Applications in Contrast Imaging

Contrast Media Basics: Important Considerations for the Pharmacist

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Summary

Pharmacists have longed played an important role in the decision-making process for drug selection and dispensing within hospitals. "A key role in a hospital pharmacist's job is determining which form of medication best suits each patient. Each decision must be made in a timely and efficient manner and requires significant input from doctors, nurses, and other healthcare professionals. Hospital pharmacists will often monitor the effects of the medications they prescribe and counsel their patients on the effects of the drugs. Another aspect of this role is to recommend administration routes and dosages, all of which are dependent on an individual's needs."*

Historically, pharmacists have had a limited role in the decision-making process for contrast media. It was not until the release of the Joint Commission's Medication Management standard in 2004 that contrast media were included as part of the definition of medication orders. While institutions have made changes in accordance with this standard, pharmacists' knowledge of contrast media remains limited. As pharmacists are called upon to provide guidance in the selection and safe use of drugs, they should be educated on the basics of US Food and Drug Administration (FDA)-approved contrast media agents.

*SOURCE: The Role of a Hospital Pharmacist; Josh Barnard, Medacs Health Care Senior Recruitment Consultants www.medacs.com/blog/2013/08/01/the-role-of-a-hospital-pharmacist

Program Overview

Applied Radiology has developed this two-part, on-demand webinar and accompanying digital monograph to increase overall understanding of the properties, clinical benefits, and safety considerations of iodinated and gadolinium-based contrast agents (GBCAs). The goal of this program is to fully prepare pharmacy personnel to make informed decisions regarding contrast media selection.

Learning Objectives

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

- Identify the differences between Ionic, Nonionic, Iso-osmolar contrast media (Iodinated & GBCAs.
- Review the important safety considerations associated with the administration of GBCAs.
- Describe and discuss important contrast media guidance documents, resources, and clinical reprints that support informed decision making in the selection of contrast media.
- Describe the clinical impact of contrast media changes and the impact on patient safety for each.
- Implement informed pharmacy practices related to the use of contrast media within their institution.

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Disclosure Statements

Rutu Patel, PharmD, RPH, has no relevant financial relationships with ineligible companies to disclose.

Program Reviewers

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Kristi Hales, Rph was a former employee of Medquest.

All relevant financial relationships for faculty and program reviewers have been reviewed and mitigated.

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This program meets all criteria and has been approved by the AHRA, *The Association for Medical Imaging Management* for 2.5 ARRT Category A CE Credits.

Accreditation Periods

ACPE Pharmacy Credits:
Release: 03/17/2024
Expiration: 03/17/2026

ARRT Category A Credits:
Release: 03/07/2024
Expiration: 03/31/2027

Obtaining Credits

To receive credits, participants must review the program materials in their entirety and complete the online post examination and evaluation. Pharmacy credits require a post examination score of 70% or higher. ARRT Category A CE credits require a post examination score of 80% or higher.

Commercial Support

This program was supported through an educational grant from Bracco Diagnostics, Inc.

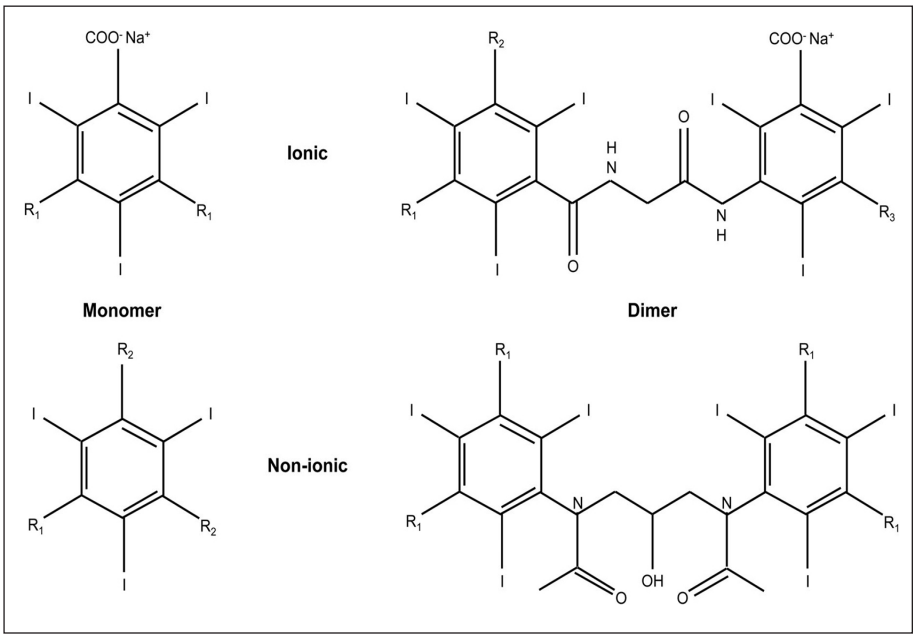
Contrast Media Basics: Important Considerations for the Pharmacist

By Rutu Patel, PharmD, RPh

The steady rise in chronic diseases and complex comorbidities continues to contribute to the need for diagnostic imaging tests, a large proportion of which utilize contrast agents.[1] While all contrast agents aim to improve the visualization of abnormalities by increasing the contrast between different types of body tissue or fluids, different classes of contrast vary in their physicochemical propertieas.[2] Furthermore, each class is reserved for specific imaging types, or modalities, which include ultrasound, nuclear, x-ray/computed tomography (CT), and magnetic resonance imaging (MRI).

