MRI for Technologists

Gadolinium-based Contrast Agents: Physicochemical Properties and Applications

PROGRAM INFORMATION

MRI for Technologists is a training program designed to meet the needs of radiologic technologists entering 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.

Original Release Date: **December 2013**
Expiration Date: **January 1, 2019**

This material will be reviewed for continued accuracy and relevance. Please go to www.icpme.us for up-to-date information regarding current expiration dates.

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.

Gadolinium-based Contrast Agents: Physicochemical Properties and Applications introduces the learner to the chemical properties of the nine currently FDA-approved MRI contrast agents, as well as why the physical characteristics of gadolinium make this rare earth metal ideal for use as an MRI contrast agent. The attributes of thermodynamics and kinetics are visualized to demonstrate the relationship between the gadolinium ion and its chelates. The critical concept of relaxivity is explained as well as its impact on image quality. Differences between older and new gadolinium-based contrast agents (GBCAs) will be discussed, their safety profiles reviewed, and imaging applications for each agent explained. Acute and delayed reactions to GBCAs are addressed, including clinical management of minor to serious events.

A note regarding off-label use of GBCAs:
Radiologists commonly use contrast media for a clinical purpose not contained in the labeling and thus commonly use contrast media off-label. By definition, such usage is not approved by the Food and Drug Administration. However, physicians have some latitude in using gadolinium chelates off label as guided by clinical circumstances, as long as they can justify such usage in individual cases. Examples include MR angiography, cardiac applications, and pediatric applications in patients younger than two years of age. In addition, no gadolinium chelate is approved in the United States for use in a power injector.

American College of Radiology website. ACR Manual on Contrast Media v9 2013.

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

- Describe the role of gadolinium-based contrast agents (GBCAs) in visualization of anatomy and differentiation of pathology from normal tissue
- Define the physicochemical similarities and differences between first generation and second generation GBCAs
- Explain the concept of relaxivity and how this chemical characteristic affects image quality
- Discuss how thermodynamic stability and kinetics affect the efficacy and safety profile of a GBCA
- Explain patient assessment and management in the event of an acute or delayed reaction to the intravenous administration of a GBCA

EDUCATIONAL CREDIT

This program has been approved by the American Society of Radiologic Technologists (ASRT) for 1.5 hours ARRT Category A+ continuing education credit.

HOW TO RECEIVE CREDIT

Estimated time to complete this activity is 1.5 hours. The posttest and evaluation are required to receive credit and must be completed online.

- In order to access the posttest and evaluation, enroll in the online course at icpme.us
- Read the entire activity.
- Log in to your account at icpme.us to complete the posttest and evaluation, accessible through the course link in your account.
- 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 be able to print a certificate of credit from your online account.

FACULTY

Peter Caravan, PhD
Associate Professor of Radiology
Harvard Medical School
Associate Director, Institute for Innovation in Imaging
Massachusetts General Hospital

Dr. Caravan received his BSc with honors from Acadia University and his PhD in chemistry from the University of British Columbia. His post-doctoral research was performed at Université de Lausanne.

Dr. Caravan has more than 15 years of academic and industrial experience in the design, synthesis, and evaluation of targeted imaging probes. Before joining Harvard Medical School and MGH, Dr. Caravan spent several years at Epix Pharmaceuticals developing tissue-specific MRI contrast agents and was ultimately responsible for all contrast agent research. He has published over 90 peer-reviewed articles on the chemistry, biophysics, and applications of imaging probes.

Dr. Caravan has contributed a highly cited review (>2000 citations) on the chemistry of gadolinium-based contrast agents as well as written several book chapters on the properties and applications of contrast agents.

Alexander Guimaraes, MD, PhD
Assistant Professor of Radiology
Harvard Medical School
Associate Radiologist
Medical Director, Martinos Center for Biomedical Imaging
Massachusetts General Hospital

Dr. Guimaraes received his MD at Harvard Medicine School and PhD at Massachusetts Institute of Technology. Both his radiology residency and fellowship were completed at Massachusetts General Hospital.

Dr. Guimaraes specializes in the both the clinical and research aspects of gastrointestinal cancers, including liver and pancreatic cancer.

His research interests are developing, analyzing, and translating novel magnetic resonance pulse sequence paradigms and applying novel targeted contrast agents for the goal of better means of quantifying angiogenesis and other relevant biomarkers in both cancer models and in humans undergoing clinical trials. These interests stem from his scientific background in magnetic resonance imaging pulse sequence design and clinical background in abdominal imaging.

Dr. Guimaraes performed post-doctoral training at the Center for Molecular Imaging Research at MGH as a clinical investigator and a member of both the mouse imaging programs and clinical discovery programs. This afforded him the unique opportunity to apply and translate novel targeted contrast agents and to develop and translate novel pulse sequence algorithms from animal models to humans suffering with cancer.

Dr. Guimaraes is now leading translational efforts at defining imaging biomarkers of therapeutic response to cancer. He is focusing on a better understanding of the relationship to tumor microvasculature, drug delivery, and targeted agents that modulate the tumor microenvironment.

ACKNOWLEDGMENT

Our thanks to Tom Schrack, BS, ARMRIT, Manager, MR Education and Technical Development, Fairfax Radiological Consultants in Fairfax, VA for his review of this material.

SPONSORED BY

icpme
Your Partner in Medical Education

SUPPORTED BY AN EDUCATIONAL GRANT FROM

BAYER Bayer HealthCare Pharmaceuticals

DISCLAIMER

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

MRI FOR TECHNOLOGISTS

Gadolinium-based Contrast Agents: Physicochemical Properties and Applications

*Please note: items in **bold** can be found in the glossary.*

After completing this material, the reader should be able to:

- Describe the role of gadolinium-based contrast agents (GBCAs) in visualization of anatomy and differentiation of pathology from normal tissue
- Define the physicochemical similarities and differences between first generation and second generation GBCAs
- Explain the concept of relaxivity and how this chemical characteristic affects image quality
- Discuss how thermodynamic stability and kinetics affect the efficacy and safety profile of a GBCA
- Explain patient assessment and management in the event of an acute or delayed reaction to the intravenous administration of a GBCA

INTRODUCTION

The use of gadolinium-based contrast agents has become an essential component of tissue visualization, revolutionizing the field of magnetic resonance imaging (MRI). Administering a GBCA helps identify and characterize normal anatomy and increase the conspicuity of lesions, abscesses, infection, and inflammation. Contrast media also improve visualization of arterial and venous anatomy and pathology.

To appreciate how the addition of a gadolinium-based contrast agent adds value to the MRI exam, the physicochemical properties of current FDA-approved agents, their similarities and differences, clinical indications, and safety profiles and precautions will be addressed.

A note regarding off-label use of GBCAs:

Radiologists commonly use contrast media for a clinical purpose not contained in the labeling and thus commonly use contrast media off-label. By definition, such usage is not approved by the Food and Drug Administration. However, physicians have some latitude in using gadolinium chelates off label as guided by clinical circumstances, as long as they can justify such usage in individual cases. Examples include MR angiography, cardiac applications, and pediatric applications in patients younger than two years of age. In addition, no gadolinium chelate is approved in the United States for use in a power injector.

American College of Radiology website. ACR Manual on Contrast Media v9 2013.

THE ROLE OF GBCAs IN MRI EXAMINATIONS

The science and art of magnetic resonance imaging are based on the acquisition of high-quality diagnostic images that depict contrast between normal and abnormal tissues for visualization of disease. Since noncontrast-enhanced MRI is noninvasive and produces high-quality diagnostic images, what is the value of introducing a GBCA to the MRI exam?

Visualization of Pathology

Gadolinium-based contrast agents allow the exploitation of physiological changes in tissue caused by disease. Studies suggest that 30-60% of all MRI exams employ the use of a GBCA to aid in the visualization of pathology[1,2]. GBCAs can be grouped into three categories: extracellular agents, blood pool agents, and liver-specific agents.

Extracellular contrast agents (ECFs) improve both image quality and tissue contrast, useful for characterizing lesions based on altered blood flow, **perfusion**, or leakiness in the microvascularity. Given that MRI is often used for imaging the central nervous system (CNS), gadolinium-based contrast agents are extremely useful for evaluating changes in the **blood brain barrier** (BBB) as well as evaluation of vascular **morphology** (**Figure 1**).

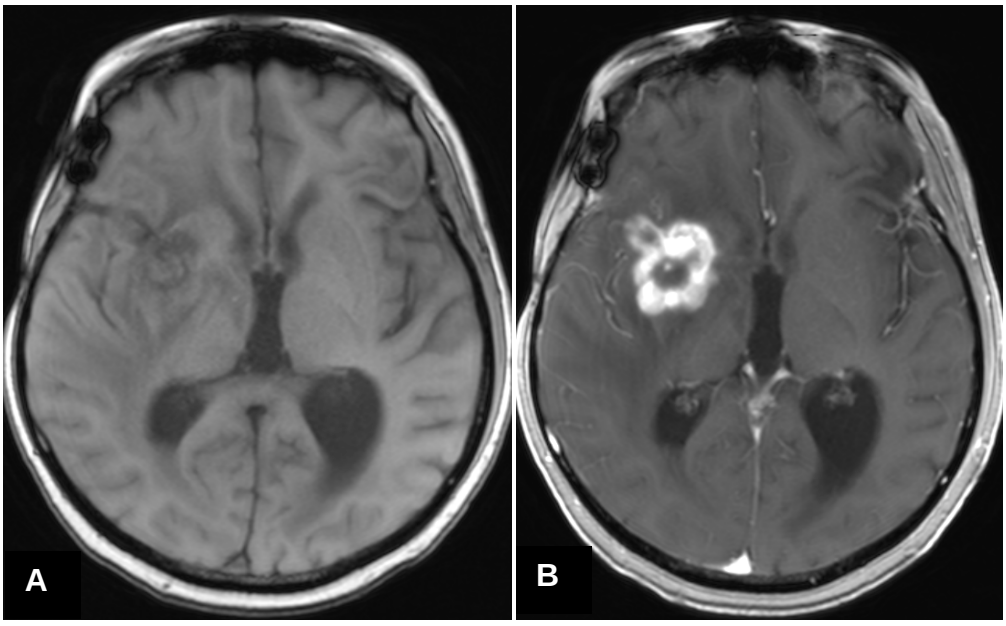


Figure 1. Breast cancer metastasis to the brain. (A) Precontrast axial T1W image shows a subtle change in mass effect compared to the contralateral hemisphere. (B) Postcontrast axial T1W image. The lesion causes leakiness in the BBB allowing it to take up the GBCA, resulting in enhancement. The lesion is very bright compared to surrounding tissue, therefore easily visualized.

Courtesy of A. Guimaraes, MD, PhD. MGH Department of Radiology.

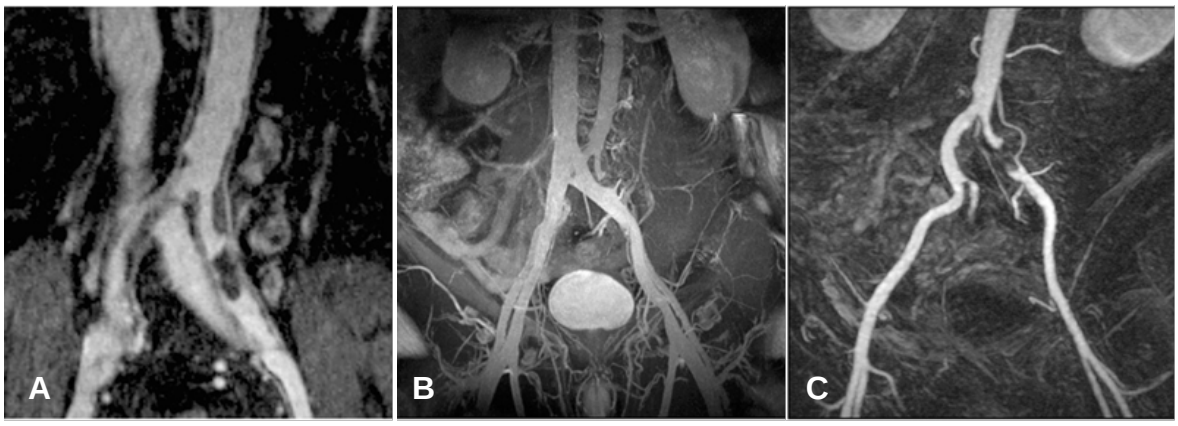


Figure 2. A 57-year-old male with aortoiliac disease. (A) Coronal 2D reformation of 3D MIP. (B) Coronal 3D MIP venous steady state. (C) Coronal 3D MIP arterial phase.

Courtesy of Lantheus Medical.

Blood pool agents persist within the blood pool and are used for visualizing pathology within the leaky blood brain barrier, assessing **stenotic** vessels, and differentiating hypervascular from nonvascular lesions (**Figure 2**).

Liver-specific agents are selectively taken up by **hepatocytes,** resulting in increased signal intensity in liver tissue. Lesions with no or minimal hepatocyte function (cysts, metastases, and the majority of hepatocellular carcinomas) generally will not take up a liver-specific agent, which helps differentiate liver lesions from normal tissue. Liver-specific agents also help assess biliary anatomy (**Figure 3**).

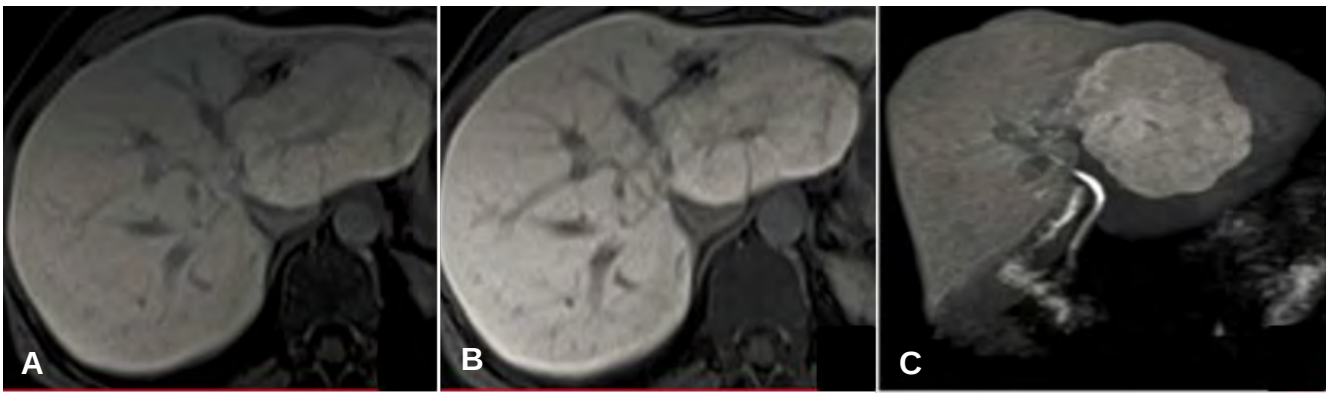


Figure 3. Coronal hepatocyte phase images post-Eovist injection. (A) 10 minutes postcontrast. (B) 20 minutes postcontrast. The lesion is increasingly hyperintense, indicating uptake of Eovist by functioning hepatocytes and ruling out hepatocellular carcinoma *(*HCC). The central region is unenhanced, consistent with the presence of a central scar typical of focal nodular hyperplasia (FNH). (C) 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 Pharmaceuticals.

CLASSIFICATION OF GADOLINIUM-BASED CONTRAST AGENTS

Extracellular Fluid Agents

The names of the FDA-approved extracellular fluid contrast agents can be confusing. Generically they all sound the same – gadobutrol, gadopentetate, gadodiamide, gadoversetamide, gadoteridol, and gadoterate. Typically they are referred to as "gad", "gado", or simply "contrast." Sometimes they are referred by their chemical name, for instance, Magnevist, which is often referred to as Gd-DPTA. **Table 1** lists the trade, generic, and chemical names of these six FDA-approved ECF contrast agents.

Trade Name	Generic Name	Chemical Name
Dotarem®	gadoterate meglumine	Gd-DOTA
Gadavist®	gadobutrol	Gd-BT-DO3A
Magnevist®	gadopentetate dimeglumine	Gd-DTPA
Omniscan™	gadodiamide	Gd-DTPA-BMA
OptiMARK™	gadoversetamide	Gd-DTPA-BMEA
ProHance®	gadoteridol	Gd-HP-DO3A

Table 1. Extracellular Contrast Agents. Note: MultiHance is identified as an ECF agent by the manufacturer but because the agent is excreted by both the renal and hepatobiliary systems, MultiHance is not included in this list.

Trade Name	Manufacturer	Approval Date
Magnevist	Bayer Healthcare Pharmaceuticals	1988
Omniscan	GE Healthcare	1993
OptiMARK	Mallinckrodt	1999
ProHance	Bracco	1992

Table 2. First generation GBCAs.

First Generation GBCAs

The FDA approved the first four gadolinium-based contrast agents in the late 1980s and early 1990s. They are referred to as "first generation" contrast agents and share similar characteristics (**Table 2**). They are all extracellular fluid agents and approved at a dose of 0.1mmol/kg (body weight). First generation GBCAs are eliminated exclusively through the kidneys. They have similar relaxivity and pharmacokinetics, and the same distribution, clearance rate, and signal-enhancing properties, which result in similar imaging efficacy.

Brand Name	Generic Name	Manufacturer	Approval Date
MultiHance®	gadobenate dimeglumine	Bracco	2004
Ablavar®	gadofosveset trisodium	Lantheus Medical	2008
Eovist®	gadoxetate disodium	Bayer Healthcare Pharmaceuticals	2008
Gadavist®	gadobutrol	Bayer Healthcare Pharmaceuticals	2011
Dotarem®	gadoterate meglumine	Guerbet	2013

Table 3. Second generation GBCAs, by date of release.

Second Generation GBCAs

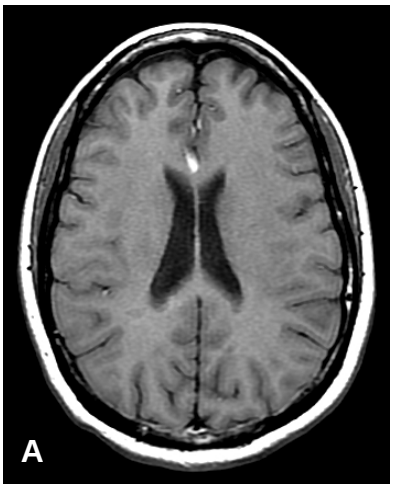
After the success of the first generation GBCAs, newer agents were developed with different pharmacokinetics and distribution properties. Additionally, these newer agents have diverse relaxivity characteristics, and in some cases, the approved dose varies from first generation contrast agents (**Table 3**).

