MRI for Technologists

Contrast Agent Safety

MRI for Technologists is a training program designed to meet the needs of radiologic technologists entering and/or working in the field of magnetic resonance imaging (MRI). These units are designed to augment classroom instruction and on-site training for radiologic technology students and professionals planning to take the review board examinations, as well as to provide a review for those looking to refresh their knowledge base in MR imaging.

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This material will be reviewed for continued accuracy and relevance.

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OVERVIEW

The skill of the technologist is the single most important factor in obtaining good quality diagnostic images. A successful MRI examination is the culmination of many factors under the direct control of the technologist.

MRI for Technologists: MRI Contrast Safety introduces the learner to the different types of MRI contrast media, visualization of normal anatomy and pathology, exam-specific agents, and how to recognize and respond to the most common adverse patient reactions.

After completing this educational material, the reader will be able to:

- Define the different types of MRI contrast media
- Determine specific contrast media appropriate for different types of MRI examinations
- Recognize and respond to the most common adverse patient reactions to MRI contrast media administration

EDUCATIONAL CREDIT

This program has been approved by the American Society of Radiologic Technologists (ASRT) for 1.0 hour ARRT Category A continuing education credit.

Note: Terms in **bold** throughout this material can be found in the glossary.

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- A passing grade of at least 75% is required to be eligible to receive credit.
- You may take the test up to three times.
- Upon receipt of a passing grade, you will receive instructions on how to print a certificate of credit.

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Contrast Agent Safety

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INTRODUCTION

The introduction of contrast media to magnetic resonance imaging revolutionized the field of MRI by increasing the intrinsic contrast between nonvascularized and vascularized tissue, including the vasculature itself. Contrast agents have widespread clinical use: they contribute to the identification and characterization of normal anatomy, increase the conspicuity of lesions such as primary or secondary tumors, abscesses, infection, or inflammation, and improve visualization of arterial and venous anatomy and pathology.

MRI contrast agents can be divided into different classes (**Table 1**).

Class of Agent	Method of Administration
Nonspecific extracellular agents (gadolinium chelates)	Intravenous
Hepatocyte-specific agents	Intravenous
Blood pool agents	Intravenous
Oral agents for gastrointestinal imaging	Oral

Table 1. Classes of MRI contrast agents.

PARAMAGNETIC PROPERTIES OF CONTRAST MEDIA

Most contrast agents are derived from **paramagnetic** substances; the majority of paramagnetic agents are nonspecific, **extracellular** agents. Gadolinium **chelates** are the best known and most widely used paramagnetic agents. Other metal **ions**, such as manganese, iron, dysprosium, and copper also have paramagnetic properties.

A common feature of paramagnetic substances is the presence of unpaired orbital electrons. After intravenous administration, an extracellular gadolinium chelate rapidly equilibrates between the intravascular and extracellular spaces. Normal living cells in the body prevent entry of nonspecific extracellular gadolinium chelates into the intracellular space.

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Paramagnetic contrast agents increase magnetic field strength in the vicinity of the gadolinium ion. Protons closely approaching a paramagnetic substance, such as gadolinium chelate, interact with the locally altered magnetic field in a manner that facilitates rapid longitudinal relaxation, resulting in shortening of the T1 relaxation time of protons in the vicinity of the gadolinium chelate.

In normal tissues that absorb the contrast agent, gadolinium chelates shorten the T1 relaxation time of protons, causing tissue protons to appear brighter on T1-weighted images and demonstrating increased signal. Thus, T1-shortening paramagnetic agents are also known as positive enhancement agents. The contrast molecule itself is not directly visualized on MRI; it is the effect of the gadolinium ion on adjacent protons that results in the increased signal intensity demonstrated on T1-weighted images. In this way, paramagnetic MR contrast agents are fundamentally different from CT or radiographic angiography contrast agents such as iodine that directly attenuate the x-ray beam.

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Paramagnetic agents, including gadolinium chelates, also act to shorten the T2 and T2* (T2 star) relaxation times of tissue protons. Unlike T1 shortening, T2 shortening causes tissues to appear darker, counteracting the positive enhancement effect of the gadolinium chelate. In most tissues, the T1-shortening effect predominates after intravenous injection of a standard 0.1 mmol/kg dose of extracellular gadolinium chelate. However, the T2* shortening effect begins to predominate as the concentration of gadolinium chelate rises. This shift explains the signal void that may be seen in normal renal collecting systems several minutes after the administration of gadolinium chelate. In certain applications such as MR brain perfusion imaging, the T2* shortening properties of gadolinium are used to clinical advantage. In this setting, the gadolinium chelate serves as a susceptibility agent, producing negative contrast enhancement (darker signal).

Gadolinium chelates are manufactured by several vendors and known by various brand names (**Table 2**). The nonspecific extracellular gadolinium chelates approved for intravenous use in the United States are Gadavist™, Eovist®, Magnevist®, Omniscan™, OptiMARK™, and ProHance®.

Another FDA-approved contrast agent, MultiHance®, is often categorized as a nonspecific extracellular agent, although it weakly binds to human serum albumin and exhibits limited specificity for **hepatocytes.** However, at this time there is no FDA clearance for MultiHance for indications other than for the central nervous system.

Ablavar®, a non-extracellular blood pool agent, completes the list. This agent binds to serum albumin, keeping it in circulation. Ablavar is FDA-approved for use in aortoiliac MR angiography.

Brand Name	Generic Name	Date of FDA Approval	Manufacturer
Magnevist®	gadopentetate dimeglumine (Gd-DTPA)	June 1988	Bayer Healthcare (Wayne, NJ)
MultiHance®	gadobenate dimeglumine (Gd-BOPTA)	December 2004	Bracco Diagnostics, Inc. (Princeton, NJ)
Omniscan™	gadodiamide (Gd-DTPA-BMA)	January 1993	GE Healthcare (Waukesha, WI)
OptiMARK™	gadoversetamide (Gd-DTPA-BMEA)	December 1999	Mallinckrodt, Inc. (St. Louis, MO)
ProHance®	gadoteridol (Gd-HP-DO3A)	November 1992	Bracco Diagnostics, Inc. (Princeton, NJ)
Ablavar®	gadofosveset trisodium	July 2008	Lantheus Medical Imaging (N. Billerica, MA)
Eovist®	gadoxetate disodium	July 2008	Bayer Healthcare (Wayne, NJ)
Gadavist™	gadobutrol	March 2011	Bayer Healthcare (Wayne, NJ)

Table 2. List of gadolinium-based contrast agents approved by the FDA as of Jun 2012[1].

Physical and Chemical Properties of Gadolinium-Based Contrast Agents

The eight currently FDA-approved gadolinium-based contrast agents (GBCAs) can be divided into three categories:

- Ionic: Magnevist, Eovist, Ablavar, MultiHance
- Nonionic: Omniscan, OptiMARK
- Macrocyclic (as opposed to linear): Gadavist, ProHance

Ionic agents dissociate into positively and negatively charged ions in the bloodstream, while the nonionic agents remain electrically neutral. Although nonionic CT contrast agents are associated with a lower incidence of adverse reactions than **ionic** CT contrast agents, this phenomenon has not been observed with MR agents, likely due to the relatively small volume of MR contrast administered for routine clinical use.

Macrocyclic agents consist of atoms surrounding a chemically-bound metal ion, as opposed to a linear bond arrangement, where the atoms are linked together in a chain-like fashion (**Table 3**).