Until recently, contrast agents were under the direct purview of radiologists, with little input and involvement from pharmacists. These agents have long been designated as prescription drugs and subject to U.S. Food and Drug Administration (FDA) regulations around investigational and new drug application processes. The Joint Commission's Medication Management standard in 2004, however, expanded the definition of medication orders to include contrast media.[3] While institutions have successfully implemented processes to ensure compliance with this standard, pharmacist knowledge of contrast media remains limited. As leaders of formulary management initiatives and the safe use of medications who are called upon to make recommendations based on sound clinical evidence, pharmacists must seek to expand their knowledge base to remain well informed.

Figure 1. Basic Structure of Iodinated Contrast Agents[5]



This article presents summaries and resources aimed at providing pharmacists with basic information on contrast agents. While contrast media are utilized across all imaging modalities, this article focuses on iodinated agents for CT imaging and gadolinium-based contrast agents (GBCAs) for MRI examinations. Webinars accompanying this article can be viewed at appliedradiology.org/pharmacy.

Iodinated Contrast Agents

The high atomic weight of iodine makes it an ideal element for use in contrast media, as it can impede the ability of x-rays to pass through tissue. The imaging properties of currently available iodinated contrast agents do not vary significantly;

Table 1. Iodinated Contrast Media Used in Clinical Practice.[6]

NAME	STRUCTURE TYPE	IODINE CONTENT (mg/mL)	OSMOLALITY (mOsm/kg)*	OSMOLALITY CLASSIFICATION	VISCOSITY (cP, 37°C)
Ionic					
Diatrizoate (Hypaque 50, Renografin)	Monomer	300	1550	HOCM	10.5
Metrizoate (Isopaque 370)	Monomer	370	2100	HOCM	3.4
Iothalamate (Conray)	Monomer	325	1843	HOCM	4.0
Ioxaglate (Hexabrix)	Dimer	320	580	LOCM	7.5
Nonionic					
Iopamidol (Isovue-370)	Monomer	370	796	LOCM	9.4
Iohexol (Omnipaque 350)	Monomer	350	884	LOCM	10.4
Iodixanol (Visipaque 320)	Dimer	320	290	IOCM	11.8
Iotrolan (Isovist)	Dimer	300	320	IOCM	8.1
Ioxaglate (Hexabrix)	Dimer	320	600	LOCM	7.5
Ioxilan (Oxilan 350)	Monomer	350	695	LOCM	8.1
Iopromide (Ultravist 370)	Monomer	370	774	LOCM	10.0
Ioversol (Optiray 300)	Monomer	300	651	LOCM	5.5
Iomeprol (Iomeron 350)	Monomer	350	618	LOCM	7.5

*For comparison, the osmolality of blood is 290 mOsm/kg.

cP=centipoise; HOCM=high-osmolar contrast media; IOCM=iso-osmolar contrast media; LOCM=low-osmolar contrast media.

rather, the attenuation they produce is directly related to amount of iodine in the path of the x-rays. However, a key differentiator among them is their safety profile, which is largely influenced by structure.[4] Iodinated contrast agents consist of a benzene ring with three iodine molecules as the backbone, along with side chains of differing size and composition (**Figure 1**).[5] Agents with a single benzene ring are classified as monomers and those with two benzene rings are known as dimers. In addition to safety, efficacy, and cost, pharmacists should be aware of three key physicochemical characteristics imparted by the structure of these agents: osmolality, ionicity, and viscosity (**Table 1**).[4,6]

Osmolality

Osmolality represents the number of osmotically active particles in a suspension per kilogram of solvent. As osmolality moves closer to that of blood, or close to "iso-osmolar," the tolerability and safety profile improves.[4] Iodinated contrast agents fall into one of three groups: high-osmolar (1800–2100 mOsm/kg) (HOCM), low-osmolar (200–900 mOsm/kg) (LOCM), and iso-osmolar (290 mOsm/kg; equal to the osmolality of blood) (IOCM).[6]

HOCM are associated with higher rates of adverse reactions and have largely been replaced by agents with improved safety profiles, especially for intravascular exams.[4] However, some older products in this category are still widely used, owing to their low cost and clinical utility in gastrointestinal and urological procedures.[7]

