributes to spin dephasing and a decrease in the
intensity of the MRI signal. In this manner, different
degrees of diffusion and perfusion within tissue contrib-
ute to contrast in the MRI. The use of a relaxivity
or susceptibility contrast agent to manipulate diffusion
coefficients, and thus serve as a contrast agent, has re-
ceived little attention. The presence of a susceptibility
agent in the blood pool can cause large changes in signal
intensity. This approach, as previously noted, is used in
one instance as a means of contrast enhancement,
specifically for the assessment of cerebral perfusion.

Relaxivity Theory

Most of the attention in the development of MRI con-
trast agents has focused on the use of paramagnetic
compounds. The most commonly used paramagnetic
ion is the gadolinium ion, which is complexed with
various ligands (such as diethylenetriamine pentaacetic
acid [DTPA] in gadopentetate dimeglumine [Magnevist,
Berlex Laboratories] and HP-DO3A in gadoteridol
[ProHance, Bracco Diagnostics]) that act as chelating
agents. Although an extensive review of relaxivity theory
is beyond the scope of this chapter, a basic conceptual
understanding is important to appreciate the physics
involved in paramagnetic contrast agent enhancement.
The presence of unpaired electrons in the paramagnetic ion is a mandatory component to cause a change in the $T_1$ and $T_2$ relaxation rates of water protons. The magnetic dipole moment created by the unpaired electrons can thereby enhance the relaxation rates of water protons either by direct interaction with the water protons or by its local magnetic field influence. Only paramagnetic ions with exceptionally slowly relaxing unpaired electrons are effective. The relaxation contributions of a paramagnetic ion are highly dependent on its spin state. If $S$ denotes the spin quantum number of the total electron spin of the paramagnetic ion, then the relaxation rate is proportional to $S(S + 1)$. A paramagnetic ion with the highest spin quantum number is desirable, provided it has slowly relaxing electrons. The gadolinium ion ($\text{Gd}^{3+}$) is a desirable feature because it allows for greater relaxation enhancement. A short residence time allows the paramagnetic ion to interact with more water molecules. In contrast agent design, a rapid exchange ($=10^6$ seconds$^{-1}$) between water molecules and the paramagnetic ion is desirable because it allows for greater relaxation enhancement. This factor is important only up to the point at which the exchange contributes as a correlation time.

Outer-sphere relaxation is a more complex concept. It does not involve a direct bonding or chemical exchange mechanism. It is the result of the relative rotational and translational diffusion of water molecules and the paramagnetic ion. Basically, the more water molecules that can approach the paramagnetic ion and interact with its dipole, the greater will be the relaxation influence of the paramagnetic ion. The more the paramagnetic ion can move through space, the greater will be its ability to interact with other water protons. The closer the water protons can approach the paramagnetic ion, the more efficient the relaxation enhancement will be. This interaction of the dipole moments of the paramagnetic ion and the water molecules in the environment has been termed a dipole-dipole relaxation process. Inner-sphere relaxation for $\text{Gd}^{3+}$ is also a dipolar process ("through space") because $\text{Gd}^{3+}$ has no scalar relaxation ("through bond").

These factors are critical in contrast agent design. For example, if the paramagnetic ion is complexed with a ligand such as DTPA, the molecular complex will rotate slower and translate slower in space. This will not allow as many water proton–paramagnetic ion interactions to occur, thereby limiting the relaxation effect. By complexing the paramagnetic ion, there will be increased distance between the water proton dipole and the paramagnetic ion dipole, decreasing the paramagnetic ion’s relaxation enhancement effect.

The Solomon-Bloembergen-Morgan equation is a mathematical expression that describes the relaxation of water protons in the presence of a paramagnetic ion species. This equation is used as a predictor of the relaxation efficiency of a paramagnetic ion species in contrast agent design. The Solomon-Bloembergen-Morgan equation consists of two parts. The first part, the dipole-dipole term, expresses a distance factor between interacting species. In one dimension, this is a statement of the inverse square law in that the magnitude of the paramagnetic effect is related to the reciprocal of the square of the distance (d$^{-2}$). In three dimensions, this becomes d$^{-6}$ expressed as r$^{-6}$ (r = radius). The dipole-dipole component is critically affected by the distance factor. Simply, the more closely a water molecule approaches the paramagnetic ion species, the more efficient will be the relaxation enhancement effect. Because the dipole-dipole component is critically affected by distance, it is important in contrast agent design to use carrier ligands that minimize this effect. Some of the carrier ligands, however, may be quite large. These ligands cause an undesirable effect from the standpoint of relaxation enhancement. The use of chelates is required because of the high toxicity of paramagnetic ions, such as gadolinium, when free in the body. Large carrier ligands and their surrounding water molecules of hydration tend to displace free or bulk water molecules from the surrounding inner sphere of influence of the paramagnetic ion, decreasing proton relaxation enhancement effects. Of all factors, this has the greatest negative impact.

The second part of the Solomon-Bloembergen-Morgan equation contains the scalar component. This term describes the probability of contact (correlation time) between the paramagnetic ion and the water proton. The total correlation time ($t_c$) between the two interacting species can be expressed mathematically for both dipole-dipole and scalar interactions as follows:

$$1/t_c = 1/t_r + 1/t_e + 1/t_m,$$

where $t_r$ is the correlation time of rotation, $t_e$ is the correlation time of electron relaxation, and $t_m$ is the correlation time of chemical exchange. Relaxivity is directly proportional to $t_c$. The critical feature of this mathematical expression is that the component of the smallest magnitude will be the most important in determining the total correlation time of interaction.

Correlation times are important in paramagnetic agent design. For example, the larger the carrier ligand to which the paramagnetic ion is bound, the slower it will rotate and translate in space, thereby increasing the magnitude of $t_r$. The total correlation time of interaction is thus increased in most instances of a large carrier ligand molecule, somewhat offsetting the distance factor for these large carrier ligands. Correlation times will always reflect the interaction possessing the shortest
time characteristic or the fastest dynamic behavior of the paramagnetic contrast agent, provided that chemical exchange is fast enough (= $10^6$ seconds$^{-1}$).

**Imaging Technique**

As is now evident, the mechanisms responsible for MRI contrast are multiple, including spin density, $T_1$, and $T_2$, susceptibility, diffusion, and perfusion. Similar to the intrinsic MRI properties of the tissues themselves, the methods of measurement of these parameters in clinical MRI are multiple. The type of MRI pulse sequence used to generate a clinical MRI image and its associated parameters profoundly affects the contrast that is visualized from the tissues.