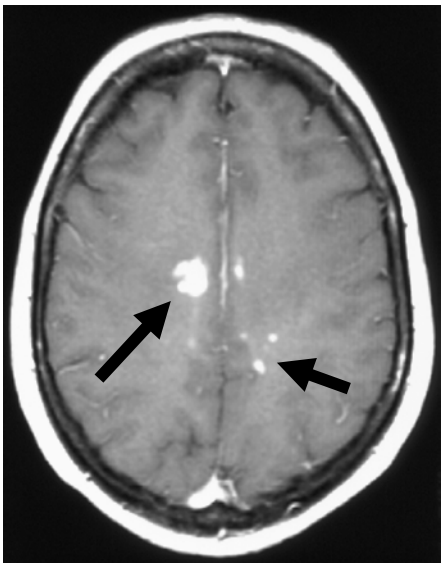
Because gadolinium contrast agents are paramagnetic they amplify the external magnetic field produced by the MRI system. Contrast agents also facilitate proton relaxation within water molecules that come into close proximity to the gadolinium ion. Both T1 **relaxivity** (r_1) and T2 relaxivity (r_2) are facilitated by paramagnetic contrast agents, but T1 effects predominate within human tissues at standard clinical doses.

Brand Name/ Manufacturer	Generic	Indication	Molecular Structure/Charge
Magnevist® Bayer Healthcare	gadopentetate dimeglumine (Gd-DTPA)	CNS/Body	Ionic, Linear
MultiHance® Bracco	gadobenate dimeglumine (Gd-BOPTA)	CNS	Ionic, Linear
Omniscan™ GE Healthcare	Gadodiamide (Gd-DTPA-BMA)	CNS/Body	Non-ionic, Linear
OptiMARK™ Covidien	gadoversetamide (Gd-DTPA-BMEA)	CNS/Liver	Non-Ionic, Linear
ProHance® Bracco	gadoteridol (Gd-HP-DO3A)	CNS	Macrocyclic
Eovist® Bayer Healthcare	gadoxetate	Liver	Ionic, Linear
Ablavar® Lantheus Medical Imaging	gadofosveset	MRA Aortoiliac	Ionic, Linear
Gadavist™ Bayer Healthcare	gadobutrol	CNS	Macrocyclic

Table 3. Gadolinium-based contrast agents and molecular structure.

The free gadolinium ion is toxic; it can become sequestered in liver, spleen, and bone, remain in the body for long periods of time, and result in cardiac- and neurotoxicity. To prevent toxicity, the gadolinium ion must be bound to a chelating **ligand** such as DTPA (pentetic acid).

Chelation of the gadolinium ion not only makes it safe but influences its biodistribution and elimination. Since Magnevist, ProHance, Omniscan, OptiMARK, Eovist and Gadavist are extracellular agents, they equilibrate rapidly after intravenous injection within the extracellular fluid space, which consists of the interstitial space and the blood pool.



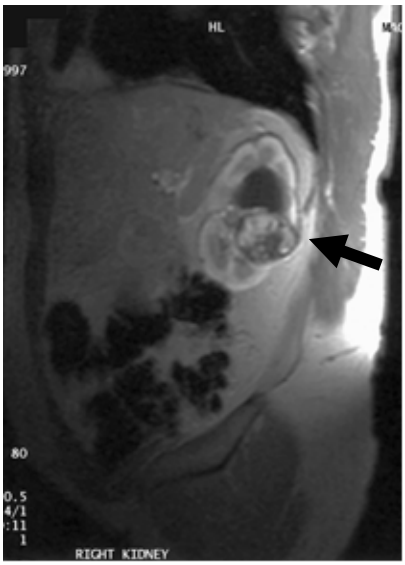


Figure 1. (Left) Axial postcontrast T1 image through the brain demonstrates brain metastases.

Figure 2. (Right) Sagittal postcontrast T1 breath-held image through the right kidney demonstrates an enhancing renal cell carcinoma.

Courtesy of Mark Flyer, MD
Maimonides Medical Center

MultiHance is predominantly an extracellular agent; however, 3%–5% of the injected dose is taken up by hepatocytes and eliminated via biliary excretion. With the exception of Eovist, and to a lesser degree, MultiHance, extracellular agents are eliminated from the body by the kidneys via glomerular filtration, with 50% of the dose eliminated within one to two hours. Eovist is eliminated differently from the other agents: 50% is eliminated by the kidneys via normal glomerular filtration and 50% via the liver.

Since MultiHance and Eovist are partially eliminated by the liver, there is potential for drug-to-drug interactions in the liver. Caution should be exercised for patients receiving chemotherapy or with certain underlying metabolic disorders. The package inserts contain full information.[2,3]

The currently approved gadolinium-based contrast agents do not cross the normal blood-brain barrier. In areas where the blood-brain barrier is disrupted, these agents can enter the interstitial spaces in neural tissue.

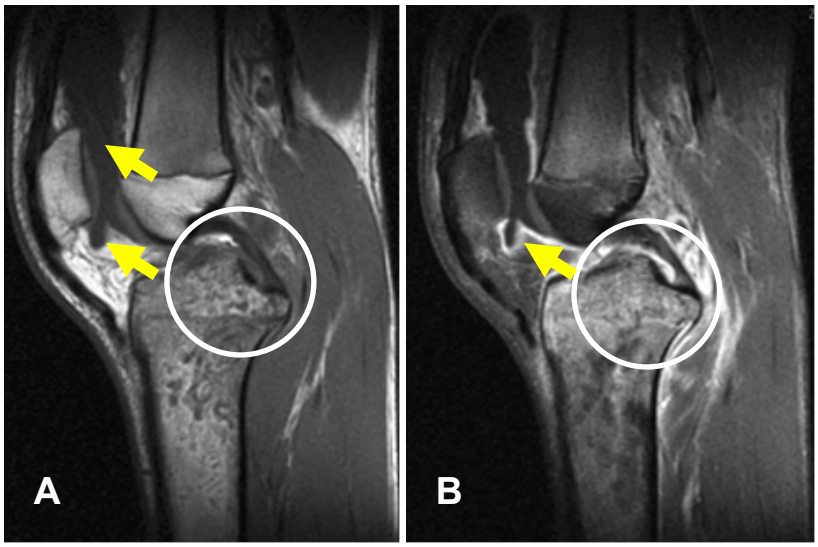


Figure 3. Sagittal T1W image of the knee. (A) Abnormal signal in the tibia and tibial head (circle) with increased fluid posterior and superior to the patella (arrows). (B) Same slice location postcontrast. Note the increased intensity of the tibia and tibial head, indicating bony infection (circle) and enhancement surrounding the fluid posterior and inferior to the patella (arrow).