The LOCM were primarily developed to avoid the safety problems associated with HOCM. The vast majority of these agents are nonionic monomers, which means they do not dissociate in water, allowing for lower osmolality. They also have fewer nephrotoxic reactions and improved intravascular tolerability.[6]

The only IOCM currently available in the U.S. is iodixanol, an agent perceived as having fewer nephrotoxic side effects than other contrast media in this class.[8,9] However, studies have failed to establish a clear advantage of its iso-osmolality over that of LOCM in terms of contrast-associated acute kidney injury (CA-AKI) or contrast-induced acute kidney injury (CI-AKI).[4,9-11]

Ionicity

Ionicity goes hand-in-hand with osmolality, and contrast media are classified as ionic or nonionic. Ionic agents dissociate in water into anion and cation components, which increases inherent osmolality; thus, ionic agents tend to fall into the high-osmolar category (**Table 1**).[6] While still water-soluble, nonionic agents do not dissociate in water, resulting in lower osmolality and fewer adverse effects.[4,12] Nonionic agents encompass both LOCM and

Table 2. Categories of Acute Reactions to Iodinated and Gadolinium-based Contrast Agents Per the American College of Radiology[4]

Mild: Signs and symptoms are self-limited without evidence of progression	
Allergic-like: ▪ Limited urticaria/pruritus ▪ Cutaneous edema ▪ Limited "itchy"/"scratchy" throat ▪ Nasal congestion ▪ Sneezing/conjunctivitis/rhinorrhea	Physiologic: ▪ Limited nausea/vomiting ▪ Transient flushing/warmth/chills ▪ Headache/dizziness/anxiety/altered taste ▪ Mild hypertension ▪ Vasovagal reaction that resolves spontaneously
Moderate: Signs and symptoms are more pronounced and commonly require medical management. Some of these reactions have the potential to become severe if not treated.	
Allergic-like: ▪ Diffuse urticaria/pruritis ▪ Diffuse erythema, stable vital signs ▪ Facial edema without dyspnea ▪ Throat tightness or hoarseness without dyspnea ▪ Wheezing/bronchospasm, mild or no hypoxia	Physiologic: ▪ Protracted nausea/vomiting ▪ Hypertensive urgency ▪ Isolated chest pain ▪ Vasovagal reaction that requires and is responsive to treatment
Severe: Signs and symptoms are often life-threatening and can result in permanent morbidity or death if not managed appropriately*	
Allergic-like: ▪ Diffuse edema, or facial edema with dyspnea ▪ Diffuse erythema with hypotension ▪ Laryngeal edema with stridor and/or hypoxia ▪ Wheezing/bronchospasm, significant hypoxia ▪ Anaphylactic shock (hypotension with tachycardia)	Physiologic ▪ Vasovagal reaction resistant to treatment ▪ Arrhythmia ▪ Convulsions, seizures ▪ Hypertensive emergency

*Cardiopulmonary arrest is a nonspecific, end-stage result that can be caused by a variety of the listed severe reactions, both allergic-like and physiologic. If etiology is unclear, assuming that the reaction is/was an allergic-like one may be judicious. Pulmonary edema is a rare severe reaction that can occur in patients with tenuous cardiac reserve (cardiogenic pulmonary edema) or in patients with normal cardiac function (noncardiogenic pulmonary edema). Noncardiogenic pulmonary edema can be allergic-like or physiologic; if etiology is unclear, assuming that the reaction is/was an allergic-like one may be judicious.

IOCM preparations. In current clinical practice, nonionic agents are used almost exclusively for examinations requiring intravascular injection.[12]

Viscosity

In contrast-enhanced CT exams, the goal is to deliver adequate iodine to the site being imaged. Viscosity, or thickness of an agent, is an important property that can impact iodine delivery (**Table 1**). It is of utmost significance in imaging procedures where injection rate plays a role.[4] Viscosity values increase with higher iodine concentrations, which can impact the ease with which contrast is injected and thereby reduce the amount of iodine delivered to the imaging site, resulting in poor visualization. An agent with high viscosity experiences resistance, or high pressure, when injected, impeding its ability to distribute into the vessel. Moreover, an agent with lower viscosity is injected at a lower pressure and may distribute easily into the vessels.[4,12] Because viscosity is dependent on temperature, iodinated agents are often warmed to body temperature to reduce thickness and permit more rapid injection rates.[4] In many exams, a delicate balance between timing and risk for adverse reactions is required to deliver a sufficient amount of iodine to the site being imaged, and viscosity is an important consideration.[4]

Of note, because contrast media are deemed to be medications, warming is overseen by the Joint Commission, which requires institutions to maintain daily temperature logs and evidence of routine maintenance of all warming devices.[4]

Safety considerations associated with iodinated contrast agents

Tables 2 and 3 summarize key safety considerations related to iodinated and gadolinium-based contrast agents that pharmacists should be mindful of.