The ultimate goal when optimizing MRI scan technique for contrast agent visualization is to suppress the contrast from unchanged tissue parameters and accentuate the contrast based on the parameter that is altered by the contrast agent. This requires knowledge of the mechanism of contrast agent enhancement, the MRI pulse technique being used to measure that parameter, and how the operator-dependent parameters can be altered to optimize the enhancement of the contrast agent being used. What follows is a discussion of the MRI pulse sequences that are commonly used in conjunction with clinical MRI contrast agents and the issues that are related to their optimization.

Conventional spin echo imaging continues to be the principal technique for visualization of contrast agents. This approach can provide images with $T_1$, $T_2$, and spin density information. In spin echo imaging, a 90-degree RF pulse is followed by a 180-degree pulse. The latter generates an MRI signal or echo at an operator-specified echo time (TE). This measurement is repeated at a repetition time (TR) also specified by the operator. In spin echo imaging, short TR and short TE times produce an image with $T_1$-weighted contrast. For example, a scan with $TR = 500$ msec and $TE = 10$ msec is $T_1$-weighted. The enhancement effect of the gadolinium chelates is typically visualized on such $T_1$-weighted scans (Fig. 14-1). Long TR and TE times produce images with $T_2$-weighted contrast. A scan with $TR = 3000$ msec and $TE = 100$ msec is thus $T_2$-weighted. During the same long TR interval used to produce a $T_2$-weighted image, an additional image can be obtained with a short or intermediate echo time. This image will have spin density or intermediate $T_1$-weighting. One of the major disadvantages of conventional spin echo imaging when used to produce $T_1$-weighted scans is the long imaging time. Imaging time is directly proportional to $TR$, which is long for a typical $T_2$-weighted pulse sequence.

In the mid-1990s, imaging techniques using magnetization transfer (MT) were introduced. The application of MT in spin echo imaging can improve the enhancement effect produced by a gadolinium chelate in the brain (Fig. 14-2). Water protons in tissue exist in three distinct pools. The protons in the free water pool exist in a narrow range of resonant frequencies and possess a long $T_2$. It is these protons that account for most of the MRI signal recorded in clinical MRI. The brain, protons in the second pool, fat, are few. The third pool of protons is the restricted pool. These protons represent structural or bound water protons associated with large molecules. Protons in the restricted pool have a large range of resonant frequencies and an extremely short $T_2$. Because the signal from this pool decays so quickly during MRI imaging (as a result of the short $T_2$), it contributes little to the image. With the application of MT, magnetization is transferred from the restricted pool to the freely mobile pool. The result is a shortening of $T_2$, with lower overall available magnetization and signal intensity. In theory, enhancement with gadolinium chelates is not mediated by macromolecular interactions and thus not suppressed by the application of MT. Accordingly, MT pulses preferentially suppress the signal from background tissue, usually improving the conspicuity of gadolinium-enhanced regions. This can lead to improved visualization of contrast enhancement at standard doses.

In areas of the body with abundant fat, scan techniques that combine $T_2$-weighting with fat suppression provide improved depiction of contrast enhancement (Fig. 14-3). Short TI inversion recovery (STIR) is one such approach. STIR suffers from poor signal-to-noise ratios and long scan times. Techniques that use a fat saturation pulse are currently more common. Frequency selective or spectral saturation exploits the slight difference in resonance frequency between fat and water. The signal from fat is saturated (removed) by the application of a frequency selective pulse. This approach can be adapted to any imaging technique and is similar in principle to spatial saturation.

Fast or turbo spin echo imaging became widely available in the mid-1990s. This approach permits $T_2$-weighted scans to be acquired in a much shorter time. With fast spin echo techniques, multiple echoes are acquired with different phase encoding values during each TR interval. Images with both proton density- and $T_2$-weighted information can be obtained in times from one fourth to one sixteenth that required for conventional spin echo techniques. The images generated from this approach arise from multiple TE data measurements, which are then averaged together for an effective TE image. Thus, image contrast is somewhat different from a conventional spin echo sequence. For example, the MRI signal from fat is more intense on a $T_2$-weighted image obtained with fast spin echo technique, reflecting in part the brighter signal that fat produces on short TE images. Despite these and other minimal shortcomings of fast spin echo sequences, they have gained widespread popularity in clinical MRI.

Another pulse technique popular in both spine and body applications is gradient echo imaging. This offers an alternative imaging approach with substantially reduced imaging time and RF power deposition. A gradient echo sequence differs from a spin echo sequence in that a 180-degree RF pulse is not used. The initial RF pulse also typically uses a flip angle of less than 90 degrees. Signal is generated after this initial pulse by manipulation of the gradient magnetic fields. By changing the operator-dependent parameters of the flip angle, TR and TE, image contrast with $T_1$, $T_2^*$, and
Figure 14–1. Glioblastoma illustrating the utility of T₁-weighted scans for detection of lesion enhancement. Precontrast T₂ (A) and T₁-weighted (B) scans are compared with postcontrast T₂ (C) and T₁-weighted (D) scans. Gadolinium chelates (ProHance in this instance) are detected in most instances using T₁-weighted scans. D. On the postcontrast T₁-weighted scan, positive lesion enhancement is noted in the region of blood-brain barrier disruption (marking the bulk of tumor mass). The contrast agent causes little or no change in signal intensity on the postcontrast T₂-weighted scan (C).
Figure 14-2. Cavernous sinus meningioma illustrating the use of magnetization transfer (MT) suppression. Precontrast T₁-weighted scans without (A) and with (B) MT are compared with postcontrast T₁-weighted scans without (C) and with (D) MT. The addition of an MT pulse shortens the T₁ of the freely mobile hydrogen pool, decreasing the signal intensity of normal brain. The effect is less on areas that demonstrate contrast enhancement, thus improving the depiction of lesion enhancement in most cases when MT is used.
spin density information can be generated. One of the major disadvantages of gradient echo imaging is that susceptibility effects become prominent. This enhanced susceptibility effect can be exploited to advantage, however, in certain clinical situations. For example, the high magnetic susceptibility of blood degradation products, such as deoxyhemoglobin, results in increased conspicuity of hemorrhage on gradient echo scans.