Courtesy of GE Medical Systems

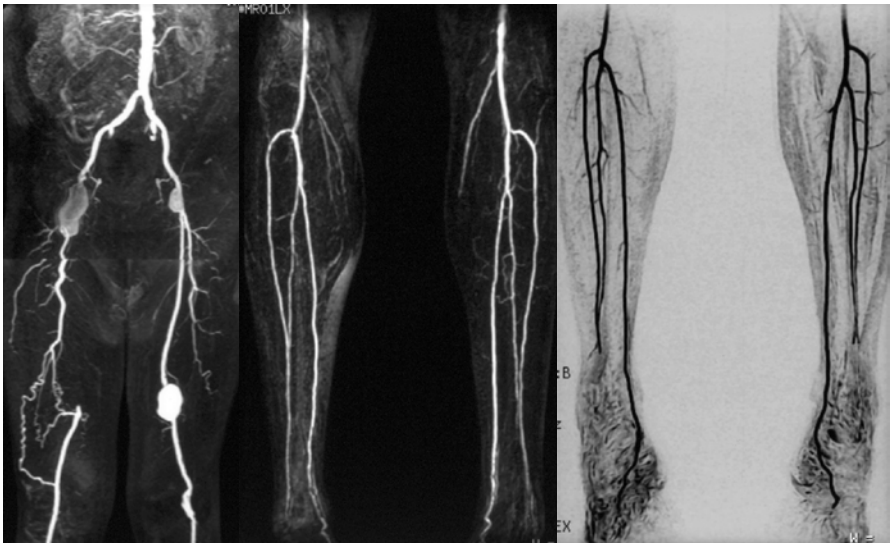


Figure 4. Gadolinium-enhanced MR angiograms of the lower extremities demonstrating peripheral runoff.

Courtesy of Mark Flyer, MD, Maimonides Medical Center

Off-label use

Over the years, radiologists and other physicians have developed many clinical applications for GBCAs not specifically approved by the FDA. Such applications constitute *off-label* use. This includes an array of important, widely used studies: MR angiography, myocardial viability and first pass perfusion imaging, brain perfusion imaging, and contrast-enhanced MR studies in pediatric patients under the age of two. Off-label use of an MRI contrast agent should not necessarily be construed as dangerous to the patient.

Gadolinium chelates are used in the evaluation of nearly all organ systems for the following:

- primary tumors and metastases (**Figures 1** and **2**)
- infectious and inflammatory processes (**Figure 3**)
- vascular anatomy and pathology (**Figures 4** and **5**)

Ionic and Nonionic Contrast Media

As previously discussed, ionic contrast media are pharmaceutical agents that dissociate into positively or negatively charged ions in water or in the bloodstream. Conversely, nonionic pharmaceutical agents have a zero-net charge, remain electrically neutral in water or the bloodstream, and do not dissociate into ions.

Iodinated contrast media used in radiographic angiography and CT imaging are also available as both ionic and nonionic compounds. Most of these agents pre-date the clinical use of MRI contrast agents by many years. Ionic compounds were introduced for radiographic contrast imaging in the early 1950s; nonionic radiographic contrast media were developed later in the mid-to-late1980s.

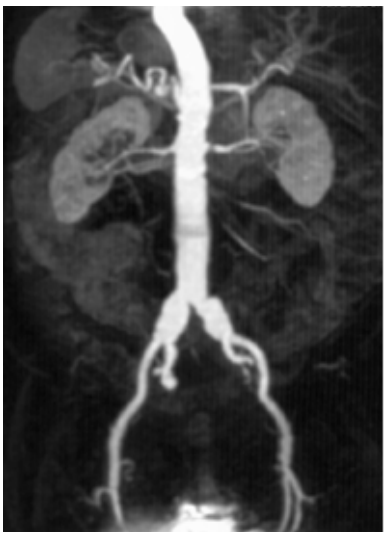


Figure 5. Gadolinium-enhanced MRA of the aortoiliac system.

Courtesy of Mark Flyer, MD
Maimonides Medical Center

Early clinical research on **iodinated** contrast agents revealed that low-**osmolar** nonionic agents were associated with a lower incidence of adverse events. However, these findings do not extrapolate to ionic and nonionic MR contrast agents. The biological mechanisms leading to adverse events from iodinated contrast media are poorly understood. It may not be valid to predict safety characteristics of MR contrast agents based on experience with radiographic contrast agents. Consider the following two points:

1. In practice, the distinction between ionic and nonionic radiographic contrast media is primarily based on differences in **osmolality** and not differences in charge. The absence of charge is important when an iodinated contrast agent is administered **intrathecally** and may be significant during intracoronary injection due to the possibility of charged molecules binding to calcium. Most ionic radiographic contrast agents are hyperosmolar, while nonionic agents are low osmolar. However, this relationship between charge and osmolality does not always hold true. For example, Hexabrix™ (loxaglate meglumine and ioxaglate sodium, Covidien) is a radiographic contrast agent that is ionic with low osmolality.

2. MRI contrast agents have strikingly different molecular structure compared to iodinated contrast media.

The actual incidence of adverse reactions to MRI contrast material is substantially lower than that for ionic or nonionic iodinated contrast materials. Cochran et al found adverse reaction rates of 6%–8% for ionic iodinated contrast agents, 0.2% for nonionic iodinated contrast agents, and 0.07% for gadolinium-based MRI contrast agents.[4] This low rate of adverse events following infusion of gadolinium-based MR contrast agents is supported by other studies.[5-7] Acute adverse events are addressed later in this material.

Osmolality vs Osmotic Load

Osmosis is defined as the diffusion of solvent molecules, such as water, from an area of lower concentration to an area of higher concentration of dissolved substance. The net result is equalization in concentration of the two solutions.

The osmolality of a chemical compound is a measure of its ability to osmose and is related to the number of particles that result when the compound is placed in solution. Osmolality is measured in units of osmoles per kilogram of water, Osm/kg, or milliosmoles per kilogram of water, mOsm/kg.

The actual incidence of adverse reactions to MRI contrast material is substantially lower than that for ionic or nonionic iodinated contrast materials.

Osmolarity is a related factor that is measured in units of osmoles or milliosmoles per liter of solution (mOsm/L). In the dilute biological fluids of the normal human body, the difference between osmolality and osmolarity is minimal, and the terms are often used interchangeably.

To avoid potentially dangerous fluid shifts, a chemical solution administered intravenously to patients should ideally have the same osmolality as that of blood. Normal blood serum osmolarity in adults is 275–300 mOsm/L.

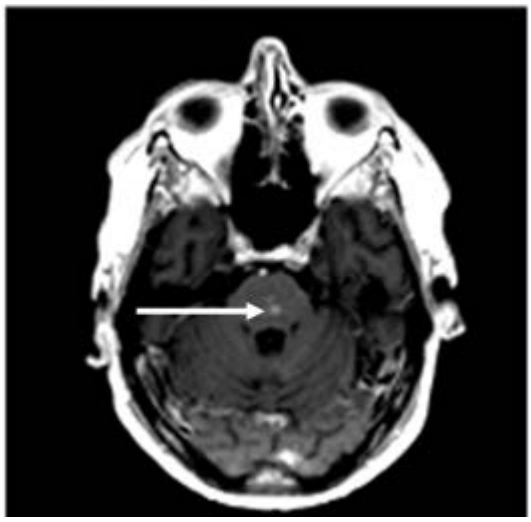


Figure 6. Axial T1W contrast-enhanced image in a 40-year-old male demonstrates a small enhancing lesion indicating central pontine myelinolysis.

Courtesy of Bayer Healthcare

Osmotic load is calculated by multiplying the milliosmoles per unit volume of agent by actual volume injected into patients. Although the osmolality of gadolinium contrast agents ranges widely from 0.688 mOsm/kg (Eovist) to 1970.0 mOsm/kg (MultiHance), the osmotic loads at a standard clinical dose of 0.2ml/kg are small compared to those of iodinated contrast agents used for CT scanning. Again, this is because the effective dose of MR contrast agents is relatively small compared to that of iodinated contrast media.

