DISCUSSION GUIDE

The Pharmacist's Role in Promoting the Safe Use of Gadolinium-based Contrast Agents

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The Pharmacist's Role in Promoting the Safe Use of Gadolinium-based Contrast Agents

This continuing pharmacy education discussion guide is designed to provide pharmacists with an overview of gadolinium-based contrast agents and aid in the oversight and use of contrast media in their institutions. The distinguishing characteristics of the various gadolinium-based contrast agents (GBCAs) are compared with regard to their relaxivity and stability, and those effects on optimal diagnostic imaging. The role of the pharmacist in improving the safety of patients who receive GBCAs is discussed, which includes considerations when evaluating agents for the pharmacy and therapeutics committee.

The estimated time to complete this activity is 60 minutes. This activity is provided free of charge and is available from June 26, 2016, to May 26, 2017.

Learning Objectives

After participating in this knowledge-based educational activity, participants should be able to

- Compare and contrast the available gadolinium-based contrast agents (GBCAs) with respect to imaging of organs and tissues, half-life, and adverse effects.
- Explain the rationale for selecting a specific GBCA for a diagnostic procedure taking into account relaxivity and stability.
- Discuss available opportunities for pharmacists to improve patient safety during diagnostic procedures.
- Explain key factors for the pharmacy and therapeutics committee to consider when deciding which GBCAs to include on the formulary.

Target Audience

This continuing pharmacy education activity was planned to meet the needs of pharmacists practicing in hospitals, health systems, and ambulatory clinics, who handle and manage contrast agents.

The Pharmacist's Role in Promoting the Safe Use of Gadolinium-based Contrast Agents

Executive Summary

Gadolinium-based contrast agents (GBCAs) were introduced in the 1980s and improved the usefulness of magnetic resonance imaging (MRI) across a broad spectrum of diseases. Currently, nine GBCAs are FDA-approved for clinical use, and nearly one-third of MRI scans involve some type of non-specific GBCA.

The characteristics that differentiate the available GBCAs include chemical structure (linear or macrocyclic); ionicity (ionic and non-ionic); and thermodynamic stability. Another key characteristic is T1 relaxivity, which is a determinant of GBCA's efficacy as measured by signal intensity, contrast enhancement, and diagnostic efficacy.

The overall safety record for the GBCAs is remarkably positive. Most acute adverse events attributed to GBCAs are mild and self-limiting. Severe adverse reactions to GBCAs are rare. Patients with significant renal disease are at risk for nephrogenic systemic fibrosis (NSF), which results in fibrosis of the skin and connective tissues throughout the body. The newest safety consideration is the potential for gadolinium deposition in the brain. Studies suggest that deposition is more likely with the less stable GBCAs – those more likely to dissociate into free gadolinium and chelate. The clinical significance of deposition of gadolinium in brain tissue is unknown.

With a variety of GBCAs from which to choose, pharmacists involved in the selection of these agents for formulary inclusion must be guided by considerations of safety, efficacy, and cost. Above all, patient safety should be the overriding factor in making these important decisions.

Reviewers and Disclosures

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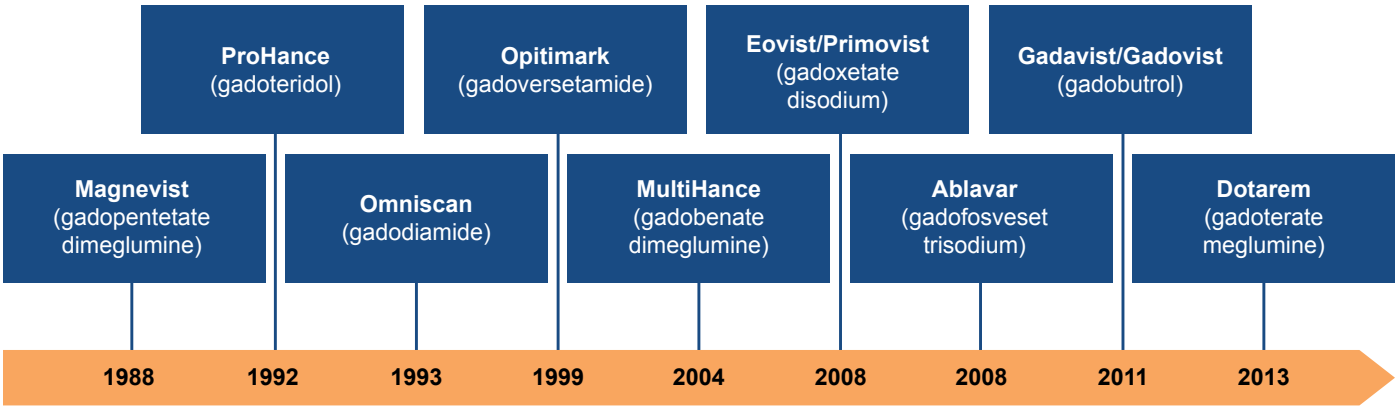
Contrast Agents and Magnetic Resonance Imaging

