Gadolinium-Based Contrast Agents: A Comprehensive Risk Assessment

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Gadolinium-based contrast agents (GBCAs) have been used in magnetic resonance imaging (MRI) since the 1980s and are now administered in up to 35% of all MRI examinations. While GBCAs were initially felt to carry minimal risk, the subsequent identification of GBCAs as the key etiologic factor in the development of nephrogenic systemic fibrosis (NSF) has raised concerns about the broader health impacts of gadolinium exposure. Clinicians, radiologists, and patients should be aware of the most up-to-date data pertaining to the risks of GBCA administration. Specific issues covered in this review article include immediate adverse reactions; pregnancy and lactation; and gadolinium deposition and toxicity, with a special focus on NSF. Practice recommendations based on the presented data, as well as current professional society guidelines, are provided for each section.
Level of Evidence: 1

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Gadolinium-based contrast agents (GBCAs) have been used in magnetic resonance imaging (MRI) since the 1980s. With the approval of gadopentetate (Magnevist) by the U.S. Food and Drug Administration (FDA) in 1988, the utilization of MRI grew at a rapid rate, soon becoming ubiquitous in clinical practice. MRI protocols incorporating GBCAs remain an important part of lesion detection and characterization throughout the body, with GBCAs administered in up to 35% of all MRI examinations.[1] Initially, the use of GBCAs was felt to carry minimal risk. While an association between the use of iodinated contrast agents for computed tomography (CT) examinations and adverse clinical outcomes in patients with impaired renal function was recognized as early as the late 1970s, GBCAs were historically administered with relatively few restrictions to patients with reduced estimated glomerular filtration rate (eGFR) and often favored in such settings over the iodinated contrast used for CT scans.[2]

The first recognition of potential nonallergic adverse effects of GBCAs came in 2006 when several authors identified a connection between GBCA administration in patients with advanced renal disease and the development of a condition called nephrogenic systemic fibrosis (NSF), a phenotype originally described almost 9 years prior.[3,4] Consequently, in June 2006, the FDA issued a statement advising caution in the use of GBCAs for patients on dialysis or with eGFR values of less than 15 mL/min/1.73-m^2. The FDA subsequently mandated a black box warning on all GBCAs and expanded this cautionary advisory to include all patients with eGFRs less than 30 mL/min/1.73-m^2.[5] Additionally, the FDA deemed gadopentetate (Magnevist), gadodiamide (Omniscan), and gadoversetamide (OptiMARK) to be contraindicated in patients with eGFRs less than 30 mL/min/1.73-m^2.

Pharmacochemical Considerations

Since 2006, GBCAs have begun to receive more intense scrutiny with respect to their safety profiles, and additional potential adverse effects of GBCA administration have been proposed. The current consensus is that such GBCA-related toxicities arise from the deposition of gadolinium ions in various tissues, a process that appears to vary in degree among GBCAs, depending on their particular structural details.[6] Because the toxicity of gadolinium and other

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lanthanide metals had been known for some time, the initial development of GBCAs required a mechanism for limiting the potential for gadolinium accumulation in the body. Accordingly, all GBCAs consist of a gadolinium ion (Gd^{3+}), a heavy metal with paramagnetic properties, complexed with a chelating ligand. The chelate is a carrier molecule, the purpose of which is to remain bound to Gd^{3+} until it is excreted, thereby preventing deposition of Gd^{3+} in tissues.

The specific properties of the chelating ligand determine how tightly the Gd^{3+} is bound, with stronger bonds indicating a lower tendency of Gd^{3+} to dissociate from the chelating ligand. Spontaneous dissociation is relatively rare at physiologic pH, while assisted dissociation occurs more readily under such conditions.[6] Assisted dissociation occurs via transmetallation, a process initially described in 1988 whereby endogenous cations such as Cu^{2+}, Zn^{2+}, and Ca^{2+} compete for binding to the GBCA chelating ligand.[7] As these cations displace the Gd^{3+}, the unchelated Gd^{3+} forms bonds with endogenous anions and can become incorporated into tissues. The avidity of Gd^{3+} binding by the chelating ligand varies widely among GBCAs. Structurally, GBCAs can be categorized as linear versus macrocyclic and as nonionic versus ionic (Table 1). Macrocyclic agents *generally* have higher stability than linear agents, and ionic agents *generally* have higher stability than nonionic agents. These relationships are intuitive when one considers the molecular structures and electrochemical properties of the chelating ligands (Fig. 1).

In light of the established role of gadolinium in NSF and other more recent gadolinium-related safety concerns, it is important for clinicians, radiologists, and patients to be adequately informed with respect to the risks of GBCA administration for MRI examinations. While many prior publications have focused on particular GBCA safety issues individually, such as gadolinium deposition in the basal ganglia or gadolinium effects on the fetus, our goal in this review is to provide a comprehensive assessment of the various established and potential risks of GBCA administration in a single publication. To this end, we discuss the most current evidence and guidelines related to the following topics: 1) GBCA-associated immediate adverse reactions; 2) GBCA use in pregnancy and lactation; 3) gadolinium deposition and toxicity; and 4) NSF.

