FROM MOLECULE TO MAGNET:
A Literature Review of Gadobenate Dimeglumine

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# TABLE OF CONTENTS

Overview ..................................................................................................................................2
Learning Objectives..................................................................................................................2
Target Audience .......................................................................................................................2
Accreditation Information.........................................................................................................3
Instructions to Receive Continuing Medical Education Credit ...................................................3
Faculty Disclosures...................................................................................................................3
From Molecule to Magnet: A Literature Review of Gadobenate Dimeglumine .........................4
References .............................................................................................................................31
Posttest ..................................................................................................................................35
Evaluation Form .......................................................................................................................39
OVERVIEW

Magnetic resonance imaging (MRI) is currently utilized for a wide variety of diagnostic applications and gadolinium (Gd)-based contrast agents can be used to further improve the sensitivity and specificity of this technique. The vast majority of contrast-enhanced MR studies utilize extracellular fluid (ECF) Gd-based contrast agents that have comparable relaxivity (and thus ability to enhance). Recent advances in contrast-enhanced MR are well documented in the literature, including the development of a Gd-based contrast agent, gadobenate dimeglumine, that possesses twice the relaxivity of conventional Gd-based agents as well as the ability to target functioning hepatocytes. The increased relaxivity allows for greater lesion-to-noise contrast in general, while the hepatocyte uptake provides increased utility in delayed liver imaging. This literature review summarizes the results of peer-reviewed scientific articles, published almost entirely in the past 5 years, in which gadobenate dimeglumine was compared with conventional Gd contrast agents for a variety of clinical applications.

LEARNING OBJECTIVES

At the conclusion of this program, participants should be able to:

• Compare and contrast properties of conventional and new MR contrast agents
• Identify advantages of increased relaxivity in MRI of the central nervous system
• Explain the utility of a dual-capability (ECF/liver) MR contrast agent for MRI of liver disease
• Describe recently published literature demonstrating the utility of new MR contrast agents for other applications, including MR angiography, breast, and cardiac imaging

TARGET AUDIENCE

The target audience for this program is radiologists.
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FROM MOLECULE TO MAGNET: A LITERATURE REVIEW OF GADOBENATE DIMEGLUMINE

INTRODUCTION
Magnetic resonance imaging (MRI) has demonstrated substantial clinical use as a robust, noninvasive diagnostic imaging modality, and its use continues to expand, as evidenced by the increasing number of procedures performed each year. Early on in the development of MRI, its high sensitivity to pathologic conditions was thought to obviate the need for contrast enhancement; however, during the 1980s it was clearly demonstrated that certain tissues and pathologic entities that have a similar appearance on noncontrast MR images were more clearly distinguishable after the administration of contrast. Dynamic contrast-enhanced MRI (ce-MRI) possesses multiplanar capability, high temporal resolution, and unparalleled soft tissue contrast in the absence of ionizing radiation, making it an indispensable tool for diagnostic imaging.

The most extensively studied and widely used contrast agents for MRI contain the paramagnetic ion gadolinium (Gd) bound to a chelate. Between 1988 and 2000, four Gd contrast agents were approved for use in the United States: gadopentetate dimeglumine (Gd-DTPA; Magnevist®); gadoteridol (Gd-HP-DO3A; ProHance®); gadodiamide (Gd-DTPA-BMA; Omniscan™); and gadoversetamide (Gd-DTPA-BMEA; Optimark®). In 2004, a fifth Gd contrast agent, gadobenate dimeglumine (Gd-BOPTA; MultiHance®), was approved for use in the United States. Gadobenate dimeglumine has been studied extensively for more than 10 years, both in Europe and in the United States, and has been demonstrated to possess properties that distinguish it from the four conventional Gd agents.

This literature review summarizes the results of peer-reviewed scientific articles, published almost entirely in the past 5 years, in which gadobenate dimeglumine was compared with conventional Gd contrast agents for a variety of clinical applications.

PROPERTIES OF Gd CONTRAST AGENTS
Some of the properties of the five Gd contrast agents currently approved for use in the United States are shown in Table 1. The four conventional contrast agents are solely extracellular fluid (ECF) contrast agents, distributing rapidly from the vasculature into the extracellular space before being renally excreted.

When patients are placed in an MR scanner, they are subjected to an external magnetic field. This magnetic field causes the hydrogen nuclei (protons) within the patient to align with it, in a longitudinal direction to the external magnetic field. When energy in the form of a radiofrequency pulse (RF pulse) is applied, the alignment of the protons is disturbed from the longitudinal direction, resulting in a decrease of the overall longitudinal magnetization and the creation of a new transverse magnetization. When the RF pulse is switched off, the newly established transverse magnetization begins to disappear while the original longitudinal magnetization...
reappears. The time needed for the protons to recover their original longitudinal magnetization is referred to as the longitudinal relaxation time (T1), while the time needed for the transverse magnetization to disappear is referred to as the transverse relaxation time (T2). The inverse of these relaxation times (1/T1 and 1/T2, respectively) are referred to as the relaxation rates (r1 and r2, respectively). The shorter the relaxation time, the higher the relaxation rate, or relaxivity. These relaxation rates vary naturally among tissues and body compartments; as a result, organs and tissues appear different on unenhanced MR images. The relaxation rate, or relaxivity, of a contrast agent indicates the degree to which the contrast agent is capable of enhancing the differences between normal tissue and lesions. The r1 relaxivity impacts the contrast on T1-weighted images and the r2 relaxivity impacts the contrast on T2-weighted images. All commonly used Gd agents are T1-relaxing agents, capable of increasing contrast on T1-weighted images. When injected at an equivalent dose, a contrast agent with a higher inherent r1 relaxivity is, therefore, better able to increase the contrast between tissue and lesion than an agent with standard r1 relaxivity. As shown in Table 1, all four of the conventional ECF contrast agents possess similar r1 relaxivities (ranging from 4.6 to 4.9 mM/s).

Table 1. Protein Interaction and “In Vivo” Relaxivity of Gd MRI Contrast Agents

<table>
<thead>
<tr>
<th>Contrast Agent</th>
<th>Brand Name</th>
<th>FDA Approval (United States)</th>
<th>Protein Interaction</th>
<th>r1* (mM·s⁻¹)</th>
<th>r2* (mM·s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extracellular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadopentetate dimeglumine (Gd-DTPA)</td>
<td>Magnevist®</td>
<td>1988</td>
<td>None</td>
<td>4.9†</td>
<td>6.3†</td>
</tr>
<tr>
<td>Gadoteridol (Gd-HP-DO3A)</td>
<td>ProHance®</td>
<td>1992</td>
<td>None</td>
<td>4.6‡</td>
<td>5.3‡</td>
</tr>
<tr>
<td>Gadodiamide (Gd-DTPA-BMA)</td>
<td>Omniscan™</td>
<td>1993</td>
<td>None</td>
<td>4.8‡</td>
<td>5.1‡</td>
</tr>
<tr>
<td>Gadoversetamide (Gd-DTPA-BMEA)</td>
<td>Optimark®</td>
<td>1999</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Combined Extracellular/Hepatobiliary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadobenate dimeglumine (Gd-BOPTA)</td>
<td>MultiHance®</td>
<td>2004</td>
<td>Weak</td>
<td>9.7†</td>
<td>12.5†</td>
</tr>
</tbody>
</table>

*r1 and r2 relaxivities indicate the efficiency in shortening T1 and T2 relaxation times, respectively.
†In heparinized human plasma at 39°C.
‡In human serum at 39°C.
NA=not available.
Gadobenate dimeglumine (Gd-BOPTA; MultiHance®) resembles the previously approved Gd ECF agents structurally and functionally but possesses two important properties that increase its potential clinical utility for ce-MRI. Due to a weak and transient interaction with serum proteins, primarily albumin, gadobenate dimeglumine has twice the relaxivity of the original four Gd contrast agents (Table 1), potentially increasing the signal of perfused tissue on T1-weighted images.

Most relaxivity studies to date have been performed at 0.5T and, although 0.5T magnets are still relatively common, scanners with up to 3.0T magnets are increasingly used in clinical practice. In order to establish optimal scanning parameters at field strengths higher than 0.5T, Pintaske and colleagues quantified the relaxation enhancement of several Gd contrast agents at clinically relevant concentrations at different magnetic field strengths. Specifically, they compared a range of concentrations of gadopentetate dimeglumine and gadobenate dimeglumine at 0.2T, 1.5T, and 3.0T. The T1 and T2 relaxation rates for gadobenate dimeglumine were 107% to 131% and 91% to 244% higher than for gadopentetate dimeglumine, respectively. Furthermore, gadobenate dimeglumine demonstrated the highest r1 relaxivity at all field strengths, and the r1/r2 ratio increased at higher field strengths for gadobenate dimeglumine but not for gadopentetate dimeglumine. The authors concluded that optimization of MR scanning with gadobenate dimeglumine would utilize very short echo times to benefit from the higher r1 relaxivity.

In addition to its higher relaxivity, the Gd-BOPTA chelate of gadobenate dimeglumine is also partially taken up by functioning hepatocytes (3% to 5% of the injected dose) and excreted through the hepatobiliary pathway. Because of this hepatocytic uptake, a certain amount of gadobenate dimeglumine persists in the liver, providing the capability for delayed enhanced imaging of the liver, a potentially important diagnostic tool. Together, these two properties yield a high-relaxivity contrast agent with dual ECF/hepatobiliary imaging capabilities. The results of numerous studies, including dosing studies and comparative trials, are outlined below and consistently demonstrate that the novel properties of gadobenate dimeglumine are advantageous for diagnostic MRI, and that this agent may provide benefit in terms of sensitivity and specificity over other Gd contrast agents for certain applications.