History

Radiologic imaging often requires contrast enhancement in order to obtain an efficacious study. During the 1970s and 1980s, when magnetic resonance imaging (MRI) was in its early stages, some researchers believed that contrast agents would not be necessary for tissue characterization with MRI.[1] However, the approval of the first gadolinium-based contrast agent (GBCA) in 1988, gadopentetate dimeglumine (Magnevist®, Bayer), marked a dramatic shift in the use of MRI and resulted in an extension of its applications and versatility.[2] During the last two decades, GBCAs have been indispensible to clinical MRI. Approximately 25-30% of all MRI scans today use some type of non-specific GBCA.[3] A timetable of the currently available GBCAs is shown in Figure 1.

Figure 1. Timetable of FDA-approved Gadolinium-based Contrast Agents[4]



Magnetic Susceptibility

Magnetic susceptibility refers to the extent a material or substance becomes magnetized when placed in an external magnetic field and it is central to many research and developmental aspects of MRI.[5] Magnetic susceptibility results primarily from an interaction between electrons within the substance and the external magnetic field. Types of magnetic susceptibility include

- **Paramagnetism** − Increases the magnetic moment parallel to the external field
- **Ferromagnetism** − Exhibits parallel alignment of magnetic moments resulting in net magnetization that persists even after the substance is removed from the external magnetic field
- **Diamagnetism** − Opposes the external magnetic field and weakens it slightly

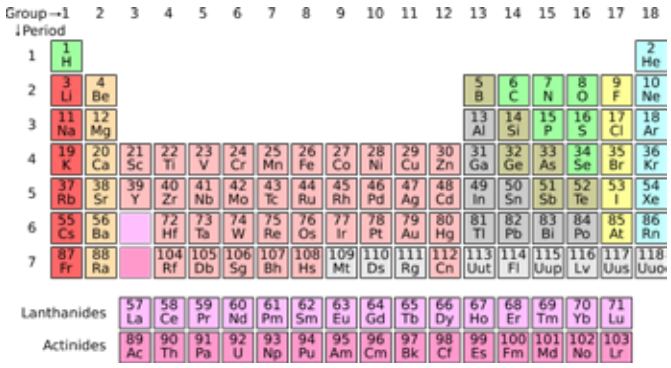
The majority of contrast agents used with MRI are based on the paramagnetic properties of gadolinium.[6] During MRI, tissues are pulsed with radiofrequency in the presence of a magnetic field, which induces excitation of protons within water molecules. The energy released when the protons relax to their ground state is recorded, which in turn produces a magnetic resonance image. Variation in the tissue signal intensity is determined by the relaxation time (T1 and T2) and proton density.[7] The effectiveness of the contrast agent in enhancing MRI depends on its relaxivity, or its capacity to modify relaxation times.

Gadolinium-based Contrast Agents

In developing a contrast agent for use with MRI, there are a number of substances with paramagnetic properties from which to choose. These include metal ions (transition metals and rare-earth metals), simple substances (oxygen), and stable free radicals (nitroxide radical). While there are many paramagnetic metal ions that could be used as MR contrast agents, gadolinium is the most commonly used. Gadolinium occupies the central position in the lanthanide (La) series of elements (Figure 2), and has an atomic number of 64 and an atomic weight of 158. With seven unpaired electrons in its 4f orbitals, gadolinium possesses the strongest paramagnetic properties of any element (Figure 3).[8] Gadolinium shortens the T1 (spin-lattice) and T2 (spin-spin) relaxation times of adjacent water protons, which causes signal enhancement at T1-weighted images.[9]

GBCAs are the only contrast agents currently used for MRI in the United States. The U.S. Food and Drug Administration (FDA) approved manganese (Mn) and iron (FE) based contrast agents in the past, but these agents did not succeed in the market and are no longer available.