Immediate Adverse Reactions

Types and Mechanisms

Immediate adverse reactions are defined as unintended side effects occurring within 1 hour of contrast agent exposure,[8] although more delayed reactions can occur.[9] These reactions are categorized as either physiologic or hypersensitivity-related (Table 2).[1,10] Physiologic reactions are likely caused by direct toxicity of the administered agent, such as contrast-related hyperosmolality and molecular binding to nonimmunologic receptors. These reactions are typically dose-dependent and/or concentration-dependent. For example, vasovagal reactions, which belong to this category, may relate to the central nervous effects of drug administration or anxiety associated with drug administration. Physiologic reactions can range from mild (eg, transient nausea and vomiting) to severe (eg, hypertensive urgency or refractory vasovagal reactions). Furthermore, at least a subset of physiologic reactions may be attributed to the Weber and Lalli effects, in which introduction of a new pharmaceutical agent to the market or to an individual patient results in increased perception and reporting of potential adverse effects.[11,12]

Hypersensitivity reactions, on the other hand, are immune-mediated, idiosyncratic, and independent of dose or concentration. The vast majority of these reactions have been termed *allergic-like* or *anaphylactoid*, signifying that they are not immunologically specific (ie, do not require previous exposure to the antigen) but nonetheless result in mast cell degranulation and complement activation. True immunoglobulin E (IgE)-mediated allergic reactions to GBCAs, as confirmed by skin testing, have been reported but are relatively rare.[13] Like physiologic reactions, hypersensitivity reactions also vary in severity and can range from mild (eg, limited urticaria) to severe (eg, anaphylactic shock).

Epidemiology and Risk Factors

In order to ascertain the rate of immediate adverse reactions, we reviewed five articles that included more than 660,000 patients who had undergone intravenous GBCA administration.[9,14–17] The adverse reaction rate varied from 0.06–0.3%. In general, lower rates were reported in retrospective trials, which may reflect a failure to capture all events. The pooled event rate was 0.1%, with 4% of reactions classified as severe (0.005% of all administrations) and 0.3% resulting in death (0.0003% of all administrations). Raisch et al systematically reviewed cases of severe adverse reactions from the FDA MedWatch database and the peer-reviewed literature through 2012, identifying 614 unique cases.[18] The majority of these cases resulted in hospitalization (53%); nearly one-third were considered life-threatening (31%); and almost one-tenth resulted in death or disability (7% and 2%, respectively). These adverse event rates are substantially lower than those observed with high-osmolar iodinated contrast agents and similar to those observed with low-osmolar iodinated contrast agents.[10]

All GBCAs have similar rates of adverse reactions.[15–18] Female gender, prior drug hypersensitivity reaction, and prior reaction to GBCAs were also associated with an increased risk of adverse reactions.[15,17] Indeed, patients with prior adverse reactions to GBCAs are roughly eight times more likely to experience a subsequent reaction, and the severity

TABLE 1. Characteristics of FDA-approved GBCAs

Chemical name	Trade name	Manufacturer	Molecular structure	Distribution	Year of FDA approval	Thermodynamic stability constant[100]	Adult dosing[23]	Biliary excretion	Global administrations (as of 2010)[77,78]	Cases of NSF[a77,78]
Gadopentetate dimeglumine (Gd-DTPA)	Magnevist	Bayer HealthCare	Linear ionic	Extracellular	1988	22.1	0.1 mmol/kg	None	105 million	179
Gadodiamide (Gd-DTPA-BMA)	Omniscan	GE Healthcare	Linear nonionic	Extracellular	1993	16.9	0.1 mmol/kg	None	49 million	505
Gadoversetamide (Gd-DTPA-BMEA)	OptiMARK	Guerbet	Linear nonionic	Extracellular	1999	16.6	0.1 mmol/kg	None	3.5 million	35
Gadobenate dimeglumine (Gd-BOPTA)	MultiHance	Bracco	Linear ionic	Extracellular	2004	22.6	0.1 mmol/kg	3%	7.5 million	2
Gadoxetate disodium (Gd-EOB-DTPA)	Eovist	Bayer HealthCare	Linear ionic	Hepatocellular	2008	23.5	0.025 mmol/kg	50%	0.4 million	0
Gadofosveset trisodium	Ablavar	Lantheus	Linear ionic	Blood-pool	2008[d]	22.1	0.03 mmol/kg	None	0.1 million	0
Gadoteridol (Gd-HP-DO3A)	ProHance	Bracco	Macrocyclic nonionic	Extracellular	1992	23.8	0.1 mmol/kg[c]	None	15 million	2
Gadobutrol (Gd-BT-DO3A)	Gadavist	Bayer HealthCare	Macrocyclic nonionic	Extracellular	2011	21.8	0.1 mmol/kg	None	6.0 million	2
Gadoterate meglumine (Gd-DOTA)	Dotarem	Guerbet	Macrocyclic ionic	Extracellular	2013	25.6	0.1 mmol/kg	None	22.4 million	1[b]

[a]Number of unconfounded single-agent cases.
[b]Patient received an unknown GBCA approximately 9 years prior.
[c]In the presence of negative or equivocal scans, a supplementary dose of 0.2 mmol/kg may be given up to 30 minutes after the first dose.
[d]No longer in production.