Extravasation, which occurs when a contrast medium leaks into surrounding tissue, is rare, occurring in 0.1% to 1.2% (1/1,000 to 1/83 patients) of power-injected CT exams.[4] It can, however, occur during hand injection, as well. Most reactions are self-limiting, impacting only the immediately surrounding vasculature. Whereas acute tissue injury is in part related to contrast hyperosmolality, most patients recover without significant sequelae, and only rarely will LOCM extravasation injury progress to a severe adverse event.[4] Currently, there are

Table 3. Safety Considerations for Non-acute Adverse Reactions to Contrast Media[4,13-15]

	SIGNS AND SYMPTOMS	CONSIDERATIONS
Iodinated contrast agents		
Contrast extravasation	▪ Swelling or tightness, and/or stinging or burning pain at the site ▪ Physical exam shows injection site to be edematous, erythematous, and tender ▪ Most reactions are limited, but they can lead to compartment syndrome, skin ulceration, and tissue necrosis	▪ Related to hyperosmolality; only rarely will a LOCM extravasation injury lead to a severe adverse event ▪ Higher-risk patients include those who cannot communicate effectively, have poor circulation in injected limb, or are severely ill/debilitated ▪ Patients with arterial insufficiency, or compromised venous or lymphatic drainage in the affected extremity, are at risk for more severe reactions; extravasations involving larger volumes of contrast media and those occurring in the dorsum of the hand, foot, or ankle are more likely to result in severe tissue injury ▪ No known effective treatment
Contrast-associated acute kidney injury (CA-AKI) and contrast-induced acute kidney injury (CI-AKI)	Acute kidney injury diagnosis is made if one of the following occurs within 48 hours after contrast administration: ▪ Absolute serum creatinine increase ≥0.3 mg/dL (>26.4 µmol/L) ▪ Percentage increase in serum creatinine ≥50% (≥1.5-fold above baseline) ▪ Urine output reduced to ≤0.5 mL/kg/hour for at least 6 hours	**CA-AKI:** ▪ CA-AKI may be caused by any nephrotoxic event (including CI-AKI) that is coincident to the intravascular administration of iodinated contrast ▪ No clear advantage of IOCM over LOCM with regard to CA-AKI or CI-AKI **CI-AKI:** ▪ Exact pathophysiology of CI-AKI is not understood; nephrotoxic effect may be proportional to dose for cardiac angiography. No evidence of a dose-toxicity relationship following IV administration when administered at usual diagnostic doses ▪ ACR position: CI-AKI is a real, albeit rare, entity ▪ Most important risk factor is pre-existing severe renal insufficiency; patients should be screened based on eGFR and personal history of kidney disease ▪ Volume expansion with saline prior to contrast administration is most effective preventative measure
Gadolinium-based contrast agents		
Contrast extravasation	▪ Lower toxicity compared to iodinated contrast agents (symptoms above)	▪ Extravasations of GBCAs usually do not cause severe injury, likely due to the smaller total volumes of contrast material that are injected at MRI
Nephrogenic systemic fibrosis	▪ Initial symptoms typically include skin thickening and/or pruritus ▪ May progress rapidly, with some patients developing contractures and joint immobility. In some patients, the disease may be fatal	▪ Almost all unconfounded cases have been reported after exposure to Omniscan, Magnevist, and/or OptiMARK ▪ Patient risk factors: dialysis, end-stage renal disease/CKD5 (eGFR <15 mL/min/1.73 m^2), severe CKD/CKD4 (eGFR 15-29 mL/min/1.73 m^2), or acute kidney injury, high single or cumulative doses GBCA with renal impairment ▪ Time between injection of GBCA and NSF onset typically occurs within days to months; however, in rare cases, symptoms have appeared years after the last reported GBCA exposure
Gadolinium retention	▪ To date, no adverse health effects have been uncovered ▪ Usually identified via a higher signal intensity in certain areas within the brain on unenhanced MRI exams or via residual Gd in brain tissue	▪ Gd retention has been observed to some extent with all the available GBCAs ▪ No reports to date suggest Gd retention is associated with histologic changes indicative of neurotoxicity, even among GBCAs with the highest rates of deposition ▪ Additional research is ongoing to elucidate the mechanisms of retention, the chelation state of these deposits, the relationship to GBCA stability and binding affinity, and theoretical toxic potential, which may be different for different GBCAs

ACR=American College of Radiology; CA-AKI=contrast-associated acute kidney injury; CI-AKI=contrast-induced acute kidney injury; eGFR=estimated glomerular filtration rate; GBCA=gadolinium-based contrast agents; Gd=gadolinium; IV=intravenous; LOCM=low osmolar contrast media; MRI=magnetic resonance imaging; NSF=nephrogenic systemic fibrosis.