Use of Gadolinium Chelates in Pregnancy

Several studies have addressed the use and safety of gadolinium chelates in pregnancy.[8-11] All GBCAs cross the placenta and accumulate in the fetal bladder, where the agents are excreted into the amniotic fluid and then swallowed by the fetus, effectively being recirculated.

In practice, gadolinium chelates should be used in pregnancy only if the expected benefit far outweighs the risk. Studies have found that less than 0.04% of administered gadopentetate dimeglumine (Magnevist) is excreted into human breast milk. The amount of contrast ingested by the infant translates to 0.0004% of the total dose given to the mother and less than 0.4% (four 10,000ths) of the amount permitted for a two-year-old child.

There is a theoretical risk of allergic reaction in the infant, but thus far it remains only theoretical as there have been no reported instances of allergic reaction in a breastfeeding infant following GBCA administration to the mother. Therefore, the guidelines from both the American College of Radiology (ACR) and the Food and Drug Administration (FDA) state that it is safe for the child of a breastfeeding mother to ingest the small amount of contrast material present in breast milk. However, if the mother remains concerned about the contrast material passing through breast milk, it is recommended that the mother practice a “pump and dump” protocol for breast milk for 24 hours following injection.[12,13]

Dosing and Administration

Recommended doses of various gadolinium chelates are shown in **Table 4**. These agents are approved for intravenous use only. Injection of gadolinium-based contrast agents should be followed by a saline flush to ensure the entire dose of the contrast agent is pushed through the IV tubing.

When administered at recommended clinical doses, gadolinium chelates do not have the nephrotoxicity of iodinated contrast materials and can therefore be used in patients with impaired renal function, including those on hemodialysis or peritoneal dialysis.

Brand Name	Generic Name	Standard Clinical Dose	Weight Example
Magnevist®	gadopentetate dimeglumine (Gd-DTPA)	0.2ml/kg	110lbs = 10ml
MultiHance®	gadobenate dimeglumine (Gd-BOPTA)	0.2ml/kg	110lbs = 10ml
Omniscan™	gadodiamide (Gd-DTPA-BMA)	0.2ml/kg	110lbs = 10ml
OptiMARK™	gadoversetamide (Gd-DTPA-BMEA)	0.2ml/kg	110lbs = 10ml
ProHance®	gadoteridol (Gd-HP-DO3A)	0.2ml/kg	110lbs = 10ml
Ablavar®	gadofosveset trisodium	0.12ml/kg	110lbs = 13.2ml
Eovist®	gadoxetate disodium	0.1ml/kg	110lbs = 5ml
Gadavist™	gadobutrol	0.1ml/kg	110lbs = 5ml

Table 4. Dosing and administration of GBCAs.[14]

The standard clinical dose for Gadavist, Eovist, and Ablavar are lower than other GBCAs. Because their concentrations are higher — Gadavist, has an osmolality of 1603.0 mOsm/kg, Eovist 0.688 mOsm/kg, and Ablavar 825.0 mOsm/kg — the dosage can be reduced. **Figures 6** and **7** are postcontrast images using Gadavist at the reduced dose.

The reported incidence of adverse reactions for all gadolinium chelates varies greatly from one patient population to the next. The most commonly reported adverse reactions for all agents are headache, nausea, taste alteration, and vertigo. **Extravasation** of gadolinium contrast agents can potentially injure soft tissue if a sufficient volume of the agent leaks into tissue surrounding the injection site. Effects of extravasation are usually transient with mild burning or pain and are rarely more serious, but can include inflammation, ulceration, or skin necrosis. Extravasation is easily preventable through proper injection technique, including careful placement of intravenous access, assurance of good blood return, and proper saline flush following contrast administration.

GENERAL BODY AGENTS

Body-specific contrast agents are categorized into three groups:

- Noncardiac chest, abdomen, and pelvis agents
- Hepatocyte-specific agents
- Oral contrast agents

Noncardiac Chest, Abdomen, and Pelvis Contrast Media

Omniscan (gadodiamide, GE Healthcare) was FDA approved in 1993 for central nervous system indications. FDA approval for Omniscan also includes specific body indications: noncardiac lesions within the thoracic, abdominal and pelvic cavities, as well as in the retroperitoneal space. Like the other contrast agents, Omniscan is approved for adults and pediatric patient ages 2-16. Approved dosage of Omniscan is 0.1mmol/kg. For example, 10ml IV contrast is the dose for a patient weighing 110lbs. The majority of gadodiamide is excreted in urine.[15] The remaining contrast is excreted in feces.

OptiMARK (gadoversetamide, Covidien) was approved by the FDA for use in 1999. It is indicated for visualization of liver lesions with abnormal vascularity. Like Omniscan, OptiMARK is also FDA approved for central nervous system imaging. Similarly, approved dosage is also 0.1mmol/kg and approximately 95% of gadoversetamide is excreted in the urine. OptiMARK differs from other contrast agents in that it comes in preloaded syringes instead of vials. Preloaded syringes deliver exact dosage and reduce the risk of infection at the injection site.[16]

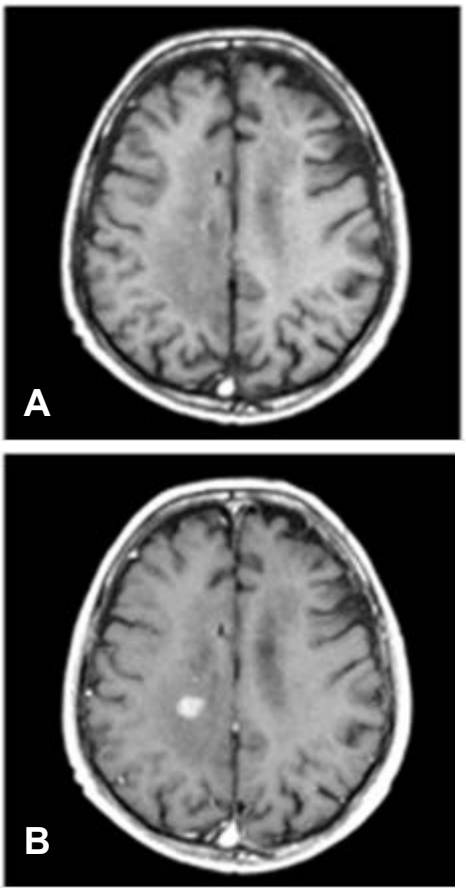


Figure 7. Axial T1W in a 69-year-old male with lymphoma.

(A) Precontrast image.
(B) Postcontrast image demonstrates the enhancing lesion.

Courtesy of Bayer Healthcare

Hepatocyte-Specific Agents

Eovist (gadoxetate disodium, Bayer Healthcare) was approved by the FDA in 2008 for liver imaging to detect and characterize lesions in adults with known or suspected focal disease. Clinically, these are patients with suspected focal nodular hyperplasia (FNH) and hepatocellular carcinoma (HCC).[17]

Eovist is an ionic linear contrast agent with a high degree of relaxivity. Greater relaxivity allows for smaller dosing compared to most other gadolinium-based contrast agents. The dose amount of Eovist is 0.025mmol/kg. For example, a 110lb patient requires only 5ml of contrast compared to the more typical dose of 10ml for a 0.1mmol/kg contrast agent. Fifty percent of Eovist is excreted through the kidneys and the other 50% through the liver.