Gd CONTRAST USE IN CENTRAL NERVOUS SYSTEM (CNS) IMAGING

Primary and Secondary CNS Tumors

Contrast-enhanced MRI is well established as a diagnostic imaging technique for evaluating neoplastic and nonneoplastic diseases of the CNS. In tumors of the CNS, the use of contrast agents has been clearly demonstrated to improve lesion detection and characterization, contributing to both the sensitivity and specificity of the study. In the case of primary tumors, the goal of ce-MRI is to determine the tumor grade and delineate, as precisely as possible, the
margins of the tumor for subsequent neurosurgical biopsy or resection, or for newer radiotherapeutic options. For metastases, it is critical that ce-MRI accurately determine the number and location of the lesions. Of particular clinical relevance is the ability to confirm the existence of small metastatic lesions in equivocal cases or to detect additional lesions in cases with only one metastatic lesion; treatment in these cases may change from surgical resection in patients with one lesion to irradiation or chemotherapy in patients with multiple lesions.10

Intravenous Gd ECF contrast agents that equilibrate rapidly between the intra- and extracellular spaces of soft tissues enter the CNS only at points where the blood-brain barrier (BBB) is nonexistent, disrupted, or damaged. Therefore, the degree of lesion enhancement is largely dependent on the extent of leakage of the BBB, the vascularity of the lesion, and the dose of contrast agent. The four original Gd contrast agents are approved for use in CNS imaging at a standard dose of 0.1 mmol/kg; however, particularly in patients with negative findings or a single metastatic lesion, a higher dose of 0.2 or 0.3 mmol/kg is recommended11-16 and, in some cases, approved.17,18 However, when used at equivalent doses, no differences have been demonstrated among these contrast agents. The use of triple doses of contrast agent necessitates use of more contrast than single dose contrast examinations and may result in an increased number of false-positive findings. False-positive findings result from increased detection of artifacts and improved display or vascular structures, such as in enhancement of nontumoral malformations.15,19

The higher-relaxivity contrast agent gadobenate dimeglumine has been demonstrated to provide greater signal enhancement of CNS lesions at lower doses than conventional agents. Large-scale, multicenter studies have confirmed the advantages of gadobenate dimeglumine-enhanced MRI of the CNS over unenhanced MRI. In addition, in these studies, a double dose (0.2 mmol/kg) of gadobenate dimeglumine was found to be a satisfactory alternative to triple doses of a standard Gd contrast agent for equivocal cases and those in which a single lesion is detected.10,19

A multicenter, randomized, double-blind clinical trial was undertaken to evaluate the efficacy and safety of gadobenate dimeglumine compared with the Gd contrast agent gadodiamide.7 In this study, 205 individuals suspected of having a CNS lesion were randomized to receive one of three different incremental contrast administration protocols: two with gadobenate dimeglumine (total administered doses of 0.15 or 0.2 mmol/kg) and one with gadodiamide (total administered dose of 0.3 mmol/kg). The cumulative doses of 0.15 and 0.2 mmol/kg gadobenate dimeglumine demonstrated equivalency with the higher cumulative dose (0.3 mmol/kg) of gadodiamide, likely due to the increased relaxivity of gadobenate dimeglumine. In a subset analysis of 82 of these patients highly suspected of having an intraaxial malignant lesion of the brain, gadobenate dimeglumine at 0.15 and 0.2 mmol/kg again offered equivalent diagnostic information as 0.3 mmol/kg of gadodiamide.20
More recently, intraindividual crossover studies have been used to compare gadobenate dimeglumine with other Gd contrast agents. Such crossover studies are designed to validate, as definitively as possible, the contrast-enhancement properties of two contrast agents in a clinical setting, even among small patient populations. In crossover studies, patients are randomized to receive an MRI examination with one contrast agent, followed at some time later (approximately 2 days to 2 weeks) by a second MRI with the second contrast agent. The two sets of postenhanced images are then compared with unenhanced images and with each other.

In a retrospective, multicenter, intrapatient comparator trial, sensitivity for lesion detection in 22 patients with intracranial metastases was compared after administration of equal doses of gadobenate dimeglumine and two conventional Gd contrast agents, gadopentetate dimeglumine and gadodiamide. The findings for the comparator agents were pooled. The sensitivity for lesion detection with gadobenate dimeglumine (93%-100%) was markedly superior to that of comparator-enhanced lesions (65%-73%) and the increase in contrast between lesion and brain compared with unenhanced images was consistently greater with gadobenate dimeglumine (+43%) vs comparators (+27%; Figure 1).

Figure 1. (A) Postcomparator image and (B) postgadobenate dimeglumine image of a metastatic brain lesion (arrow) from a patient with lung cancer. Reproduced with permission from Colosimo C et al. Detection of intracranial metastases: a multicenter, intrapatient comparison of gadobenate dimeglumine-enhanced MRI with routinely used contrast agents at equal dosage. Invest Radiol. 2001;36:72-81.

A prospective, intraindividual crossover study of 27 patients with primary and secondary brain tumors was performed in which equal doses (0.1 mmol/kg) of gadobenate dimeglumine and gadopentetate dimeglumine were directly compared based on qualitative (global contrast enhancement, lesion-to-brain contrast, lesion delineation, internal lesion morphology and structure, tumor vascularization, and global image preference) and quantitative (region-of-interest) parameters. Some of the imaging parameters utilized in this study are shown in Table 2.
The results from this crossover study demonstrated that the standard dose of gadobenate dimeglumine (0.1 mmol/kg) provided significantly superior contrast enhancement of intraaxial tumors, both qualitatively and quantitatively, when compared with an equal dose of gadopentetate dimeglumine (Figure 2).

Table 2. Parameters Used for Brain MRI*21

<table>
<thead>
<tr>
<th>Sequence</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>Number of Slices</th>
<th>Slice Thickness (mm)</th>
<th>Interslice Gap (%)</th>
<th>FOV (cm)</th>
<th>Matrix Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precontrast imaging sequences</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-W SE</td>
<td>500</td>
<td>15</td>
<td>18</td>
<td>5</td>
<td>25</td>
<td>25</td>
<td>256 x 256</td>
</tr>
<tr>
<td>T2-W fast SE</td>
<td>3000</td>
<td>90</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Postcontrast†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-W SE loop</td>
<td>NA</td>
<td>NA</td>
<td>18</td>
<td>5</td>
<td>25</td>
<td>25</td>
<td>256 x 256</td>
</tr>
</tbody>
</table>

FOV=field of view; MRI=magnetic resonance imaging; NA=not applicable/not available; SE=spin-echo; T1-W=T1-weighted; T2-W=T2-weighted; TR=repetition time.

*Two 1.5T MRI systems (Magnetom Vision [Siemens Medical Systems, Erlangen, Germany] and Edge [Marconi, Cleveland, Ohio]) were used.
†Contrast agent administered intravenously at an injection rate of 2 mL/s using a power injector (Tomoset [Brukea, Etlingen, Germany] or Spectris [Medrad, Indianola, Pa]) and a 20-gauge needle.

Figure 2. (A) Gadopentetate dimeglumine and (B) gadobenate dimeglumine image of a metastatic brain lesion from a patient with renal cell cancer. Equal doses of contrast agent were injected (0.1 mmol/kg). The larger metastasis (open arrow) appears more intense, and the smaller metastasis (solid arrow) is more clearly visible with gadobenate dimeglumine. Reproduced with permission from Knopp MV et al. Primary and secondary brain tumors at MR imaging: bicentric intraindividual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine. Radiology. 2004;230:55-64.
Recently, results of a large, US, intraindividual study were published in which 157 patients underwent two temporally separated 1.5T MR imaging examinations. The patients were randomized to receive standard doses (0.1 mmol/kg body weight) of gadobenate dimeglumine or gadopentetate dimeglumine. Contrast agent administration (volume, speed of injection), imaging parameters before and after injection, and time between injections and postinjection acquisitions were identical for both examinations. Three blinded neuroradiologists evaluated qualitative parameters (lesion border delineation, definition of disease extent, visualization of internal morphologic features of the lesion, enhancement of the lesion) and quantitative parameters (percentage of lesion enhancement, contrast-to-noise ratio [CNR]). In addition, overall diagnostic preference in terms of lesion conspicuity, detectability, and diagnostic confidence was assessed. Readers 1, 2, and 3 demonstrated overall preferences for gadobenate dimeglumine in 75, 89, and 103 patients, compared with that for gadopentetate dimeglumine in six, 10, and three patients, respectively. An example of the results is shown in Figure 3. Significant ($P<0.0001$) preference for gadobenate dimeglumine was demonstrated for all diagnostic information end points, percentage of lesion enhancement, and CNR. The superiority of gadobenate dimeglumine was significant ($P<0.001$) for all lesion types, both intraaxial and extraaxial. The authors concluded that gadobenate dimeglumine provides significantly better enhancement and diagnostic information compared with gadopentetate dimeglumine for MRI of the CNS.

Figure 3. (A) Transverse T1-weighted MR image in a 61-year-old man with metastatic lung cancer after administration of 0.1 mmol/kg of gadopentetate reveals multiple enhancing lesions in right cerebellum and posterior medulla. (B) Image acquired with identical parameters as in A after administration of 0.1 mmol/kg of gadobenate reveals improved contrast enhancement of lesions seen with gadopentetate and unequivocal detection of two additional metastatic lesions (arrows) in right cerebellar hemisphere. Reproduced with permission from Maravilla KR et al. Contrast enhancement of central nervous system lesions: multicenter intraindividual crossover comparative study of two MR contrast agents. Radiology. 2006;240:389-400.
MRI is also the diagnostic imaging method of choice for neuroimaging in pediatric patients because of its high sensitivity and the advantage of avoiding the ionizing radiation associated with computed tomography (CT) imaging. As in adults, Gd contrast agents have demonstrated great utility in detection and characterization of CNS lesions in pediatric patients, with no real differences in efficacy among the four conventional agents. In a recent study of 63 children with tumors of the brain or spine, equivalent standard doses of gadobenate dimeglumine and gadopentetate dimeglumine were compared for qualitative and quantitative lesion evaluation. Table 3 shows some of the imaging parameters used in this study. Pre- to postdose changes were significantly better with gadobenate dimeglumine for border delineation and contrast enhancement and nonsignificantly better for visualization of internal morphology compared with gadopentetate dimeglumine. The authors concluded that gadobenate dimeglumine may be clinically advantageous for detection and diagnosis of small or poorly enhancing tumors of the brain and spine in children. The study indicated that further research is needed; the FDA has not yet approved gadopentetate dimeglumine for enhancement of CNS lesions in children and adolescents.