Figure 2. Periodic Table of Elements

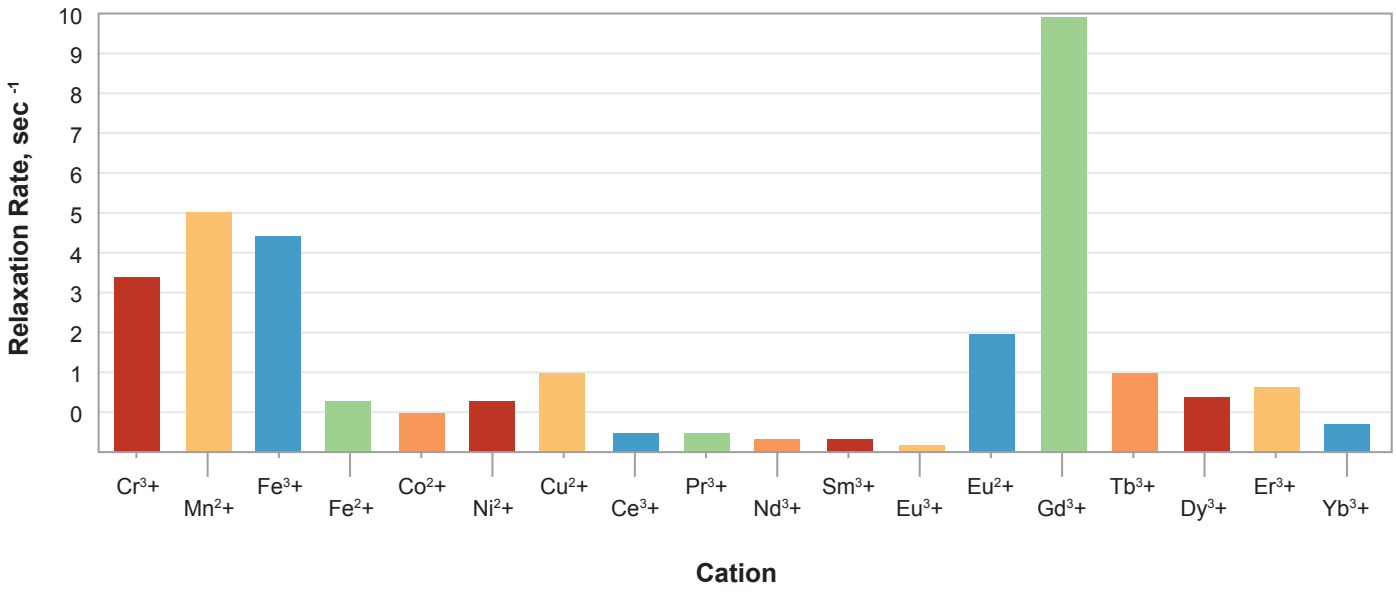


Characteristics of GBCAs

Gadolinium Toxicity

Free gadolinium is a toxic lanthanide heavy metal with an ionic radius similar to that of calcium. The similarity of gadolinium to calcium can lead to competitive inhibition of biological processes and cause toxicities (e.g., cardiactoxicity, neurotoxicity).[7] In addition, free gadolinium can block calcium-dependent enzymes such as S-transferases, dehydrogenases, kinases, ATPase, and glutathione,[10] stimulate expression and release of cytokines involved in tissue fibrosis and development,[11] and inhibit phagocytosis.[12]

Figure 3. T1 Relaxivity of Gadolinium (Gd) Compared with Other Cations[8]



In order to reduce the toxicity associated with gadolinium, it is chelated with diethylenetriamine penta-acetic acid (DTPA). DTPA is suitable for combination with gadolinium and results in a strongly paramagnetic, stable complex that is well tolerated in animals.[13] In addition to helping prevent precipitation at tissue pH, chelation with DTPA facilitates organ distribution as well as rapid and complete excretion, and substantially reduces toxicity.[14]