Hepatocytes are the main cell type in the liver, comprising 70-80% of its mass. They are directly involved in protein synthesis, carbohydrate metabolism, and cholesterol and bile creation. Following injection, Eovist is quickly distributed into the extracellular space. Over time, 50% of the contrast is selectively taken up by hepatocytes intracellularly. This intracellular hepatocyte phase occurs approximately 20 minutes after injection. Liver lesions with functioning hepatocytes appear hypointense, while lesions without functioning hepatocytes appear hyperintense (**Figure 8** and **9**).

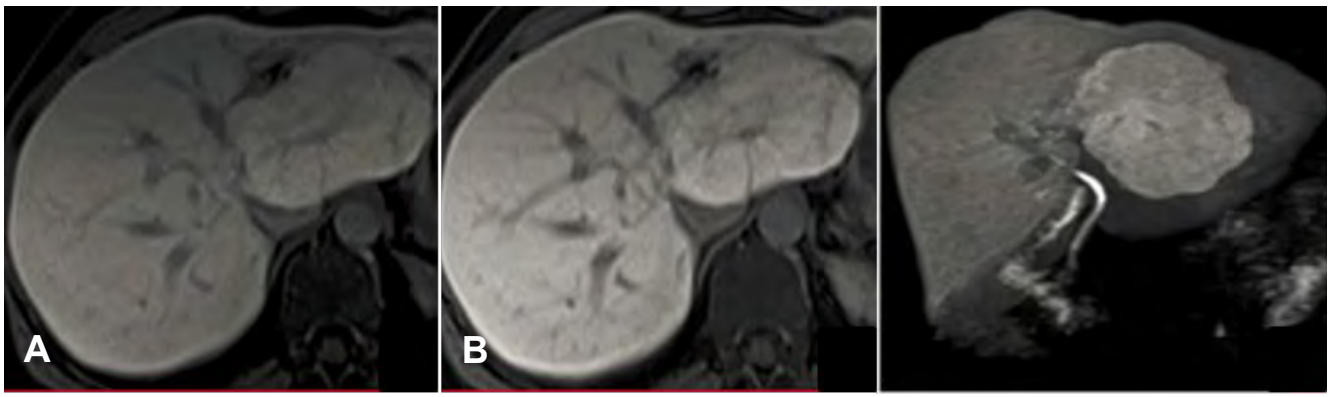


Figure 8. Coronal hepatocyte phase images post-Eovist injection. (A) 10 minutes postcontrast. (B) 20 minutes postcontrast. The lesion is increasingly hyperintense, indicating uptake of Eovist by functioning hepatocytes and ruling out HCC. The central region is unenhanced, consistent with the presence of a central scar typical of FNH.

Figure 9. (Right) Coronal T1 hepatocyte phase MIP 35 seconds post-Eovist injection. Note hyperenhancing mass typical of FNH and the biliary excretion into the common bile duct and duodenum.

Courtesy of Bayer Healthcare

Oral MR Agents

Although several oral MR contrast agents have been approved by the FDA, none of them has been widely applied in clinical practice. In 1993, Imagent GI® (perflubron, Alliance Pharmaceutical Corp.) was the first oral MRI contrast agent approved for human use in the United States. Imagent GI is an inert perfluorocarbon in which all of the hydrogen atoms have been replaced by fluorine atoms and one bromine atom. As a result, Imagent GI produces a signal void within the bowel lumen on T1- and T2-weighted images. Imagent GI moves through the gastrointestinal tract rapidly and has the unfortunate tendency to leak per rectum after oral administration. Along with its relatively high cost, Imagent GI failed to gain clinical acceptance and was withdrawn from the market shortly after its approval.

Lumenhance® (manganese chloride tetrahydrate, Bracco)[18] and FerriSeltz®[19] (ferric ammonium citrate, Otsuka Pharmaceutical Co. Ltd.) were approved as oral MR contrast agents in 1997. Both were primarily T1-shortening agents that produced bright intraluminal signal on T1-weighted images and low signal on T2-weighted images. The clinical efficacy of both agents was limited by a tendency to become diluted as they moved distally beyond the duodenum. Both products have been discontinued.

GastroMARK™ (ferumoxsil, AMAG Pharmaceuticals) was approved in 1996 and is the only oral agent still available in the United States. It is an iron particulate agent similar to ferumoxide (Feridex®, Bayer Healthcare) except that it is formulated for oral use. When administered orally, GastroMARK causes intraluminal signal loss on T1- and T2-weighted images.[20]

There are several explanations for the limited utilization of oral MR contrast. One is their limited efficacy, which explains the continued use of "off the shelf" methods to visualize the bowel on MR images. For example, dilute barium has been used as a reasonably effective method to produce negative contrast in the bowel lumen on T1-and T2-weighted images. Metamucil® (psyllium, Proctor & Gamble) has also been used with some success. The hypertonicity of Metamucil serves to draw water into the colon, thereby distending the bowel lumen and producing low intraluminal signal intensity on T1-weighted images. Both dilute barium and Metamucil have been used in conjunction with intravenous gadolinium chelate administration. The intravenous contrast agent serves to enhance the bowel wall and areas of inflammation, abnormal thickening, or neoplastic involvement of the bowel wall.

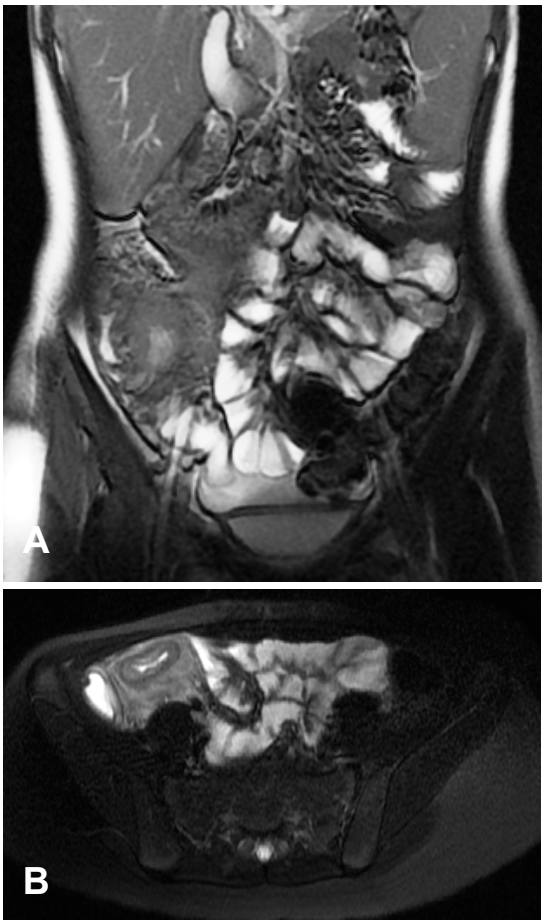


Figure 10. Volumen® used as a positive oral contrast agent in the small bowel.
(A) Coronal FIESTA™ image.
(B) Axial T2W fat-suppressed image.

MR imaging of the small bowel has become effective when using barium sulfate solutions often used in CT as a positive contrast agent. Volumen® (Bracco) has been shown to be an effective and inexpensive positive contrast agent when used for MR imaging of the small bowel because of its high-signal intensity and bowel-coating property (**Figure 10**).