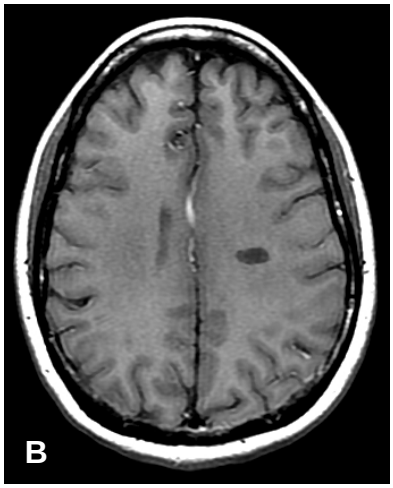
PROPERTIES OF GADOLINIUM-BASED CONTRAST AGENTS

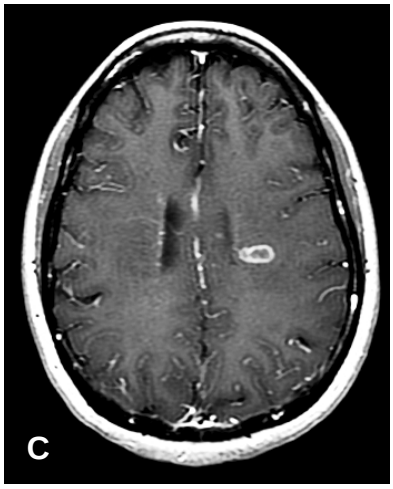
Similarities of GBCAs

Although development of gadolinium-based contrast agents continues to evolve, first and second generation share the following characteristics:

- All gadolinium-based contrast agents are **hydrophilic**, meaning “water loving.” They are extremely water **soluble** and partition into water as opposed to fat.
- All gadolinium-based contrast agents use an octadentate **chelator** (eight chemical bonds) to bind the gadolinium ion. The element, gadolinium, is a rare earth metal and toxic to the human body. The GBCA chelator strongly binds to the gadolinium ion to prevent its release into the body, allowing the gadolinium compound to be excreted intact.
- The chemical structure of gadolinium-based contrast agents varies, but each has one open site that allows for water to bind to the gadolinium ion, resulting in relaxation of the water molecule.







Differences among GBCAs

There are several factors that differentiate GBCAs:

Ionicity

There are two classifications of GBCAs: electrically-charged ionic compounds and nonionic which carry no net charge. The ionicity of a GBCA impacts the concentration and **osmolality** at which the contrast agent is formulated.

Chelation

The word “chelate” comes from Greek meaning “claw.” All gadolinium-based contrast agents are compounds bound with an octadentate chelator, but there are differences in the type of chelation used.

There are two types of chelation used in formulating gadolinium-based contrast agents: linear (acyclic) chelators based on DTPA and cyclic (macrocyclic) chelators based on DOTA. The degree to which the chelator binds to the gadolinium ion varies, and the rate at which free gadolinium can be released *in vivo* depends on the chemical structure of the contrast agent and type of chelator used.

Relaxivity

Relaxivity is the mechanism that produces tissue contrast, allowing the radiologist to not only better visualize but also to *characterize* abnormalities (**Figure 4**). Image quality is dependent upon the degree of relaxivity of the contrast agent, and gadolinium has proven to be efficient for producing relaxation in tissues in MRI.

Figure 4. Axial brain images. (A) Standard T1W-image. Fat is bright because it has a short T1; CSF is dark because it has a very long T1. (B) Precontrast T1W-image. (C) Postcontrast T1W enhancement of a metastatic tumor, demonstrating the extremely short T1 of the lesion.

Courtesy of Fairfax Radiological Consultants, Fairfax, VA.

Safety Considerations

There are several factors related to the safety profile of gadolinium-based contrast agents.

First and foremost are the physicochemical properties of gadolinium-based contrast agents: chelation, thermodynamics, and kinetics. As we will discuss, these properties relate to the overall safety of GBCAs and the incidence of nephrogenic systemic fibrosis (NSF). NSF has been associated with the release of free gadolinium in patients with impaired renal function. Recall that gadolinium on its own is toxic, and the release of gadolinium into the body would therefore have a toxic effect. The ability of a gadolinium compound to bind tightly and hold onto the gadolinium ion is directly related to the safety of a contrast agent.

Another safety consideration is patient tolerance which can be affected by the delivery and formulation of a GBCA. The symptoms and management of adverse events (AEs) and NSF will be discussed later in this material.

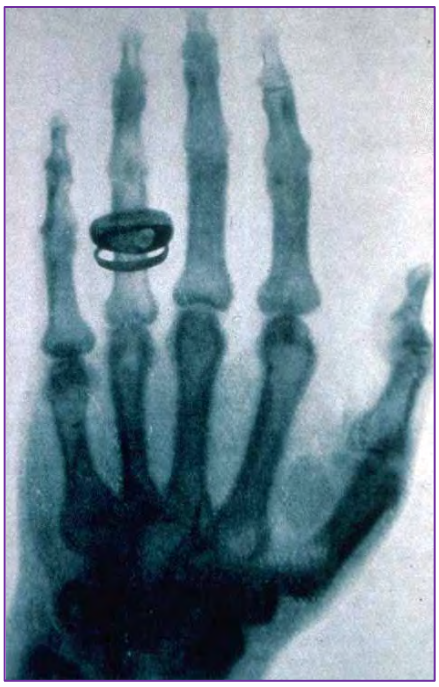
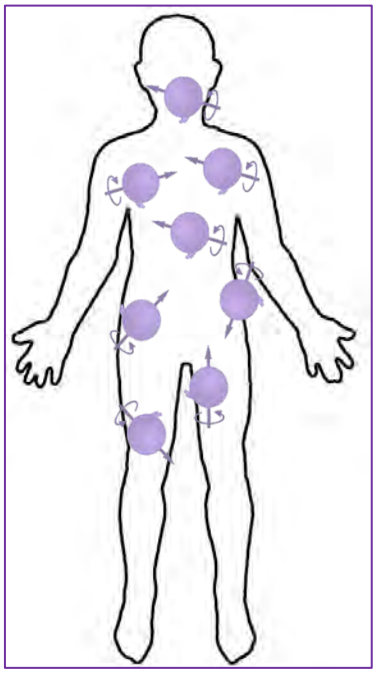


Figure 5. An 1896 x-ray (or Röntgen ray) taken by Wilhelm Röntgen (1845-1923), the discovery for which he was awarded the 1901 Nobel Prize in Physics.

Available at Wikimedia Commons.



PHYSICS 101

Images created by x-ray and computed tomography are based on the density of tissue, that is, soft tissue and dense bone tissue (**Figure 5**). MR images are created by the detection of hydrogen atoms (protons) within the body, which is a medium of mostly water and fat (**Figure 6**).

GBCAs used in MR are detected *indirectly* by their effect on water. Recall that the water molecule is composed of two hydrogen atoms and one oxygen atom (H_2O). Hydrogen is a primary element of all body tissues, including fat which is easily seen on MRI. In addition to being the most plentiful element in the body, which is 60% water[3], hydrogen is also the simplest element with an atomic number of 1, since it contains a single proton and a single electron.

Figure 6. MRI images are created by imaging protons moving through a medium.

Relaxivity

The hydrogen atom, with its single proton, possesses a physical property called **spin**. The spinning hydrogen proton creates a very small magnetic field with associated north and south poles. Thus the hydrogen proton is an electrically charged, spinning particle that generates its own weak magnetic force. The random movement of spinning hydrogen protons in a fluid is called **Brownian motion** (**Figure 7**).

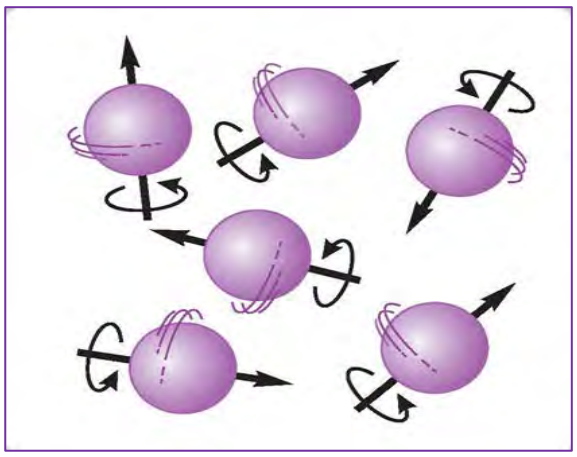


Figure 7. Illustration of Brownian motion, the random movement of particles suspended in a fluid.

In order for relaxation to occur, the hydrogen proton must encounter a fluctuating magnetic field, which in MRI is provided by a superconducting magnet. The MRI scanner contains a large magnet that aligns protons along the magnet's B_0 axis. Relaxivity occurs when protons are excited by a radiofrequency field transmitted at the **Larmor frequency**. When the excitation pulse is removed, protons "relax" back to their initial state and produce signals that can be detected. This rapid process forms the basis of the MR image.

To enhance relaxation, a compound with unpaired electrons is introduced. Consider that a single unpaired electron is 660 times more magnetically potent than a proton. The gadolinium ion has seven unpaired electrons, making it a very powerful local magnet.

Because gadolinium has T1-shortening properties, introduction of the intravenous gadolinium compound **catalytically** acts on hydrogen protons to change the enhancement properties of tissue in close proximity to the agent. Enhancing tissue exhibits a very short T1, resulting in higher signal intensity than non-enhancing tissue. Because contrast-enhanced tissues appear brighter, visualization of pathology is improved.

The extent to which the contrast agent can change T1 or T2 is denoted as r_1 or r_2. The mathematical definition of relaxivity is the change in 1/T1 or 1/T2 normalized to the concentration of the contrast agent:

$$r_1 = \frac{\Delta(1/T_1)}{[Gd]}$$

$$r_2 = \frac{\Delta(1/T_2)}{[Gd]}$$

The mechanism of relaxivity

Recall that when the magnetic field of a MRI scanner fluctuates close to the Larmor frequency of water, relaxation will occur.

Figure 8. ANIMATION. Gadolinium molecule surrounded by unrelaxed water molecules represented in red. As relaxation occurs, the water molecules change color to the relaxing light blue.

To view the full discussion and animation, click here: www.YouTube/ICPMEducation_relaxation.

The rate of relaxation is dependent on the chemical environment. For example, in the presence of cerebral spinal fluid (CSF) or grey matter, water undergoes relaxation at different rates. The rate of relaxation of these tissues provides tissue contrast in MR. Because of the chemical structure of gadolinium contrast, the rate of relaxation can be enhanced with the introduction of a GBCA.

Recall that the gadolinium ion has seven unpaired electrons that create a powerful molecular magnet. The gadolinium ion is chelated to form a gadolinium complex. Relaxation occurs when water binds to and is released from the gadolinium complex.

After the water molecule associates with the gadolinium complex and is relaxed, the water can then dissociate and another water molecule will take its place. That water molecule will be relaxed and in turn undergo exchange with another water molecule. In this relaxation and exchange process, the GBCA can relax a large proportion of the water in the tissue. This **water exchange** occurs very rapidly, at about a million exchanges per second (**Figure 8**). It is this rapid process that makes GBCAs a very effective MRI contrast agent.

When a GBCA is introduced, it acts catalytically to relax water in the body, affecting millions of water molecules per second. A very small amount of GBCA has a very large effect on water, allowing for the administration of GBCAs at a small volume compared to the volume of water present in the body.

The relaxivity values of all currently FDA-approved GBCAs are similar with a few exceptions; MultiHance has a relaxivity rate about 50% greater than the other agents, and the relaxivity of Ablavar is about six times greater than for the first generation GBCAs (**Table 4**).

Trade Name	Generic Name	r_1 at 1.5T*	r_2 at 3.0T*
Ablavar	gadofosveset trisodium	28.0	9.9
Dotarem	gadoterate meglumine	3.6	3.5
Eovist	gadoxetate disodium	4.7	4.3
Gadavist	gadobutrol	5.5	5.0
Magnevist	gadopentetate	4.1	3.7
MultiHance	gadobenate dimeglumine	6.3	5.5
Omniscan	gadodiamide	4.3	4.0
OptiMARK	gadoversetamide	4.7	4.5
Prohance	gadoteridol	4.1	3.7

Table 4. Relaxivities of FDA-approved contrast media[4].

*in $L \bullet mmol^{-1}$, in plasma at 37^0C

NOTES

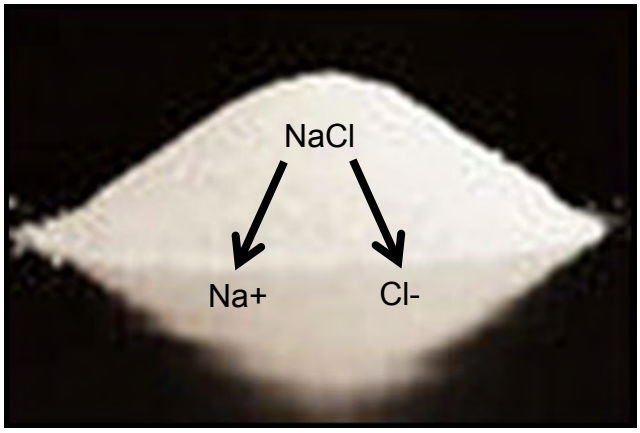


Figure 9. Table salt, or sodium chloride, is an ionic compound.

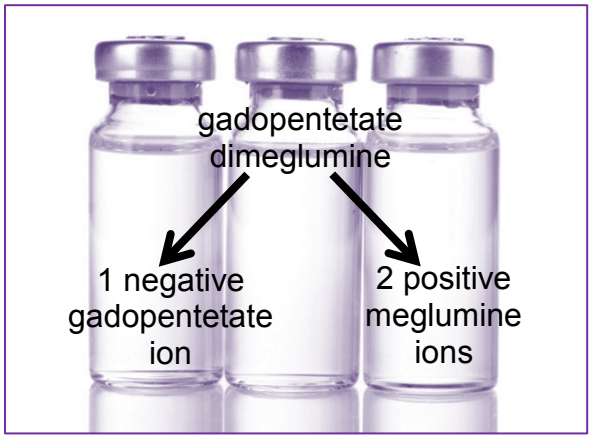


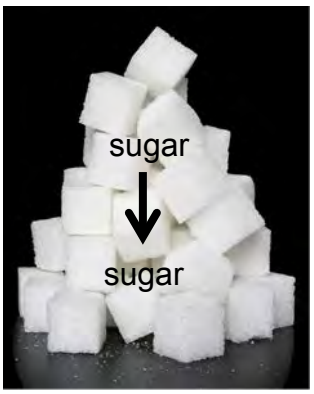
Figure 10. Gadopentetate dimeglumine, Magnevist, is an ionic contrast agent.

IONICITY, OSMOLALITY, AND FORMULATION

Ionic vs Nonionic Compounds

Ionic compounds dissolve in water and dissociate into individual positively and negatively charged **ions**. For example, when sodium chloride (NaCl), table salt, is dissolved in water, it produces positively charged sodium ions and negatively charged chloride ions (**Figure 9**).

This same principle applies to ionic contrast agents. For example, gadopentetate dimeglumine, Magnevist, is an ionic contrast agent. Dissolved in water, gadopentetate dimeglumine dissociates to produce one negatively charged gadopentetate ion and two positively charged counter ions, meglumine (**Figure 10**).



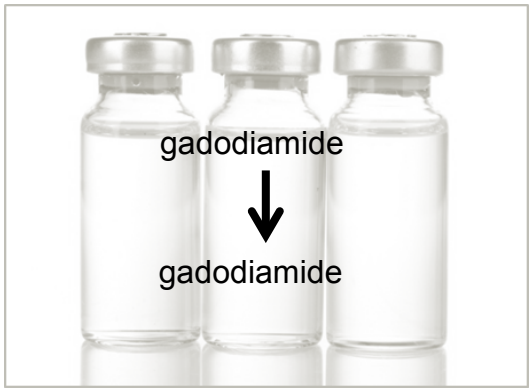


Figure 11. (Left) Example of a nonionic compound. Sugar dissolved in water provides no counter ion.

Figure 12. (Right) Omniscan is an example of an nonionic contrast agent.

Nonionic compounds dissolve in water to give a single uncharged ion. An example is sucrose, table sugar, which dissolves in water *unchanged* to give sucrose. Again, this same principle applies to nonionic contrast agents. For example, gadodiamide, Omniscan, is a nonionic contrast agent. When dissolved in water, it gives no counter ion (**Figures 11-12**).

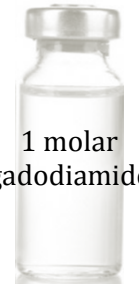
Ionicity and Osmolality

The distinction between ionic and nonionic compounds is important in terms of osmolality, the measure of the number of particles in solution. At the same concentration, ionic compounds have higher osmolality than nonionic compounds.

For example, a 1 molar (M) solution of gadopentetate dimeglumine, Magnevist, consists of 1 molar gadopentetate ions and 2 molar meglumine ions, resulting in a 3 osmolar solution:

1 molar gadopentetate dimeglumine = 1 molar gadopentetate ions + 2 molar meglumine ions = 3 osmolar solution

Gadodiamide, Omniscan, consists of 1M gadodiamide ions and therefore is a 1 osmolar solution:



1 molar gadodiamide = 1 osmolar gadodiamide

The osmolality of a gadolinium contrast agent is also an important characteristic. **Osmosis** is the process by which a higher concentrated fluid can permeate through a membrane into a less concentrated fluid until there is equalization on both sides of the membrane. GBCAs are formulated to be hyperosmotic, that is, characterized by increased osmolality as compared to blood plasma. Theoretically, if the osmolality of the blood plasma upon injection of the GBCA is too high, then water will be drawn out from the blood and endothelial cells to maintain osmotic balance. If this disruption in osmotic balance is large enough, it can lead to adverse events as are sometimes seen with ionic x-ray contrast media; however, given the small volume of GBCA injected, the likelihood of an adverse event is very small.