Factors Affecting GBCA Stability

Stability refers to the ease with which a gadolinium chelate will dissociate into free gadolinium and chelate in the body, which is not desirable due to the potential toxicities of free gadolinium. Ionicity and structure are the two main factors affecting the stability of GBCAs. The GBCAs are grouped based on ionicity and structure in Table 1.[15-23]

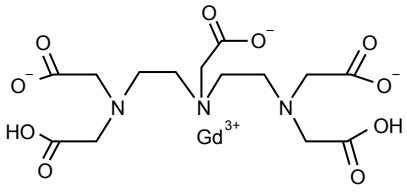
Ionic GBCAs are more stable than non-ionic GBCAs because ionic compounds have electrostatic forces of positive and negative ions. Non-ionic agents are less stable and more likely to dissociate into free gadolinium and chelate.

Structure has a significant impact on the stability of GBCAs. There are 2 structurally distinct categories of GBCAs: linear ("open chain") or macrocyclic. In a linear structure, or open-chain molecule, the ligand is not fully closed and the gadolinium ion easily dissociates. In macrocyclic molecules the gadolinium is "caged" in the preorganized cavity of the ligand and is less likely to dissociate (Figure 4).[24] Other factors that are often included in the discussion of iodinated contrast agents are osmolality and viscosity. These factors are not as important with respect to GBCAs because the volume of GBCA administered is smaller (less than 20 mL versus up to 150 mL for iodinated agents) and the rate of administration is slower (1-2 mL/sec versus 5-8 mL/sec for iodinated agents).

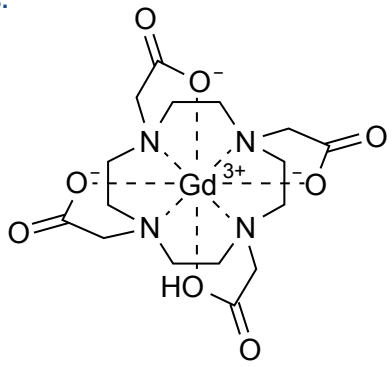
Table 1. Characteristics of Gadolinium-based Contrast Agents[15-23]

Contrast Agents	Stucture / Ionicity
Gadobenate dimeglumine (MultiHance®, Bracco Diagnostics)	Linear Ionic
Gadobutrol (Gadavist®, Bayer Healthcare)	Macrolytic Non-ionic
Gadodiamide (Omniscan®, GE Healthcare)	Linear Non-ionic
Gadofosveset trisodium (Ablavar®, Lantheus Medical Imaging)	Linear Ionic
Gadopentetate dimeglumine (Magnevist®, Bayer Healthcare)	Linear Ionic
Gadoterate meglumine (Dotarem®, Guerbet)	Macrolytic Ionic
Gadoteridol (ProHance®, Bracco Diagnostics)	Macrolytic Non-ionic
Gadoversetamide (Optimark®, Mallinckrodt Inc.)	Linear Non-ionic
Gadoxetate disodium (Eovist®, Bayer Healthcare)	Linear Ionic

Figure 4. The Structure of Gadolinium-based Contrast Agents.



Omniscan (gadodiamide)
Linear structure



Dotarem (gadoterate meglumine)
Macrocyclic structure

Measuring Stability

Thermodynamic stability is the standard way to measure the stability of a metal chelate. The bound chelate has a higher energy level and the dissociated chelate has a lower energy level. The rate at which the chelate dissociates is described by the thermodynamic stability constant (Log K-therm).[25] GBCAs with a linear structure dissociate very quickly at a pH of 1 compared to GBCAs with a macrocyclic structure. Because thermodynamic stability is not a perfect measure, other methods for measuring the stability of metal chelates have been used. Conditional stability is similar to thermodynamic stability, but it is measured at a physiologic pH instead of a pH of 1.[26] Perhaps the most useful measure of stability is kinetic stability, which measures the time required for the chelate to dissociate (Figure 7).[26]