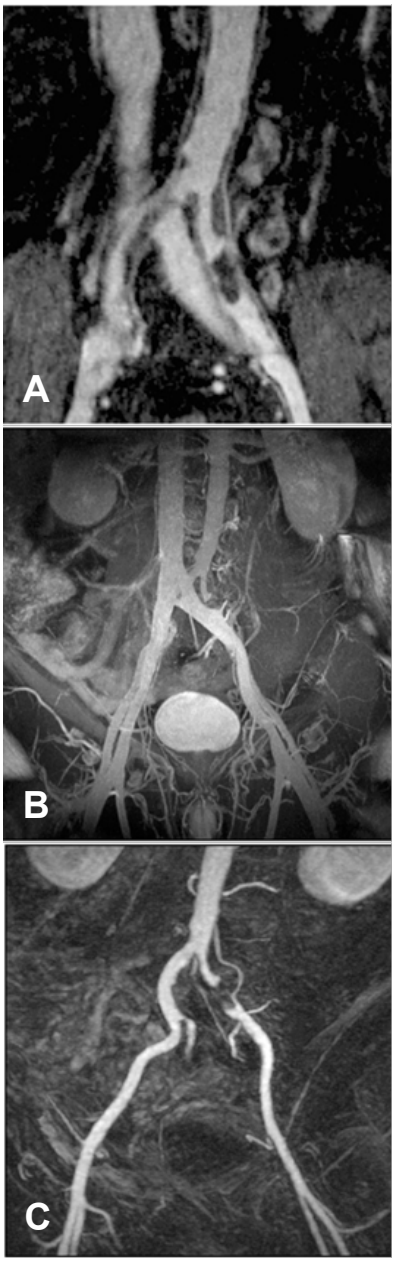


Figure 11. 57-year-old male with aortoiliac disease.

(A) Coronal 2D reformation of 3D MIP.

(B) Coronal 3D MIP venous steady state.

(C) Coronal 3D MIP arterial phase.

For more information, click here. Ablavar.com

Another reason for the limited utilization of oral MR contrast agents is that abdominal MR applications have primarily focused on specific organs. For example, MR imaging is often requested for evaluation of indeterminate lesions in the liver, pancreas, kidneys, or adrenal glands. MR imaging is less often used for general abdominal complaints such as abdominal pain or nausea and vomiting. CT scanning is typically used for these indications, which often require a careful assessment of the gastrointestinal tract in addition to the abdominal organs. However, with the introduction and widespread availability of high quality breath-hold sequences, the volume of abdominal MR examinations has grown, and the clinical indications have broadened. MR imaging is increasingly being used instead of CT to evaluate bowel pathology such as inflammatory bowel disease and malignant conditions. These studies typically involve the use of an intravenous gadolinium chelate, but there is still a need for an effective oral MR contrast agent.

BLOOD POOL AGENTS

Blood pool agents, also known as intravascular agents, have stimulated much interest among radiologists. The advantages of blood pool agents over standard MR contrast agents is that they remain in the blood for a long period of time, providing a large imaging window of opportunity. Currently, the only FDA-approved blood pool agent used for imaging aortoiliac occlusive disease (AIOD) by MRA is Ablavar (gadofosveset trisodium, Lantheus Medical Imaging), formerly known as Vasovist® (gadofosveset trisodium, Bayer Healthcare, Inc.) (**Figure 11**).

The long pooling time of Ablavar is a result of a reversible chemical bond to serum albumin. When bound to albumin, the chemical structure of Ablavar is large enough to prevent ready diffusion out of the capillaries into the extracellular fluid space, resulting in a prolonged half-life within the blood pool. This mechanism also decreases the T1 relaxation time for water protons, permitting the added benefit of using a much lower concentration level. Lantheus Medical recommends a dosage of

0.003mMol/kg, virtually half the dose of most gadolinium-chelate contrast agents. It should be noted that the FDA guidelines for glomerular filtration rate (GFR) to reduce nephrogenic systemic fibrosis (NSF) risk remains the same at 0ml/min/1.73m^2 even for low-concentration contrast agents. Nephrogenic systemic fibrosis is discussed later in this material.

The primary use of Ablavar is for imaging blood vessels. In contrast-enhanced MRA examinations using extracellular gadolinium chelates, arterial phase images are obtained to visualize the target arterial bed. The timing of image acquisition relative to the injection of contrast material is critical to ensure adequate T1 shortening of the blood pool during image acquisition. The use of blood pool agents provides a much broader window during which vascular images can be obtained. Typically an arterial phase image is acquired in the same manner as with a conventional gadolinium chelate. However with Ablavar, a window of several hours follows contrast administration, during which steady-state (or equilibrium phase) images of the vascular system can be acquired. During this time period, high resolution images can be obtained using image acquisition times that are too long for arterial phase imaging. The prolonged blood pool half-life of Ablavar also allows imaging of multiple vascular territories after a single intravenous injection, and high resolution images of the venous system can be acquired.[21]

A potential problem when using any blood pool agent is the overlap of arteries and veins on steady-state images. In most vascular beds, the arterial and venous anatomy is relatively straightforward, and overlap does not occur. However, in some vascular territories, eg, below the knees, overlap could be confusing.

POTENTIAL ADVERSE EVENTS

Although rare, GBCA administration can result in three types of adverse events:

- Nephrogenic Systemic Fibrosis
- Acute Adverse Events
- Spurious Hypocalcemia

Nephrogenic Systemic Fibrosis

Nephrogenic Systemic Fibrosis (NSF) is a potentially serious adverse reaction to intravenously administered gadolinium chelates. The first case of NSF was recognized in California in 1997 and published in 2000.

In 2006, the Food and Drug Administration issued a warning regarding the link between NSF and gadolinium exposure.[22] As of February 2009, there have been 584 reported cases of single-agent NSF globally (**Table 5**). While the number of cases is large enough to justify action, when compared to the millions of patients that have safely received gadolinium-based contrast agents, the incidence of NSF is extremely rare.

No patient with normal kidney function has ever been reported to have acquired NSF following administration of gadolinium-based contrast agents.

Symptoms

Typical symptoms of NSF begin with mild to moderate swelling of the distal extremities followed several weeks later by **induration** of the skin (**Figures 12-14**). Induration of this nature can be extremely painful to the patient and cause significant loss of skin flexibility. Acute disability commonly follows to the point where the patient becomes wheelchair-bound. Internal organs such as the liver, heart, and lungs are often involved and are believed to account for the significant mortality rate of NSF patients.[23]

NSF is reported almost exclusively in patients with severe, Stage 5 chronic kidney disease (CKD), although a very small number of NSF cases have been noted in Stage 3 and 4 CKD. No patient with normal kidney function has ever been reported to have acquired NSF following administration of a gadolinium-based contrast agent.[24] Because the mortality rate among patients with Stage 5 CKD is significant, determining a precise mortality rate of victims of NSF is not easily discernible because a cardiovascular event is typically the primary cause of death in both Stage 5 CKD patients and NSF patients.[25]

Agent	# Reported Cases	Doses Given (in millions)
Omniscan™	438	47
Magnevist®	135	95
OptiMARK™	7	0.8
Gadavist™	2	6.0*
Prohance®	1	12.3
MultiHance®	0	6.0
Ablavar®	0	0.05
Eovist®	0	0.15

*up to Oct 2010 vs Feb 2009 for the others

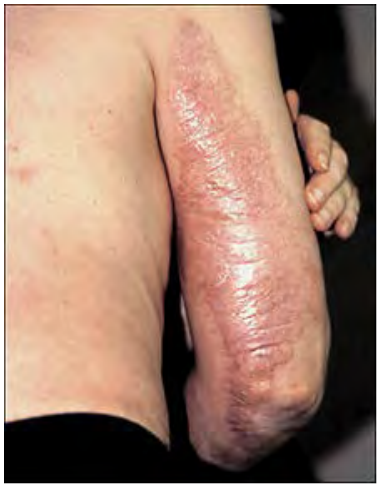
Table 5. Reported cases of NSF per GBCA dose in millions.