6

no known effective treatments for contrast extravasation.

The incidence of acute reactions, which are categorized as allergic-like (true allergic, "anaphylactoid," "allergic-like," or "idiosyncratic") or physiologic, is correlated with osmolality. HOCM are associated with higher incidence rates than are LOCM or IOCM.[4] Acute reactions to LOCM tend to be mild and non-life-threatening, typically requiring only observation and supportive measures.[4] Severe, life-threatening adverse events are rare and unpredictable; however, most occur within 20 minutes after contrast injection.[4]

Table 2 shows the standard classification of acute reactions in both iodinated and GBCAs. Current estimates suggest that severe acute reactions to LOCM occur in only 4 in 10,000 (0.04%) patients.[4] In general, patients with a history of allergic reactions are at elevated risk for contrast-related allergic reactions, with the risk being 5-fold higher among patients with a history of prior reactions to contrast who are exposed to the same agent, and 2- to 3-fold higher among patients with non-contrast-related allergies.[4] It is important to note that patients with shellfish or povidone-iodine allergies are not at higher risk for reactions to iodinated contrast media than are patients with other allergies.[4]

CA-AKI and CI-AKI are two distinct clinical conditions that can occur after administration of iodinated contrast media. CA-AKI describes the sudden deterioration in renal function that occurs within 48 hours following iodinated contrast medium administration, but the contrast medium may or may not be the cause of the deterioration.[4] In CI-AKI, the deterioration in renal function is caused by the administration of the iodinated contrast medium (**Table 3**). The risk for either condition is higher in patients with impaired renal function; these patients are typically screened beforehand via estimated glomerular filtration rate or assessment of their history of renal disease. The risks and benefits of a given iodinated agent must always be weighed carefully before administering contrast to any patient. Currently, the position of American College of Radiology (ACR) Committee on Drugs and Contrast Media is that "CI-AKI is a real, albeit rare, entity."[4]

Gadolinium-based Contrast Agents

Gadolinium (Gd) is a heavy earth metal in the lanthanide series valued for its paramagnetic properties. It forms a 3+ charge with seven unpaired electrons that attract nearby protons, such as those found in water. In MRI, the resulting Gd3+ complex produces tissue differentiation and enhanced signal intensity by reducing the relaxation times of nearby protons within a magnetic field.[16] Owing to Gd's inherent toxicity as an ion, all GBCAs are bound by chelates.

Seven GBCAs are currently available in the U.S., 2 of which are the same molecule (**Table 4**).[4,17-23] In recent years, the production of Ablavar (gadofosveset), OptiMARK (gadoversetamide), and Magnevist (gadopentetate dimeglumine) has been discontinued voluntarily by their manufacturers and are not discussed here.[24-26] Pharmacists should be aware of several characteristics that differentiate the available GBCAs: structure (macrocyclic vs linear), ionicity (ionic vs nonionic), relaxivity (standard vs high), and concentration (0.5 M vs 1.0 M) (**Figure 2**; **Table 4**).

Structure and ionicity

Chelate structure and ionicity are important considerations in selecting a GBCA, as they influence the overall stability of the chelate-Gd3+ complex. It is postulated that the Gd3+ ion in GBCAs with lower stability may have a propensity to dissociate from the chelate or undergo transmetallation with other metallic ions, which can ultimately impact patient safety.[4] In general, linear nonionic agents are the least stable, whereas linear ionic agents are moderately stable.[29] Macrocyclic GBCAs are the most stable, owing to their cage-like configuration that binds Gd3+ more tightly than linear chelates (**Figure 2**).[29]

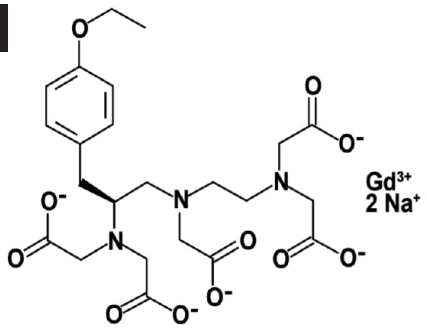
Relaxivity and concentration

Similar to how the efficacy of an iodinated contrast agent is dependent upon iodine delivery at the imaging site, the efficacy of a GBCA relies on the intrinsic relaxivity of the agent.[30] Relaxivity represents the ability of a GBCA to increase the relaxation rates of the surrounding water proton spins.[31] The higher the relaxivity of an agent, the better its ability to create contrast between abnormal lesions and background tissues.[31] Of the available GBCAs, ProHance (gadoteridol), Omniscan (gadodiamide), and Dotarem/Clariscan (gadoterate meglumine) are formulated at 0.5 M concentration and classified as non-protein binding extracellular fluid agents (ECF), meaning they distribute from the vasculature to the extracellular space rapidly after injection.[31,32] These agents are also categorized as having standard relaxivity, despite differences in their structure and ionicity.[28] All 4 agents are approved at a dose of 0.1 mmol/kg, with ProHance allowing for an additional dose of up to 0.2 mmol/kg, if needed.[17,18,22,23]