Echo planar imaging (EPI) became widely available for clinicians in the late 1990s. EPI-based techniques are used to decrease motion artifact with uncooperative patients by shortening scan time and to acquire brain perfusion studies. High-quality images can be acquired in seconds as opposed to minutes. Fast spin echo scans, for example, require several minutes for acquisition. EPI scans can be proton density-, T₁-, or T₂-weighted. In combination with bolus contrast injection, EPI is used to view the first pass of a gadolinium chelate through the brain. Tissue perfusion can thus be assessed.

For perfusion imaging, the contrast medium (typically one of the approved extracellular gadolinium chelates) is injected as a bolus using an MRI-compatible power injector. Images are acquired very rapidly, about one per second, during and immediately after injection. This makes possible observation of the first pass of the contrast agent through the brain. In all other applications, T₁-weighted scans are used to detect a gadolinium chelate. In brain perfusion studies, T₂*-weighted scans are used. These scans provide the high temporal resolution needed and also are quite sensitive to the very concentrated contrast medium within the vascular bed. On T₂*-weighted scans, the gadolinium chelates cause a reduction in signal intensity as opposed to the increase in signal intensity seen on T₁-weighted scans. After acquisition, processing software can be used to produce relative cerebral blood volume (rCBV) and relative mean transit time (rMTT) images. Perfusion imaging can detect brain ischemia far sooner than standard T₁-weighted
scans, with important clinical applications in infarct detection and evaluation.

Development History

Before 1982, the relaxation effects of the paramagnetic metals, which include gadolinium, were well known. However, the toxicity of these metals in their ionic forms appeared to prevent their use in humans. To design a safe agent, it was proposed that the metal ion be tightly bound by a chelate. Thus, the paramagnetic effect could be expressed, yet toxicity limited, by achieving rapid and total renal excretion. The gadolinium ion emerged as the most favorable choice because of its large paramagnetic effect or, more specifically, enhancement of $T_1$ relaxation.

The clinical safety of these agents is largely dependent on the stability of the chelate in vivo (Fig. 14–4). Key factors determining safety include thermodynamics, solubility, selectivity, and kinetics. There must be a high affinity of the chelate for the metal ion, which is reflected by the thermodynamic binding constant of the complex ($K_{eq}$). If the agent is not sufficiently soluble, precipitation of the gadolinium ion can occur, with potential toxicity. The chelate must also have high selectivity for the gadolinium ion itself. This requirement is such that metal exchange with endogenous ions, such as zinc and copper, does not occur. Last, but not least, the compound must exhibit slow kinetics in regard to release of the gadolinium ion. This makes possible near-complete excretion of the complex in the setting of normal renal function. One way to assess kinetics is by the rate of dissociation of the complex in acid solution. Table 14–1 presents a comparison of the three agents available in the United States on the basis of these and other chemical characteristics. High thermodynamic stability, slow kinetics of dissociation (small $k(\text{obs})^{-1}$), low osmolality, and low viscosity are favorable features.

The gadolinium chelates, the major class of contrast agents currently used in MRI clinical practice, enhance $T_1$ relaxivity. Positive lesion enhancement is seen on $T_1$-weighted scans. Changes on $T_2$-weighted scans are generally not appreciable. Although these agents primarily affect $T_1$ relaxation rates, producing positive enhancement, they also affect $T_2$. In most clinical situations, $T_2$ effects have little contribution. However, at very high concentrations, negative enhancement can be seen. For example, on postcontrast scans of the bladder, some urine may be of low signal intensity. This occurs as a result of layering of contrast and hyperconcentration posteriorly when the patient is supine. The low signal intensity reflects the $T_2$ contribution.

Administration of a gadolinium chelate can substantially improve lesion identification and characterization. Within the CNS, lesion enhancement occurs as a result of disruption of the blood-brain barrier (BBB). For extra-axial abnormalities and lesions outside the CNS, contrast enhancement is governed by differences in tissue vascularity. At a standard dose (0.1 mmol/kg), lesion enhancement on MRI using a gadolinium chelate is equivalent or slightly superior to that on x-ray CT using an iodinated agent. However, unlike CT, adjacent bone or calcification does not obscure abnormal contrast enhancement.

Over the past decade, research has focused in part on the development of new gadolinium chelates with improved tolerance. Increased emphasis has been placed on physicochemical properties, including osmolality, viscosity, and stability of the metal chelate in vivo. Agents with lower osmolality and viscosity can be administered faster and generally at higher doses, important features for first-pass perfusion studies. Other avenues of research include development of compounds with higher relaxivity. Both approaches seek to lower the toxicity of the agent for a given effective dose. One step in development has paralleled the history of the iodinated agents. Nonionic (neutral) compounds, such as ProHance, have been perfected since the initial develop-

<table>
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<th>Table 14–1. Physicochemical properties of the gadolinium chelates in clinical use in the United States</th>
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<tr>
<td>Trade name</td>
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<tr>
<td>ProHance</td>
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<td>Magnevist</td>
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mented in clinical studies. The latter class of agents may to increase blood pool residence time are being evalu-
clinical use; agents that bind to human serum albumin benate dimeglumine, Bracco Diagnostics) are also in
chelates targeted in part to the liver (MultiHance, gado-
Magnevist, is awaiting approval in Europe. Gadolinium gadobutrol, Schering AG), from the manufacturer of
use outside the United States, and a third (Gadovist,
insertion. T2*- (susceptibility) weighted scans are used for
patients are taken up by lymph nodes and bone marrow
determines their distribution. Larger particles are
phagocytosed by macrophages of the reticuloendothelial system, with uptake in normal liver and spleen. Smaller
particles are taken up by lymph nodes and bone marrow and have a long residence time in the bloodstream.

In the presence of a sufficient concentration of iron particles, there is selective T2 shortening with profound
signal loss. Because MRI signal intensity is decreased in normal liver and spleen (with large iron particles), focal
areas of replacement, such as metastatic disease, are seen as areas of higher signal intensity. Iron particles exhibit
a monophasic effect on signal intensity because progressively larger doses can only further reduce signal intensity until the level of background noise is reached.

**GADOLINIUM CHELATES**

This discussion is limited to gadolinium chelates that have been developed for use as contrast media in MRI and the intravenous application of these agents. In the past, clinical trials were conducted in Europe examining the oral use of gadolinium chelates. However, no agent is currently approved for such an indication in the United States. The gadolinium chelates are paramagnetic agents, developing a magnetic moment when placed in a magnetic field (the scanner). The large magnetic moment enhances the relaxation rates of water protons in the vicinity of the agent. On T1-weighted images, there is a resultant increase in signal intensity when sufficient contrast material is present. T1-weighted scans are used largely for the detection of these agents. In routine clinical practice, both pre- and postcontrast T1-weighted scans are acquired. This enables certain identification of the presence of contrast material postinjection. T2* (susceptibility) weighted scans are used for visualization of these agents in one application only, that being first-pass brain imaging. In this instance, because T2 relaxation is enhanced (with T2 shorter), the result is a decrease in signal intensity.