Ionicity and Adverse Events

The relationship between the iodine-based contrast agents used in CT and adverse events is well known. The research on CT contrast media has shown that ionic agents have a significantly higher **adverse event** rate compared to nonionic agents. Is the same true of MR contrast agents?

The answer is no. Because of the smaller volume of contrast administered in MRI, there is no established safety benefit of using a GBCA based on ionicity. Given data from multicenter clinical trials and post-marketing surveillance, it is well accepted that adverse event profiles for all MR contrast agents are similar despite differences in ionicity and osmolality.

Formulation and Dose

There are differences in the formulation of gadolinium-based contrast agents related to osmolality and sometimes the **viscosity** of a contrast agent.

The standard GBCA formulation concentration is 0.5 molar, although nonionic agents can sometimes be formulated at higher concentrations. For example, gadobutrol, Gadavist, is formulated at 1M, two times higher than most of the other approved gadolinium-based contrast agents. This higher concentration allows the dose to be given in a smaller volume. Therefore, instead of administering the standard GBCA dose volume of 20cc, Gadavist is administered at a dose volume of 10cc, resulting in nearly equivalent image contrast but at lower volume.

THERMODYNAMICS AND KINETICS OF GBCAS

Thermodynamics

Thermodynamics is the branch of physics that deals with the relationship of heat and mechanical energy and the conversion of one into the other. In the field of gadolinium-based contrast agents, thermodynamics relates to the change in energy associated with the binding of the gadolinium ion to its chelator. Thermodynamics addresses the affinity of the chelator for the gadolinium ion.

All gadolinium-based contrast agents use chelators that have a very high affinity for gadolinium. But these chelators also have high affinity for metal ions other than gadolinium, for instance, zinc and iron.

The gadolinium ion itself has a high affinity for other things in the body like phosphate and bicarbonate, both of which are present at high concentrations in plasma. Gadolinium forms an insoluble salt with phosphate or bicarbonate, preventing the free gadolinium from binding again to its chelator.

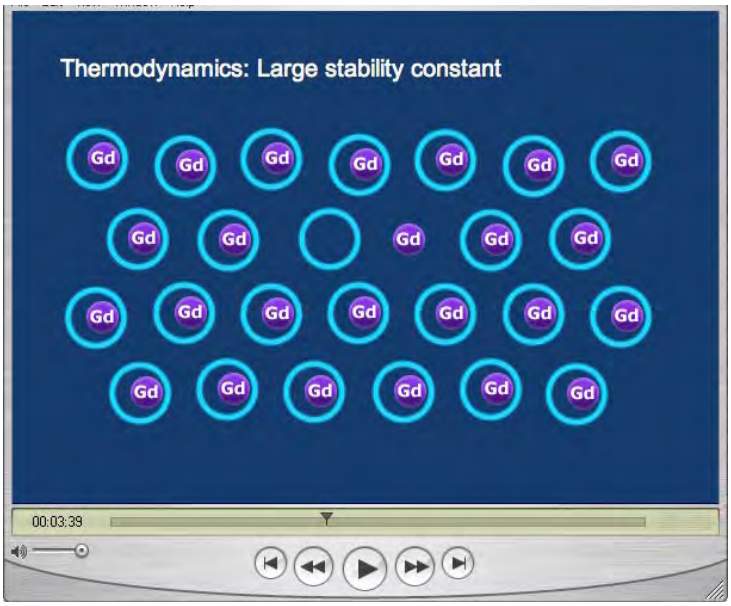


Figure 13. ANIMATION. Thermodynamics and Kinetics.

To view the full discussion and animation, click here: www.YouTube/ICPMEducation.

While thermodynamics determines the end-product of the chemical reaction between the chelator, the gadolinium ion, and other metals, it does not tell us how quickly it takes this chemical reaction to reach the end product. That is the role of **kinetics.**

Kinetics

Kinetics is the branch of chemistry concerned with the *rate* of a chemical reaction. The study of kinetics reveals how quickly free gadolinium is released from the chelated compound. At the pH of blood, 7.4, the release of free gadolinium is very slow, but the rate of release can be catalyzed by the presence of acid, metal ions, and phosphate.

The concepts of thermodynamics and kinetics can be challenging to understand. **Figure 13** illustrates these concepts as they relate to gadolinium-based contrast agents.

The Role of Thermodynamics and Kinetics in GBCAs

The relationship between thermodynamic stability and kinetic inertness of a gadolinium-based contrast agent is directly related to the chemical structure of the agent (**Figure 14**).

Linear nonionic compounds, Omniscan and OptiMARK, release 2% of their gadolinium in a phosphate-rich serum within an hour of administration and have the lowest thermodynamic stability; the chelating structure of these agents does not hold onto the gadolinium ion as tightly as the other GBCAs.

The linear ionic chelators, Ablavar, Eovist, Magnevist, and MultiHance, are in the middle of the spectrum. They have higher thermodynamic stability and are more kinetically inert than the linear nonionic compounds.

The macrocyclic contrast agents, Dotarem, Gadavist, and ProHance, vary in their thermodynamic stability but are by far the most kinetically inert contrast agents. They release free gadolinium extremely slowly, requiring over 10,000 hours to release just 2% of free gadolinium in the presence of other metal ions.

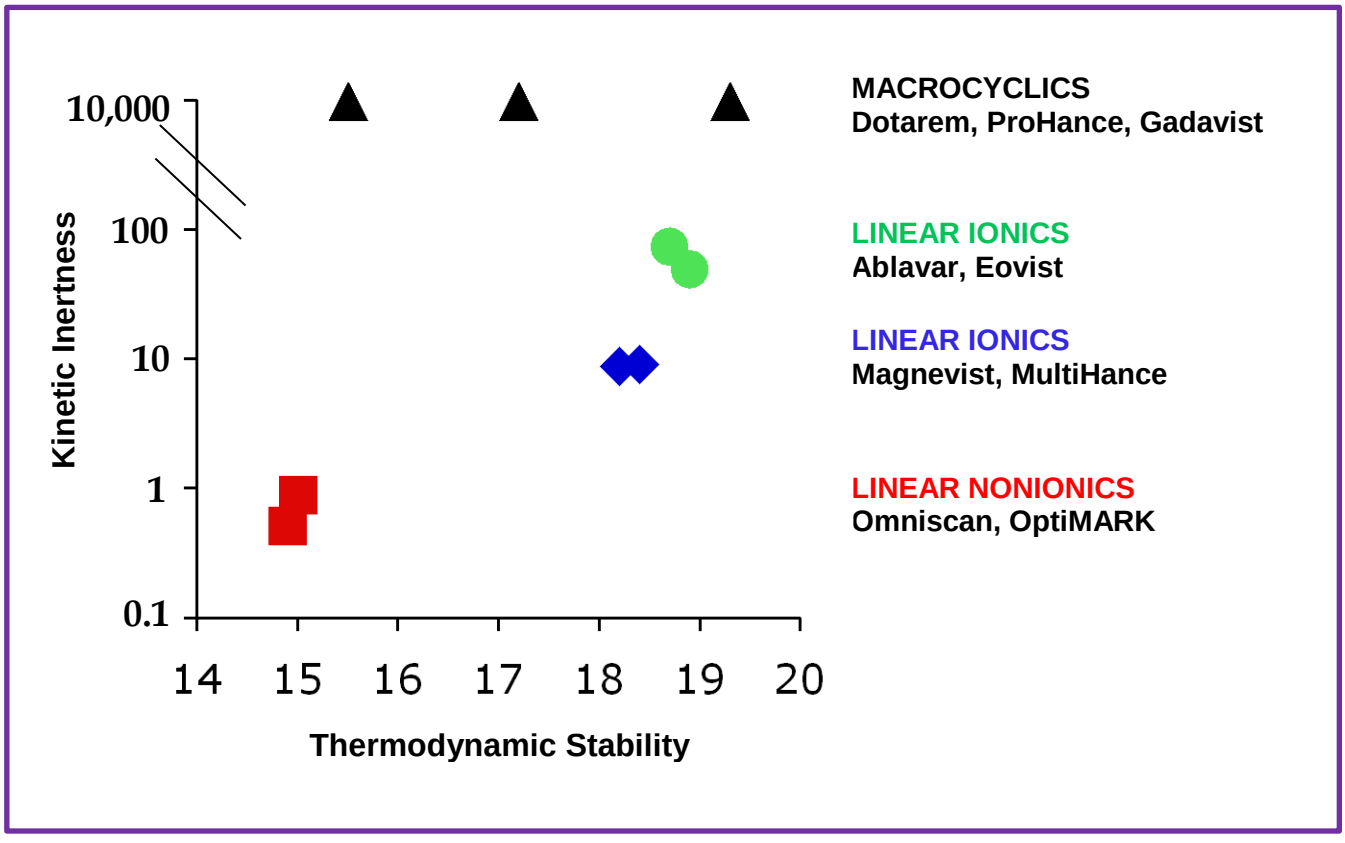


Figure 14. Kinetic inertness and thermodynamic stability. On the *x* axis is thermodynamic stability, how tightly a chelate holds onto gadolinium ions; on the *y* axis is kinetic stability, the time it takes to release 2% of free gadolinium in a phosphate-rich serum.[5]

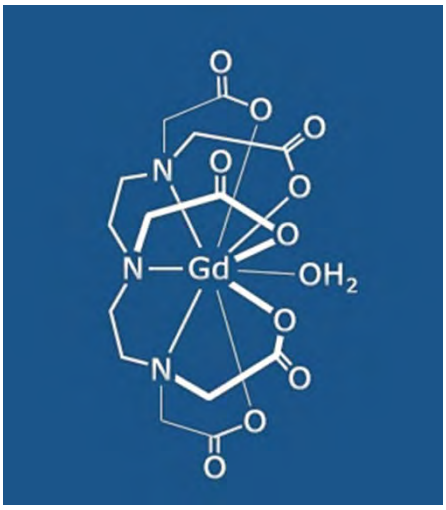


Figure 15. Linear chelation.

Figure 16. Macrocyclic chelation.

To view the full discussion and animation about the mechanism of linear and macrocyclic chelators, click here: www.YouTube/ICPMEducation**.**

The Importance of Chelation

Why is macrocyclic chelation more kinetically inert than linear chelation?

There are two types of chelation used in the formulation of gadolinium-based contrast agents: linear chelation and macrocyclic chelation. The type of chelation used is directly related to the kinetic inertness of the GBCA.

Linear chelators

Linear chelators wrap around the metal ion like a snake coiling around an egg. Because of this coiled structure, linear chelators can “unwrap” as well. Recall that chelators have an affinity for gadolinium as well as other metal ions. The unwrapping of the linear chelator is the result of the breaking of one oxygen bond, and then another, allowing the release of the gadolinium ion and replacement by another metal ion like zinc or iron (**Figure 15**).

Macrocyclic chelators are bound in such a way that it is much more difficult for the gadolinium ion to be released. The unwrapping of the macrocyclic chelator occurs when an oxygen bond breaks and two nitrogen bonds break *simultaneously,* releasing the gadolinium ion. The probability of two nitrogen bonds breaking at the same time is highly unlikely. It is much more probable that the first broken nitrogen bond would reform, preventing the release of the gadolinium ion. For this reason, macrocyclic chelation tends to be more chemically inert (**Figure 16**).

THE SAFETY OF GBCAs

We have learned that thermodynamic stability and kinetic inertness not only define the nature of a GBCA but can be predictors of the risk of an adverse event (AE).

Acute and Delayed Adverse Events

There are two types of adverse reactions to contrast agents: acute and delayed. Acute events, primarily contrast **extravasation** and allergic reactions, may appear to be relatively straightforward but can quickly escalate. Delayed events can ultimately become much more serious, specifically the development of **nephrogenic systemic fibrosis** (NSF).

Contrast Extravasation

Contrast extravasation is the unintentional or accidental extravascular (outside the vessel) injection of intravascular (inside the vessel) contrast. Causes can be dislodgment of the cannula, contrast leakage from the vessel puncture site, or rupture of the vessel wall (commonly called "blowing a vein")[6]. Because of the low volumes of contrast administered in MRI, the incidence of contrast extravasation is extremely low.

Risk factors

There are several patient risk factors for contrast extravasation. Patients who may be at risk for contrast extravasation should be closely monitored throughout the MRI examination.

- Patients who have difficulty with communication
  - Infants and children
  - Elderly (hard of hearing, dementia)
  - Debilitated
- Patients with altered circulation
  - Peripheral vascular disease (PVD)
  - Diabetes mellitus (DM)
  - Raynaud's disease
  - Venous thrombosis
- Site of IV placement
  - Hand
  - Wrist
  - Foot
  - Ankle
- Indwelling lines that have been in place >24 hours
- Multiple injections into the same vein

Signs and symptoms of extravasation

A patient complaint of stinging or burning at the IV site is an indication of extravasation. Swelling of the skin and irritation in the subcutaneous soft tissues is often the cause of this stinging and burning. There may also be **edema** at the injection site, and the area may become red and tender (**Figure 17**). It is possible that the patient may be unaware of an extravasation, and careful observation of the IV site is essential.

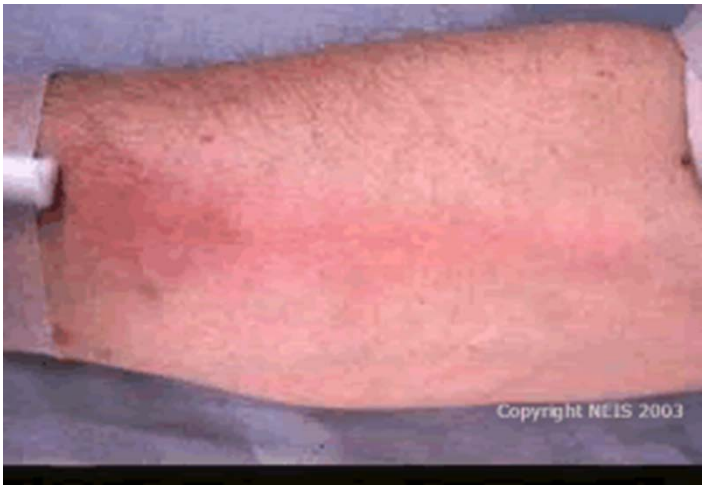


Figure 17. Contrast extravasation. Note the redness and tenderness distal to the IV site.

Available at The National Extravasation Information Service.

Classification of contrast extravasation

The incidence of contrast extravasation is quite low, on the order of 0.05% to 0.1%, and classified as minor, moderate or severe[7,8]. The classifications for contrast extravasation are based on the administration of CT contrast agents which are administered at significantly larger volumes than MRI contrast (20cc GBCA vs 120cc iodinated CT contrast).

Treatment for contrast extravasation

If the patient complains of burning or stinging at the site or if redness or tenderness is observed, STOP the injection immediately and:

- Check for diminishing perfusion of blood flow distal to the site where the extravasation occurred
- Check for capillary refill
- Ensure pulses and sensation are intact

If possible, elevate the affected site above the heart to encourage lymphatic and blood flow to diminish the amount of swelling in the affected area. Monitor the patient closely and discharge them *only* after the swelling resolves.

Treatment for minor contrast extravasation is ice and/or warm packs for patients without symptoms other than localized swelling. The patient should be closely monitored and discharged only after the swelling resolves.

Moderate contrast extravasation is accompanied with inflammation that peaks within 24-48 hours. Because the body typically compartmentalizes the fluid and absorbs it into the vasculature, inflammation is usually self-limiting and resolves within 48 hours.

Severe cases of contrast extravasation can result in the development of **compartment syndrome**, when the **fascial** planes swell in one area and perfusion distal to the IV site is diminished. Chronic inflammation, **fibrosis,** or **atrophy** can develop as well. Ulceration and tissue necrosis can occur as soon as six hours after extravasation, and an urgent plastic surgery consult is required.

Increased swelling and pain within two-to-four hours after the extravasation and any evidence of blistering, ulceration, **induration**, or altered tissue perfusion may also require a plastic surgery consult.

Acute Allergic Reactions

Acute allergic reactions can also occur with MRI agents; however, **anaphylactic** reactions are three times less likely to occur with gadolinium-based MRI contrast agents than with the iodine-based contrast agents used in CT[9].

Treatment

Benadryl® can be administered in cases of a mild allergic reaction like rash or **urticaria**.

For patients with moderate signs of hypotension or sudden respiratory complaints (bronchospasm or shortness of breath), epinephrine, H2 blockers (acid reducers), and steroids along with Benadryl are recommended[10].

Severe anaphylactoid reactions require supportive measures to maintain patient respiratory and systemic stability. In rare cases, patients may require respiratory assistance in the form of assisted breathing or intubation and alpha or beta agonists, eg, epinephrine, for systemic blood pressure support. In extremely rare cases, death has been reported[11].

Incidence

The incidence of mild to moderate reactions to a gadolinium-based contrast agent is very low at 0.0004 – 0.7%; for severe anaphylactoid reactions, the incidence is extremely low at 0.001 – 0.01%[12].

An adverse event is 2.3 to 2.7 times more likely in patients with a history of allergy to iodinated contrast, 4 times higher if there is any history of allergy or asthma, and 8 times higher if the patient had a previous gadolinium contrast reaction[13]. As always, obtaining the patient's history of prior imaging studies is essential.

Steroid pretreatment

There is no consensus regarding the value of using steroids as a pretreatment for patients who have had previous allergic reactions to gadolinium- or iodine-based contrast agents. Although there have been no controlled trials to determine the efficacy of steroid pretreatment, the practice is widely used.

A sample steroid pretreatment regimen:

- 50mg prednisone by mouth every 6 hours (at 13, 7, and 1 hour prior to IV contrast agent administration)
- 25-50mg Benadryl by mouth 1 hour prior to IV contrast agent administration

If the patient cannot tolerate oral medications, other protocols allow for equivalent intravenous steroids. There are also acute protocols that allow for intravenous steroids to be given as short as four hours before imaging.

Nephrogenic Systemic Fibrosis

Nephrogenic systemic fibrosis is a **fibrosing** disease that primarily involves the skin and subcutaneous soft tissue but can affect the vital organs as well, depending on where the free gadolinium collects (**Figure 18**). Symptoms include skin thickening and itching and can progress rapidly into contractures and joint immobility (**Figure 19**). In rare cases, NSF can cause death.