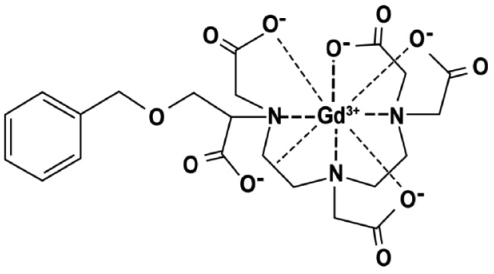
Gadavist (gadobutrol) is also an ECF agent, but it is formulated at a higher concentration—1.0 M—than the aforementioned agents.[21] Gadavist also exhibits relaxivity values similar to those of the standard relaxivity agents (**Table 4**); however, despite formulation at a 2-fold higher concentration, it is approved for the same 0.1 mmol/kg dose,

Figure 2. Linear and Macrocyclic Gadolinium-based Contrast Agents. (A) Linear Ionic Agents; (B) Linear Nonionic Agent; (C) Macrocyclic Agents.[27]

A

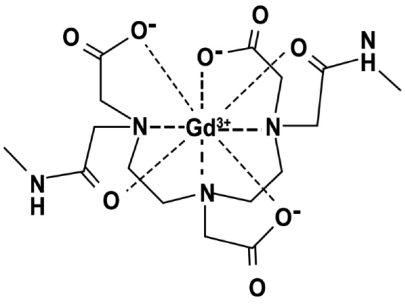


Gadoxetate disodium
Gd-EOB-DTPA
Eovist



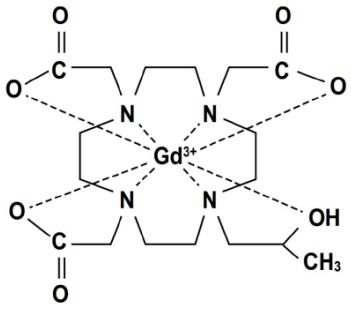
Gadobenate dimeglumine
Gd-BOPTA
MultiHance

B

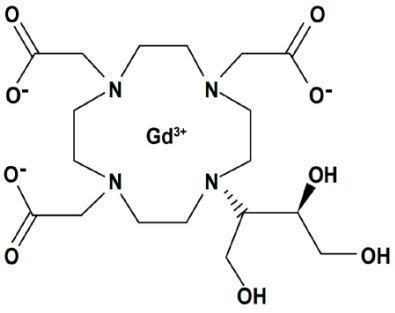


Gadodiamide
Gd-DTPA-BMA
Omniscan

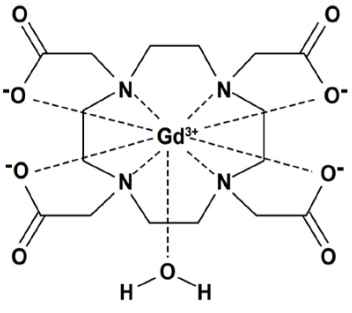
C



Gadoteridol
Gd-HP-DO3A
ProHance



Gadobutrol
Gd-BT-DO3A
Gadavist/Gadovist



Gadoterate meglumine
Gd-DOTA
Dotarem/Clariscan

Table 4. U.S. Food and Drug Administration-approved Gadolinium-based Contrast Agents.[4,17-23,28]