**Agents in Current Clinical Use**

Because of their molecular size, the agents in current clinical use do not cross an intact BBB. Disruption of the BBB or abnormal vascularity allows accumulation of a gadolinium chelate in lesions, thus providing contrast enhancement. As a group, these agents have a good overall safety profile. The majority of adverse reactions are mild and transient. Although they are rare, severe anaphylactoid reactions have been documented. Diagnostic use should be carried out under the direction of a physician, with adequate preparation for treatment of a major untoward event. The possibility of a reaction is considered to be higher in patients with previously documented sensitivity to iodinated agents, gadolinium chelates, or multiple drugs or with history of asthma. The gadolinium chelates are given according to weight. The standard dose is 0.1 mmol/kg, which is equivalent to 0.2 ml/kg. Magnevist, ProHance, and Omniscan (gadodiaimide, Nycomed) are all formulated at a 0.5 mol/L concentration. Except for dose, the clinical approval for these three agents is similar. Broad indications exist for their use in the CNS and body. None are formulated with antimicrobial preservatives. Most vials sold are for single-patient use only.

Magnevist is known to be excreted in breast milk. This is believed to be true, although not studied, for the other gadolinium chelates. If given to lactating mothers, the recommendation has been historically that breastfeeding should be discontinued for several days. One study demonstrated that the actual dose delivered to the infant is very low; thus, this recommendation (to discontinue breast-feeding) is now in question. The gadolinium chelates do cross the placenta and should not be used during pregnancy except under extenuating circumstances. There are no adequate, well-controlled studies examining safety in pregnant women.

Gadolinium is a metal of the lanthanide series, which are rare-earth elements. The safety of this class of agents is based on the use of chelates, firmly holding the gadolinium ion and ensuring rapid and complete excretion. If dechelated, the gadolinium ion can be deposited in liver, brain, and bone marrow. Gadolinium toxicity is known from industrial accidents. From a theoretical perspective, based on stability in vivo, ProHance is the safest agent and Omniscan the least. An increase in urinary zinc excretion has been documented after Omniscan injection (far greater than that observed with any other agent), reflecting in vivo transmetallation and release of free gadolinium ion.

**Magnevist**

In 1988, Magnevist was approved by the U.S. Food and Drug Administration (FDA) for intravenous injection. This agent was the first gadolinium chelate evaluated in humans and served as the model for development of the
agents that followed. It is a linear chelate with a net charge of \(-2\), counterbalanced by the two N-methylglucamine salts. The osmolality is 1960 mOsm/kg water at 37°C and the viscosity 2.9 cP. Thus, Magnevist has an osmolality 6.9 times that of blood plasma and is markedly hypertonic. The agent, like ProHance and Omniscan, is distributed in the extracellular space and excreted exclusively by glomerular filtration (in the urine). Approval is for adults and children (2 years of age and older). This approval is for the intracranial space (adults and children), spine (adults and children), and body (chest, abdomen, and pelvis, but excluding the heart, and in adults only). Nausea is reported as an adverse reaction with an incidence of 2.5% (according to the package insert). An intravenous injection rate of not more than 10 ml per 15 seconds is recommended.

**ProHance**

ProHance was approved for clinical use in the United States in 1992. This agent was the first ring chelate developed, accounting for its high stability in vivo and favorable safety margin. The ligand carries a charge of \(-3\) and the gadolinium ion a charge of \(+3\), with the combination (or chelate) carrying no charge. Thus, ProHance is a neutral or nonionic agent. The osmolality is 630 mOsm/kg water at 37°C and its viscosity 1.3 cP. Thus, ProHance has an osmolality only 2.2 times that of blood plasma. The agent is much less viscous than Magnevist, a difference quite noticeable to the individual performing the injection. Approval is for adults and children (2 years of age and older) in the brain (intracranial), spine, and associated tissues. ProHance is also approved for use in adults to visualize lesions in the head and neck. Nausea and taste paresthesia are reported as adverse reactions with an incidence of 1.4% (according to the package insert). In adults, there is approval for an additional dose of 0.2 mmol/kg, supplementing the initial dose of 0.1 mmol/kg (for a total of 0.3 mmol/kg). In clinical practice, scans are typically performed either after a standard dose or a single high-dose injection. The latter is most commonly used in the evaluation of intracranial metastatic disease (Fig. 14-5). In the multicenter U.S. trial (published in 1994) comparing 0.1 and 0.3 mmol/kg ProHance for the detection of brain metastases, an improvement of 32% in number of lesions detected was demonstrated at high dose. These trials established not only the greater efficacy for lesion detection but also the overall cost-effectiveness of this approach. Additional diagnostic value for high-dose administration has been demonstrated for a broad range of poorly enhancing disease. ProHance is approved for bolus injection. Single-dose (prefilled) syringes have also become available, with the field moving in this direction for packaging of all MRI contrast media.

**Omniscan**

Omniscan was approved for clinical use in the United States in 1993. This agent features a variant of the linear chelate used in Magnevist. The ligand carries a charge of \(-3\), with the gadolinium chelate itself thus carrying no charge. Neutrality is achieved, however, at the cost of a substantial decrease in the stability of the chelate in vivo. The osmolality is 783 mOsm/kg water at 37°C and the viscosity 1.4 cP. Thus, Omniscan has an osmolality 2.8 times that of blood plasma. CNS (brain and spine) approval is for adults and children (2 years of age and older). Approval for use in the body is restricted to adults and includes the intrathoracic (noncardiac), intrabdominal, pelvic, and retroperitoneal regions. An adverse effect on embryofetal development has been shown with Omniscan in rabbits. Nausea, headache, and dizziness occurred in clinical trials in 3% or less of patients (as reported in the package insert). In adults, there is approval for an additional dose of 0.2 mmol/kg. Omniscan, like ProHance, is approved for bolus injection.