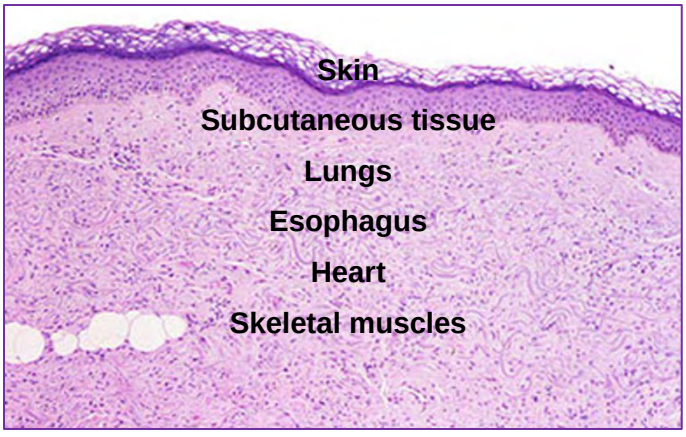


Figure 18. Range of NSF manifestations.

Cowper SE. Nephrogenic Systemic Fibrosis [ICNSRF Website]. 2001-2013. Available at http://www.icnfdr.org/ Accessed November 5, 2013.

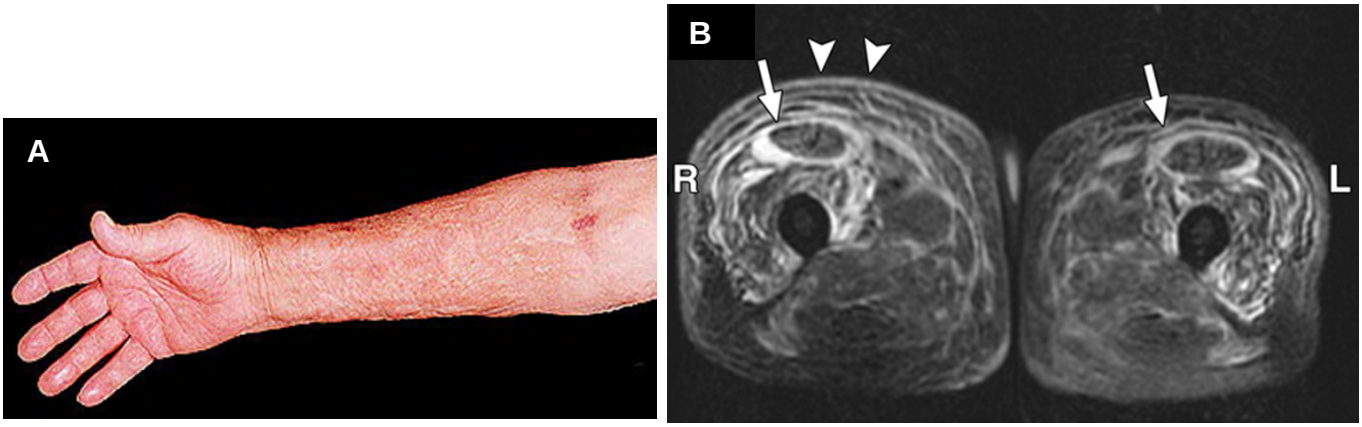


Figure 19. Nephrogenic Systemic Fibrosis. (A) Skin thickening associated with NSF.

Cowper SE. Nephrogenic Systemic Fibrosis [ICNSRF Website]. 2001-2013. Available at http://www.icnfdr.org/ Accessed November 5, 2013.

(B) 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.

Courtesy of Martin Prince, MD, PhD, Weill Cornell Medical College.

Patient risk factors for NSF

The association between nephrogenic systemic fibrosis and exposure to gadolinium is well-established. NSF has also been associated with:

- Chronic renal disease (eGFR <15ml/min/1.73m^2)
- Acute renal injury
- High doses of gadolinium contrast (>0.1mmol/kg)

Other known associations have occurred in patients with **lactic acidosis**, **hemochromatosis** or **hemosiderosis**, and high iron concentration. Patients who are hypercalcemic or hyperphosphatemic or taking erythropoietin for low hemoglobin or any immunosuppressive therapies also have been known to be affected. Patients with diabetes often have renal injuries with concomitant **vasculopathies**, and patients with liver injury can have **hepatorenal syndrome** and therefore both groups may have chronic renal failure.

Patients should be carefully screened to determine if they are at risk. Screening questions should include:

- Patient over 60
- History of renal disease
- Dialysis
- Kidney transplant
- Single kidney

Estimated glomerular filtration rate

Glomerular filtration rate (GFR), is a measurement of renal function and determined by the serum **creatinine** level in the blood. GFR estimates how much blood passes each minute through the kidney's tiny filters called glomeruli. The creatinine level is combined with several other variables to *estimate* the GFR, sometimes referred to as eGFR.

MR contrast-enhanced imaging is contraindicated in patients on dialysis and patients with the following risk factors:

- Severe or end-stage renal disease with eGFR <30
- eGFR 30-40 without dialysis*
- Acute renal failure

*Patients with of eGFR 30-40 should also be considered at risk as eGFR levels may fluctuate[14]. Ironically, it has been shown that patients with acute renal failure are at higher risk for NSF than patients with chronic renal failure[15].

The Modification of Diet in Renal Disease (MDRD) is the equation used to calculate serum creatinine[16]. eGFR calculation is related to age and gender; males have a higher risk of NSF than females, as do African Americans to Caucasians. eGFR values are reported in mg/dl:

$$eGFR(ml/min/1.73^2 = 175\ x\ (serum\ creatinine)^{-1.154}\ x\ (age\ in\ years)^{-0.203}$$
$$if\ female\ multiply\ by\ 0.742$$
$$if\ African\ American\ multiply\ by\ 1.212$$

There is no scientific evidence that determines the time interval prior to GBCA injection when an eGFR should be obtained in at-risk patients. However, based on expert opinion and a need to maintain patient safety, the ACR Committee on Drugs and Contrast Media recommends a new eGFR be obtained within time intervals in outpatients who are identified by screening as at increased risk (**Table 5**)[17].

Prior eGFR level ($ml/min/1.73m^2$)	Last eGFR prior to MRI	Obtain a new GFR prior to MRI
None available	N/A	Within 6 weeks
>60	>6 months	Within 6 weeks
>60	<6 months *(stable state*)*	New eGFR not needed
>60	<6 months *(possibly unstable state**)*	Within 3 weeks
30-59	>2 weeks	Within 2 weeks
<30	>1 week	Within 1 week
On dialysis	N/A	New eGFR not needed

** patient does not have a known condition that might result in acute deterioration of renal function*

*** patient has a known condition that might result in acute deterioration of renal function. Such conditions include severe dehydration, febrile illness, sepsis, heart failure, recent hospitalization, advanced liver disease, and abdominal surgery*

Table 5. When a new eGFR should be obtained in outpatients with risk factor(s) for compromised renal function.

From American College of Radiology website. ACR Manual on Contrast Media v9 2013.

Relationship of NSF to the Chemical Structure of GBCAs

Kinetic inertness is the most important measure for predicting NSF. Most of the cases of NSF have occurred with the linear nonionic agents, which are not as stable or chemically inert as macrocyclic agents. The hypothesis is that chelators that tightly bind the gadolinium ion have less risk of causing NSF than compounds that are more willing to release the gadolinium ion.

Recall that all extracellular contrast agents are excreted through the kidneys and have a very short half-life in the body. In a patient with normally functioning kidneys, GBCA clears the body in about 90 minutes. In a patient with renal insufficiency, the amount of time the contrast agent is in the body increases by several hours or even days. Impaired kidney function increases the probability that free gadolinium will remain in the body, potentially triggering a toxic response.

Within approximately 24 hours, free gadolinium interacts with **monocytes** and **macrophages** to produce profibrotic **cytokines** that can stimulate the overproduction of **collagen** and lead to the observable manifestations of NSF.

There is no laboratory test for NSF[18]. Confirmation of this diagnosis is determined by observation of clinical symptoms, history of gadolinium exposure, and deep skin biopsy to confirm the presence of gadolinium in soft tissues and collagen bundles.

Association of NSF to Gadolinium and GBCAs

While we have learned that the association between NSF and gadolinium exposure is well-established, the precise relationship between NSF and the different formulations of gadolinium is controversial and not well understood.

Gadolinium-based contrast agents are stratified based on the number of documented cases of NSF (**Table 6**). The greatest number of documented NSF cases are Group I agents associated with Omniscan, Magnevist, and OptiMARK. Group II agents are associated with few if any cases: MultiHance, ProHance, Dotarem and Gadavist. Group III is comprised of the newest agents and have, at least to this point, no associated, reported cases of NSF: Ablavar, the blood pool agent, and Eovist, the liver-specific contrast agent.

Group I: Agents associated with the greatest number of NSF cases: Gadodiamide (Omniscan – GE Healthcare) Gadopentetate dimeglumine (Magnevist – Bayer HealthCare Pharmaceuticals) Gadoversetamide (OptiMARK – Covidien)
Group II: Agents associated with few, if any, unconfounded cases of NSF: Gadobenate dimeglumine (MultiHance – Bracco Diagnostics) Gadoteridol (ProHance – Bracco Diagnostics) Gadoteric acid (Dotarem – Guerbet) Gadobutrol (Gadavist – Bayer HealthCare Pharmaceuticals)
Group III: Agents that have only recently appeared on the market: Gadofosveset (Ablavar – Lantheus Medical Imaging) Gadoxetic acid (Eovist – Bayer HealthCare Pharmaceuticals)

Table 6. GBCA risk stratification from American College of Radiology Manual on Contrast Media, Version 9. Available at American College of Radiology.

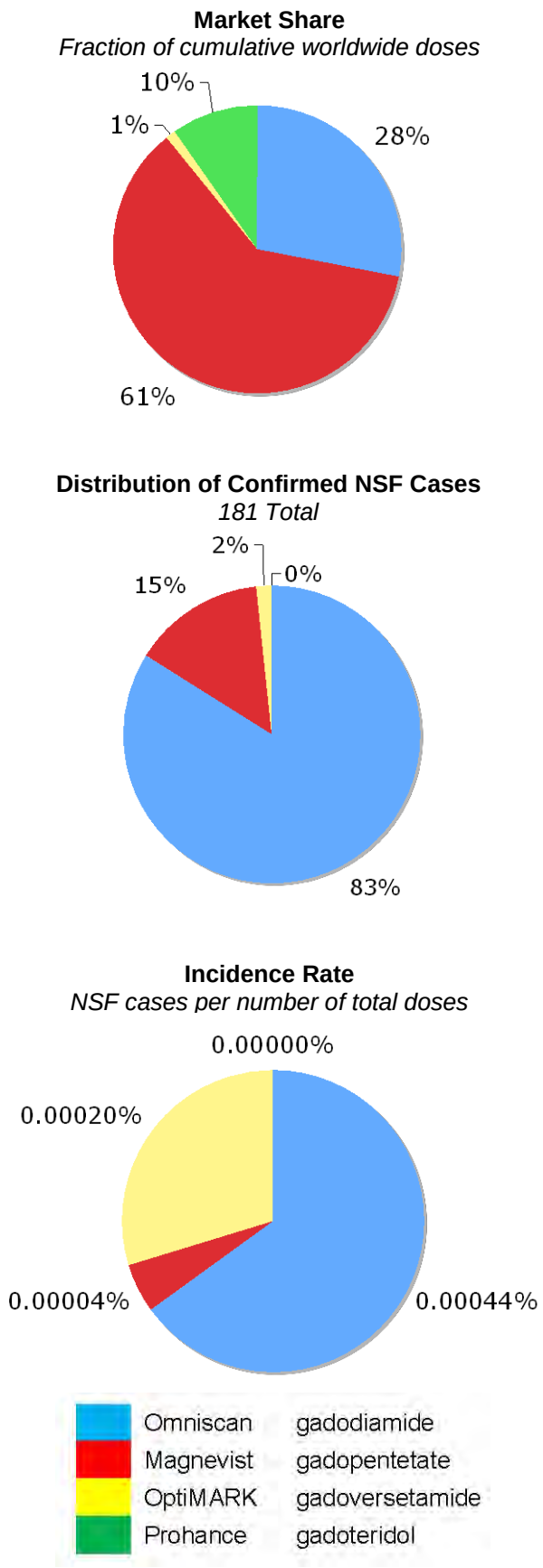


Figure 20. Documented cases of NSF by market distribution, and incidence rate[19].

The relationship between documented cases of NSF and gadolinium-based contrast agents can be viewed from a variety of perspectives (**Figure 20**).

When comparing market share against the number of NSF cases worldwide, Magnevist (gadopentetate dimeglumine) has the greatest market share but a comparatively low incidence of NSF relative to its market share. Conversely, the incidence of NSF is higher with Omniscan (gadodiamide) and OptiMARK relative to their market share[20].

NOTES

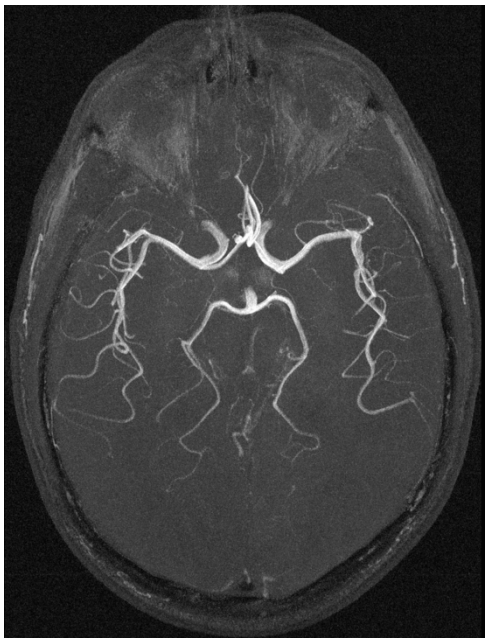


Figure 21. Heavily T1-weighted image exploits the ability of the extracellular agent to remain in the vasculature within the first few seconds of administration for rapid imaging and exquisite definition of the circle of Willis.

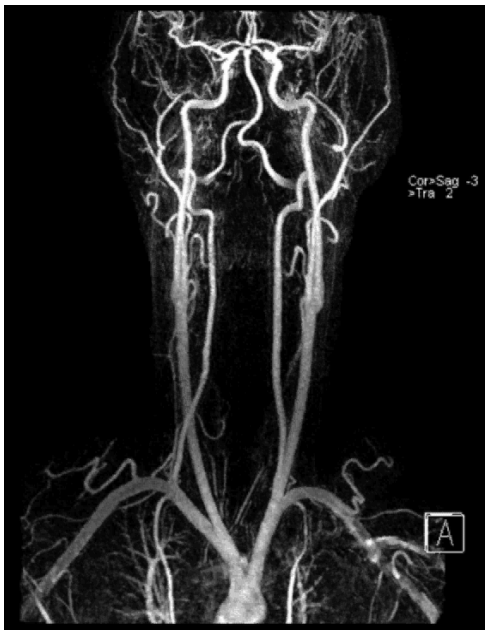


Figure 22. MOVIE. 3T MRA of the vasculature from the aortic arch to the circle of Willis using an 8-channel phased array coil, 20cc Gd-DPTA, 2cc/sec; 0.6mm x 0.8mm x 0.9mm, 30cm FOV, TR 3.9, TE 1.5.

Images courtesy of A. Guimaraes, MD, PhD. MGH Department of Radiology.

APPLICATIONS OF FIRST GENERATION CONTRAST AGENTS

Recall that first generation contrast agents were developed in the late 1980s and early 1990s, and they share similar imaging properties and clinical utility. All are extracellular fluid contrast agents; they have similar distribution properties, relaxivity values, no protein-binding properties, and they are primarily excreted through the kidneys.

This older generation of GBCAs is used for dynamic contrast-enhanced (DCE) imaging to enhance lesions based on differences in perfusion and differences in leaky microvasculature. **Kinetic modeling** can be used to quantify permeability by measuring changes in R1 (relaxation rate of tissue), an imaging technique primarily used to differentiate lesions in breast and prostate imaging.

Within the central nervous system, extracellular contrast agents are used to exploit r2* properties since these agents not only affect T1 relaxation but T2 and T2* relaxation. T2* effects allow dynamic assessment of **relative cerebral blood flow** and **relative cerebral blood volume**.

Extracellular contrast agents can also be used to assess anatomic changes in the vasculature using **angiography**, important not only in the central nervous system but in the peripheral vasculature.

MR Angiography

With improved coils and higher field strength magnets, spatial information can be rapidly encoded through the first pass after contrast administration, when the GBCA is primarily in the arterial blood pool, to obtain high-resolution MR angiography (MRA) images. Vasculature can be exquisitely captured within a very short period of time (**Figures 21-22**).

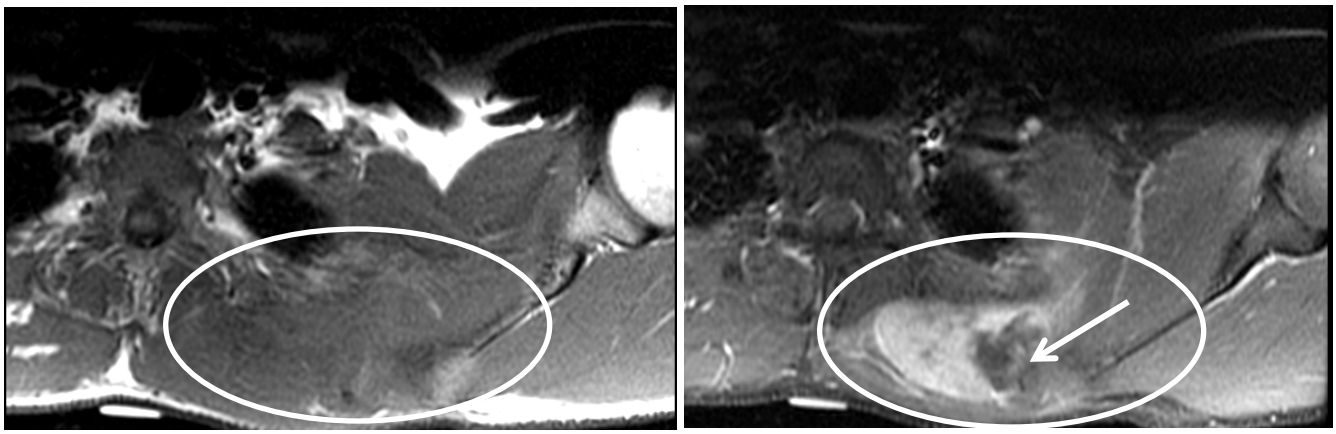


Figure 23. Recurrent Ewing's sarcoma. (A) Precontrast, the lesion is not easily seen posterior to the scapula (circle). (B) Postcontrast the lesion avidly enhances (circle) along with possible necrosis due to lack of uptake of contrast (arrow).