Table 3. Parameters Used for Pediatric MRI of the Brain and Spine

<table>
<thead>
<tr>
<th>Sequence</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>Number of Excitations</th>
<th>FOV (cm)</th>
<th>Slice Thickness (mm)</th>
<th>Interslice Gap (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unenhanced T2-W images</td>
<td>2500–5000</td>
<td>20–80/150</td>
<td>0.75–2</td>
<td>10–48</td>
<td>3–6</td>
<td>0–20</td>
</tr>
<tr>
<td>Unenhanced and CE T1-W images</td>
<td>400–750</td>
<td>≤25</td>
<td>2</td>
<td>10–48</td>
<td>3–6</td>
<td>0–20</td>
</tr>
</tbody>
</table>

CE=contrast-enhanced; FOV=field of view; MRI=magnetic resonance imaging; T1-W=T1-weighted; T2-W=T2-weighted; TE=echo time; TR=repetition time.

*Magnetic field strengths varied (0.5T [n=13]; 1.0T [n=4]; 1.5T [n=46]). Whole brain imaging was performed with axial and sagittal planes using a dedicated head coil. Spine imaging was performed with the sagittal plane using a surface coil. For unenhanced imaging, T1-W and conventional or fast T2-W spin-echo (SE) sequences were used. For contrast-enhanced imaging, T1-W SE sequences were used.

The clinical impact of increased enhancement has significance both for intracerebral primary lesions (e.g., gliomas) as well as for metastatic lesions. For gliomas, the goals of presurgical planning are to identify, as accurately as possible, enhancing tumor margins in order to guide surgical resection or delineate radiosurgical target volumes as well as to differentiate “operable” vs “nonoperable” lesions. For postsurgical evaluation, increased enhancement permits improved detection of comparatively small areas of residual tumor. In addition, for low field strength techniques such as intra-operative MRI, increased enhancement provides greater effectiveness for detection and definition of the full extent of tumor during the surgical procedure.

For secondary brain metastases, increases in accuracy of estimation of the number of lesions contribute to improved selection of the most appropriate treatment option. A growing trend in the treatment of both primary and secondary neoplastic brain lesions is the use of noninvasive stereotactic radiosurgery techniques, such as Gamma Knife and CyberKnife. In order to
determine the specific brain areas to treat, stereotactic radiosurgery techniques often rely heavily on the results of a high-resolution pretreatment MRI. Such pretreatment MRIs require high sensitivity and specificity in order for the treatment to provide the optimal patient outcome. It is not unusual for such high-resolution pretreatment MRIs to demonstrate a greater tumor volume or additional metastatic lesions compared with the diagnostic MRI. Prestereotactic radiosurgery MRIs are often performed with thin slices, specialized sequences, and double or triple doses of Gd contrast agents in order to achieve the highest possible resolution. The use of a higher relaxivity contrast agent such as gadobenate dimeglumine provides greater enhancement without the need for double and triple doses, potentially saving time as well as money while improving patient outcomes.

**Brain Perfusion Imaging**

MR brain perfusion imaging is used to characterize blood flow through the brain and is quantified as blood flow per unit time through 100 g tissue. Perfusion imaging permits physiologic information to be obtained that is relevant to the state and progression of pathologic processes. After rapid injection of a bolus of contrast, T2-weighted imaging sequences are used in combination with rapid, serial acquisitions, a technique also known as dynamic susceptibility contrast-enhanced MRI (DSC-MRI).\(^{25,26}\) The susceptibility effect of the passing contrast agent results in a significant decrease in the signal intensity in the tissue. To quantify the data, the time-signal intensity curve is converted to a time-concentration curve on a pixel-by-pixel basis, providing quantification of the regional cerebral blood volume (rCBV) and regional cerebral blood flow (rCBF). The most common clinical indications for brain perfusion MRI include cerebrovascular disease, brain tumor evaluation, and monitoring of the patient following radiotherapy, but it is also increasingly used for the evaluation of patients with dementia.

The amount of signal drop depends not only on the MR sequence used, but also on the dose, concentration, and relaxivity of the contrast agent used. To date, most perfusion studies use higher than the standard dose (ie, 0.15 or 0.2 mmol/kg) of a conventional Gd contrast agent to achieve an overall signal drop of approximately 20%. Recently, the higher relaxivity gadobenate dimeglumine was compared with gadobutrol, a Gd contrast agent available in Europe that is formulated at a higher concentration (1.0M) than those available in the United States (0.5M). One might predict that both the higher relaxivity of gadobenate dimeglumine and the higher concentration of gadobutrol would permit MR perfusion imaging at standard concentrations. Recently, Essig and colleagues\(^{26}\) showed this to be the case: both gadobutrol and gadobenate dimeglumine allowed the acquisition of high-quality perfusion maps on a 1.5T magnet using standard doses of contrast agent (0.1 mmol/kg body weight). Furthermore, the susceptibility effect was comparable for both agents and was deemed stronger than that for conventional MR contrast agents. A similar comparison of gadobenate dimeglumine and gadobutrol for perfusion
imaging was performed at 3.0T and, as expected, similar results were obtained: at 3.0T, the T2 relaxation effects of 0.1 mmol/kg of gadobutrol or gadobenate dimeglumine were nearly identical and were sufficient for assessment of brain perfusion.\textsuperscript{27} Rollin and colleagues also demonstrated clinical utility of diffusion and perfusion imaging with gadobenate dimeglumine for the characterization of intraaxial brain lesions in 28 patients: rCBV correlated with the grade of glioma and was useful for distinguishing lymphoma from high-grade glioma and, in most cases, recurrent tumor from radionecrosis. Differentiating between low- and high-grade gliomas was not possible until a significant increase in intensity was revealed on signal-intensity time curves after the first pass of gadopentetate dimeglumine.\textsuperscript{28} The combination of perfusion MR imaging with gadopentetate dimeglumine revealed increases in rCBV values in recurrent tumors, but low rCBV values in radionecrosis due to vascular injury.\textsuperscript{28}

**Multiple Sclerosis (MS)**

Gd-enhanced MRI has become a critical tool in the diagnosis and assessment of the progression of MS. The location, number, and dimension of clinically silent, demyelinating plaques can be monitored using serial MRI examinations. Furthermore, plaques can be classified as acute (moderate to intense enhancement with Gd contrast), subacute (absence of contrast enhancement, but high signal intensity on T2-weighted images and hypointense on T1-weighted images), or chronic (no contrast enhancement, but slightly hyperintense on T2-weighted images).\textsuperscript{29} The presence of acute lesions, which have surrounding edema and breakdown of the BBB, is of particular clinical importance because these lesions represent early events in the physiologic process that ultimately lead to demyelination.\textsuperscript{29}

Double or triple doses of standard Gd contrast agents may be necessary to achieve sufficient sensitivity to detect acute MS plaques and to better assess disease progression.\textsuperscript{30,31} Alternatively, neuroimaging with the higher relaxivity gadobenate dimeglumine may allow for visualization of plaques at single doses or reveal additional, smaller plaques at higher doses.\textsuperscript{29} Preliminary results of a multicenter study on detection of plaques in patients with a probable diagnosis of MS and patients with clinical symptoms of acute relapse using different doses of gadobenate dimeglumine have been promising.\textsuperscript{29} These data demonstrate that gadobenate dimeglumine is safe and effective for the detection of MS plaques: greater numbers of MS plaques were visible with increased time and increased contrast dose (Figure 4).\textsuperscript{29}
Figure 4. T1-weighted images of a patient with multiple sclerosis enhanced with gadobenate dimeglumine. Images were acquired (A) 5 minutes and (B) 20 minutes after administration of 0.1 mmol/kg gadobenate dimeglumine and (C) 5 minutes after a second bolus for a total dose of 0.2 mmol/kg. Reproduced with kind permission of Springer Science and Business Media from Tartaro A. MultiHance in multiple sclerosis: update of a study in progress. Eur Radiol. 2004;14 (suppl 7):O16-O19.

CONTRAST USE IN ABDOMINAL IMAGING

Liver Imaging

Nonenhanced T1- and T2-weighted MRI sequences, together with fast imaging techniques, allow rapid imaging of the entire liver. However, the use of IV agents provides more accurate characterization of all histologic types of liver lesions as well as a better assessment of the full extent of malignant liver lesions. Furthermore, contrast agents are useful for the characterization of diffuse liver disease, hepatitis and cirrhosis, and extrahepatic disease. Nonspecific extracellular Gd-based chelates have been available the longest and utilized for the greatest number of clinical applications and, in addition, have the best documented safety profile. The use of Gd-based contrast agents is now considered essential for a comprehensive MRI evaluation of the abdomen.

Dynamic contrast-enhanced studies of the liver typically include precontrast images and 2-dimensional (2D) or 3-dimensional (3D) T1-weighted images obtained during the arterial, portal venous, and equilibrium phases of contrast enhancement. During the hepatic arterial phase, enhancement occurs in the arterial tree and in liver tumors that are arterially perfused, and is also useful for detection of perfusion abnormalities. An improved rate of detection of hepatocellular carcinoma (HCC) has been demonstrated for Gd-enhanced MRI during the arterial phase.