Efficacy of GDCAs

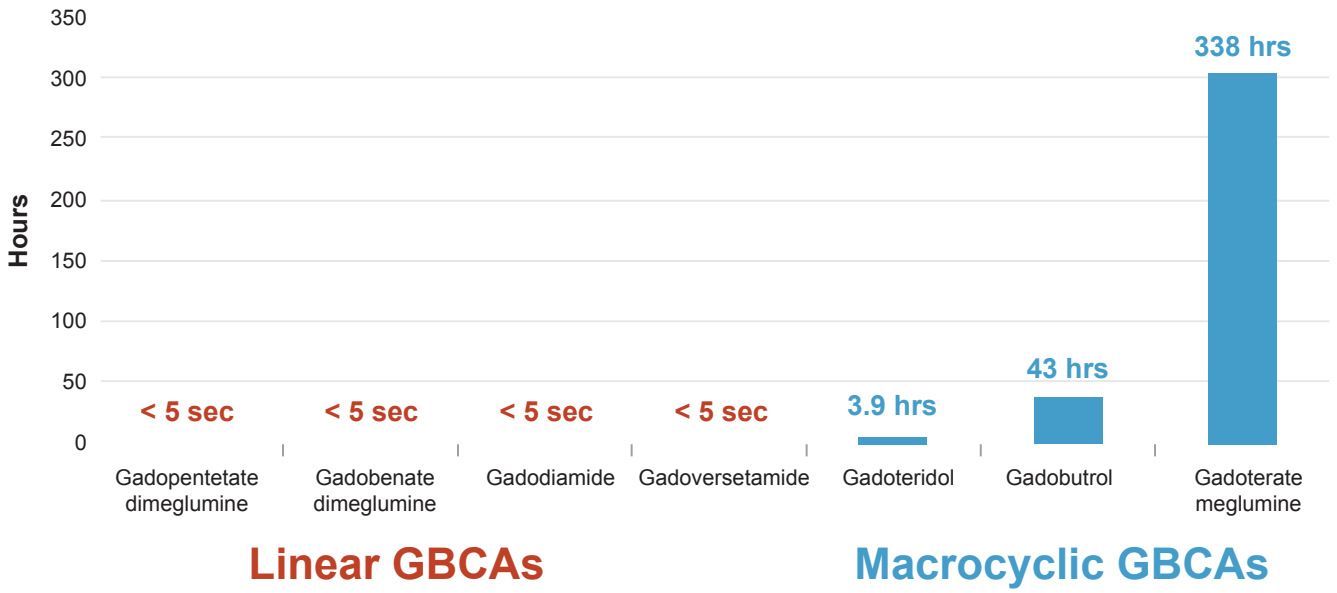
At clinical doses, GBCAs shorten the T1 relaxation times of perfused tissues after intravenous injection resulting in an enhanced image.

T1 relaxivity is the degree to which a contrast agent can shorten the T1 relaxation times of tissues after intravenous injection. The greater the T1 shortening, the brighter the enhancement on T1-weighted MR images. As shown in Table 3, a range of T1 relaxivity exists among the general-use gadolinium agents, with approximately a factor of two between the agent with the highest relaxivity (gadobenate dimeglumine) and the agent with the lowest relaxivity (gadoterate meglumine).[27] It has been suggested that higher relaxivity contrast agents result in better enhancement and possibly a better diagnosis, although there are no definitive data that indicate better patient outcomes.

Table 3. T1 Relaxivity of General-use Gadolinium Agents[27]

Contrast Agent	T1 Relaxivity (1.5T)
Gadobenate dimeglumine	6.3
Gadobutrol	5.2
Gadoversetamide	4.7
Gadodiamide	4.3
Gadopentetate dimeglumine	4.1
Gadoteridol	4.1
Gadoterate meglumine	3.6

Figure 7. Kinetic Stability of Gadolinium-based Contrast Agents[26]



In a double-blind, randomized, intraindividual, prospective crossover study in 151 patients, Maravilla and colleagues compared gadobenate dimeglumine with gadopentetate dimeglumine for enhanced MRI of central nervous system (CNS) lesions.[28] Patients underwent two temporally separated 1.5-T MRIs. In randomized order, gadobenate followed by gadopentetate was administered to group A (*n*=78); the order of administration was reversed in group B (*n*=79). Three blinded neuroradiologists evaluated images using objective image interpretation criteria for diagnostic information endpoints and quantitative parameters. Results of this study showed a significant increase in measurements of contrast enhancement with gadobenate (T1 relaxivity = 3.6) compared with those of gadopentetate (T1 relaxitity = 6.3) for MRI of CNS lesions.