Epidemiology

As described earlier, there are several manufacturers of FDA-approved gadolinium-based chelates on the market. Magnevist (ionic) and Omniscan (nonionic) are by far the most frequently used in the U.S. and are therefore most often associated with NSF. Of the two, Omniscan accounts for the majority of NSF cases.[26]

Again, it is important to note that no other patient factor other than CKD has been associated with NSF. Neither race, gender, age, timing of dialysis treatment, nor renal transplantation appears to be a factor in patients with Stage 5 CKD who develop NSF.[27]

Why does NSF occur? It is believed that after the administration of GBCAs to patients with CKD, gadolinium can be become separated from its chelate. Once separated, free-roaming gadolinium accumulates in the soft tissues. Within approximately 24 hours, free gadolinium interacts with monocytes and macrophages to produce profibrotic **cytokines**. The cytokines are believed to bind to their cognate receptors to stimulate the overproduction of collagen, thus leading to the observable manifestations of nephrogenic systemic fibrosis. Confirmation of the diagnosis of NSF comes from observation of clinical symptoms, history of gadolinium exposure, and deep skin biopsy indicating gadolinium in the soft tissues and collagen bundles. There is no laboratory test for NSF.[28]



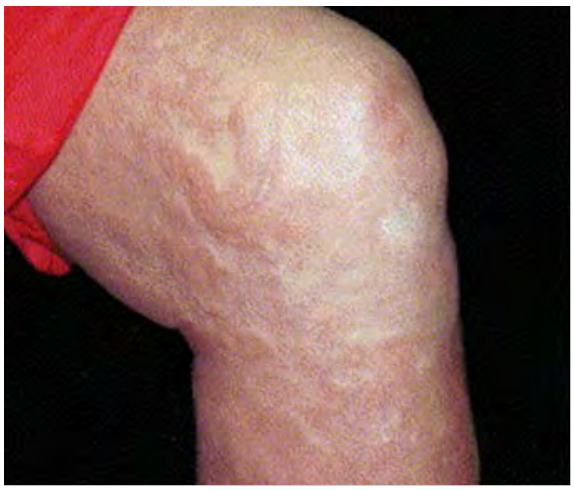


Figure 12. (Left) Sclerotic plaque on the back of the upper arm of a patient demonstrates induration of the skin typical of NSF. For more Information, click here. Uremic Frost

Figure 13. (Right) Typical "orange peel" appearance and induration of the thigh, knee, and upper calf of a patient with NSF For more information, click here. Internal Medicine News

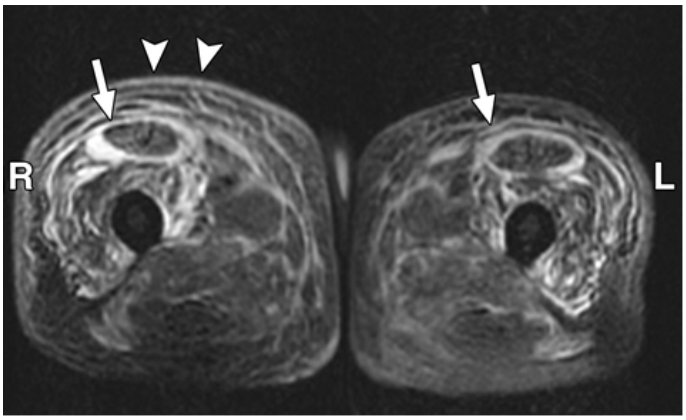


Figure 14. Axial T2W image with fat suppression of the left and right thighs demonstrates dermal thickening (arrow heads) and edema and inflammatory changes in the skeletal muscles (arrows) consistent with NSF.

For more information, click here.
American Journal of Roentgenology

Treatment

There are no known accepted effective treatments for NSF. However, there have been reported cases of spontaneous recovery and positive effects from attempted treatment with oral and topical corticosteroids. Other attempted treatment methods have included oral thalidomide, pentoxifylline, and IV sodium thiosulfate. While each of these attempts has demonstrated positive results in small samples of NSF patients, none has shown enough of a statistically significant benefit to be considered an effective NSF treatment protocol. There is no prophylactic treatment for NSF.[29]

Year	Event
1988	FDA approval for gadopentetate dimeglumine (Magnevist)
1991	ASRT proposes that administration of contrast media is within the scope of practice of radiologic technologists
1992	FDA approval for gadoteridol (ProHance)
1993	FDA approval for gadodiamide (Omniscan)
1997	First case of NSF identified
1999	FDA approval for gadoversetamide (OptiMARK)
2000	First report of 15 patients with NSF
2003	GE Healthcare purchases Nycomed/Amersham
2004	FDA approval for gadobenate dimeglumine (MultiHance)
2005	GE Healthcare and Novation sign agreement for injectable contrast media
2006	Gadolinium “trigger” proposed for NSF
2007	FDA calls for “boxed warning” for gadolinium-based contrast agents
2008	First lawsuit alleging that “[T]he chemical make-up of Omniscan makes it more likely that gadolinium will become free within the bodies of recipients, thereby making it more likely that kidney patients will develop NSF”

Table 6. MR Contrast Agent and Nephrogenic Systemic Fibrosis Timeline[31]

Warning: Nephrogenic Systemic Fibrosis

Gadolinium-based contrast agents increase the risk for nephrogenic systemic fibrosis (NSF) in patients with:

- acute or chronic severe renal insufficiency (glomerular filtration rate <30ml/min/1.73m^2) **or**
- acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.

In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle and internal organs.

Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any readministration.

Prevention

To prevent the onset of NSF, the Food and Drug Administration, along with other global government health agencies, has provided guidelines to identify those patients at risk for NSF. Since NSF is known to affect patients with severe CKD and the mechanism for the onset of NSF is the separation of gadolinium from its chelate, it is logical to identify and distinguish those patients based on measured kidney health. Thus, in 2007, the FDA issued a black box warning on all gadolinium-based contrast agents.[30]

Today, all MR facilities follow procedures to measure the GFR in at-risk patients prior to IV gadolinium administration. Since these guidelines were issued, the reported cases of NSF have been virtually zero. In addition to identifying patients at risk for NSF, some gadolinium-based IV contrast manufacturers have developed IV contrasts with lower gadolinium concentration, as discussed earlier. **Table 6** shows the timeline of GBCA approval and first documented case of NSF.

Acute Adverse Events

Developing nephrogenic systemic fibrosis is not the only risk of gadolinium-based contrast agent administration. While also rare, acute adverse events can occur. These adverse events range from very mild side effects, which are non-allergic events, to more serious allergic reactions that require medical intervention (**Table 7**). A “side effect” is *predictable* and can be desirable or undesirable even with correct dosage. A “reaction” is *unintended and harmful*, even with correct dosage. It is important that the MRI technical staff be prepared to differentiate between mild side effects and more serious reactions and be able to manage each type of adverse event.