TRADE NAME	PROHANCE	OMNISCAN	MULTIHANCE	EOVIST	GADAVIST	DOTAREM/ CLARISCAN*
Manufacturer	Bracco Diagnostics	GE Healthcare	Bracco Diagnostics	Bayer Healthcare	Bayer Healthcare	Guerbet/ GE Healthcare
Generic name	Gadoteridol	Gadodiamide	Gadobenate dimeglumine	Gadoxetate disodium	Gadobutrol	Gadoterate meglumine
Year approved	1992	1993	2004	2008	2011	2013/2019
FDA approved to image	▪ CNS in adults & pediatrics ▪ Head and neck in adults	▪ CNS in adults & pediatrics (2-16 years of age) ▪ Body (excluding the heart) in adults & pediatrics (2-16 years of age)	▪ CNS in adults & pediatrics (including term neonates) ▪ MRA in adults, to evaluate known or suspected renal or aorto-ilio-femoral occlusive vascular disease	▪ Liver	▪ CNS in adults & pediatrics (including term neonates) ▪ Assess presence and extent of malignant breast disease ▪ MRA to evaluate known or suspected supra-aortic or renal artery disease in adults & pediatrics (including term neonates) ▪ Assess myocardial perfusion (stress, rest) and late gadolinium enhancement in adult patients with known or suspected coronary artery disease	▪ CNS in adults & pediatrics (including term neonates)
Structure	Macrocyclic	Linear	Linear	Linear	Macrocyclic	Macrocyclic
Ionicity	Nonionic	Nonionic	Ionic	Ionic	Nonionic	Ionic
Relaxivity at 1.5T	4.39 ± 0.47	4.47 ± 0.08	6.20 ± 0.36	7.24 ± 0.15	4.61 ± 0.18	3.91 ± 0.13
Concentration (molar)	0.5	0.5	0.5	0.25	1.0	0.5
Approved dose (mmol/kg)	▪ Adults: 0.1 + 2nd dose of 0.2 up to 30 min after 1st dose if needed ▪ Pediatrics: 0.1	0.1 (0.05 for kidney only)	▪ Adults & pediatrics ≥2 years of age: 0.1 ▪ Pediatrics <2 years of age: 0.05-0.1 (CNS imaging only)	0.025	0.1	0.1
ACR group	II	I	II	III†	II	II
More information	www.braccoimaging.com/us-en#	www.gehealthcare.com/products/contrast-media/	www.braccoimaging.com/us-en#	www.radiologysolutions.bayer.com/	www.radiologysolutions.bayer.com/	www.gehealthcare.com/products/contrast-media/ www.guerbet.com/en-us

*Clariscan, a generic version of Dotarem, was approved by the U.S. Food and Drug Administration in November 2019.
†Data remains limited regarding nephrogenic systemic fibrosis risk, but for which few, if any unconfounded cases of NSF have been reported.
ACR=American College of Radiology; CNS=central nervous system; cP=centipoise; FDA=U.S. Food and Drug Administration; MRA=magnetic resonance angiography.

delivering the same amount of Gd as the other agents, but in half the volume.[21,28]

Eovist (gadoxetate disodium) is one of the two high-relaxivity agents.[28] Eovist behaves differently from the other GBCAs in that it is selectively taken up by hepatocytes, allowing for better visualization in liver tissue. As a result, it is approved solely for liver imaging.[20]

Unlike the other 6 agents, MultiHance (gadobenate dimeglumine) possesses a hydrophobic side chain that allows it to transiently interact with serum albumin molecules (**Figure 2**).[31] This interaction allows the Gd to influence more of the surrounding water molecules, translating to a higher relaxivity value.[31]

Safety considerations associated with GBCAs

Tables 2 and 3 present key safety considerations related to GBCAs. As with the iodinated agents, extravasation can occur with these agents. Owing to the smaller volume injected for MRI exams, however, the reactions associated with GBCAs are generally not as severe.[4]

Acute reactions to GBCAs are classified similarly to those of iodinated contrast agents (**Table 2**). Compared with their iodinated counterparts, both ionic and nonionic GBCAs can be injected, with little or no difference in risk for acute reactions and discomfort.[33] The overall incidence of adverse reactions to GBCAs is low, with rates ranging from 0.07% to 2.4%.[4] Most are mild and transient, with skin reactions, nausea with or without vomiting, headache, paresthesias, and dizziness being most common.[4] Allergic-like reactions are also rare, with incidence ranging between 0.004% to 0.7%, and life-threatening cases between 0.001% to 0.01%.[4] Patients at risk for acute reactions include those with previous reactions to GBCAs and those with a history of asthma or other allergies.[4] To alleviate these risks, common practice at many institutions is to administer premedication to such patients.[4]

Nephrogenic systemic fibrosis (NSF) is a rare but often debilitating, scleroderma-like condition that presents with fibrotic changes such as thickening, induration, and tightening of the skin that can potentially progress to joint contractures and decreased mobility.[4] It can also impact the internal organs, especially the lungs, as well as the esophagus, heart, and skeletal muscles.[4] A diagnosis of NSF is established using a scoring system based on clinical, laboratory, and histopathological assessments of patients presenting with a clinical picture of NSF.[34]

NSF was first described in 2000 among renal dialysis patients exhibiting symptoms of sclero-myxedema, including thickening and hardening of the skin of the extremities.[35] However, the link to Gd was not established until 2006.[36] While the exact mechanism by which this condition occurs is still not fully understood, it is widely accepted that exposure to GBCA in conjunction with pre-existing acute or chronic renal impairment (chronic kidney disease [CKD] stages 4 and 5; glomerular filtration rate [GFR] <30 mL/min/1.73 m^2) increase the risk for NSF.[37]

Furthermore, most confirmed NSF cases have occurred with linear agents of lower stability (ie, Omniscan, Magnevist, OptiMARK), suggesting that dissociation or transmetallation of Gd3+ ion plays a role in the mechanism. In response, the ACR established groupings based on the number of unconfounded cases associated with each GBCA (**Table 4**). According to this grouping: the GBCAs with the most reported NSF cases are classified as Group I; agents associated with few, if any, cases of NSF are in Group II; Group III agents are those that have only recently appeared on the market, and thus have insufficient real-life data to determine their risk for contributing to NSF.[4] Thus, identifying patients at risk for developing NSF is critical before administering Group I and III GBCAs.[4]

In 2013, a report from Japan suggested that the unenhanced MR images of some patients exposed to multiple administrations of GBCAs may exhibit increased signal intensity in specific regions of the brain.[38] This finding was attributed to the abnormal retention of Gd compounds in these areas.