During the portal venous phase, enhancement of the hepatic parenchyma is maximized revealing hypovascular lesions such as cysts or hypovascular metastases; these appear as
areas of absent or diminished enhancement.32,34 Tissues with enlarged extracellular space (eg, focal liver lesions such as hepatocellular adenomas, hepatocellular carcinoma and hypervascular metastases, and focal nodular hyperplasia) and scar tissue associated with cirrhosis are usually best visualized during the delayed phase.36,37 Typical contrast enhancement patterns for a variety of benign and malignant lesions of both hepatocellular and nonhepatocellular origin have been identified, aiding in lesion characterization.34,36,37

In the last decade, much effort has been focused on developing a liver-specific contrast agent. Gadobenate dimeglumine not only has a higher relaxivity than conventional ECF contrast agents, but it also possesses a unique route of elimination: in addition to renal excretion, 2% to 4% of the injected dose of gadobenate dimeglumine is excreted by the biliary route, resulting in uptake by functioning hepatocytes.38,39 Therefore, in addition to dynamic liver imaging, delayed images during the hepatobiliary phase can be acquired starting from 40 minutes and extending to at least 2 hours after contrast injection. These delayed images provide important information regarding the cellular makeup of a lesion, thereby helping to detect and characterize a variety of primary and secondary liver lesions.

In the absence of an approved and established comparator, the utility of gadobenate dimeglumine for MRI of the liver was originally validated against established techniques such as unenhanced MRI, conventional CT, CT during arterial portography (CTAP), and ce-CT. Findings from a multicenter phase 3 clinical trial demonstrated the utility of gadobenate dimeglumine for both dynamic and delayed imaging of focal lesions of the liver.40,41 Dynamic imaging was performed immediately after a rapid bolus of 0.05 mmol/kg gadobenate dimeglumine and delayed imaging 60 to 120 minutes after an IV infusion of another 0.05 mmol/kg. Compared with precontrast, gadobenate dimeglumine demonstrated increased efficacy for detecting lesions and increasing lesion conspicuity when used for dynamic and delayed imaging in 126 patients with suspected or known focal liver lesions.40 Significantly more lesions were detected on combined pre- and postcontrast images compared with precontrast alone; all reviewers reported a decreased mean size of the smallest detected lesion; lesion conspicuity was increased on postcontrast images; and gadobenate dimeglumine significantly increased the overall diagnostic confidence of the readers compared with precontrast images.40

What about the accuracy of the characterization of the additional lesions detected with gadobenate dimeglumine? Pirovano and colleagues41 looked at the ability of gadobenate dimeglumine to accurately differentiate benign from malignant lesions and to facilitate the correct specific diagnosis using histologic proof as a reference. The accuracy for gadobenate dimeglumine was found to be 90.7%. Another study evaluated the value of adding delayed imaging with gadobenate dimeglumine to precontrast and dynamic postcontrast imaging for the detection and characterization of 98 focal liver lesions in 48 patients.42 The delayed-phase images showed homogeneous enhancement of the liver parenchyma along with distinctive enhancement features of metastases and HCCs. The authors postulated that the pattern of enhancement observed with delayed imaging, ie, homogeneous enhancement of the
parenchyma, would be advantageous because it would aid in the detection of small metastases and it would allow for a longer imaging window, which could be useful in patients with poor breath-holding ability.42

Several publications have evaluated the use of gadobenate dimeglumine for imaging specific liver pathologies, particularly those that frequently demonstrate atypical findings after dynamic imaging with standard Gd agents. Grazioli and colleagues43 looked at HCCs after delayed MRI with gadobenate dimeglumine. Quantitative and qualitative evaluations of the images were correlated with histologic findings. A total of 34 patients with HCC and varying degrees of diffuse liver disease underwent MRI before and 60 minutes after administration of 0.1 mmol/kg gadobenate dimeglumine. The investigators found that the signal enhancement of liver parenchyma after administration of gadobenate dimeglumine (ie, delayed imaging alone) was influenced to a large degree by the extent to which the functionality of the liver parenchyma was compromised. Residual hepatocytic functionality allowed uptake of gadobenate dimeglumine into certain HCCs, subsequently affecting the CNR on delayed images.43 Increased intralesional fatty metaplasia was also shown to contribute to worsening of lesion conspicuity.

Delayed imaging with gadobenate dimeglumine was also used to describe the morphologic and functional characteristics of FNH, a relatively common benign lesion of hepatocellular origin. Typical FNH lesions appeared isointense or hyperintense relative to the surrounding normal liver parenchyma. Of 100 FNH lesions studied, 21 lesions displayed atypical morphologic features sufficient to prevent definitive diagnosis on precontrast and dynamic postcontrast images. Nevertheless, about 2% to 4% of gadobenate dimeglumine is taken up by functioning hepatocytes, which can cause a marked hyperintensity of the liver lasting up to 120 minutes postinjection. Delayed-phase contrast imaging with gadobenate dimeglumine thus permitted correct characterization of 90% of the 21 atypical lesions as hyperintense or isointense.44

A particular challenge in diagnostic liver imaging is the accurate differentiation between the benign lesions FNH and hepatic adenoma (HA). FNH is not associated with any malignant potential and therefore, once FNH is confirmed, the patient is typically managed conservatively. Grazioli and colleagues45 published the results of a study in which 73 patients with confirmed FNH and 35 patients with confirmed HA or the similar liver adenomatosis (LA) received gadobenate dimeglumine followed by both dynamic and delayed imaging to determine whether these two benign entities could be accurately distinguished. The authors confirmed that accurate differentiation of FNH and HA could not be achieved on the basis of precontrast and dynamic imaging alone; however, at 1 to 3 hours after contrast material injection, 97% of FNHs appeared hyper- or isointense, while 100% of HA and LA lesions appeared hypointense, demonstrating excellent accuracy in the differential diagnosis of these two benign lesions (Figure 5). The overall different enhancement patterns of FNH vs HA and LA were ascribed to the different structural and functional characteristics of the lesions and to their capacity for uptake of gadobenate dimeglumine by the functioning hepatocytes in these lesion types.46
Figure 5. Image of a 56-year-old asymptomatic woman with both focal nodular hyperplasia (FNH) and hepatic adenoma (HA). Hepatobiliary phase T1-weighted gradient-echo image acquired 2 hours after injection of gadobenate dimeglumine shows the FNH (arrowhead) is hyperintense to the normal parenchyma and the HA (arrow) is hypointense. The hypointense appearance of HA indicates that this lesion should be considered for resection, while the hyperintense appearance of FNH indicates a true benign lesion requiring only follow-up. Reproduced with permission from Grazioli L et al. Accurate differentiation of focal nodular hyperplasia from hepatic adenoma at gadobenate dimeglumine-enhanced MR imaging: prospective study. Radiology. 2005;236:166-177.

In order to directly compare gadobenate dimeglumine with other approved agents (ie, the ECF agent gadopentetate dimeglumine and the liver-specific superparamagnetic iron oxide [SPIO] ferumoxides), intraindividual studies have recently been performed.46,47 Schneider and colleagues46 compared low-dose (0.05 mmol/kg) gadobenate dimeglumine with standard-dose (0.1 mmol/kg) gadopentetate dimeglumine in a crossover study of 41 patients with known primary or secondary liver lesions. Blinded readers evaluated images for confidence in lesion detection; lesion number, character, and diagnosis; enhancement pattern; lesion-to-liver contrast; and benefit of dynamic and delayed scans.

Several of the imaging parameters from this study are shown in Table 4. Overall, 0.05 mmol/kg gadobenate dimeglumine was equivalent to 0.1 mmol/kg gadopentetate dimeglumine for dynamic imaging and superior for delayed imaging of the liver (Figure 6).46 In an intraindividual comparison between gadobenate dimeglumine and ferumoxides in 83 FNH lesions, gadobenate dimeglumine was shown to be significantly superior to ferumoxides for identifying and characterizing FNH.47 For detection of liver metastases, delayed imaging with gadobenate dimeglumine has shown comparable diagnostic performance to ferumoxides and better diagnostic performance than dynamic imaging with gadobenate dimeglumine.46
Table 4. Parameters Used for Liver MRI*46

<table>
<thead>
<tr>
<th>Sequence</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>Slice Thickness (mm)</th>
<th>FA</th>
<th>FOV (mm)</th>
<th>Interslice Gap (%)</th>
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<tr>
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<td>4.1</td>
<td>6–8</td>
<td>80°</td>
<td>350</td>
<td>25</td>
<td>107 x 256</td>
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<tr>
<td>T2-W Turbo SE</td>
<td>3200</td>
<td>138</td>
<td>6</td>
<td>180°</td>
<td>350</td>
<td>25</td>
<td>116 x 256</td>
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<td>Postcontrast imaging sequence†</td>
<td></td>
<td></td>
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<tr>
<td>T1-W FLASH-2D</td>
<td>174.9</td>
<td>4.1</td>
<td>6–8</td>
<td>80°</td>
<td>350</td>
<td>25</td>
<td>107 x 256</td>
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</table>

FA=flip angle; FLASH=fast low-angle shot; FOV=field of view; MRI=magnetic resonance imaging; SE=spin-echo; T1-W=T1-weighted; T2-W=T2-weighted; TE=echo time; TR=repetition time.

*1.5T (Siemens Vision; Siemens Medical Systems, Erlangen, Germany) using a body phased array coil.
†Performed during arterial (25–30 seconds postinjection), portal venous (70–90 seconds postinjection), equilibrium (~5 minutes postinjection), and delayed (1–2 hours postinjection) phases; contrast administration was carried out using a power injector at a constant injection rate of 2 mL/s.