**OptiMARK**

OptiMARK successfully completed phase III clinical trials in the late 1990s and received FDA approval for a dose of 0.1 mmol/kg (with limited indications) in the year 2000. OptiMARK is similar in design, distribution in the body, and use to the three extracellular gadolinium chelates previously approved by the FDA. Results from U.S. clinical trials were reported in 1999. Adverse events were seen in 73% of patients who received OptiMARK. In this trial, 163 patients received OptiMARK and 42 patients received a placebo. Adverse events were reported in 50% of the placebo group. The rate of adverse events increased with dose (doses of 0.1, 0.3, and 0.5 mmol/kg were evaluated). In a second trial, also published in 1999, OptiMark was compared with Magnevist. In this trial, 37 of 99 patients (37%) receiving OptiMARK experienced an adverse event; events in 9 patients (9%) were considered likely related to the contrast agent. Reaction rates were similar with Magnevist. Forty-five of 94 patients (48%) receiving Magnevist experienced an adverse event; events in 13 patients (14%) were considered likely related to the contrast agent. The most common reported adverse event attributed to either OptiMARK or Magnevist was taste perversion (6%). Urticaria occurred with an incidence of less than 2%.

**Adverse Reactions**

Although the gadolinium chelates are commonly thought not to be associated with any adverse reactions, this is not true. Other than pain at the injection site, which may or may not, in reality, be related to contrast injection, the two most common mild reactions encountered (attributed to contrast injection) are nausea and hives. On the basis of U.S. clinical trials published in the journal *Radiology*, there is no statistically significant difference between the agents in terms of incidence of these two adverse reactions. Nausea is reported in 1.5% of patients receiving Magnevist, 1.2% of patients receiving ProHance, and 1.6% of patients receiving Omniscan. With regard to hives, these were reported in 0.3% of patients receiving Magnevist, 0.2% of patients receiving ProHance, and 0.7% of patients receiving Omniscan.
scan. Severe anaphylactoid reactions occur, but are very rare, with all agents. Patients with asthma, multiple allergies, or known drug sensitivities (including to iodinated contrast media) are at increased risk. Health care personnel should be aware of the potential for severe anaphylactoid reactions in association with the use of gadolinium chelates and be prepared should complications arise. All agents for intravenous use in MRI should only be administered to a patient when a physician is readily available, in the near vicinity, in case such an untoward event is encountered.

Agents in Clinical Trials

Contrast media currently in clinical trials include new extracellular gadolinium chelates (similar to Magnevist, ProHance, and Omniscan), hepatobiliary gadolinium chelates, and intravascular agents. Of this group, MultiHance is somewhat unique, with intended applications including both the CNS and body. MultiHance is excreted principally by the kidneys and to a small extent by the liver. The latter feature markedly improves the performance of this agent in the liver. MultiHance also binds slightly to proteins, improving its relaxivity (enhancement effect) regardless of location in the body. Thus, at an equivalent dose, it exhibits a superior contrast effect compared with other chelates regardless of body region.

Of the agents with some hepatobiliary excretion, MultiHance is the farthest along in regard to approval status. This agent is currently awaiting approval in the United States. However, MultiHance is already ap-
proved and in clinical use in most of Europe. When used in the liver, both dynamic and delayed scans provide valuable information. Before its clinical approval, dynamic imaging with the extracellular gadolinium chelates will continue to play a major role in liver MRI.

**MultiHance**

MultiHance is the first agent in a new class of gadolinium chelates with initial extracellular distribution, weak protein binding, and subsequent renal and hepatobiliary excretion. A substantial increase in enhancement is seen with MultiHance, when compared at the same concentration with the three gadolinium chelates in current clinical use, because of the weak protein binding. In one experiment, peak signal intensity enhancement in brain tumors was 87% after 0.1 mmol/kg MultiHance versus 64% after 0.1 mmol/kg Magnevist, which has no protein binding. A similar increase in enhancement has been observed in an infarct model. In the CNS, MultiHance at a dose of 0.2 mmol/kg should provide roughly the same lesion enhancement as seen with 0.3 mmol/kg of a conventional agent (see Fig. 14-5).

Phase I, II, and III clinical trials have been performed in Europe and Japan, with 975 individuals receiving MultiHance. These trials included imaging of the CNS, chest (heart), and abdomen. In Phase IIb-III studies, nausea was reported in 1.1% of subjects. In addition to being an excellent extracellular contrast agent for application in the CNS, MultiHance is a superior agent for liver imaging because of its hepatobiliary excretion (Fig. 14-6). With its clinical introduction, MultiHance will replace conventional extracellular gadolinium chelates for liver applications. In addition to dynamic scans, as acquired with conventional agents, delayed scans can also be obtained after MultiHance injection (for liver imaging). On delayed scans, there is clearance of the agent from the extracellular space with uptake in hepatocytes and biliary excretion. Delayed scans are particularly useful for the detection of small liver metastases. Liver-lesion contrast is highest 60 to 120 minutes after injection, and detection of lesions less than 1 cm in size is markedly improved. MultiHance is the lead agent in this class in terms of both clinical experience and stage of evaluation. MultiHance is currently approved for clinical use in most of Europe.

Phase II U.S. clinical trials with MultiHance have also been completed. The agent was evaluated in both the liver and CNS. In the former trial, which was a study of focal liver lesions, 222 patients were enrolled at 14 sites. Based on the judgment of the on-site investigator, postcontrast scans improved diagnostic confidence to a degree sufficient to change patient management in 22% and 41% of patients, depending on the dose administered. Dynamic and delayed postcontrast scans proved complementary; both were of substantial diagnostic value (Fig. 14-7).

**Gadovist**

Clinical trials with Gadovist have been performed in Europe and Japan since 1992. Gadovist, like ProHance, demonstrates high in vivo stability as a result of the ring shape of the chelate. As with ProHance, this enables safe injection of up to 0.3 mmol/kg and formulation at twice the normal concentration (1.0 molar vs. 0.5 mol/L). Gadovist was approved in Switzerland in 1998 for CNS use in adults (at doses of 0.1 and 0.3 mmol/kg). Both the 0.5 and 1.0 mol/L formulations were approved. The latter has advantages for perfusion studies, specifically for the diagnosis of stroke, detection of focal cerebral ischemia, and evaluation of tumor perfusion.

**Eovist**

Eovist is a new gadolinium chelate that, like MultiHance, has renal and hepatobiliary excretion. Eovist has been evaluated in European clinical trials; the focus has been for liver use. As with MultiHance, both dynamic (extracellular phase) and delayed (hepatobiliary phase) scans can be acquired when imaging the liver. Eovist provides improved detection of hepatic lesions over conventional extracellular gadolinium chelates, such as Magnevist.