Mild Side Effects/ Reactions	Moderate Reactions	Severe Reactions
Nausea, vomiting*	Tachycardia/bradycardia	Laryngeal edema
Altered taste*	Bronchospasm, wheezing	Convulsions (severe or rapidly progressing)
Sweats***	Hypertension	Profound hypotension
Cough***	Laryngeal edema	Unresponsiveness
Itching**	Generalized or diffuse erythema	Clinically manifest arrhythmias
Rash, hives**	Mild hypotension	Cardiopulmonary arrest
Warmth***	Dyspnea	Death†
Pallor (paling of the skin)***		
Nasal stuffiness**		
Headache***		
Flushing/swelling of eyes, face***		
Dizziness***		
Chills***		
Anxiety***		
Shaking***		

* *side effect*
** *reaction*
*** *side effect or reaction*
† *not listed but presumed*

Table 7. ACR Categories of Reactions to GBCAs.[32]

Moderate to severe acute adverse reactions to GBCAs are similar to reactions experienced from administration of iodinated contrast. MRI technical staff must be trained in recognizing adverse effects and have on-site equipment and medications available and ready. Typically, patients are immediately transported out of the imaging room so that equipment used for patient monitoring and treatment do not become magnetic missiles, endangering the patient and staff.[33]

The FDA requires that all adverse events associated with gadolinium administration be reported into an Adverse Event Reporting System (AERS), also known as MedWatch. The reports are made available on a quarterly basis for public review.[34]

Excluding NSF, there were a total of 40 deaths attributable to GBCA administration reported to the FDA from 2004-2009. While unforeseen and tragic, this translates to a death rate of less than one in one million GBCA administrations. Most if not all deaths were due to allergic, anaphylactoid, anaphylaxis, or hypersensitivity-type reactions.[35]

Risk factors

To prevent patients from experiencing a negative reaction to gadolinium administration, these risk factors should be considered prior to the scan:[36]

- Previous reaction to GBCA
- History of asthma, beyond seasonal
- History of allergies, particularly to aspirin
- Previous allergic reactions to iodinated contrast agents
- Tenuous health; may not survive anaphylactic shock

ACR Guidelines

The American College of Radiology offers these contrast reaction treatment guidelines[37]:

- Rapid recognition, assessment, and diagnosis
- Competent personnel capable of cardiopulmonary resuscitation and/or advanced cardiac life support
- Oxygen, IV, continuous monitoring, epinephrine at a concentration of 0.3 mg

While GBCAs are extraordinarily safe and most acute reactions are mild, severe reactions can be life-threatening. MRI personnel must remain vigilant when administering gadolinium, especially to at-risk patients.[38]

Spurious Hypocalcemia

Two of the extracellular gadolinium contrast agents approved in the United States — gadodiamide (Omniscan) and gadoversetamide (OptiMARK) — can cause temporary reductions in laboratory serum calcium measurements over the 24-hour period after contrast administration. The reductions in reported serum calcium levels are artifactual, that is, they are not the result of true reduction in calcium levels in the body but of false values reported when a colorimetric assay is used to measure serum calcium postcontrast administration. Such false readings may increase the risk for a number of adverse outcomes for both patient and healthcare provider, including errors in diagnosis, inappropriate treatment, and increased healthcare costs.

The main risk associated with **spurious** hypocalcemia is that a patient could be erroneously diagnosed with low serum calcium and treated with unnecessary and perhaps even life-threatening interventions. There have been several documented cases of patients incorrectly treated with oral calcium supplements or intravenously administered calcium due to falsely lowered measurements of serum calcium.[39] The actual prevalence of inappropriate therapy due to spurious hypocalcemia is unknown because the majority of patients at risk have not been identified or adequately followed.

Steps can be taken to minimize the risks associated with spurious hypocalcemia and spurious normocalcemia. Increasing the awareness of the problem through education obviously reduces such risk. Some clinical laboratories have implemented a policy whereby serum calcium measurements are repeated in patients with hypocalcemia detected within 24 hours after a contrast-enhanced MR examination. The simplest solution is to use a contrast agent that does not interfere with the colorimetric serum calcium assay or to inform the patient of the potential for artificially altered serum calcium levels if they undergo laboratory blood tests within 24 hours of contrast administration.

SUMMARY

MRI remains a critical imaging modality in the characterization of normal tissue and the diagnosis of most abnormal conditions and disease states. The use of gadolinium-based contrast agents enhances the conspicuity of pathology with MRI. GBCAs continue to be used safely, and since the implementation of FDA guidelines in 2007, there have been no reported cases of NSF. Gadolinium administration remains a safe and effective adjunct to high-quality diagnostic MR imaging.

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GLOSSARY

chelate
the formation or presence of two or more separate coordinate bonds between a multiple bonded ligand and a single central atom; used in the synthesis of gadolinium contrast agents to make them effective and safe

cytokine
any of various proteins, secreted by cells, that carry signals to neighboring cells

extracellular
literally, outside the cell as compared to *intracellular* or inside the cell

extravasation
escape of fluids from a vessel into surrounding tissues. In giving IV gadolinium contrast, extravasation occurs when some of the contrast material leaks out of the vessel into the surrounding soft tissues. While not a safety concern, extravasation irritates the tissues and can be painful.

hepatocyte
the liver's main cell type that comprises 70-80% of the liver's mass

iodinated contrast/iodine
a nonmetallic chemical element with an atomic weight of 53. Its high atomic weight makes it the most widely used element in CT contrast agents.

ion/ionic
a negatively or positively charged atom or molecule

induration
hardening or thickening of the skin

intrathecal/intrathecally
an injection into the spinal canal (intrathecal space surrounding the spinal cord)

ligand
an ion or molecule that binds to a central metal atom

linear contrast agent
a structural class of GBCA chelates that binds gadolinium ions with a chain structure

macrocyclic contrast agent
a structural class of GBCA chelates that binds atoms around a chemically-bound metal ion

nonionic
an atom that is neither negatively nor positively charged but is neutral

osmolality
measured in units of osmoles per kilogram of water or milliosmoles per kilogram of water; a measure of the ability of a chemical compound to cause osmosis

osmolarity
measured in units of osmoles or milliosmoles per liter of solution

osmosis
the diffusion of solvent molecules, such as water, from an area of lower concentration of dissolved substance to an area of higher concentration of dissolved substance; the net result is that the concentrations of the two solutions equalize

paramagnetic
an element that is slightly attracted to a magnetic field yet not ferrous, eg, gadolinium, which amplifies the external magnetic field produced by the MRI system

relaxivity
the ability, expressed numerically, of a GBCA to cause T1 relaxation in tissues that come in close proximity to the contrast material. The higher the numeric value, the greater the relaxivity, resulting in brighter signal from the tissue as compared to lower values.

spurious
not genuine or authentic; as used in *spurious hypocalcemia*, a falsely depressed calcium level

ABBREVIATIONS OF TERMS

ACR	American College of Radiology
AERS	Adverse Event Reporting System
AIOD	aortoiliac occlusive disease
CKD	chronic kidney disease
FDA	Food and Drug Administration
FNH	focal nodular hyperplasia
GBCA	gadolinium-based contrast agent
GFR	glomerular filtration rate
HCC	hepatocellular carcinoma
MRA	magnetic resonance angiogram/angiography
NSF	nephrogenic systemic fibrosis
Osm/kg	osmoles/kilogram of water
mOsm/kg	milliosmoles per kilogram of water
r_1	T1 relaxivity
r_2	T2 relaxivity
T2*	T2 star