Figure 6. Unenhanced (A, B), gadobenate dimeglumine–enhanced (0.05 mmol/kg) (C, E, G, I), and gadopentetate dimeglumine–enhanced (0.1 mmol/kg) (D, F, H, J) images of a 56-year-old man with a history of colorectal carcinoma. Unenhanced T1-weighted (A) and T2-weighted (B) images show a large, irregular lesion in liver segment 8 (large arrows). An additional lesion (small arrows) can be noted in segment 7 on the outer border of the liver. In the arterial phase (C, D), inhomogeneous, peripheral enhancement of the two lesions can be seen with no significant differences in contrast enhancement despite the half dose of gadobenate dimeglumine. In the portal-venous (E, F) and equilibrium (G, H) phases, some filling in of the lesion in the periphery can be noted; however, both lesions remain hypointense throughout all early phases. One hour post–0.05 mmol/kg gadobenate dimeglumine injection (I), both metastases can be clearly identified, with depiction of a peripheral hypointense rim (arrow) in the large metastasis in liver segment 8; however, as images acquired approximately 1 hour after administration of 0.1 mmol/kg gadopentetate dimeglumine show (J), both lesions can be identified but the contrast is low between the lesions and the surrounding liver tissue. Reproduced with permission from Schneider G et al. Low-dose gadobenate dimeglumine versus standard dose gadopentetate dimeglumine for contrast enhanced magnetic resonance imaging of the liver: an intra-individual crossover comparison. Invest Radiol. 2003;38:85-94.
In general, in these comparative studies with other ECF and liver-targeted MRI contrast agents, the use of the dual ECF/hepatocellular contrast agent gadobenate dimeglumine has been demonstrated to show equivalence at a lower dose. It may be that when used at a comparable full dose, there may be additional benefits from the increased enhancement for detection and characterization of a variety of malignant and nonmalignant hepatocellular lesions. Importantly, gadobenate dimeglumine has displayed safety and pharmacokinetic profiles similar to the other ECF contrast agents in patients with normal and impaired renal and hepatic function.49-51

**MRI of the Colon**

Another clinically important application in diagnostic radiology is colon imaging: the ability to noninvasively image colon pathology has the potential to significantly improve colon cancer detection rates. Typically, MRI of the colon requires oral or aboral contrast, frequently in combination with IV contrast. Recently, a preliminary report was published in which an MR colonography was performed after injection of gadobenate dimeglumine without patient preparation.52 Because this contrast agent exhibits some degree of hepatobiliary excretion, it was hypothesized that it could be used for ce-MRI of the colon in a technique called “bile tagging.” In this pilot study of six volunteers, gadobenate dimeglumine–enhanced MRI of the colon demonstrated excellent intraluminal contrast enhancement within 24 hours of IV administration of contrast, and the enhancement was of sufficient intensity to allow for 3D visualization, thus achieving a virtual colonoscopy in the absence of any patient preparation (Figure 7).52 Although the clinical potential of this initial observation is uncertain, further studies in this area may lend support to the use of gadobenate dimeglumine for this important application.

*Figure 7. (Left) Maximum intensity projection of magnetic resonance (MR) colonography 24 hours postinjection of 0.1 mmol/kg gadobenate dimeglumine. Homogeneous signal is shown in all segments of the colon within the field of view. Acquisition as a 3D set allows realtime fly-through visualization in any direction. (Right) Virtual 3D MR colonoscopy with fly-through cinematic display performed on a 3D workstation. Reproduced with permission from Knopp MV et al. Bile-tagged 3D magnetic resonance colonography after exclusive intravenous administration of gadobenate dimeglumine, a contrast agent with partial hepatobiliary excretion. Invest Radiol. 2001;36:619-623.*
MR ANGIOGRAPHY (MRA)

In many clinical situations ce-MRA is replacing conventional catheter angiography for diagnostic assessment of the vasculature, particularly for patients in which ionizing radiation or nephrotoxicity are of increased concern. Contrast-enhanced MRA relies on the T1-shortening effect of Gd contrast agents in the blood. Arteries are visualized soon after injection of contrast, whereas veins are enhanced after a delay in image acquisition, thus emphasizing the critical nature of timing for ce-MRA. Common applications for ce-MRA include imaging of carotid arteries, the aorta, renal arteries, and the peripheral vasculature. High-resolution, rapid imaging methods enable noninvasive imaging of atherosclerotic artery walls and assessment of lumen stenosis.

ECF contrast agents, which lack the capacity for interaction with serum proteins, have been the most widely studied for ce-MRA, and all represent suitable choices for first-pass ce-MRA studies. Most studies in the literature utilize these conventional Gd contrast agents, frequently at up to triple dose (0.3 mmol/kg) to maximize vessel imaging, particularly for small vessels. Gadobenate dimeglumine, with its increased relaxivity in blood, has been demonstrated to be well suited for this application.

Early studies aimed at establishing dosing for ce-MRA with gadobenate dimeglumine in various vascular territories. In the abdominal aorta and renal arteries, gadobenate dimeglumine–enhanced MRA was found to be superior to unenhanced MRA, and the change increased with increasing dose, reaching a plateau at 0.1 mmol/kg. An analogous study was performed for MRA of the pelvic arteries and a similar result was found: gadobenate dimeglumine was safe and effective for MRA and provided improved imaging compared with unenhanced images, and the most appropriate dose was 0.1 mmol/kg. For whole-body MRA, a dose of 0.3 mmol/kg of a standard Gd ECF contrast agent is used to ensure diagnostic quality. With gadobenate dimeglumine, a dose of 0.2 mmol/kg was found to be sufficient to render diagnostic image quality and thereby exclude vascular disease in all segments. Although a higher signal-to-noise ratio (SNR) was achieved with 0.3 mmol/kg, no further clinical benefit was achieved at this dose.

In the absence of an MRA-approved comparator, early MRA studies were performed comparing gadobenate dimeglumine with other diagnostic techniques. In a small study of five healthy volunteers and six patients, whole-body MRA (from supra-aortic vessels to distal runoff vessels) with gadobenate dimeglumine was evaluated by two blinded readers. According to the two readers, gadobenate dimeglumine had overall sensitivities of 91% and 94%, and specificities of 93% and 90%, for the detection of substantial vascular disease (ie, luminal narrowing >50%) compared with conventional digital subtraction angiography (DSA). When compared with conventional duplex sonography, venography, and arteriography in 19 patients with peripheral vascular malformations, gadobenate dimeglumine–enhanced MRA, particularly when used with short tau inversion recovery (STIR) sequences, was valuable for the assessment of vascular malformations of the extremities. However, in this case, performing conventional angiography was still necessary to reveal vascular detail and thereby make definitive treatment decisions.
As for other applications, the results of an intraindividual crossover MRA study remain the most compelling evidence for the superiority of one contrast agent over another. A crossover study was performed that, first, compared the vascular contrast properties of various doses (0.0125, 0.05, and 0.2 mmol/kg) and flow rates (0.5 and 2.0 mL/s) of gadobenate dimeglumine and, second, compared equivalent doses (0.1 mmol/kg) of gadobenate dimeglumine and gadopentetate dimeglumine administered at the same flow rate (2.0 mL/s) for imaging of the abdominal aorta in healthy volunteers. The dose of 0.2 mmol/kg of gadobenate dimeglumine demonstrated higher maximum intensities, longer median peak widths, and larger areas under the curve than the lower doses. In the comparison with gadopentetate dimeglumine, with the same dose in the same individuals, gadobenate dimeglumine demonstrated significantly better vascular enhancement characteristics in terms of signal peak duration, maximum signal intensity, and area under the enhancement curve. In addition, most of the image readers assessing overall vascular contrast preferred images enhanced with gadobenate dimeglumine.58

A second crossover study compared 0.1 mmol/kg gadobenate dimeglumine with 0.1 mmol/kg gadopentetate dimeglumine in 21 healthy volunteers for ce-MRA of the peripheral runoff vasculature.59 The authors found that the standard dose of gadobenate dimeglumine demonstrated greater vascular enhancement than gadopentetate dimeglumine, particularly in the smaller vessels.

Recently, in another crossover study, 0.1 mmol/kg of gadobenate dimeglumine was compared with 0.2 mmol/kg of the conventional Gd contrast agent gadopentetate dimeglumine for MRA of the renal arteries in 34 patients.60 Table 5 shows some of the imaging parameters used in this study. No qualitative difference was found by either of the two blinded readers. Quantitatively, significantly increased SNR and CNR were found with gadobenate dimeglumine at the descending aorta; these ratios were numerically higher, although not significantly so, at the infrarenal aorta (Figure 8). The authors concluded that gadobenate dimeglumine at 0.1 mmol/kg is comparable to gadopentetate dimeglumine at 0.2 mmol/kg. Furthermore, the authors postulated that the benefit of gadobenate dimeglumine for peripheral vessels may be due to not only the increased relaxivity but also the weak interaction with serum proteins, resulting in reduced extravasation into the tissue, although this effect is likely very small.60

The majority of studies used to establish the diagnostic accuracy of noninvasive imaging techniques for assessing carotid artery stenosis use DSA as the reference standard; however, due to the limited number of projections available with conventional DSA, there may be underestimation of the degree of stenosis, particularly when the stenotic lumen has an asymmetric shape. The implication of this underestimation with DSA is an apparent overestimation of stenosis by MRA. A recent paper compared the accuracy of unenhanced MRA, gadobenate dimeglumine–enhanced MRA, DSA, and rotational angiography for depiction of the degree of internal carotid artery (ICA) stenosis.61 This study confirmed that conventional DSA underestimates the degree of ICA stenosis and found that ce-MRA with gadobenate dimeglumine correlated best with rotational angiography.
Given this good correlation, as well as the safety and rapidity of ce-MRA, the authors concluded that ce-MRA should be considered the technique of choice. The authors further postulated that the choice of the higher relaxivity contrast agent likely contributed to the results.61

Table 5. Parameters Used for MRA*60

<table>
<thead>
<tr>
<th>Scanner</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>FA</th>
<th>FOV</th>
<th>Slice Thickness</th>
<th>Matrix Size</th>
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<td>30°–45°</td>
<td>1.00–2.86</td>
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<td>Magnetom</td>
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<td>25°–45°</td>
<td>350–500</td>
<td>174–240</td>
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</table>

FA=flip angle; FOV=field of view; MRA=magnetic resonance angiography; TE=echo time; TR=repetition time.

*1.5T MRI system (Magnetom Vision [n=22], Magnetom Symphony [n=5], or Magnetom Sonata [n=7]; Siemens Medical Systems, Erlangen, Germany) with a phased-array surface coil and sequential 3D phase-encoded spoiled sequence during breath-holding; contrast was administered using a power injector and a constant injection rate of 2 mL/s.