**AngioMARK**

The ligand in AngioMARK is a derivative of that used in Magnevist, with an additional protein-binding diphenylcyclohexyl group attached to the chelate by a phosphodiester linkage. The agent binds strongly to plasma albumin after injection, achieving greater signal enhancement for longer periods of time when compared with a conventional extracellular gadolinium chelate. The slower molecular tumbling of the albumin-bound chelate affords a five- to 10-fold enhancement in relaxivity over existing gadolinium chelates. AngioMARK is designed for vascular indications, including peripheral, carotid, and coronary artery disease. In phase I, doses from 0.05 to 0.15 mmol/kg were evaluated. No clinically significant adverse events were reported in 63 normal individuals. A phase II safety and efficacy trial (for peripheral and carotid disease) has been completed in the United States using a dose of 0.05 mmol/kg. In a more recent phase II feasibility trial for imaging coronary arteries, the agent was administered at a dose of 0.1 mmol/kg.

**Low Dose**

The choice of contrast dose for screening MRI exams of the head and spine is now discussed, focusing on the issue of low (half) dose: 0.05 mmol/kg. The discussion is pertinent to the use of the gadolinium chelates (approved worldwide) with extracellular distribution and renal excretion (only). Data from clinical trials strongly support a dose not lower than 0.1 mmol/kg for screening MRI exams of the head and spine. The use of a lower dose, with proven lower efficacy, places the patient at risk of adverse reactions because of contrast administration, yet does not ensure the one result for which contrast was administered: improving lesion detection and differential diagnosis. The choice of dose in certain specialty applications, specifically for the study of pitu-


Figure 14–6. Metastases (adenocarcinoma, unknown primary). The value of dynamic scans for lesion characterization and delayed scans for lesion detection (using MultiHance, a gadolinium chelate with both renal and hepatobiliary excretion) is evident. A lesion adjacent to the anterior margin of the left lobe is questioned on the precontrast T$_2$-weighted scan (A) and confirmed on the precontrast T$_1$-weighted scan (arrow) (B). The lesion enhances to isointensity with normal liver on dynamic imaging (consistent with a metastasis) (C) and is best identified on the delayed scan at 80 minutes after MultiHance injection (D, arrow). Closer to the dome of the diaphragm, precontrast T$_2$- (E) and T$_1$-weighted (F) scans appear normal prospectively, as does the dynamic postcontrast scan (G). However, an additional metastasis (arrow) is clearly visualized on the delayed scan at this level (H). In retrospect, the lesion is seen (albeit poorly) on the precontrast T$_2$-weighted scan (E). No additional metastatic lesions were noted.
FIGURE 14–6 Continued. I and J. Both metastases were poorly detected by enhanced spiral computed tomography.
FIGURE 14–7. Metastases from colon carcinoma. The value of delayed postcontrast scans in additional planes (other than axial) using MultiHance is evident. No abnormality was noted on the precontrast T2-weighted scan (not shown). A, Two areas of abnormal low signal intensity are seen in the liver on the precontrast T1-weighted scan. B, The more posterior of the two enhances on the dynamic scan obtained immediately after contrast injection, consistent with normal liver (focal sparing from fatty infiltration). The lesion more laterally demonstrates mild inhomogeneous enhancement that progresses slightly from immediately (B) to 5 minutes (C) postcontrast. Lesion margins are also indistinct on the dynamic scans. These features are consistent with a metastasis. D, This metastasis (arrow) is clearly seen on the delayed scan obtained 80 minutes after MultiHance injection.
itary microadenomas and acoustic schwannomas, is also discussed. Excluded from commentary is the choice of dose for contrast-enhanced magnetic resonance angiography (CE-MRA), an area of current controversy. However, in CE-MRA, doses higher than 0.1 mmol/kg are commonly used. The reason for addressing the issue of dose in some depth is the practice at some MRI sites of splitting a 20-ml vial of contrast (intended for single-patient use) into two doses of 10 ml, each for different patients. This practice cannot be justified on a scientific basis and raises important ethical and legal issues.

Clinical Trial Experience

In the referenced literature, only a small number of studies exist that compare results in the CNS over a range of contrast dose, from very low (0.025 mmol/kg) to high (0.3 mmol/kg). In 1987, the first experience with a gadolinium chelate (Magnevist or gadolinium DTPA) in intracranial tumors was published. This study, which evaluated doses of 0.05 to 0.2 mmol/kg in 11 patients, concluded that a dose of 0.1 mmol was both safe and suitable. Also noted was that a dose of 0.2 mmol/kg increased diagnostic yield in selected cases. In a follow-up 1990 report, which evaluated doses of 0.025 to 0.2 mmol/kg, a dose of 0.1 mmol/kg was recommended for routine study of intracranial tumors. This study also noted that the use of 0.2 mmol/kg further increased tumor-brain contrast. In the largest series published with gadolinium DTPA, doses of 0.025, 0.05, and 0.1 mmol/kg were evaluated in 88 patients. This study, which appeared in 1992, confirmed the conclusion of earlier investigations that a dose of 0.1 mmol/kg was more effective for enhancing intracranial tumors than lower doses (on both mid- and high-field units).

The advent of clinical trials with ProHance in the late 1980s provided a second opportunity to examine dose and efficacy. In a study of 14 patients, doses of 0.05 to 0.3 mmol/kg were evaluated. The authors concluded that lesion enhancement was sufficient for clinical diagnosis in all cases at a dose of 0.1 mmol/kg. However, doses higher than 0.1 mmol/kg further improved lesion enhancement. A 1991 study examined 40 patients given doses of 0.05 to 0.3 mmol/kg. The authors concluded that lesion contrast improved with dose and that the lowest dose evaluated, 0.05 mmol/kg, was inadequate for the evaluation of most CNS tumors.