In addition to general-use GBCAs, there are two agents that are organ specific.

- **Gadofosveset trisodium (Ablavar®)** is an intravenous blood pool contrast agent with a protein-binding moiety attached to it that makes it excellent for vascular imaging. The protein-binding moiety allows the contrast agent to bind reversibly to endogenous serum albumin, resulting in longer vascular residence time than non-protein binding contrast agents. The binding to serum albumin increases the T1 relaxivity and decreases the relaxation time of water proteins, resulting in increased signal intensity of blood on T1-weighted images.[15]

- **Gadoxetate disodium (Eovist®)** is a contrast agent used for liver imaging. The relatively large magnetic moment produced by this agent results in a local magnetic field, yielding enhanced relaxation rates of water protons and leading to an increase in signal intensity of blood and tissue.[17] The lipophilic moiety of gadoxetate disodium results in higher T1 relaxivity and 50% hepatocyte uptake. When injected intravenously, 50% of gadoxetate disodium is excreted renally and 50% excreted into the bile. This agent allows detection of small metastases in the liver as well as characterization of liver lesions.

GBCA Safety

GBCAs are considered safe when administered at clinically recommended doses to patients who do not have significant renal impairment. Patients should be screened for risk factors for acute adverse events and nephrogenic systemic fiborsis (NSF). Renal function is an important consideration when screening patients who are to receive a GBCA as most GBCAs are eliminated via glomerular filtration. The exceptions are gadobenate dimeglumine, of which about 4% is eliminated hepatically, and gadoxetate disodium, which is eliminated 50% renally and 50% hepatically.[29] The elimination half-life of commercially available GBCAs ranges from 1 to 2 hours.[15-23] In addition, recent concerns about gadolinium deposits in brain tissue is a consideration when evaluating agents.

Acute Adverse Events

Most acute adverse events associated with GBCAs are mild and self-limiting and often include nausea, vomiting, headache, and urticaria.[30] Severe anaphylactoid reactions and death are possible, but rare. Severe reactions to contrast agents can occur even without prior exposure. Such reactions are referred to as anaphylactoid reactions, because they have similar signs and symptoms to anaphylactic reactions. In a retrospective study of patients who had been given GBCAs between August 2004 and July 2010, the incidence of immediate hypersensitivity reactions to magnetic resonance contrast media was 0.08%, and the recurrence rate of hypersensitivity reactions was 30% in patients with previous reactions.[30]

Individuals with a history of asthma, allergies, and prior adverse reaction to a GBCA are at increased risk for allergic-like reactions to GBCAs.[30] There are approved pretreatment regimens and emergency premedication regimens for patients at risk.

- **Elective Pretreatment Regimen.** Prednisone 50 mg by mouth administered 13 hours, 7 hours, and 1 hour before contrast media injection plus diphenhydramine 50 mg by mouth administered 1 hour before contrast injection.[27]

- **Emergency Premedication Regimen.** Methylprednisolone sodium succinate 40 mg i.v. or hydrocortisone sodium succinate 200 mg i.v. every 4 hours until contrast study plus diphenhydramine 50 mg i.v. 1 hour prior to contrast injection.[27]

Nephrogenic Systemic Fibrosis

Nephrogenic systemic fibrosis (NSF) is characterized by thickening and hardening of the skin of the extremities. It is a fibrosing disorder that occurs predominantly in patients with end-stage chronic kidney disease, particularly patients who are on dialysis.[27,32] Initially, patients may have nonspecific complaints that include joint pain, stiffness, and swelling of the extremities. NSF may manifest as a range of cutaneous lesions, and the skin may be variably affected with subtle, superficial papules and plaques; deeper dermal or subcutaneous induration; or extension of joints, resulting in severe contractures (Figure 5).[33-34]

The acute phase of NSF is characterized by erythema, ulceration, and pain. NSF then progresses to a more chronic phase, with progressive hyperpigmentation, hardening, and tethering of the skin (Figure 6).[32] If NSF invades the joints, joint immobilization occurs and results in serious debilitation.