†Slice thickness = 1.00–2.86 mm (n=32); slice thickness = 3.33 mm (n=2).

‡Matrix size = 174–240 x 512 (n=32); 256 x 256 (n=2).

Figure 8. Magnetic resonance angiograms of the abdominal aorta and renal arteries in a 79-year-old woman after injection of (A) 0.1 mmol/kg gadobenate dimeglumine or (B) 0.2 mmol/kg gadopentetate dimeglumine. The aneurysm of the infrarenal abdominal aorta (solid arrow) and stenosis of the left proximal renal artery (open arrow) are depicted equally well on both anteroposterior maximum intensity projection images, but there is better depiction of the inferior mesenteric artery (arrowhead) and more intense and homogeneous signal intensity above and below the aortic bifurcation with 0.1 mmol/kg gadobenate dimeglumine. Reproduced with permission from Prokop M et al. Contrast-enhanced MR angiography of the renal arteries: blinded multicenter crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine. Radiology. 2005;234:399-408.
DYNAMIC ce-MRI OF THE BREAST

Contrast-enhanced MRI of breast tissue to detect cancer relies on the increased neoangiogenic status of breast tumors. Compared with normal breast tissue, breast tumors have increased vascularity, more and larger vessels, increased permeability, and increased interstitial space.62 Early MRI of the breast relied on direct visual comparison of pre- and postcontrast images: malignant foci demonstrate high enhancement and late washout. More recently, new methods (eg, digital subtraction, calculation of dynamic time-intensity curves, 3D maximum projection algorithms) allow for sensitive detection and characterization of breast lesions, assisting in planning individualized treatment for each patient.63

The indications for dynamic ce-MRI imaging of the breast include preoperative pathologic staging of multifocal, multicentric, or synchronous bilateral cancer, particularly in patients with dense or mixed breasts63; postoperative assessment to evaluate positive margins at pathology or to distinguish scar tissue from recurrence64,65; evaluation of the effect of neoadjuvant therapy64; searching for occult breast cancer in patients with lymph node metastases but no evidence of tumor by x-ray mammography or ultrasound (ie, carcinoma of unknown primary syndrome)65; screening of women carriers of genetic mutations in breast cancer susceptibility genes67,68; and, finally, special cases in which the diagnosis is undefined after x-ray mammography and ultrasound.62,63

All of the conventional-relaxivity Gd contrast agents have demonstrated good sensitivity in dynamic ce-MRI of the breast; however, the specificities vary among studies.69 The efficacy and safety of gadobenate dimeglumine was demonstrated in a multicenter study involving 189 patients with known or suspected breast cancer.69 Some of the imaging parameters used in this study are shown in Table 6. Several doses of gadobenate dimeglumine (0.05, 0.1, and 0.2 mmol/kg) were compared with each other and with 0.1 mmol/kg gadopentetate dimeglumine. Significant dose-related increases in global lesion detection were noted for patients receiving gadobenate dimeglumine. Sensitivity for lesion detection was comparable for 0.1 and 0.2 mmol/kg, and specificity was highest for 0.1 mmol/kg. Higher detection scores and sensitivity values for lesion characterization were found for 0.1 mmol/kg gadobenate dimeglumine than for 0.1 mmol/kg gadopentetate dimeglumine. Specificity was higher at 0.1 mmol/kg gadobenate dimeglumine because of a comparatively higher false-positive rate among the 0.2 mmol/kg dose group. The authors concluded that, although their findings were preliminary, a dose of 0.1 mmol/kg gadobenate dimeglumine may offer advantages over other doses and other agents at the same dose for breast lesion detection and characterization.69
Table 6. Parameters Used for Dynamic ce-MRI of the Breast.\textsuperscript{a}

<table>
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<tr>
<th>Sequence</th>
<th>TR (ms)</th>
<th>FA</th>
<th>FOV (cm)</th>
<th>Slice Thickness (mm)</th>
<th>Interslice Gap (%)</th>
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<td>3D T1-W spoiled GRE\textsuperscript{†}</td>
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<td>(&lt;36)</td>
<td>(&lt;3)</td>
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</table>

FA=flip angle; FOV=field of view; GRE=gradient echo; T1-W=T1-weighted; TR=repetition time.

\textsuperscript{a}1.5T systems (Magnetom Vision and Magnetom SP4000 [Siemens, Erlangen, Germany]); 1.0T systems (Magnetom Harmony [Siemens] and Gyroscan NT [Philips, Eindhoven, The Netherlands]); and 0.5T system (Signa Contour [General Electric Medical Systems, Milwaukee, Wis]) used with dedicated double breast coil.

\textsuperscript{†}Precontrast and 0, 2, 4, 6, and 8 minutes postcontrast; contrast was administered using a power injector at a constant injection rate of 0.8 mL/s.

A retrospective evaluation of the MRI results from this study demonstrated that high-quality vascular maps were obtained from doses as low as 0.05 mmol/kg of gadobenate dimeglumine and that these maps were superior to those obtained with gadopentetate dimeglumine.\textsuperscript{70} Furthermore, the authors found vascular asymmetry to be associated with ipsilateral invasive breast cancer with a high degree of sensitivity (88\%) and specificity (82\%) (Figure 9).\textsuperscript{70} Finally, these conclusions were echoed in a commentary by a well-known breast radiologist who further postulated that in terms of clinical practice, it will be necessary to demonstrate that vascular mapping with gadobenate dimeglumine, along with morphologic and kinetic information, improves the interpretation of breast MR images.\textsuperscript{71}

Figure 9. Maximum-intensity–projection reconstruction 2 minutes after IV injection with 0.05 mmol/kg gadobenate dimeglumine. The increased vascularity in the left breast is associated with bifocal invasive ductal carcinomas (arrows) in the lower quadrants. Reproduced with permission from Sardanelli F et al. Gadobenate dimeglumine-enhanced MR imaging breast vascular maps: association between invasive cancer and ipsilateral increased vascularity. Radiology. 2005;235:791-797.
The results of an intraindividual comparison of standard doses of gadobenate dimeglumine and gadopentetate dimeglumine for accuracy of detection and characterization of breast lesions in 26 women were recently published. A T1-weighted 3D gradient-echo sequence was used, and images were acquired before and at 0, 2, 4, 6, and 8 minutes after injection of either gadopentetate dimeglumine or gadobenate dimeglumine at an identical flow rate of 2 mL/sec. As for other intraindividual comparisons, separate and combined assessment of unenhanced, contrast-enhanced, and subtracted images was assessed in blinded fashion by two readers. Accuracy for lesion detection was determined against a final diagnosis based on findings at conventional x-ray mammography, sonography, and surgery. Dynamic ce-MRI of the breast with gadobenate dimeglumine depicted significantly more lesions (45 of 46) than did that with gadopentetate dimeglumine (36 of 46), and detected lesions were significantly more conspicuous with gadobenate dimeglumine (Figure 10). The authors concluded that detection of breast lesions and accurate identification of malignant lesions at MRI are significantly superior with gadobenate dimeglumine in comparison with gadopentetate dimeglumine. The lower 0.05 mmol/kg contrast dosage produced significantly higher infarcted signal intensity relative to normal myocardium.

Figure 10. Transverse MR images of a dynamic series in a 36-year-old patient with 4 histologically confirmed IDC lesions in the right breast. (A) MIP reconstruction of subtracted images obtained with 0.1 mmol/kg gadopentetate dimeglumine clearly reveals three lesions (arrows). (B) On subtracted MIP reconstruction obtained with 0.1 mmol/kg gadobenate dimeglumine, lesions are more conspicuous and more strongly enhanced. An additional small, histologically confirmed lesion (arrow), which is not seen on A, is clearly visible with gadobenate dimeglumine. Reproduced from Pediconi F et al. Breast lesion detection and characterization at contrast-enhanced MR mammography: gadobenate dimeglumine versus gadopentetate dimeglumine. Radiology. 2005;237:45-56.

CARDIAC MRI

Until recently, due to technical difficulties, cardiac MRI was considered to be of limited clinical utility; however, recent technological developments have rapidly improved the potential of this important application. In an early study to assess the feasibility of gadobenate dimeglumine for ce-cardiac MRI to detect acute myocardial infarction (AMI), Holman and colleagues imaged 24 patients within 13 days of a first AMI. T1-weighted images were obtained before, immediately after, and 15, 30, and 45 minutes following injection of either 0.05 or 0.1 mmol/kg gadobenate dimeglumine. Optimal infarct delineation was achieved 15 to 45 minutes after administration of 0.05 mmol/kg gadobenate dimeglumine and the image quality, as measured by CNR and signal intensity, was improved with 0.05 mmol/kg compared with 0.1 mmol/kg.
More recently, 103 patients with AMI were evaluated using dynamic and delayed ce-MR with 0.05 mmol/kg gadobenate dimeglumine and the results compared with precontrast MR images, electrocardiography, single-photon emission computed tomography (SPECT), and echocardiography. Some of the imaging parameters used in this study are shown in Table 7.

Dynamic imaging with gadobenate dimeglumine was more sensitive than delayed imaging (72% vs 56%) and similar in specificity (98% vs 99%). SPECT was sensitive (96%) but not specific (63%). In contrast, echocardiography was specific (92%) but not sensitive (32%). The authors concluded that dynamic gadobenate dimeglumine–enhanced MRI is moderately sensitive, very specific, and well tolerated for MRI of patients with AMI.

Table 7. Parameters Used for Cardiac MRI

<table>
<thead>
<tr>
<th>Sequence Description</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>Slice Thickness (mm)</th>
<th>FOV (cm)</th>
<th>T (ms)</th>
<th>FA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precontrast imaging sequence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG gated, T1-W SE</td>
<td>1 x R-R interval</td>
<td>25</td>
<td>8</td>
<td>35</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Postcontrast imaging sequences</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TurboFLASH</td>
<td>4.7</td>
<td>2</td>
<td>10</td>
<td>25</td>
<td>300</td>
<td>8˚</td>
</tr>
<tr>
<td>T1-W SE</td>
<td>1 x R-R interval</td>
<td>25</td>
<td>8</td>
<td>35</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

ECG = electrocardiogram; FA = flip angle; FOV = field of view; MRI = magnetic resonance imaging; NA = not applicable/not available; SE = spin-echo; T1-W = T1-weighted; TE = echo time; TR = repetition time.