Many studies have since been published on this important finding, with some studies quantifying levels of elemental Gd using inductively coupled plasma mass spectroscopy (ICP-MS) in the brain tissue of patients exposed to GBCAs.[13-15] These studies found that Gd retention can occur to some extent with all GBCAs, regardless of structure or number of doses.[13-15] In July 2015, the FDA responded by issuing an initial Safety Announcement regarding its investigation of the risk of Gd retention in the brain following repeated use of GBCAs.[39] After further review, the FDA began requiring GBCA manufacturers to develop a Medication Guide for patients.[40] The agency also required manufacturers to further assess the safety of these contrast agents through human and animal studies.[40]

It is important to note there have been no reports to date suggesting that Gd retention is associated with histologic changes indicative of neurotoxicity, even among GBCAs with the highest rates of retention.[4]

The Evolving Role of the Pharmacist

Pharmacists are pivotal players in ensuring the safe and appropriate

Table 5. Resources for Pharmacists.

RESOURCE	DESCRIPTION	WHERE TO OBTAIN MORE INFORMATION
ACR Manual on Contrast Media	Guide to enhance the safe and effective use of contrast media	▪ Full copy available at: https://www.acr.org/Clinical-Resources/Contrast-Manual
Prescribing information	FDA-approved indications and usage, dosing recommendations, how supplied (fill sizes, NDC numbers), important safety information	▪ Specific to a product ▪ Housed on manufacturer website or can be searched on FDA website: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
Formulary kit	Product-specific information that can help inform formulary decisions	▪ Specific to a product; can be obtained from contrast manufacturer, if available
Peer-reviewed publications	Key journal articles evaluating the safety and efficacy of contrast agents	▪ PubMed.gov ▪ Publisher/journal websites ▪ Reprints may be available through contrast manufacturers via sales representatives
FDA website	Safety notifications/updates and information pertaining to specific products, including prescribing information, medication guides, approval history, and FDA letters	▪ Drug safety and availability notices available at: https://www.fda.gov/drugs/drug-safety-and-availability ▪ Drugs@FDA database available at: https://www.accessdata.fda.gov/scripts/cder/daf/
Manufacturer representatives	On- or off-label information available through product manufacturers	▪ Manufacturer Medical Information phone numbers ▪ Sales representatives for on-label information ▪ Medical Science Liaisons

ACR=American College of Radiology; FDA=U.S. Food and Drug Administration; NDC=national drug code.

procurement, storage, distribution, and administration of all drugs, including contrast media. Despite this responsibility, many pharmacy and radiology departments historically have had very little interaction, with radiology directing all the logistics related to contrast media. That has begun to change in recent years as radiology and pharmacy departments have begun partnering to improve contrast management for medical imaging.

Indeed, today's pharmacists are increasingly involved in the ordering, procurement, and delivery of contrast agents to specific radiological areas. In collaboration with radiologists, pharmacists play a role in the yearly review of the contrast agents utilized within the institution. As gatekeepers of medications, they are also engaged in the routine audit of areas in which contrast agents may be stored.

Perhaps the most pivotal role pharmacists play within institutions is in the formulary decision-making process. As equal members of multidisciplinary formulary committees, pharmacists share the responsibility of promoting appropriate evidence-based, safe, and cost-effective use of all drugs, including contrast agents. Thus, they must remain current on all developments related to contrast media. To this end, **Table 5** provides resources for obtaining additional information related to iodinated and gadolinium-based contrast agents.

Summary

Contrast agents are powerful tools that dramatically improve the diagnostic efficacy of imaging examinations. Pharmacists must be aware of the attributes and properties that differentiate these products. Among the iodinated contrast agents, osmolality, ionicity, and viscosity are key physicochemical properties. Similarly, among the GBCAs, important characteristics include their structure, ionicity, relaxivity, and concentration.

As pharmacists embrace their role in contrast selection, a better understanding of the various agents' indications for use, safety profiles, and product attributes will allow them to determine the most appropriate, cost-effective choices for formulary inclusion and specific imaging examinations and patient types. In the process, they will be empowered to forge closer and stronger partnerships with radiology in the use and management of these vital tools of medical imaging.

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