Prior to 2006, it appeared that the amount of GBCA administered to patients was excreted shortly afterward or that any amount retained by the body long term was small enough to be inconsequential.[35] In 2006, however, a possible relationship was suggested between NSF and GBCA in patients with significant renal disease.[36-37]

A dermatopathologist published the first paper about NSF in 2000, in which cases of NSF were described as dating back to 1997.[38] Whereas GBCAs have been approved for use since 1988, it is unclear why a case of NSF was not described until over a decade later. In fact, when NSF was first reported, there was no knowledge of its relationship to gadolinium.

The dissociation of gadolinium from its chelate is thought to activate circulating fibrocytes and initiate a fibrotic cascade that results in fibrous tissue developing in the skin and other organs.[39]

There is no cure for NSF. Treatments include extracorporeal photophoresis, thalidomide, and plasmapheresis, but none is universally effective. Patients with NSF have been known to improve as renal function improves, but this is not the case with 100% of NSF patients. Approximately 5% of patients experience a fulminant course, and some patients die as a result of complications of NSF.[40]

Although it is generally accepted that NSF is associated with GBCA exposure, the precise relationship between NSF and different GBCA formulations is not completely understood. Most cases of NSF were reported after exposure to gadodiamide, gadopentetate dimglumine, and gadoversetamide. These cases were referred to as un-confounded, which meant

Figure 5. NSF contractures resulting from inhibition of joint flexion and extension

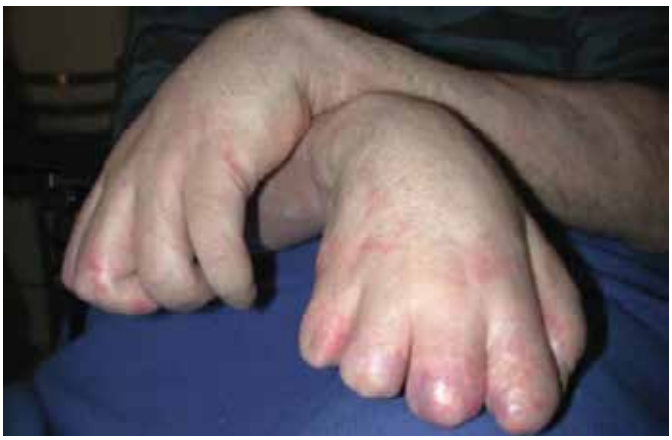


Figure 6. Progressive hyperpigmentation, hardening, and tethering of the skin

that patients only had exposure to one of these three contrast agents. The association of NSF with GBCAs in patients with poor renal function has led practitioners to avoid the use or reduce the dose of GBCA in patients with an estimated glomerular filtration rate (GFR) of less than 30 mL/min.[27]

GBCAs are classified by the American College of Radiology based the number of cases associated with each agent (Table 2).[27] Group 1 agents are those associated with the highest number of NSF cases; Group 2 agents are those associated with few or no un-confounded cases of NSF; and Group 3 agents are relatively new to the market so there are insufficient data to define their association with NSF. Due to widespread screening for renal function prior to the administration of GBCAs coupled with the use of the most stable contrast agents (i.e., avoidance of Group 1 agents in patients with renal impairment), NSF has been largely eliminated since 2009.[24]

Gadolinium Deposits in Tissue

Evidence of gadolinium deposition in bone tissue was established in 2004. A study analyzed gadolinium deposition in femoral heads after total hip replacement surgery and reported that inductively coupled mass spectroscopy showed gadolinium deposition in bone tissue, with deposition 2.5 times greater with gadodiamide than with gadoteridol.[41]

More recently, concerns regarding gadolinium deposition in the brain have surfaced. In 2014, Kanda and colleagues examined the correlation between the extent of prior GBCA administrations and high signal intensity in the dentate nucleus and globus pallidus on enenhanced T1-weighted magnetic resonance images.[42] Of 381 patients who had an MRI of the brain, 19 patients who had at least six contrast-enhanced examinations were compared with 16 patients who had at least six unenhanced examinations. Results showed that signal intensity ratios were significantly greater in patients who had undergone GBCA-enhanced examinations compared with those who had undergone unenhanced examinations (p<0.001).