*1.0T MRI scanner (Magnetom Impact; Siemens, Erlangen, Germany) used with linearly polarized 180-mm body coil.
†All patients received a single intravenous bolus injection by hand at a rate of between 1.3 and 3.8 mL/s.
‡TurboFLASH = single-shot inversion recovery prepared T1-weighted gradient echo sequence (Siemens); acquisitions were cardiac gated with midline of k space in mid-diastole; new image initiated every second heartbeat beginning 1.3 x R-R interval, 450 ms after the R wave.
§Postcontrast T1-W SE sequence repeated beginning 15 and 30 minutes after the administration of contrast.

The differentiation between viable and nonviable myocardium after MI is critical for predicting the success of revascularization and recovery of regional function. A study was performed to determine the contrast enhancement pattern in patients with subacute MI after revascularization, and to correlate this pattern with myocardial viability. The authors found that, within the first 5 minutes of injection, midwall and/or subendocardial enhancement with gadobenate dimeglumine was associated with viable myocardium, and that midwall hypoenhancement is associated with microvascular obstruction correlating with scar formation. Although this study was small (7 patients), ce-MRI with gadobenate dimeglumine can detect MI, and furthermore, using this method to detect nonviable infarction appears to be feasible.
Delayed imaging (15 to 30 minutes following administration of ECF contrast) has also been shown to allow assessment of myocardial viability in patients with acute and chronic ischemic heart disease.\textsuperscript{78,79} Results of an intraindividual comparison between gadopentetate dimeglumine and gadobenate dimeglumine for assessment of viability in 23 patients with clinically proven MI were recently published.\textsuperscript{80} Patients received two cardiac MR examinations within 2 days, one with a double dose (0.2 mmol/kg) of gadopentetate dimeglumine and the other with a single dose (0.1 mmol/kg) of gadobenate dimeglumine, followed by assessment of myocardial viability. Of the 61 infarcts evaluated, there was no statistically significant difference found in the mean CNR ratio between the double dose of gadopentetate dimeglumine and the single dose of gadobenate dimeglumine, suggesting diagnostically equivalent efficacy.

SAFETY OF MRI CONTRAST AGENTS

When choosing among available Gd contrast agents, an important consideration is not only properties that relate to relaxivity and tissue specificity, but also characteristics that relate to safety, which is directly related to chelate stability and adverse event rates (Tables 8 and 9).\textsuperscript{4,17,18,81-85} Among the five Gd contrast agents approved for use in the United States, gadoteridol, gadopentetate dimeglumine, and gadobenate dimeglumine have relatively high thermodynamic and conditional stability constants. Gadodiamide and gadoversetamide have the lowest stability constants of the group. The stability of the different agents is also reflected in the excess chelate in the formulation: excess chelate is considered necessary in the less stable agents to minimize the probability of transmetallation with trace amounts of zinc in the blood, resulting in release of free Gd.\textsuperscript{86-89} Gadodiamide and gadoversetamide are both formulated with considerably greater amounts of excess chelate than the other available agents.\textsuperscript{18,81} Interestingly, gadobenate dimeglumine has no excess chelate in the approved formulation.\textsuperscript{82}

Table 8. Physicochemical Properties of Gd Contrast Agents\textsuperscript{4,17,18,81-84}

<table>
<thead>
<tr>
<th>Contrast Agent</th>
<th>Brand Name</th>
<th>Molecular Structure</th>
<th>Thermodynamic Stability Constant (log $K_{eq}$)</th>
<th>Conditional Stability Constant at pH 7.4</th>
<th>Viscosity (mPa • s at 37°C)</th>
<th>Metal Chelate (mg/mL)</th>
<th>Excess Metal Chelate (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadopentetate dimeglumine (Gd-DTPA)</td>
<td>Magnevist&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Linear, ionic</td>
<td>22.1</td>
<td>18.1</td>
<td>1.96</td>
<td>2.9</td>
<td>469</td>
</tr>
<tr>
<td>Gadoteridol (Gd-HP-D03A)</td>
<td>ProHance&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Cyclic, nonionic</td>
<td>23.8</td>
<td>17.1</td>
<td>0.63</td>
<td>1.3</td>
<td>279.3</td>
</tr>
<tr>
<td>Gadodiamide (Gd-DTPA-BMA)</td>
<td>Omniscan™&lt;sup&gt;™&lt;/sup&gt;</td>
<td>Linear, nonionic</td>
<td>16.9</td>
<td>14.9</td>
<td>0.79</td>
<td>1.4</td>
<td>287</td>
</tr>
<tr>
<td>Gadoversetamide (Gd-DTPA-BMEA)</td>
<td>Optimark&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Linear, nonionic</td>
<td>16.6</td>
<td>15.0</td>
<td>1.11</td>
<td>2.0</td>
<td>330.9</td>
</tr>
<tr>
<td>Gadobenate dimeglumine (Gd-BOPTA)</td>
<td>MultiHance&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Linear, ionic</td>
<td>22.6</td>
<td>18.4</td>
<td>1.97</td>
<td>5.3</td>
<td>334</td>
</tr>
</tbody>
</table>
Differences in chelate stability have clinically important consequences both in vitro and in vivo. In vitro, dissociation of the less stable Gd-chelate complexes has been demonstrated to interfere with the most common colorimetric laboratory assay for serum calcium, causing a result of spurious hypocalcemia. A false diagnosis of hypocalcemia may result in improper and possibly life-threatening yet unnecessary treatment of the patient. Alternatively, a spurious hypocalcemia may mask a true hypercalcemia. A thorough evaluation of the extent to which various commercially available Gd-containing contrast agents interfere with the measurement of calcium was recently published. Serum and plasma from healthy volunteers were spiked with various concentrations of gadopentetate dimeglumine, gadobenate dimeglumine, gadodiamide, or gadoversetamide and a commonly used, colorimetric laboratory assay for calcium was performed. The authors found that gadopentetate dimeglumine and gadobenate dimeglumine generate no interference with colorimetric methods for calcium determination, whereas strong interference was shown for gadodiamide and gadoversetamide under clinically relevant conditions. In vivo, less stable Gd contrast agents may undergo transmetallation, resulting in release of free Gd and retention of these ions in the body.

In terms of adverse events (AEs), a retrospective analysis was recently published in which the safety of gadobenate dimeglumine was assessed from a total of 3092 subjects who had received gadobenate dimeglumine in 79 clinical trials. Data from comparisons with other contrast agents as well as studies in children, subjects with hepatic or renal impairment, or subjects with coronary artery disease were reviewed. All showed a similarly low overall incidence of AEs, the most common of which were headache, nausea, taste perversion, and urticaria (hives) (Table 9). Furthermore, all have been studied and shown to be safe for use in patients with renal impairment; in addition, gadobenate dimeglumine has also been evaluated and found to be safe in patients with hepatic impairment. This comparable safety profile for gadobenate dimeglumine is notable in light of its unique dual route of elimination.

Evaluation of postmarketing safety surveillance data after more than 1.5 million applications of gadobenate dimeglumine has demonstrated that in total, 413 of 2982 (14%) adult subjects receiving gadobenate dimeglumine reported at least one AE definitely or potentially related to the contrast agent, an incidence similar to that observed with placebo (21/127, 17%) or active controls (59/723, 8%). In intraindividual crossover studies, 23 of 287 (8%) subjects receiving gadobenate dimeglumine experienced AEs compared with 25 of 295 (9%) receiving gadopentetate dimeglumine. No increase in the AE rate was observed in children and, in addition, no worsening of renal or liver function was observed in subjects with hepatic or renal impairment. In addition, no detrimental effect on cardiac electrophysiology could be observed from a retrospective analysis of ECG parameters in more than 1000 patients and healthy volunteers. The AE reporting rate from postmarketing safety surveillance of gadobenate dimeglumine was 0.05%. Serious AEs occurred rarely. The most frequently reported serious AEs were dyspnea, nausea, urticaria, hypotension, and anaphylactoid reactions. Therefore, in this
In general, Gd contrast agents have been utilized in the vast majority of ce-MRI procedures; they are considered to have an excellent safety record and lack the nephrotoxicity associated with large administered volumes of iodinated contrast media. These agents cannot be differentiated based on the associated mild AEs; however, differences in chelate stability may have important clinical consequences.

Nephrogenic systemic fibrosis (NSF) is a potentially fatal, idiopathic skin condition that was first described in 2000; however, the first cases were seen in 1997.98 Now, more than 200 cases are registered in the national database. The disease is seen days or weeks following administration of a Gd-based contrast agent, predominantly in patients that have severe or end-stage renal disease.99,100 Clinically, NSF is comprised of a scleroderma-like set of findings, with thickening and fibrosis of the skin that tends to occur in the lower extremities and the distal portions of the upper extremities. It has subsequently been found to also involve other muscles, including those of the heart and diaphragm.