Courtesy of A. Guimaraes, MD, PhD. MGH Department of Radiology.

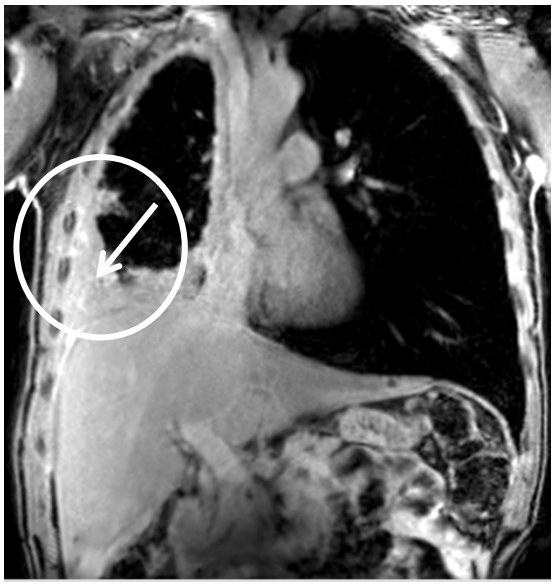


Figure 24. Mesothelioma. Postcontrast image shows an avidly enhancing ring of tissue in the right hemithorax extending through the diaphragm (arrow), with extension through the chest wall (circle).

Courtesy of A. Guimaraes, MD, PhD. MGH Department of Radiology.

Malignant Lesion Detection, Characterization, and Metastasis

Most extracellular agents are used for detecting and characterizing lesions. **Figure 23** shows pre- and postcontrast images of a patient with a history of Ewing's sarcoma. **Figure 24** shows an example of **mesothelioma** and demonstrates diaphragmatic extension and chest wall involvement. These pathologic findings are all better visualized by the exquisite soft tissue contrast of contrast-enhanced MRI.

Benign Lesion Detection and Characterization

ECF agents are also useful for defining benign vascular lesions. **Figure 25** shows the typical enhancement pattern following the blood pool of a liver hemangioma in T2W, arterial, portal-venous, and equilibrium phases; **Figure 26** is an example of **Budd-Chiari syndrome**, which is a thrombosis of the hepatic vein.

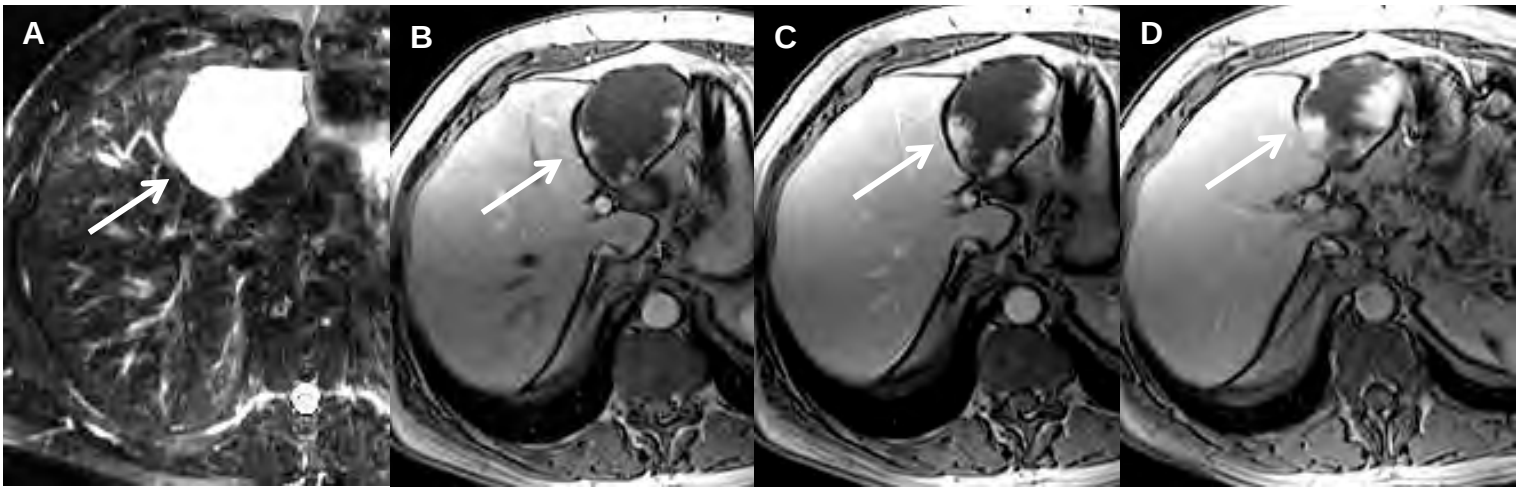


Figure 25. Liver hemangioma. (A) T2W shows a bright lesion with classic peripheral nodular enhancement that follows the blood pool. (B, C, D) In the arterial, portal-venous, and equilibrium phases, note the classic peripheral nodular enhancement with delayed filling.

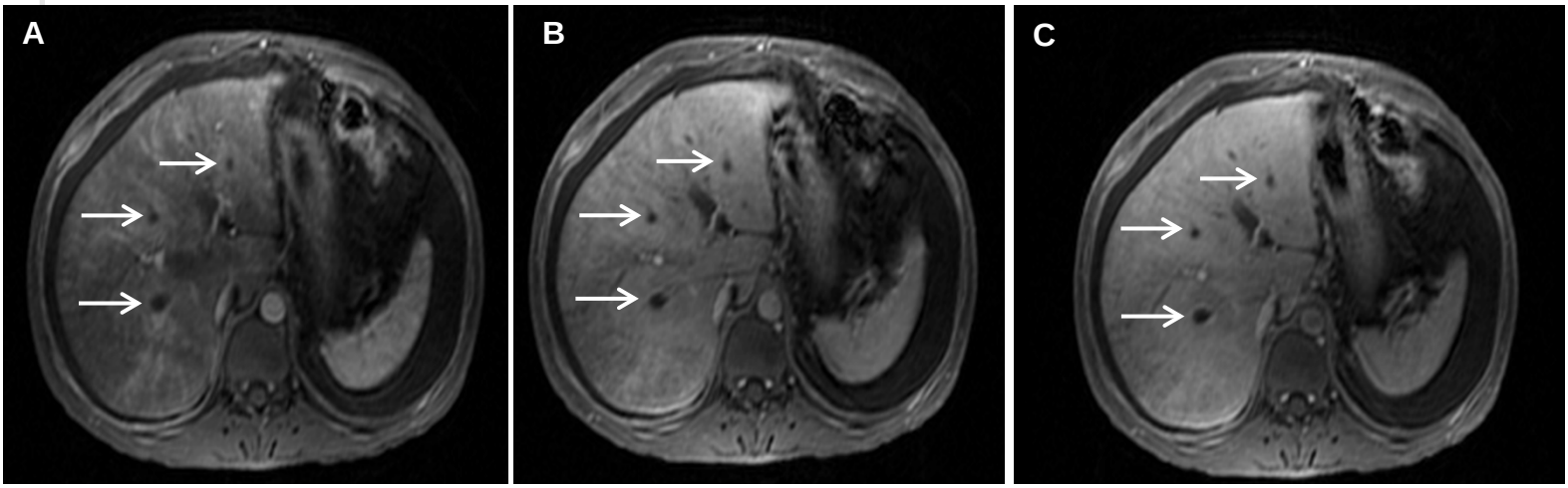


Figure 26. Budd-Chiari syndrome, a thrombosis of the hepatic vein. Note the heterogeneous appearance of altered perfusion in the (A) arterial, (B) portal-venous, and (C) delayed phases, as well as the lack of enhancement of the hepatic vein, which is nodular and hypointense.

Images courtesy of A. Guimaraes, MD, PhD. MGH Department of Radiology.

MR Arthrography

MR arthrography is a technique that increases intra-articular contrast to better visualize small labral or tendon tears, similar to x-ray arthrography.

MR arthrography consists of an injection of a mixture of a GBCA and an iodinated contrast agent used in CT scanning. The iodinated contrast allows the visualization of needle placement under fluoroscopy and confirms that the joint space has been accessed. The GBCA provides the contrast mechanism under MR visualization (**Figure 27**).

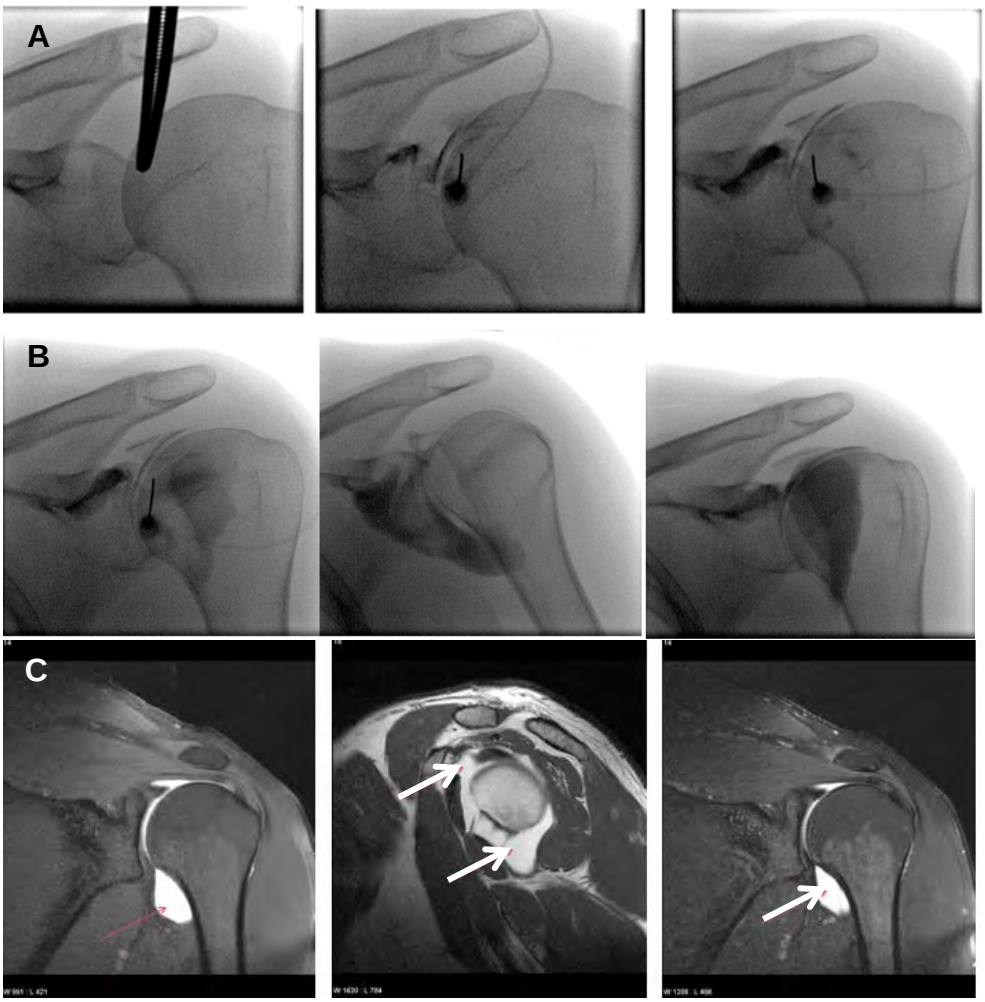


Figure 27. MR arthrogram. (A, B) Images demonstrating needle placement. (C) Contrast fills and well defines the joint space, allowing visualization of subtle changes in the glenoid and surrounding tissues (arrows).

Courtesy of J. Frank Simeone, MD, Massachusetts General Hospital.

Dynamic-susceptibility Contrast Imaging

Dynamic-susceptibility contrast imaging (DSC), also known as bolus-tracking MRI, is a dynamic method for measuring perfusion and other hemodynamic parameters[21]. *Susceptibility* in the context of MR imaging relates to the loss of MR signal[22]. Using a very rapid bolus, dramatic changes in T2* are apparent, and changes in relative cerebral blood flow and relative cerebral blood volume can be quantified (**Figures 28-29**).

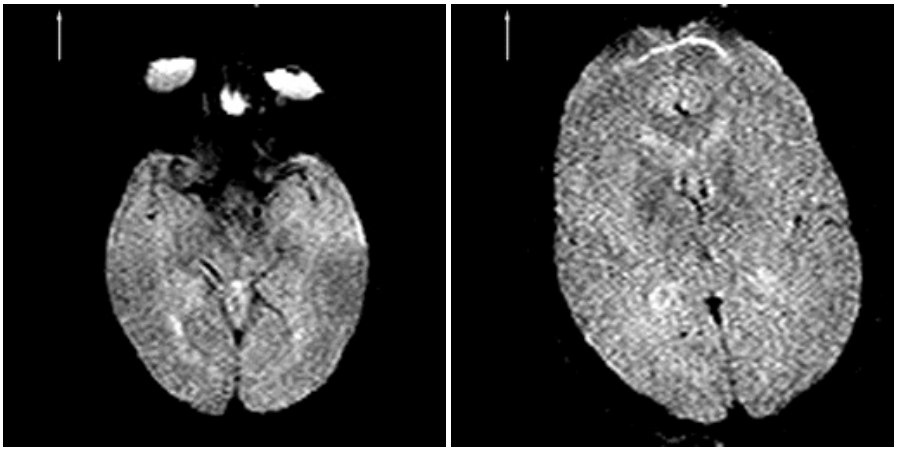


Figure 28. (L) MOVIE. Normal perfusion of the brain using dynamic-susceptibility contrast imaging.

Click here to view the movie:
www.YouTube/ICPMEducation

Figure 29. (R) MOVIE. Dynamic-susceptibility contrast imaging revealing altered perfusion and delayed transit through the right hemisphere. Diagnosis is right middle cerebral artery (MCA) stroke.

Click here to view the movie:
www.YouTube/ICPMEducation.

Movies courtesy of A. Guimaraes, MD, PhD. MGH Department of Radiology.

APPLICATION OF SECOND GENERATION AGENTS

Since 2004, five second generation gadolinium–based contrast agents have been introduced. While these newer GBCAs have many similarities with first generation agents, second generation GBCAs have different and, in some cases, improved properties.

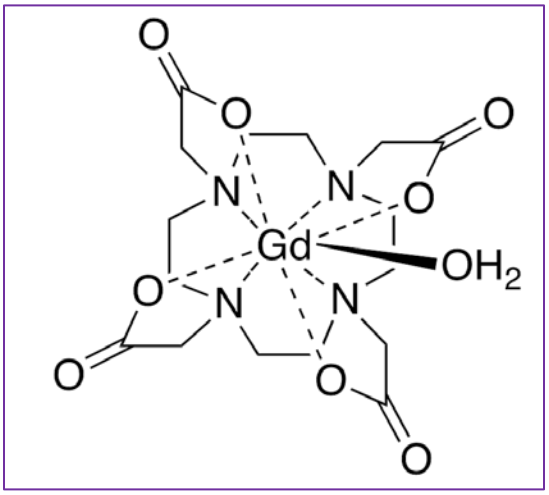


Figure 30. Chemical structure of Dotarem / Gd-DOTA / gadoterate meglumine.

Dotarem

Gadoterate meglumine, trade name Dotarem, is an extracellular fluid agent and has been in clinical use in Europe for many years. Dotarem has a safety record similar to first generation GBCAs and was approved by the FDA for use in the United States in 2013.

Chemical structure

Dotarem is an ionic macrocyclic agent with a single negative charge (**Figure 30**). In chemical **assays** of thermodynamic stability and kinetic inertness, Dotarem performs the best of all the GBCAs. The formulation and relaxivity properties of Dotarem are typical of first generation extracellular agents.

Clinical indications

Dotarem is indicated for intravenous use in the brain, spine, and associated tissues in adult and pediatric patients (≥ two years of age) for detection and visualization of areas with disruption of the blood brain barrier or abnormal vascularity (**Figure 31**).

Safety

In a recent study of more than 84,000 patients who were given Dotarem, adverse events such as nausea, vomiting, and urticaria were observed in 0.34% of the examinations and were primarily rated as minor[23]. Eight patients (0.0001%) reported serious adverse events. The adverse event rate was significantly higher in patients with a history of allergies and in patients with a previous allergic reaction to contrast media. There was no increase in the incidence of adverse events in patients with renal impairment. It was concluded that Dotarem has a low rate of adverse events and produces good or excellent image quality in most patients, with or without patient risk factors.

Doterem is classified as a Group II mid-risk agent for NSF by the American College of Radiology.