Unlike NSF, which occurs in patients with impaired renal function, gadolinium deposition in the brain occurs in patients with normal renal function. Moreover, the T1 shortening effect on the global pallidus and dentate nuclei observed with repeated prior administration of GBCA is dose-dependent.[43] Similar to NSF, study data support the concept that gadolinium deposition in the brain appears to be dependent on chelate stability.[35] Therefore, gadolinium deposition in the brain is more likely to occur with less stable GBCAs, and at a much lower rate or not at all with more stable GBCAs.

The form of gadolinium in the brain is undefined because the tests used to measure gadolinium do not distinguish between the free ion and the intact chelate. However, it is known that some gadolinium crosses the blood-brain barrier and is deposited in the neuronal interstitium.[35] The clinical significance of gadolinium deposition in brain tissue is unknown.

Table 2. Classification of GBCAs According to Number of NSF Cases[27]

Group 1	Group 2	Group 3
gadodiamide (Omniscan®) gadopentetate dimeglumine (Magnevist®) gadoversetamide (Optimark®)	gadobenate dimeglumine (MultiHance®) gadoteridol (ProHance®) gadobutrol (Gadavist®) gadoterate meglumine (Dotarem®)	gadofosveset trisodium (Ablavar®) gadoxetate disodium (Eovist®)

Conclusion

Gadolinium-based contrast agents have been a powerful tool for improving the efficacy of MRI studies. Factors such as ionicity and structure are keys to differentiating GBCAs and selecting the most appropriate agent for a given patient. Although GDCAs are generally safe, it is important to screen patients for prior sensitivity and poor renal function.

The three important factors to consider when choosing a GBCA for inclusion on the formulary are safety, efficacy, and cost. Knowledgeable radiologists and pharmacists should both have input on this important decision. Ideally formularies include both general-use, and specialty agents. When selecting a general-use GBCA safety should be of utmost importance.

The Pharmacist's Role in Promoting the Safe Use of Gadolinium-based Contrast Agents

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Take Test and Process CPE

Assessment Test Study Aid

This assessment test is provided as a study aid only. Follow the instructions above to complete this assessment test and the evaluation online to obtain CE credit for this activity.

1. Which of the following gadolinium-based contrast agents (GBCAs) has a macrocyclic structure?

A. Gadoversetamide (Optimark)
B. Gadopentetate dimeglumine (Magnevist)
C. Gadoxetate disodium (Eovist/Primovist)
D. Gadobutrol (Gadavist/Gadovist)

2. Which of the following GBCAs has the highest degree of hepatocyte uptake and biliary excretion?

A. Gadoxetate disodium (Eovist/Primovist)
B. Gadoterate meglumine (Dotarem)
C. Gadodiamide (Omniscan)
D. Gadobenate dimeglumine (MultiHance)

3. The most important factor in determining which GBCAs to include on the formulary is the following:

A. Cost
B. Support from the manufacturer
C. Multiple packaging options
D. Patient safety

4. How can the hospital pharmacist reduce the risks associated with GBCAs?

A. Recommend contrast-enhanced CT scanning instead of MRI for patients with renal insufficiency
B. Provide valium to reduce feelings of claustrophobia
C. Include a macrocyclic agent on the formulary
D. Recommend corticosteroids for patients with hives

5. The risk of an acute adverse reaction to GBCAs is increased in which of the following groups of patients?

A. Patients with a history of previous adverse reaction to GBCA.
B. Patients with hepatic disease.
C. Patients with impaired renal function.
D. Patients with hypertension.

6. Which of the following statements about gadolinium deposition in the brain is well documented?

A. It is strongly associated with depression and cognitive dysfunction.
B. It occurs predominantly in the dentate nuclei and globus pallidus.
C. Gadolinium does not cross an intact blood brain barrier.
D. It is mainly associated with macrocyclic agents.

7. The best rationale for including more than one brand of GBCA on the formulary is the following:

A. It is important to maintain relationships with more than one supplier.
B. It is useful to stock a general GBCA and one or two specialized agents for specific clinical indications.
C. Stocking more than one brand can provide leverage in negotiating a good price.
D. Different physicians prefer different agents.

8. The risks of NSF and gadolinium tissue deposition after GBCA administration are greatly reduced with which class of agents?

A. Non-chelated gadolinium agents
B. Nonionic linear agents
C. Macrocyclic agents
D. Extracellular agents

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