Thus, phase II and III clinical trials, which are the only dose-ranging studies to date, conclude that a dose of 0.1 mmol/kg (using a gadolinium chelate with extracellular distribution and renal excretion) is sufficient for screening the CNS. No data are provided to support a lower dose, and indeed the evidence points to this being markedly inferior. Figures 14-8, 14-9, and 14-10 show the difference between lesion enhancement with half-dose (0.05 mmol/kg) and full dose (0.1 mmol/kg). Metastases can be readily missed at doses lower than 0.1 mmol/kg (see Fig. 14-8). Other intra-axial lesions may not enhance sufficiently at doses lower than 0.1 mmol/kg to permit the identification of BBB disruption, the very reason for contrast injection (see Fig. 14-9). Simi-

![Figure 14-7 Continued. E and F, Acquisition (in the delayed time frame) of additional breathhold images in the sagittal plane led to a change in patient management. These scans show clearly the metastasis (E, arrow) noted on axial imaging but also identify an additional metastasis (F, arrow) adjacent to the diaphragm. G, The enhanced computed tomography scan was difficult to interpret prospectively (without reference to the magnetic resonance image) because of extensive focal fatty infiltration.](image-url)
Figure 14–8. Metastatic disease, comparison of half- (A) and standard dose (B) postcontrast scans. A single brain metastasis (B, arrow) is well seen when the standard dose (0.1 mmol/kg) of contrast is administered. Enhancement after half-dose is poor; the metastasis is difficult to identify. This lesion was also not clearly seen on the precontrast T2-weighted scan (not shown), as is often the case with small brain metastases.

Figure 14–9. Subacute infarction, comparison of half- (A) and standard (B) dose. The patient presented 12 days previously with a left hemispheric stroke. Precontrast scans were normal, including both fast T2-weighted and fluid-attenuated inversion recovery sequences. In subacute brain infarction, there may be sufficient resolution of vasogenic edema to make the lesion difficult to identify on precontrast scans. In this setting, the lesion can be identified on postcontrast scans as a result of blood-brain barrier disruption. The scan obtained after standard dose contrast administration (B, 0.1 mmol/kg) demonstrates multiple areas of abnormal cortical enhancement (arrows), confirming the clinical diagnosis. At half-dose, enhancement is subtle and less widespread; identification of the abnormality is not assured.

Figure 14–10. Dural inflammation, comparison of half (A) and standard (B) dose. A, Enhancement of extra-axial abnormalities can also be poor with half-dose. Dural enhancement, in this instance resulting from previous hemorrhage, is clearly seen (arrow) at standard contrast dose (0.1 mmol/kg).

Larly, extra-axial abnormalities may not be recognized at half-dose (see Fig. 14-10).

Phase II and III clinical trials also provided the impetus for the examination of high doses in selected patient populations. It is important to note that extensive clinical experience exists with high contrast dose (0.3 mmol/kg with ProHance or Omniscan) in the study of brain metastases. Clinical trials examining this issue have established not only the greater efficacy for lesion detection (with a dose of 0.3 mmol/kg) but also the overall cost effectiveness of this approach.

Specialty Applications

Limited clinical trials have been published in only two specialty areas regarding possible use of doses lower than 0.1 mmol/kg. In a 1995 study limited to acoustic schwannomas, with a sample of 39 patients, it was suggested that a dose of 0.1 mmol/kg may not be necessary for detection of acoustic schwannomas, and that half-dose might be sufficient. This result is to some extent expected, given the intense enhancement (often 1000%) of acoustic schwannomas on MRI after gadolinium chelate injection (using standard dose). Of all brain lesions, acoustic schwannomas display by far the greatest magnitude of contrast enhancement.

In a 1991 study of pituitary adenomas, 11 microadenomas and 12 macroadenomas were evaluated with half-dose only. There was no comparison with full-dose exams. On the basis of this limited number, it was stated that the half-dose study appeared comparable to full-dose techniques for the detection of micro- and macroadenomas. Again, theoretical considerations support the choice of a lower dose in this area, given the intense enhancement of the normal anterior pituitary and infundibulum, two structures that lie outside the BBB.

It should be noted that even in these two specialty areas the support for half-dose is limited. Both studies commented on the need for confirmation of their results, which has never been done, in larger populations.
Neither study addresses contrast dose at low fields. One study was performed at 0.5 and 1.5 T and the other at 1.0 and 1.5 T. Low-field systems are poor candidates for thin-slice high-resolution imaging, as required in the pituitary and internal auditory canal. High-quality imaging at low field requires careful selection of imaging technique; higher dose is typically advocated, not lower dose. Both of the publications referenced also examined half-dose in patient populations with a specific known diagnosis. In real-world imaging of the sella and internal auditory canal, other diseases need to be considered and would likely not be as well depicted at a lower contrast dose.

OTHER APPROVED AGENTS

Feridex (ferumoxides, Berlex Laboratories) is a reddish-brown colloid of superparamagnetic iron oxide particles that also contain dextran formulated for intravenous use. The agent is taken up by cells of the reticuloendothelial system (RES). Its principal use is as a liver agent. The iron enters the normal body iron metabolism cycle after injection. Feridex shortens T2, producing signal loss on T2-weighted scans. Tissues with decreased RES function, so contrast between normal liver and lesions is increased. Feridex is approved in the United States for intravenous use in adults only and only for liver imaging. The dose is diluted in 100 ml and given over 30 minutes. Feridex is contraindicated in patients with known allergic or hypersensitivity reactions to parenteral iron or dextran. Anaphylactic-like reactions and hypotension have been seen after injection. Acute severe back, leg, or groin pain can occur within 1 to 15 minutes after injection alone or with other symptoms, such as hypotension and dyspnea. In clinical trials, this pain was severe enough to cause interruption or discontinuation of the infusion in 2.5% of patients (12.5% of patients with cirrhosis).

Teslascan (Mn DPDMP, Nycomed) is a manganese chelate approved for liver imaging at a dose of 5 \( \mu \text{mol/kg} \) (0.1 ml/kg). The dose is given by intravenous administration over 1 minute. Postcontrast images are typically acquired with a slight delay, 15 minutes or longer, after injection. The ion responsible for enhancement, manganese, is different when compared with the gadolinium chelates. The agent was designed to be incorporated into hepatocytes. Postcontrast, moderate enhancement of normal liver parenchyma is seen, improving, in some instances, lesion conspicuity and differential diagnosis. In phase I, facial flushing and warmth were observed in 35 of 40 individuals. Dose-dependent increases in heart rate and blood pressure were also seen.

Subsequent clinical trials were conducted with lower doses and slower intravenous injection, resulting in fewer side effects. Mild to moderate adverse events were reported in 17% of patients in a phase III study published in 1997. Mn DPDMP dechelates in vivo, accounting for the high incidence of flushing and enhancement of the intestinal mucosa and pancreas. The DPDMP ligand does not facilitate transport of manganese into any organ, except the kidney, but does reduce distribution to the heart. The instability of the complex in vivo has raised concerns regarding potential toxicity from free manganese (known to accumulate in the brain and leading to a parkinsonism-like syndrome). In preclinical evaluation, Teslascan injection caused skeletal abnormalities in fetal rats; Mn\(^{2+}\) was the causative agent. There was also an increased rate of fetal demise in rabbits at 10 times the recommended clinical dose.