To date, the vast majority of NSF cases (~90%) have occurred following administration of one particular Gd-based contrast agent, gadodiamide (Omniscan™).101 The exact pathophysiology of NSF is not completely understood; however, several lines of evidence support a mechanism of transmetallation. Transmetallation involves the dissociation of Gd from its chelate and exchange of the Gd in the Gd-chelate complex with another ion. Free Gd ions, known to be toxic, would then be available to accumulate in the tissue. As discussed above, there are significant differences in the Gd-chelate stability among the different Gd-based contrast agents, and those less stable contrast agents, such as gadodiamide, are believed to be more readily involved in the process of transmetallation.102 Patients who have renal dysfunction are less able to clear the contrast agent, resulting in a significantly longer half-life for the contrast agent, and potentially more serious consequences of transmetallation.103

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**Table 9. Reported Incidences of Common Adverse Events With US-FDA–Approved Gd Contrast Agents**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Gadobenate dimeglumine (N=2367)</th>
<th>Gadopentetate dimeglumine (N=1068)</th>
<th>Gadoteridol (N=1709)</th>
<th>Gadodiamide (N=700)</th>
<th>Gadoversetamide (N=1663)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache (%)</td>
<td>1.9</td>
<td>3.6</td>
<td>0.4</td>
<td>4.4</td>
<td>7.5</td>
</tr>
<tr>
<td>Nausea (%)</td>
<td>1.3</td>
<td>1.5</td>
<td>1.1</td>
<td>3.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Taste perversion (%)</td>
<td>1.1</td>
<td>0.3</td>
<td>1.2</td>
<td>2.6</td>
<td>5.7</td>
</tr>
<tr>
<td>Urticaria (%)</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
<td>0.1</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Adapted from Shellock FG et al. Safety of gadobenate dimeglumine (MultiHance): Summary of findings from clinical studies and postmarketing surveillance. Invest Radiol. 2006;41:500-509.
The American College of Radiology recently updated their MR safety guidelines to include recommendations for the prevention of NSF. Screening patients for a history of renal or kidney disease is recommended. Virtually all data suggest that the vast majority of NSF patients have had either severe or end-stage renal disease at the time of diagnosis or of Gd-based MR contrast agent. The official staging system of the National Kidney Foundation includes a glomerular filtration rate (GFR) for each stage of chronic kidney disease. Glomerular filtration rates between 30 and 59 mL/min/1.73 m² have stage 3 or moderate chronic kidney disease. Patients with glomerular filtration rates between 15 and 29 mL/min/1.73 m² have stage 4, or severe chronic kidney disease; those with glomerular filtration rates between <15 mL/min/1.73 m² have stage 5, or end-stage disease. The guidelines caution against use of a Gd-based MR contrast agent in patients with stage 3 to 5 renal disease. When risk-benefit assessment warrants contrast administration in these patients, the lowest dose possible should be considered. The guidelines further caution against the use of gadodiamide in patients who have any degree of renal dysfunction. Additional administrative procedures that should be instituted include requiring explicit orders from a radiologist to administer a specific Gd-based contrast agent to an individual patient, as opposed to accepting an order by protocol or from a referring physician. In addition, it is recommended that the risks and benefits of contrast-enhanced MR are explained to patients and their consent obtained. Cooperation between radiologists and nephrologists is required to identify and manage patients at risk for the development of NSF to prevent this rare but serious adverse event.

CONCLUSIONS

The clinical utility of diagnostic MRI is expanding, due in large part to the contribution of new contrast agents that are improving existing uses of MRI and MRA and making possible novel and exciting applications. Conventional ECF Gd contrast agents have been instrumental in demonstrating the potential improvement of ce-MRI over noncontrast MRI. Gadobenate dimeglumine is a new contrast agent with the ability to function as both an ECF and a hepatocyte-specific contrast agent, allowing both dynamic- and delayed-phase hepatic imaging. In addition, gadobenate dimeglumine has twice the relaxivity of the conventional Gd contrast agents. Many clinical studies, both inter- and intraindividual, have demonstrated superior sensitivity and specificity of gadobenate dimeglumine for a variety of applications compared with the conventional Gd contrast agents, likely due to these unique properties.
REFERENCES


81. Optimark® 0.5 mmol/ml (gadoversetamide injection) [prescribing information]. St. Louis, Mo: Mallinckrodt Inc.; revised January 2003.


FROM MOLECULE TO MAGNET:
A Literature Review of Gadobenate Dimeglumine

Posttest

1. Which statement best describes the four conventional gadolinium (Gd)-based contrast agents?
   a. They all have similar r1 relaxivities, ranging from 4.6 to 4.9 mM-'s-', and are all renally excreted
   b. They are all IV extracellular fluid (ECF) contrast agents that are most useful for delayed hepatic parenchymal imaging but can also be used for dynamic liver imaging
   c. All four have similar r2 relaxivities, ranging from 4.6 to 4.9 mM-'s-', but differ significantly in their r1 relaxivities
   d. None is useful for first-pass contrast-enhanced magnetic resonance (MR) angiography

2. Gadobenate dimeglumine differs from the four conventional Gd-based contrast agents in that it
   a. Has been shown to be inferior for delayed hepatic parenchymal imaging
   b. Has been approved in the United States for much longer
   c. Possesses twice the relaxivity as well as being excreted to a small degree by the hepatobiliary pathway
   d. Has a far superior safety record

3. Which of the following is not a factor in the degree of central nervous system lesion enhancement?
   a. The extent of leakage of the blood-brain barrier
   b. The vascularity of the lesion
   c. The dose of contrast agent
   d. The number of lesions

4. Intraindividual crossover studies are designed to compare the contrast-enhancement properties of two contrast agents in a clinical setting. In this type of study
   a. Contrast agents are differentially tagged and patients receive both contrast agents simultaneously
   b. Patients are randomized to receive an MR imaging (MRI) with one contrast agent, followed at approximately 2 days to 2 weeks with an MRI using the second contrast agent
   c. Patients are randomized to receive an MRI with one contrast agent, followed at approximately 6 months with an MRI using the second contrast agent
   d. Postcontrast images are assessed independently of unenhanced images

5. Which phases are normally included during dynamic contrast-enhanced studies of the liver?
   a. Arterial and portal-venous, but not equilibrium
   b. Arterial and equilibrium, but not portal-venous
   c. Portal-venous and equilibrium, but not arterial
   d. Arterial, portal-venous, and equilibrium
6. Due to its unique route of elimination, gadobenate dimeglumine is useful for delayed imaging as well as dynamic imaging of the liver. Dynamic imaging can be performed immediately after a rapid 0.05-mmol/kg bolus, and, following an IV infusion of another 0.05 mmol/kg, delayed imaging can be performed
   a. 5 to 10 minutes later
   b. 60 to 120 minutes later
   c. 8 to 10 hours later
   d. 2 weeks later

7. Grazioli and colleagues recently demonstrated that delayed imaging with gadobenate dimeglumine is useful for distinguishing between focal nodular hyperplasia and
   a. Hepatic adenoma
   b. Infantile hepatic hemangioma
   c. Peliosis hepatis
   d. Colonic polyps

8. In general, comparative studies of gadobenate dimeglumine with conventional Gd-based extracellular fluid agents for the detection and characterization of a variety of malignant and nonmalignant hepatocellular lesions have demonstrated
   a. Equivalence at a lower dose and superiority at a comparable dose for gadopentetate dimeglumine
   b. Superiority at a lower dose for gadopentetate dimeglumine
   c. Equivalence at a comparable dose for gadobenate dimeglumine
   d. Equivalence at a lower dose and superiority at a comparable dose for gadobenate dimeglumine

9. Contrast-enhanced MRI (ce-MRI) of breast tissue relies on the altered neoangiogenic status of breast tumors. Compared with normal breast tissue, breast tumors have
   a. Fewer, smaller vessels
   b. Decreased permeability
   c. Increased vascularity
   d. Decreased interstitial space

10. High-quality vascular breast maps have been obtained from doses as low as 0.05 mmol/kg gadobenate dimeglumine. In addition, vascular asymmetry has been associated with ipsilateral invasive breast cancer with
    a. A sensitivity of 88% and a specificity of 82%
    b. A sensitivity of 68% and a specificity of 62%
    c. A sensitivity of 98% and a specificity of 92%
    d. A sensitivity of 58% and a specificity of 52%

11. The use of MRI for contrast-enhanced imaging of the heart has advanced greatly. Dynamic imaging of the heart with gadobenate dimeglumine has been demonstrated to be well tolerated and to have
    a. High sensitivity and moderate specificity
    b. Moderate sensitivity and high specificity
    c. Low sensitivity and moderate specificity
    d. Moderate sensitivity and low specificity
12. Which of the following has been demonstrated to have a lower stability constant and to interfere with a common colorimetric laboratory assay for calcium?
   a. Gadobenate dimeglumine
   b. Gadodiamide
   c. Gadopentetate dimeglumine
   d. Gadoteridol

13. Which statement **best** describes the adverse event (AE) rates for the various Gd-based contrast agents?
   a. Gadodiamide and gadoversetamide have significantly higher rates of mild AEs
   b. Gadopentetate dimeglumine has a significantly higher rate of AEs
   c. In general, Gd-based MRI contrast agents have a poor safety record
   d. All have a similarly low overall incidence of AEs

14. The homogenous enhancement of the liver parenchyma seen on delayed images with gadobenate dimeglumine has been postulated to be advantageous for all of the following reasons **except**
   a. It would allow for a shorter imaging window
   b. It would aid in the detection of small metastases
   c. It would allow for a longer imaging window
   d. It would be less susceptible to perfusion abnormalities

15. Dynamic ce-MRI of the breast is not indicated in which of the following clinical situations or patient groups?
   a. Preoperative pathologic staging of multifocal, multicentric, or synchronous bilateral cancer
   b. Screening of low-risk patients
   c. Postoperative assessment to evaluate positive margins
   d. Evaluation of the effect of neoadjuvant therapy

*A score of 70% or higher is required to receive continuing education credit for this activity.*
FROM MOLECULE TO MAGNET:
A Literature Review of Gadobenate Dimeglumine

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E-mail:____________________________________________________________________________________

Signature:____________________________________________________________________________________

Posttest Answers (circle the correct answer)

1. a b c d 5. a b c d 9. a b c d 13. a b c d
2. a b c d 6. a b c d 10. a b c d 14. a b c d
3. a b c d 7. a b c d 11. a b c d 15. a b c d
4. a b c d 8. a b c d 12. a b c d

Evaluation

1. Extent to which the objectives were achieved: 1 2 3 4 5
2. Potential impact on your practice: 1 2 3 4 5
3. Detail of information presented: 1 2 3 4 5
4. Extent to which commercial bias appeared: 1 2 3 4 5
5. Suggestions for future CME topics:__________________________________________________________