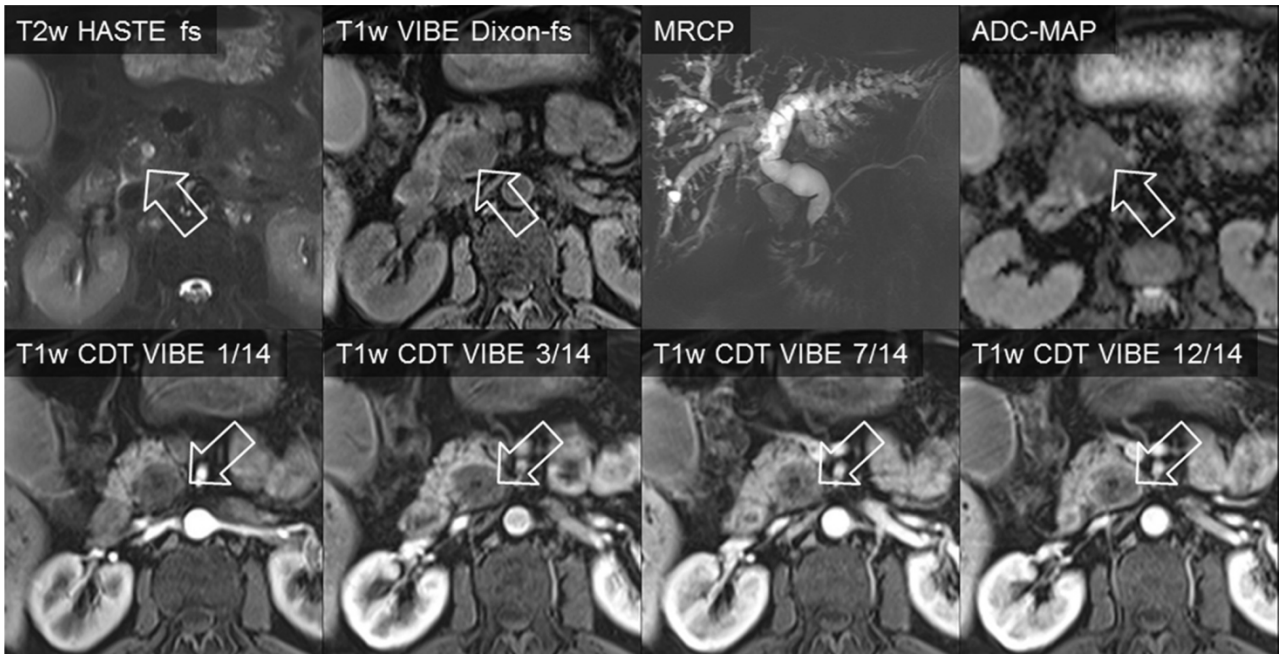


Figure 31. 57-year-old male with adenocarcinoma of the pancreas. After administration of Dotarem, the axial T1 and T2W images show a T2 mildly hyperintense mass with intrahepatic cholestasis. The mass is seen on MRCP and decreased ADC. On the CDT-VIBE, the tumor is clearly shown to be hypovascular with gradual development of peripheral enhancement consistent with adenocarcinoma of the pancreas.

Courtesy of Henrik Michaely, MD, Institute of Clinical Radiology and Nuclear Medicine, University Medical Centre Mannheim, Mannheim, Germany.

Gadavist

Gadobutrol, trade name Gadavist, is an extracellular contrast agent approved by the FDA in 2011. Compared to first generation gadolinium-based contrast agents, Gadavist has about 25% greater relaxivity than other ECF contrast agents. The higher relaxivity produces greater enhancement in T1-weighted imaging.

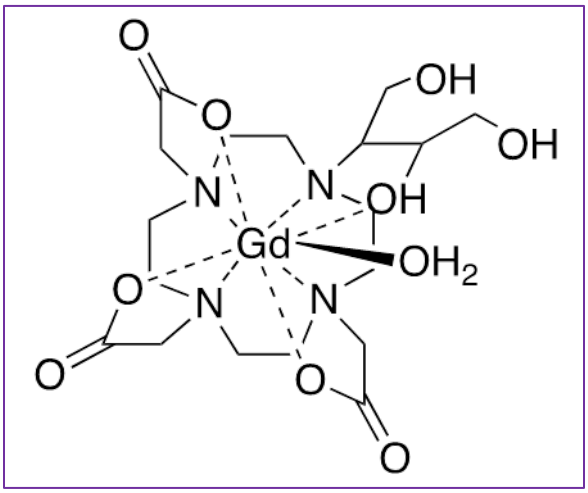


Figure 32. Chemical structure of Gadavist / GD-BT-DO3A / gadobutrol

Chemical structure

Gadavist is a nonionic macrocyclic agent (**Figure 32**). Because of the nonionic nature of Gadavist, it is formulated at double the concentration compared to most GBCAs, meaning an equivalent dose can be administered at half the volume.

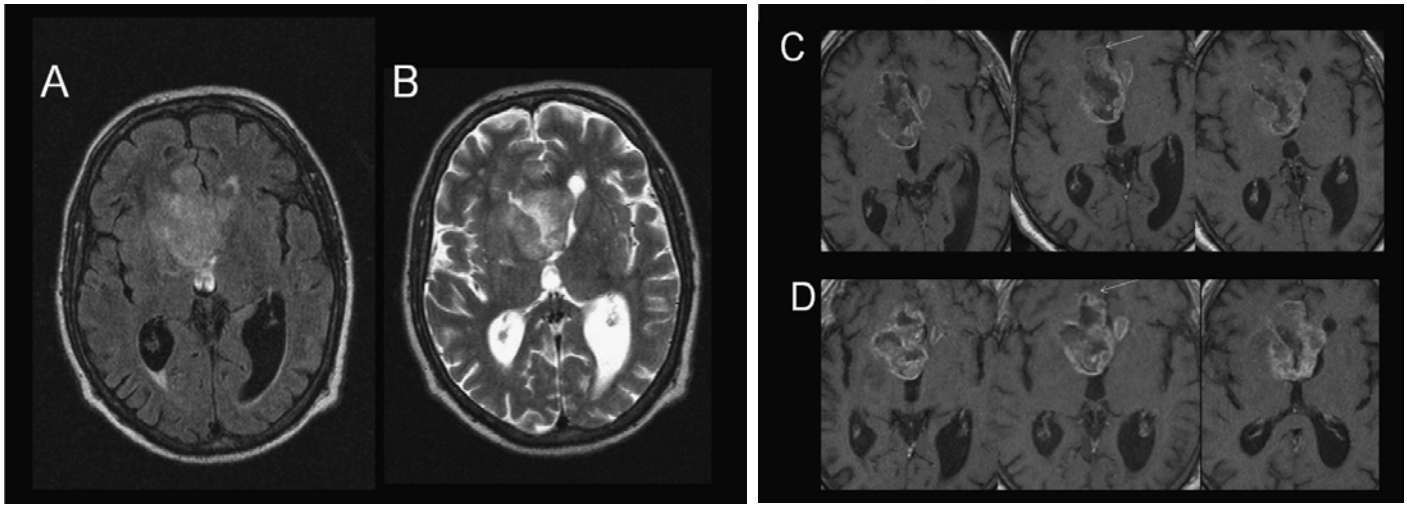


Figure 33. 69-year-old male with butterfly glioma. (A, B) FLAIR and T2W images using Gadavist shows the typical butterfly appearance and infiltration of the partially necrotic tumor into both frontal lobes. Three consecutive T1W images were acquired after a single dose of Dotarem (C) and Gadavist (D). Because of the higher concentration formulation of Gadavist, the enhancement margins are better defined and the internal structures of the tumor are better differentiated.

Courtesy of Nicoletta Anzalone, MD Department of Neuroradiology, Scientific Institute H.S. Raffaele, Milan, Italy.

Does this lower volume affect image quality? A 2003 study reviewed the use of Gadavist in brain perfusion studies where, T2*-weighted imaging was used to evaluate the effect of the high concentration of Gadavist on first pass[24].

The higher formulated concentration of Gadavist results in administration of a tighter bolus and greater drop in signal on first pass. This drop in signal is much greater for the 10cc bolus of the 1.0 mol/L formulation compared to the 20cc bolus of the 0.5 mol/L formulation, resulting in better delineation of the perfusion rate.

In a 2013 multicenter study comparing Gadavist to Dotarem, there was increased conspicuity of lesions based on their enhancement at the equivalent time post-injection of Gadavist[25] (**Figure 33**).

Clinical indications

Gadavist is indicated for intravenous use in adults and pediatric patients (≥ two years of age) for detection and visualization of areas with disrupted blood brain barrier or abnormal vascularity of the central nervous system.

Safety

Gadavist is classified as a Group II mid-risk agent for NSF by the American College of Radiology.

MultiHance

Gadobenate dimeglumine, trade name MultiHance, is a slightly different class of contrast agent. It has the same Gd-DPTA core molecule as Magnevist, but the benzyl group added to the MultiHance formulation provides weak serum protein binding that results in slightly higher relaxivity. MultiHance was approved by the FDA in 2004.

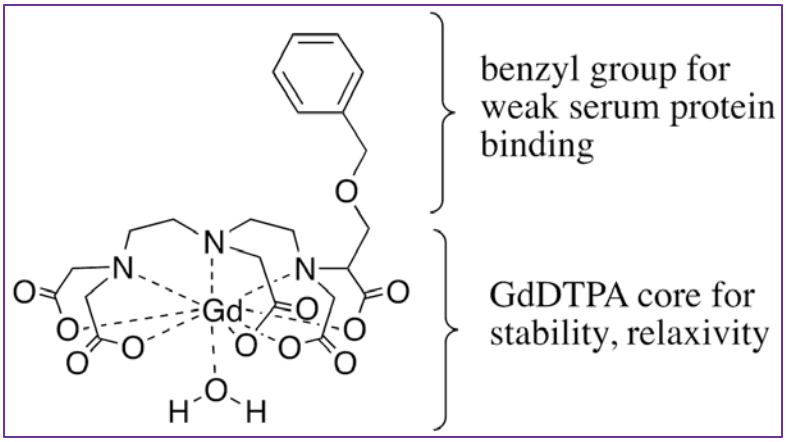


Figure 34. Chemical structure of MultiHance / gadobenate dimeglumine / Gd-BOPTA.

Chemical structure

MultiHance is a linear ionic contrast agent (**Figure 34**). The distribution of MultiHance is similar to other extracellular agents although it is classified as a weak protein-binding agent. Compared to the other ECFs, MultiHance has higher relaxivity by about a factor of two. Recall that with a higher relaxivity agent, better conspicuity of lesions at a lower dose can be achieved.

MultiHance demonstrates weak and transient interactions with serum proteins that cause slowing in the tumbling of the molecule, resulting in increases in relaxivity in solutions containing serum proteins. The improved relaxation effect contributes to increased contrast-to-noise ratio and lesion-to-brain ratio, potentially improving visualization[26].

Clinical indications

Like Dotarem and Gadavist, MultiHance is indicated for central nervous system studies.

Safety

MultiHance is classified as a Group II mid-risk agent for NSF by the American College of Radiology. It has a similar adverse event profile to other first generation GBCAs.

For an angiographic comparison of MultiHance, Gadavist, and Dotarem, see **Figure 35**. **Figure 36** is a comparison of MultiHance to a first generation extracellular agent.

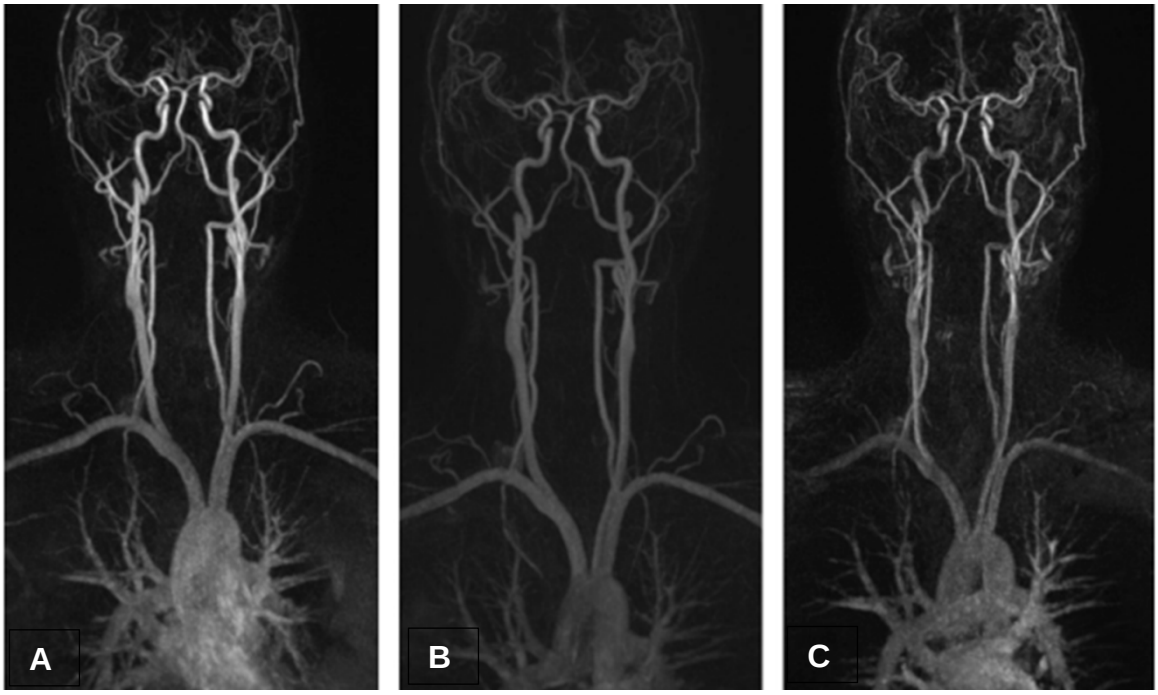


Figure 35. MRA of the supra-aortic vessels. Comparison of signal intensity and image contrast using (A) Gadavist, (B) MultiHance, and (C) Dotarem. Note the higher signal intensity and image contrast in the macrocyclic contrast agents, Gadavist and Dotarem. No significant differences in edge blurring are visible.

Courtesy of J. Harald Kramer, MD, Institute for Clinical Radiology, Ludwig Maximilians University Hospital Munich, Munich, Germany.

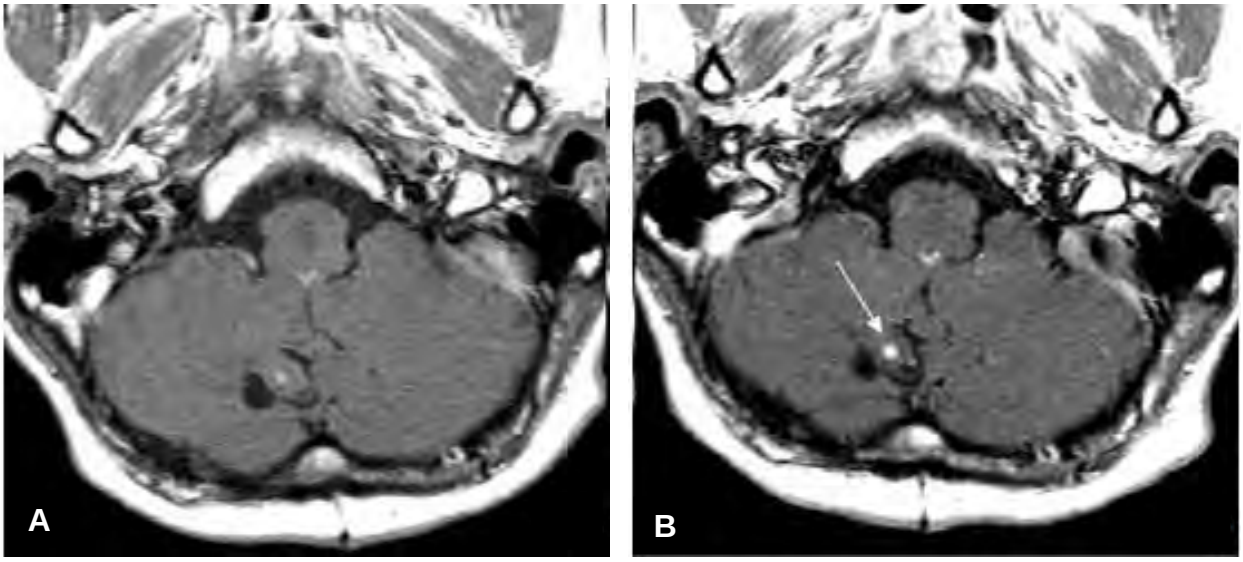


Figure 36. Axial image of the brain. (A) First generation ECF agent (B) MultiHance. The higher relaxivity and increased contrast-to-noise properties of MultiHance increase the conspicuity of the small lesion in the right hemisphere of the cerebellum (arrow) using the same pulse sequence.

Courtesy of A. Guimaraes, MD, PhD. MGH Department of Radiology.

Ablavar

Gadofosveset trisodium, trade name Ablavar, is designed to have reversible binding to the blood protein albumin. This structure creates longer retention times within the blood pool and provides a large imaging window of opportunity for MR angiographic studies. Ablavar is given at a lower dose of 0.03mmol/kg. It was approved by the FDA in 2008.

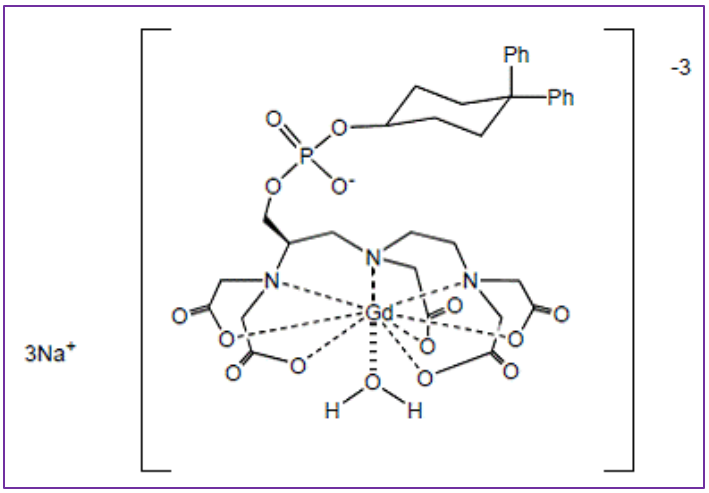


Figure 37. Chemical structure of Ablavar / gadofosveset trisodium / MS325

Chemical structure

Ablavar, like MultiHance, is also based on the ionic linear Gd-DTPA core molecule but has two aromatic rings (denoted by Ph) bound to the chelator making the molecule more **lipophilic** or fat soluble (**Figure 37**). The combination of lipophilicity and negative charge causes Ablavar to bind with serum albumin. The strong serum protein binding (80-90% bound to albumin, with the remaining 10-20% filtered through the kidneys) creates a large chemical structure that prevents ready diffusion out of the capillaries into the extracellular space, resulting in a prolonged half-life within the blood pool and consequently that large imaging window of opportunity for MR angiography.