The market acceptance in the United States of Feridex and Teslascan has been poor. Reasons for low utilization of these agents include the inability to obtain dynamic postcontrast scans, limited diagnostic value, and the high number of adverse reactions (relative to the gadolinium chelates).

ORAL CONTRAST MEDIA

Four different oral contrast media have been approved for clinical use in the United States. In Europe, but not in the United States, an oral formulation of Magnevist is also available. Imagent (PFOB, Alliance) was approved in the early 1990s but is no longer marketed. GastroMARK (AMI 121, Mallinckrodt) was the second agent to market. LumenHance (Bracco Diagnostics) and FerriSeltz (Nyomed) were approved by the FDA in 1999. Imagent was highly effective in producing low signal intensity in the bowel. It is tasteless, water insoluble, and nontoxic. However, complete bowel opacification was difficult and side effects were high because of the rapid transit of the agent through the bowel. The majority of the agent is eliminated rectally within the first few hours after administration.

GastroMARK is a dark-brown aqueous suspension of superparamagnetic iron oxide. The recommended dose is 600 ml (900 ml maximum) administered orally at a rate of 300 ml over 15 minutes. Depending on the section of the bowel that is to be opacified, imaging is performed from between 30 minutes to several hours postadministration. A substantial time delay after administration (4-7 hours) is recommended for delineation of the lower gastrointestinal tract. GastroMARK is approved for oral use in adults only to enhance delineation of the upper gastrointestinal tract. The approval (according to the package insert) states that usefulness in the lower gastrointestinal tract is limited by transit time and dilution. With pancreatic and gastric masses, clinical trials demonstrated increased confidence in delineating the mass in 44% to 49% of cases. In clinical reports, efficacy in bowel marking was significant for the small bowel and cecum but not significant with all scan sequences for the sigmoid colon.

The formulation for LumenHance contains manganese (Mn\(^{2+}\)) chloride as the active ingredient. The agent is supplied as an off-white powder with strawberry flavoring. Each packet is dissolved to yield 300 ml; the instructions for use specify that the first packet be given 45 to 90 minutes, the second packet 30 to 45 minutes, and the third packet less than 30 minutes before imaging. LumenHance is approved for oral use in patients older than 16 years for enhanced delineation of the...
upper gastrointestinal tract. Clinical trials demonstrated that there was additional information on the postdose scans in 50% to 54% of patients. The agent provides both improved lesion visualization and the ability to distinguish the bowel from other normal and abnormal structures. On imaging, LumenHance has a dual T₁ and T₂ effect. The agent is hyperintense on T₁-weighted scans; clinical trials report good to excellent bowel marking on such scans. The agent is hypointense on T₂-weighted scans; clinical trials also demonstrate improved bowel marking on such scans. The latter feature (low signal intensity on T₂-weighted scans) makes LumenHance useful in MRI cholangiography. The agent lowers the signal intensity of the duodenum and small bowel, which might otherwise interfere with visualization of the biliary system on cholangiographic-type sequences.

The active ingredient in FerriSeltz is ferric ammonium citrate. The package insert states that two packets (6 g) are to be dissolved in 600 ml of water and administered orally over 15 to 30 minutes. Imaging is to be initiated within 5 to 20 minutes after administration. FerriSeltz is approved for use only in adults for enhanced bowel delineation of the upper gastrointestinal tract. T₁-weighted scans are used to visualize the agent. In clinical trials, investigators found increased intraluminal signal intensity, improved contrast enhancement of the gastrointestinal tract, and improved signal homogeneity in 89% to 98% of patients after ingestion. New or additional radiologic information was provided in clinical trials in 64% of patients and information that changed diagnosis, management, or surgical approach in 15%.

### OFF-LABEL CONTRAST USE

The definition of off-label use, as it pertains to diagnostic radiology, is the use of an approved contrast agent for a clinical purpose not stipulated in the package insert. Off-label use is common in clinical practice in the United States. Addressing legal issues, off-label use is not a violation of U.S. law, provided that the use is in the course of routine medical practice and not part of an investigation into safety or effectiveness and not commercialized through advertising. Off-label use is possible because the FDA does not have the authority to regulate the use of approved contrast media in any manner that radiologists believe, in their professional judgment, would best serve the patient. Furthermore, the use of an approved contrast agent for a clinical purpose not explicitly contained in the labeling does not expose the radiologist to malpractice liability. Reimbursement, however, limits off-label use. Off-label use may or may not be reimbursed, depending on the specific application and local insurance carrier. In Europe, the situation is similar in regard to off-label use and the ramifications thereof.

Off-label use is important to ensure that the patient, in many situations, receives the best diagnostic exam. For example, no MRI contrast agent is approved in the United States for use in patients younger than 2 years. This is at odds with standard clinical practice. Published clinical trials have established safety and guidelines for the use of gadolinium chelates in young children and infants. Particularly in hospital settings, gadolinium chelates are commonly administered to patients younger than 2 years because contrast use can be important for lesion detection and appropriate differential diagnosis. An even more significant example of off-label use is the injection of gadolinium chelates for MRA exams (CE-MRA). No agent has specific approval for this indication. Off-label use of the gadolinium chelates for CE-MRA is common and accepted practice throughout the United States.

The subject of off-label use is very important in clinical practice; thus, the issue bears re-explaining, perhaps in a manner more understandable to the average user. Contrast media are approved with certain indications. This does not, however, limit how a physician can use an agent. Almost 85% of all MRI contrast use is in the head and spine, and all agents have approval here for patients older than 2 years. Comparatively, very few doses are used in other areas. Some agents have “whole body approval”; however, this refers specifically to the chest, abdomen, and pelvis. None of the agents are approved for the heart, breast, or musculoskeletal system or for MRA. Diagnostic radiologists commonly use contrast media in these and other off-label applications. Such use often constitutes the best of medical care.

### CONCLUSION

The gadolinium chelates play a major role in the evaluation of patients by MRI. These agents improve both the sensitivity and specificity of the exam. In many cases, particularly in the CNS, lesions cannot be identified before contrast administration. Lesion delineation, assessment of lesion activity, and differential diagnosis are improved with the addition of postcontrast scans. The scope of applications continues to expand, as the modality and clinical experience mature. New agents on the horizon include gadolinium chelates with enhanced relaxivity (greater contrast effect at the same dose), hepatobiliary distribution, and intravascular distribution.