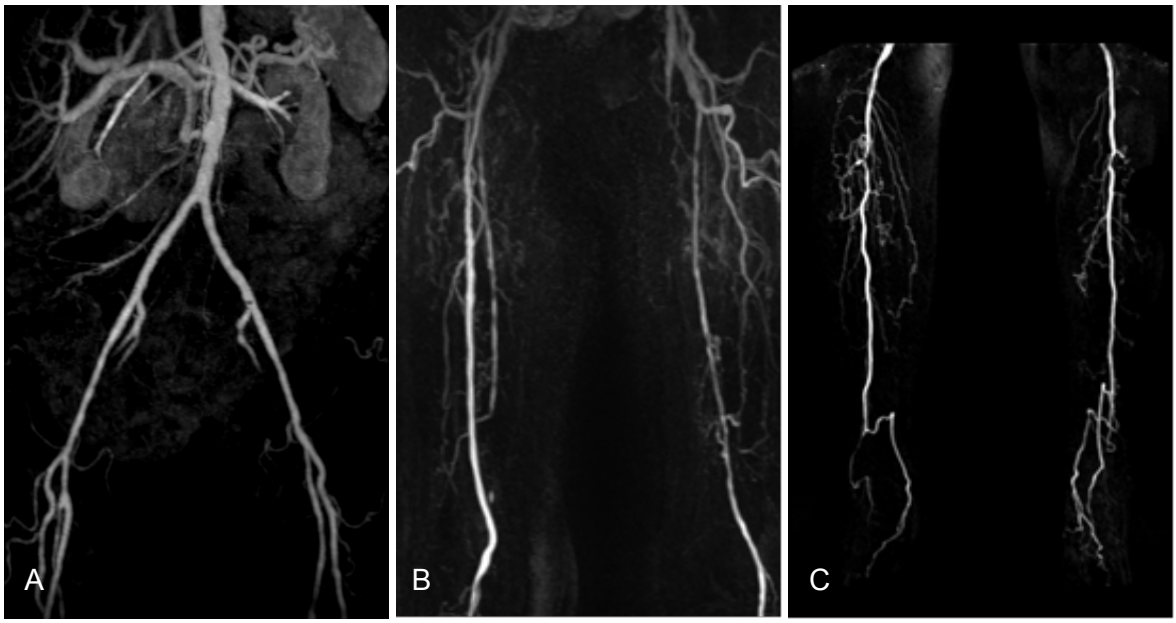
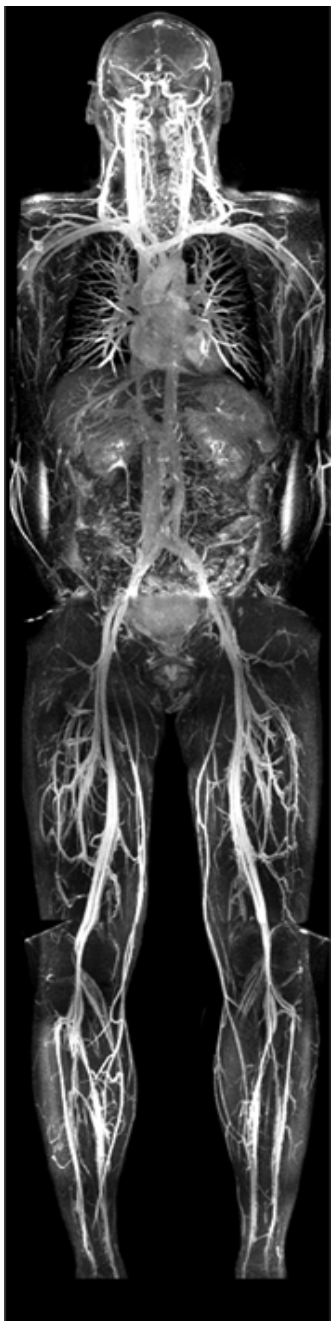


Figure 38. Peripheral MRA using Ablavar. (A) Aortoilliac. (B) Femoropopliteal. (C) Tibials.

Courtesy of Mark Lewis, MD, Norfolk and Norwich University Hospital, Norwich, UK.

Clinical indications

Ablavar is approved for MR angiography in aortoiliac occlusive disease. Because of its blood pool properties, it is used off-label for cerebral, carotid, peripheral, and coronary MR angiography, as well as the great vessels. It produces excellent quality images of all chambers of the heart and coronary arteries and exquisitely depicts renal stenosis. It has also been used off-label for venography.



As a result of its long-lived intravascular state, Ablavar allows for visualization of the entire vascular system without significant enhancement of the peripheral tissues. In combination with improved technology that allows for more rapid imaging and whole body registration, the previous inability to perform whole body angiography has become a reality. **Figure 38** demonstrates peripheral MRA and **Figure 39** shows a complete vascular assessment using Ablavar.

Mechanism of action

When Ablavar is injected into the blood stream, it rapidly binds to serum albumin, which causes an increase in relaxivity and the MR signal to be further enhanced. **Figure 40** is an illustration and animation that shows the molecule glowing brightly upon binding to the protein, reflecting the higher relaxivity and signal increase due to protein binding. The protein binding also restricts the compound to the blood vessels.

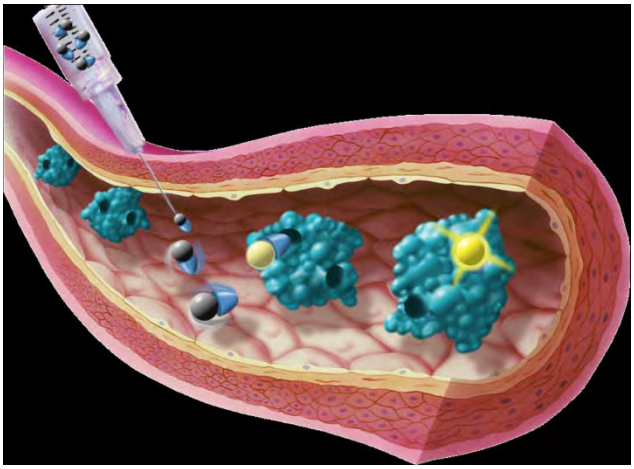
Safety

Since Ablavar was recently approved in the United States, its safety profile is not as well established. The literature indicates that adverse events associated with Ablavar are similar to those seen with other GBCAs, eg, hives and urticaria.

Because of its formulation, Ablavar is highly thermodynamically and kinetically stable, it is currently classified as a Group III low-risk agent for NSF.

Figure 39. Whole body scan using Ablavar.

Courtesy of A. Guimaraes, MD, PhD. MGH Department of Radiology.



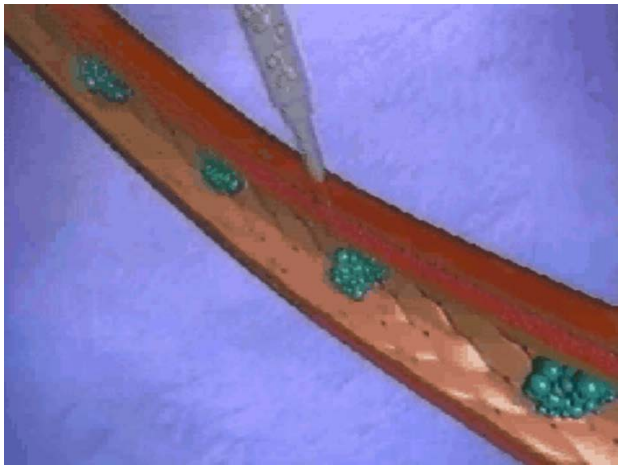


Figure 40. (Left) Reversible binding of Ablavar to serum albumin. (Right) **MOVIE**. Animation of the GBCA molecule binding to the protein.

Click here to view the movie: www.YouTube/ICPMEducation.

Courtesy Peter Caravan, PhD.

Eovist

Gadoxetic disodium acid, trade name Eovist, is a gadolinium-based MRI contrast agent approved by the FDA in 2008. It is the first and currently only GBCA approved for the detection and characterization of known or suspected focal liver lesions in adults.

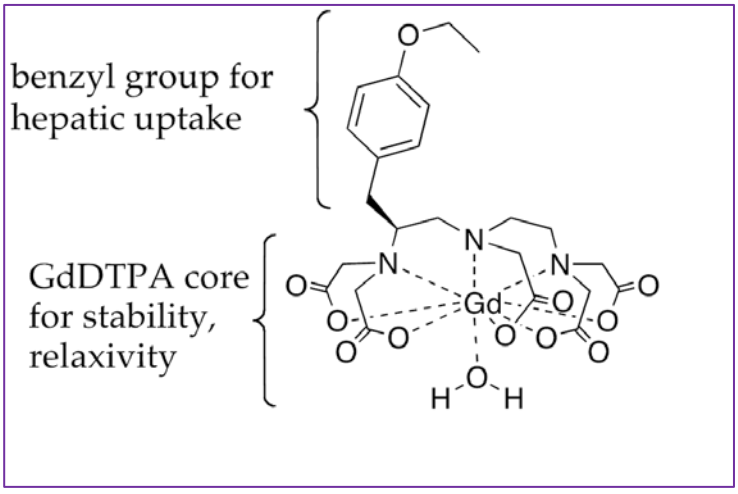


Figure 41. Chemical structure of Eovist / gadoxetate disodium / Gd-EOB-DTPA

Chemical structure

Eovist is based on the ionic linear Gd-DTPA and is similar to MultiHance with the added benzyl group. A change in the orientation of a couple of atoms differentiates Eovist from MultiHance (**Figure 41**).

Clinical indications

The clinical utility of Eovist is in imaging hepatic focal nodular hyperplasia, adenoma, and metastasis. Eovist is also used for MRA or imaging of vascular lesions, **arteriovenous malformation** (AVM), **hemangioma**, and **hepatocellular carcinoma**.

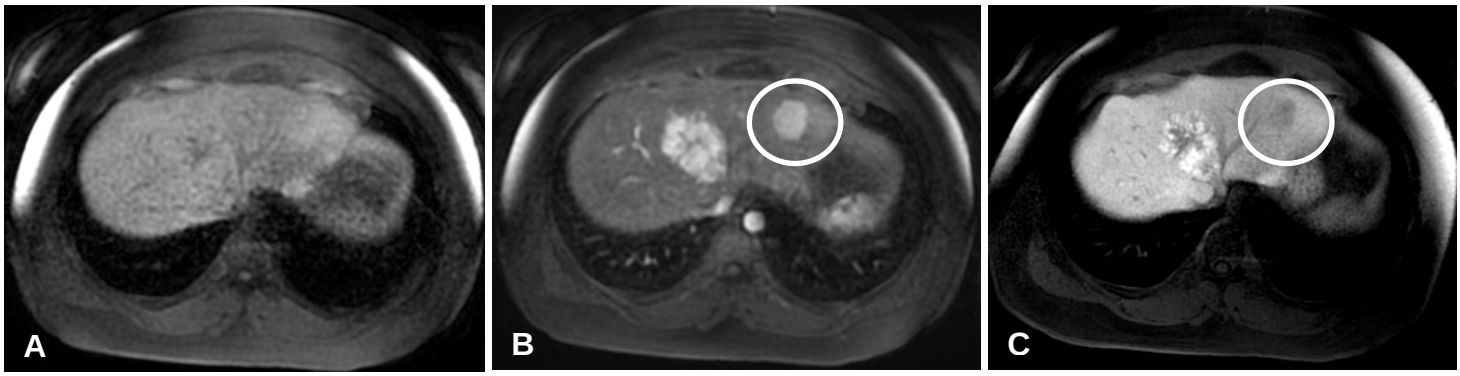


Figure 42. T1W images of the liver. (A) Precontrast. (B) Postcontrast arterial phase. (C) Delayed hepatobiliary phase (20 minutes post-injection) demonstrates two arterially-enhancing lesions within the left lobe of the liver. On the delayed phase image, the lesion on the left shows no uptake of Eovist, consistent with an adenoma. The second lesion demonstrates contrast uptake and a central scar, consistent with focal nodular hyperplasia.

Courtesy of A. Guimaraes, MD, PhD. MGH Department of Radiology.

Mechanism of action

Eovist is unique in that about 50% of the contrast material is excreted through the liver and into the bile. Eovist has some weak protein binding and thus slightly higher relaxivity compared to first generation gadolinium-based contrast agents. Although Eovist has a very high percentage of hepatic clearance, it is approved at a much lower dose than most GBCAs — a quarter of the standard dose at 0.025 mmol/kg as compared to 0.1 mmol/kg for most GBCAs.

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 without functioning hepatocytes appear hypointense, while lesions that have functioning hepatocytes appear hyperintense. Liver lesions that are not comprised of hepatocytes will not take up contrast and thus will not enhance.

Figure 42 shows pre- and postcontrast liver images using Eovist. **Figure 43** demonstrates the four phases of contrast.

Safety

Because of its formulation, Eovist is highly thermodynamically and kinetically stable, it is currently classified as a Group III low-risk agent for NSF.

Because of the high percentage of hepatic clearance, there has been concern that Eovist is contraindicated in patients who have hepatitis or cirrhosis. So far, Eovist has been found safe for these patient cohorts; patients with cirrhosis are often evaluated with Eovist because of its ability to distinguish perfusion anomalies as compared to small hepatocellular carcinomas.

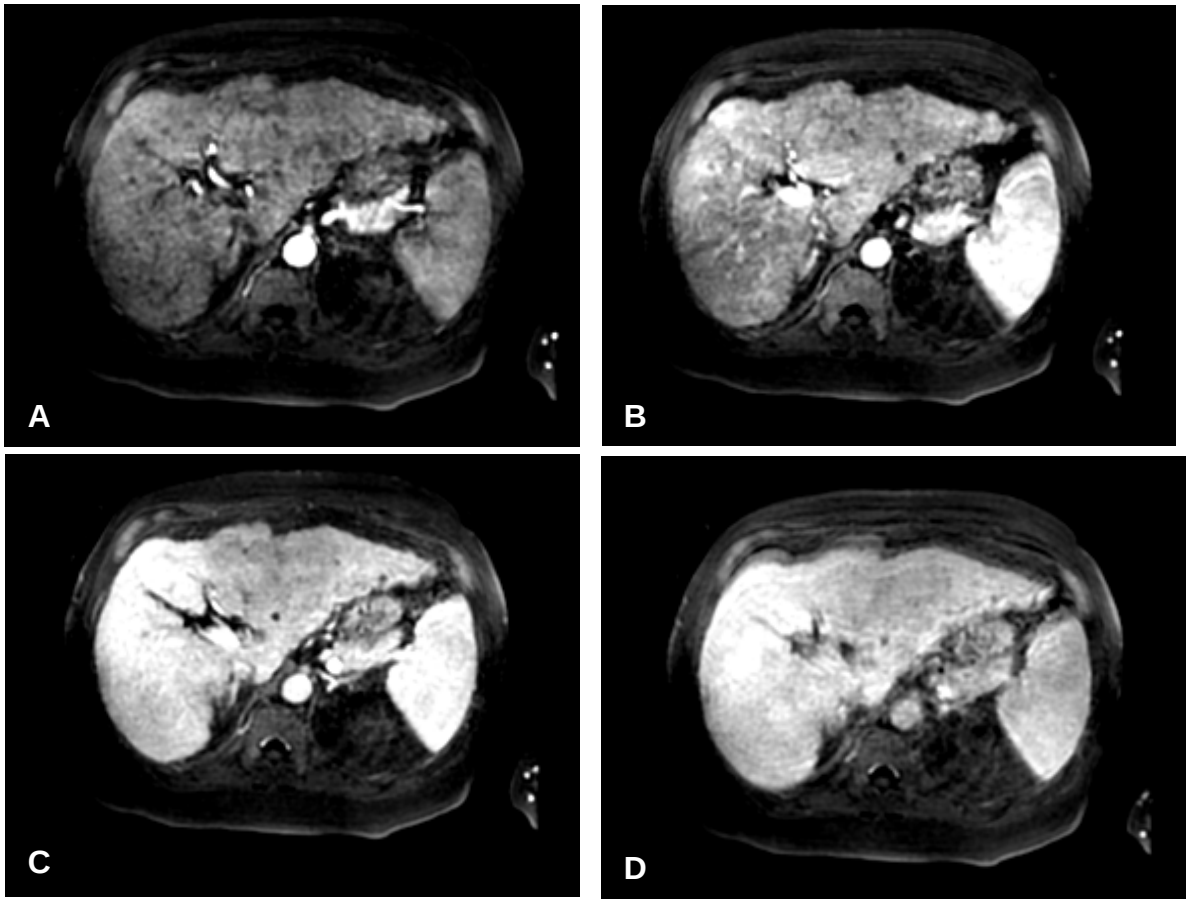


Figure 43. T1-weighted imaging demonstrating the four phases of contrast. (A) Early arterial phase. (B) Arterial phase. (C) Portal venous phase. (D) Delayed hepatobiliary phase (20 minutes post-injection). Note the nodular morphology to the liver contour compatible with cirrhosis. There is a diffuse region encompassing the entirety of the left lobe that demonstrates mild, heterogeneous contrast uptake. On delayed hepatobiliary phase imaging, this region shows decreased uptake and is compatible with a diffuse infiltration hepatocellular carcinoma.

Courtesy of A. Guimaraes, MD, PhD. MGH Department of Radiology.

SUMMARY

MRI remains a critical imaging modality in the characterization of normal tissue and the diagnosis of most abnormal conditions and disease states. The addition of gadolinium-based contrast agents enhances the conspicuity of pathology using MRI. Gadolinium-based contrast agents continue to be a safe and effective adjunct for producing high quality, diagnostic MR images with little to no risk to the patient.

The use of particular contrast agents for specific clinical indications is the choice of the end user and clinical facility based on their needs and interpretation of published performance and safety data.

REFERENCES

1. Data from Massachusetts General Hospital Department of Radiology.

2. Colletti PM. Nephrogenic systemic fibrosis and gadolinium: a perfect storm. AJR Am J Roentgenol. 2008;191(4):1150-1153.

3. United States Department of the Interior website. What does water do for you? Available at: http://ga.water.usgs.gov/edu/propertyyou.html. Accessed October 30, 2013.

4. Rohrer M, Bauer H, Mintorovitch J, Requardt M, Weinmann HJ. Comparison of magnetic properties of MRI contrast media solutions at different magnetic field strengths. Invest Radiol. 2005;40(11):715-724.

5. Kinetic inertness and thermodynamic stability. Adapted from Frenzel, et al. *Invest Radiol*. 2008;43:817; Port, et al. *Biometals*. 2008:21:469-490.

6. University of California San Francisco website. Contrast extravasation. Available at: http://www.radiology.ucsf.edu/patient-care/patient-safety/contrast/iodinated/contrast-extravasation. Accessed November 1, 2013.

7. Davenport MS, Wang CL, Bashir MR, Neville AM, Paulson EK. Rate of contrast material extravasations and allergic-like reactions: effect of extrinsic warming of low-osmolality iodinated CT contrast material to 37 degrees C. Radiology. 2012;262(2):475-484.

8. American College of Radiology website. ACR Manual on Contrast Media v9 2013. Available at: http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/Contrast%20Manual/2013_Contrast_Media.pdf. Accessed September 26, 2013.

9. Widmark JM. Imaging-related medications: a class overview. *Proc (Bayl Univ Med Center).* 2007;20(4):408-417.

10. Jung JW, Kang HR, Kim MH, et al. Immediate hypersensitivity reaction to gadolinium-based MR contrast media. Radiology. 2012;264(2):414-422.

11. Prince MR, Zhang H, Zou Z, Staron RB, Brill PW. Incidence of immediate gadolinium contrast media reactions. *AJR Am J Roentgenol.* 2011;196(2):W138-143.

12. Prince MR, 2011.

13. Prince MR, 2011.

14. American College of Radiology website. ACR Manual on Contrast Media v9 2013.

15. American College of Radiology website. ACR Manual on Contrast Media v9 2013.

16. National Kidney Disease Education Program website. GRF MDRD Calculator for Adults. Available at: http://nkdep.nih.gov/lab-evaluation/gfr-calculators/adults-conventional-unit.shtml. Accessed November 7, 2013.

17. American College of Radiology website. ACR Manual on Contrast Media v9 2013.

18. Girardi M, Kay J, Elston DM, Leboit PE, Abu-Alfa A, Cowper SE. Nephrogenic systemic fibrosis: clinicopathological definition and workup recommendations. J Am Acad Dermatol. 2011;65(6):1095-1106.

19. Broome DR. Nephrogenic systemic fibrosis associated with gadolinium based contrast agents: a summary of the medical literature reporting. Eur J Radiol. 2008;66(2):230-234.

20. Broome DR, 2008.

21. Calamante F. Perfusion MRI using dynamic-susceptibility contrast MRI: quantification issues in patient studies. Top Magn Reson Imaging. 2010;21(2):75-85.

22. MR-TIP website. Available at: http://www.mr-tip.com/serv1.php?type=db1&dbs=dynamic%20susceptibility. Accessed November 8, 2013.

23. Maurer M, Heine O, Wolf M, et al. Tolerability and diagnostic value of gadoteric acid in the general population and in patients with risk factors: results in more than 84,000 patients. Eur J Radiol. 2012;81(5):885-890.

24. Tombach B, Benner T, Reimer P, et al. Do highly concentrated gadolinium chelates improve MR brain perfusion imaging? Intraindividually controlled randomized crossover concentration comparison study of 0.5 versus 1.0 mol/L gadobutrol. Radiology. 2003;226(3):880-888.

25. Anzalone N, Scarabino T, Venturi C, et al. Cerebral neoplastic enhancing lesions: multicenter, randomized, crossover intraindividual comparison between gadobutrol (1.0M) and gadoterate meglumine (0.5M) at 0.1 mmol Gd/kg body weight in a clinical setting. Eur J Radiol. 2013;82(1):139-145.

ABBREVIATION GLOSSARY

ADC	apparent diffusion coefficient
AE	adverse event
ACR	American College of Radiology
AVM	arteriovenous malformation
B_1	magnetic field for RF transmission pulse oriented 90° to the main magnetic field (B_0)
BBB	blood brain barrier
cc	cubic centimeter; 1/1000 of a liter; also 1 milliliter (mL)
CNS	central nervous system
CSF	cerebrospinal fluid
CTA	computed tomography angiography
DCE	dynamic contrast-enhanced
DM	diabetes mellitus
DSC	dynamic-susceptibility contrast
ECF	extracellular fluid (contrast agent)
FHN	focal nodular hyperplasia
eGFR	estimated glomerular filtration rate
GBCA	gadolinium-based contrast agent
GFR	glomerular filtration rate
HCC	hepatocellular carcinoma
M	molar, as relates to mole, a unit of measurement in chemistry
MCA	middle cerebral artery
MDRD	Modification of Diet in Renal Disease
MIP	maximum intensity projection
mmol	millimole; 1/1000 of a mole
MRA	magnetic resonance angiography
MRCP	magnetic resonance cholangiopancreatography
NSF	nephrogenic systemic fibrosis
PVD	peripheral vascular disease
r_1	T1 relaxivity
R_1	relaxation rate
r_2	T2 relaxivity
RF	radiofrequency

GLOSSARY OF TERMS

affinity
in chemistry, a special attraction or force between particles that cause them to combine

anaphylactic/anaphylaxis
a systemic or generalized hypersensitivity reaction from exposure of a sensitized individual to a specific antigen, like shellfish, nuts, or penicillin, which otherwise are harmless to non-sensitized individuals. Unlike an allergic reaction, anaphylaxis can result in complete airway obstruction, shock, and even death. An *anaphylactoid* reaction resembles anaphylaxis but does not involve an immunological mechanism; sometimes called *pseudoanaphylactic*.

angiogenesis/angiogenic
the formation of new blood vessels, especially blood vessels that supply oxygen and nutrients to cancerous tissues

angiogram/angiography
an imaging technique used to visualize blood vessels

arteriovenous malformation (AVM)
a vascular abnormality where arteries and veins are connected and bypass the capillary system. AVMs can appear anywhere in the body but are usually found in the central nervous system.

arthrogram/arthrography
a series of joint images acquired after a mixture of saline, radiopaque contrast material, and dilute gadolinium-based contrast agent is injected directly into the joint under x-ray guidance for the purpose of evaluating inter-articular injury or integrity; can be acquired via x-ray, CT, or MRI

assay
a type of chemical or biological measurement or test

atrophy
the wasting away of an organ or part or a body from degeneration or decline

blood brain barrier (BBB)
a naturally occurring barrier that separates the circulating blood and brain extracellular fluid in the central nervous system. Occurs along the capillaries and consists of tight junctions around capillaries that do not exist in normal circulation outside of the brain. Inhibits passage of certain materials from the blood into brain tissue.

blood pool agents
in MRI, a gadolinium-based contrast agent that persists within the blood pool for an extended period of time and allows for visualization of pathology within the leaky blood brain barrier, assessment of stenotic vessels, and differentiation of hypervascular from nonvascular lesions

Brownian motion
a random movement of microscopic particles suspended in a fluid; also called *Brownian movement.* Named for Scottish botanist and scientist, Robert Brown (1773–1858).

Budd-Chiari syndrome
a rare condition caused by obstruction of the hepatic venous outflow and characterized by hepatomegaly, ascites, and abdominal pain; prognosis is poor if the condition is left untreated. Named for English physician George Budd (1808-1882) and Austrian pathologist Hans Chiari (1851-1916).

catalyst/catalytic
in chemistry, a catalyst is a substance that accelerates the rate of a chemical reaction or process without being affected itself

chelation/chelate/chelator
to combine a metal ion with a chemical compound to form a ring; used in the synthesis of gadolinium contrast agents to ensure their efficacy and safety

collagen
a class of extracellular protein especially found in the skin, bone, cartilage, tendons, and teeth that forms strong, insoluble fibers and serves as connective tissue between cells

compartment syndrome
occurs when pressure within the muscles builds to a dangerous level that can decrease blood flow; compartments are groupings of nerves, muscles, and blood vessels in the arms or legs, and the syndrome develops when swelling or bleeding occurs within a compartment

creatinine
byproduct of normal breakdown of creatine phosphate in the body; serum creatinine levels are used as a measurement of kidney function

cytokines
one of several proteins secreted by cells that carry signals to neighboring cells

edema
excessive accumulation of fluid in tissue spaces that causes swelling of the area

electron
a negatively charged subatomic particle that typically orbits the nucleus of an atom

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

extravasation, contrast agent
the unintentional or accidental extravascular injection of an intravascular contrast agent

fascia/fascial
a layer or band of fibrous tissue that connects and/or supports muscles or organs

fibrosis/fibrotic
the formation of an abnormal fibrous (fiber-like) tissue in an organ or part as a result of inflammation, irritation, or healing

glomerular filtration rate
volume of blood that passes through the kidney's filters (glomeruli) each minute

hemangioma
a benign, vascular tumor in which proliferation of blood vessels results in a mass; they can be present at birth or develop during life; they can occur anywhere in the body but are most often noticed in the skin and subcutaneous tissues

hemochromatosis
a rare, inherited metabolic defect caused by deposit of iron-containing substances; usually affects the liver, spleen, and pancreas

hemosiderosis
excessive deposit of hemosiderin, an iron-containing protein that results from disorders of iron metabolism and breakdown of red blood cells

hepatocellular carcinoma (HCC)
a primary malignancy that arises from the liver itself and usually develops in the setting of chronic liver disease or cirrhosis, for which the long-term prognosis is poor; also called *hepatoma*

hepatocyte
a liver cell

hepatorenal syndrome
acute renal failure in people with liver or biliary tract disease

hydrophilic
a molecule or molecular entity that has an affinity for water and tends to be water soluble; literally, "water loving"

induration
an abnormally hard spot

inert
having no inherent power of action, as opposed to active or labile; in chemistry, having little to no ability to react

ion/ionic
a negatively or positively charged atom or molecule

kinetics
the branch of chemistry that studies the rates of chemical reactions; in relationship to GBCAs, kinetics reveals how fast free gadolinium is released from its chelator

kinetic modeling
in MRI, measuring the MRI signal change as a function of time before, during, and after GBCA injection, and then subjecting that signal vs time data to a mathematical model to determine how rapidly the GBCA is transported from the blood into the extravascular extracellular space; most commonly using in cancer imaging to characterize different lesion types as benign or malignant

lactic acidosis
a type of metabolic acidosis caused by an accumulation of lactic acid, typically due to lack of oxygen to the tissue

Larmor frequency
the frequency at which magnetic resonance is produced in a sample of hydrogen nuclei or other types of nuclei used in MRI; the frequency at which the hydrogen nuclei precess when disturbed from their alignment in the B_0 magnetic field. The Larmor frequency is determined by the equation

$$w = \gamma B_0$$

where γ equals the gyromagnetic ratio and B_0 is the magnetic field strength. Named for Irish physicist and mathematician Joseph Larmor (1857-1942).

lipophilic
a molecule or molecular entity that has an affinity for lipids and tends to be fat soluble; literally, “fat loving”

macrophage
a large white blood cell that occurs primarily in the connective tissue and bloodstream that ingests foreign particles and infectious microorganisms; part of the body’s immune system

mesothelioma
a malignant tumor of the lung or lining of the pleural and abdominal cavities and often associated with exposure to asbestos

molar (M)
pertaining to a solution containing one mole of solute per liter of solution; solute is the substance dissolved in a given solution

monocyte
a large circulating white blood cell formed in bone marrow and the spleen that ingests foreign particles and cell debris; part of the body’s immune system

morphology
the form or shape of an organism

nephrogenic systemic fibrosis (NSF)
a rare but potentially serious condition that has been associated with the use of gadolinium-based contrast agents in patients with kidney disease

nonantigenic
a substance that does not stimulate the production of antibodies, as opposed to antigenic/antigen

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

osmolality
a measure of the ability of a chemical compound to cause osmosis; measured in units of osmoles per kilogram of water (Osm/kg) or milliosmoles per kilogram of water (mOsm/kg)

osmosis
the diffusion of solvent molecules, such as water, from an area of lower concentration of dissolved substances to an area of higher concentration of dissolved substance; the net result is that the concentrations of the two solutions will equalize; GBCAs are formulated to be *hyperosmotic*, that is, with increased osmolality, as compared to blood plasma

perfusion
blood flow within capillaries to reach an organ or tissues

proton
a subatomic, positively charged particle; the hydrogen atom is sometimes referred to as a proton; hydrogen MRI and proton MRI refer to the same thing.

relative cerebral blood flow (rCBF)
cerebral blood flow (CBF) is the blood supply to the brain in a given time; in an adult the cerebral blood flow is typically 750 milliliters per minute or 15% of the cardiac output; relative CBF is the ratio of blood flow in one part of brain compared to another part, for example CBF in a stroke lesion relative to CBF in the same region in the contralateral hemisphere

relative cerebral blood volume (rCBV)
cerebral blood volume (CBV) is the volume of blood in a mass of brain tissue; normal gray matter/white matter amounts are approximately 7.2 and 3.6 mL of blood per 1000g of tissue. Relative CBV is the ratio of blood volume in one part of the brain compared to another part of the brain.

relaxivity
the extent to which one millimolar concentration of contrast agent can change 1/T1 or 1/T2; denoted as r_1 or r_2, respectively

soluble/solubility
capable of being dissolved; the property of being soluble

spin
the intrinsic angular momentum of an elementary particle, like a nucleus; in MRI, the hydrogen proton creates its own tiny magnetic field and begins spinning once subjected to the MRI magnet

stenosis/stenotic
abnormal narrowing of a vessel

thermodynamics
the branch of physics that studies the relationship of heat and mechanical energy and the conversion of one into the other; in relationship to GBCAs, thermodynamics relates to the change in energy associated with the binding of the gadolinium ion to its chelator, that is, the affinity of the chelator for the gadolinium ion

urticaria
a skin condition characterized by welts or wheals that itch intensely and can be caused by an allergic reaction, infection, or stress; commonly called *hives*

vasculopathy
any disease or disorder of the blood vessels

viscosity/viscous
the extent to which a fluid resists the tendency to flow and is dependent on the friction of the fluid's component molecules as they slide past one another; a viscous material is sticky, thick, or adhesive

water exchange
in relationship to GBCAs, a rapid process of water molecules dissociating from the gadolinium ion and being replaced by another water molecule, resulting in relaxation of the water molecules and consequent detection of the GBCA

PHYSICOCHEMICAL PROPERTIES OF GADOLINIUM-BASED CONTRAST AGENTS FOR MRI

First Generation GBCAs

Brand name	Magnevist	Omniscan	OptiMARK	ProHance
Generic Name	gadopentetate dimeglumine	gadodiamide	gadoversetamide	gadoteridol
Chemical Name	Gd-DTPA	Gd-DTPA-BMA	GD-DTPA-BMEA	Gd-HP-DO3A
Manufacturer	Bayer Healthcare Pharmaceuticals	GE Healthcare	Mallinckrodt	Bracco
Approval Date	1988	1993	1999	1992
Mechanism of Action	extracellular distribution renal excretion	extracellular distribution renal excretion	extracellular distribution renal excretion	extracellular distribution renal excretion
Molecular/ Chemical Structure	ionic linear	nonionic linear	nonionic linear	nonionic macrocyclic
Molecular Weight	939.0	573.6	661.8	558.7
Protein Binding Characteristic	no binding	no binding	no binding	no binding
Thermodynamic Stability (log *K*)	22.5	16.9	16.8	23.8
Conditional Stability Constant at pH 7.4 (log Kcond)	18.4	15.0	14.9	17.2
Osmolality (Osm/kg)	1.96	0.79	1.11	0.63
Viscosity (mPa · s at 37°C)	2.9	1.4	2.0	1.3
T1 Relaxivity (1.5T, plasma) ($L/mmol \cdot s^{-1}$)	4.1	4.3	4.7	4.1
T1 Relaxivity (3T, plasma) ($L/mmol \cdot s^{-1}$)	3.7	4.0	4.5	3.7
Formulation Concentration (M)	0.5	0.5	0.5	0.5
Excess Ligand (mol %)	0.20%	5%	10%	0.10%
Class	ECF	ECF	ECF	ECF
Indications	CNS Head and Neck Body	CNS Body	CNS Liver	CNS Head and Neck
Standard Dosage (mmol/kg)	0.1	0.1	0.1	0.1
Half-life (normal subjects)	1.6 hr	1.5 hr	1.7 hr	1.5 hr

PHYSICOCHEMICAL PROPERTIES OF GADOLINIUM-BASED CONTRAST AGENTS FOR MRI

Second Generation GBCAs

Brand name	MultiHance	Ablavar	Eovist	Dotarem	Gadavist
Generic Name	gadobenate dimeglumine	gadofosveset trisodium	gadoxetate disodium	gadoterate meglumine	gadobutrol
Chemical Name	Gd-BOPTA	MS-325	Gd-EOB-DTPA	Gd-DOTA	GD-BT-DO3A
Manufacturer	Bracco	Lantheus Medical	Bayer Healthcare Pharmaceuticals	Guerbet	Bayer Healthcare Pharmaceuticals
Approval Date	2004	2008	2008	2013	2011
Mechanism of Action	extracellular distribution weak protein binding higher relaxivity	albumin binding blood pool localization high relaxivity	hepatocyte specific	extracellular distribution renal excretion	extracellular distribution renal excretion
Molecular/ Chemical Structure	ionic linear	ionic linear	ionic linear	ionic macrocyclic	nonionic macrocyclic
Molecular Weight	1058.2	958.0	682.0	753.9	604.72
Protein Binding Characteristic	weak reversible binding	strong reversible binding	weak binding	no binding	no binding
Thermodynamic Stability (log *K*)	22.6	22.1	23.5	25.6	21.8
Conditional Stability Constant at pH 7.4 (log Kcond)	18.4	18.9	18.7	18.8	15.5
Osmolality (Osm/kg)	1.97	0.825	0.688	1.35	1.6
Viscosity (mPa · s at 37°C)	5.3	1.8	1.19	2.4	4.96
T1 Relaxivity (1.5T, plasma) (L/mmol · s^{-1})	6.3	27.7	6.9	3.6	5.2
T1 Relaxivity (3T, plasma) (L/mmol · s^{-1})	5.5	9.9	6.2	3.5	5
Formulation Concentration (M)	0.5	0.25	0.25	0.5	1
Excess Ligand (mol %)	0	1.30%	*	0	0.10%
Class	ECF liver	blood pool	liver	ECF	ECF
Indications	CNS Renal MRA Aorto-iliac MRA	Aorto-iliac MRA	Liver	CNS	CNS
Standard Dosage (mmol/kg)	0.1	0.03	0.025	0.1	0.1
Half-life (normal subjects)	1.2 - 2 hrs	16.3 hr	0.9 hr	1.7 hr	1.8 hr

*** amount of excess chelate not provided in package insert**