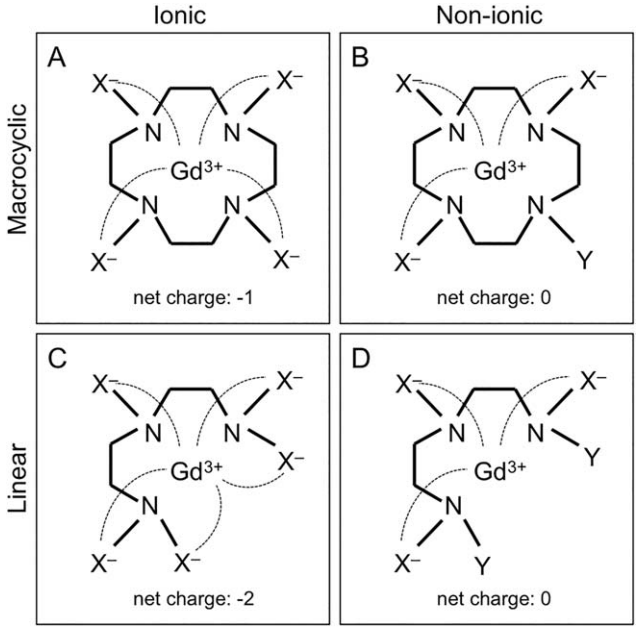

FIGURE 1: Structural and electrochemical differences among GBCAs. All GBCAs consist of a gadolinium ion (Gd^{3+}) complexed with a chelating ligand. The GBCAs can be divided according to the structure of the chelating ligand (macrocyclic: A,B versus linear: C,D) and according to the net charge of the gadolinium-chelate complex (ionic: A,C versus nonionic: B,D). Although not true for all GBCAs, the macrocyclic agents are *generally* more stable than the linear agents. For the two prototypical macrocyclic compounds shown in A and B, the Gd^{3+} is completely encircled by the chelating ligand, creating a molecular cage that reduces the likelihood of dissociation. In contrast, for the two prototypical linear compounds shown in C and D, the chelating ligand forms an incomplete ring around the Gd^{3+}. Regarding net charge, the ionic agents are *generally* more stable than the nonionic agents. For the two prototypical ionic compounds shown in A and C, the chelate includes greater than three negatively charged moieties (X^-) that form electromagnetic associations (dotted lines) with the Gd^{3+}, resulting in a relatively strong bond that decreases the likelihood of dissociation. Such GBCAs are termed *ionic* due to their net negative charges. In contrast, for the two prototypical nonionic compounds shown in B and D, the chelate includes only three negatively charged moieties (X^-) that form electromagnetic associations (dotted lines) with the Gd^{3+}, resulting in a relatively weak bond that increases the likelihood of dissociation. Such GBCAs are termed *nonionic* due to their net neutral charges and include various neutral moieties (Y) incapable of forming electromagnetic associations the Gd^{3+}.

of the subsequent reaction can be greater than that of the initial reaction.[1,10] However, lack of reaction during a previous GBCA administration is not predictive of decreased risk.[9] While there is no immunologic crossreactivity between iodinated contrast agents and GBCAs, prior reaction to an iodinated agent is an indicator of increased risk for hypersensitivity reactions to GBCAs.[1] Furthermore, there may be little-to-no crossreactivity even among different GBCAs.[13]

Prevention

Corticosteroid premedication is a widely used technique intended to reduce the incidence and severity of contrast-induced hypersensitivity reactions. Such regimens are likely effective in preventing many mild reactions.[1,19] However, breakthrough reactions (ie, those occurring despite premedication) are seen in up to one-third of pretreated patients.[9,15] Similarly, patients with prior severe reactions are still at risk for developing severe reactions even when pretreated.[20] No randomized, controlled clinical trials have been performed to evaluate whether premedication truly reduces the risk of severe adverse reactions.[10] While the risks associated with short corticosteroid courses are low, these agents must be used with caution in patients with uncontrolled hypertension, diabetes, and active infections.[21] To this point, corticosteroid premedication for inpatients may prolong admission and thus increase the risk for hospital-associated infections.[22] Anaphylactoid reactions have also been reported with corticosteroids, most frequently with intravenous formulations.[10]

Recommendations on Acute Adverse Reactions

The FDA advises caution when using GBCAs in patients with prior hypersensitivity reactions and in patients with asthma and allergic disorders, although the FDA is somewhat inconsistent on this point. The FDA considers a prior hypersensitivity reaction to any GBCA to be a contraindication for gadoversetamide (OptiMARK) and gadobenate (MultiHance) administration. In contrast, the FDA considers other GBCAs to be contraindicated only in the setting of a prior hypersensitivity reaction to the specific GBCA in question.[23] We found no evidence to support this discrepancy, and the American College of Radiology (ACR) and European Society of Urogenital Radiology (ESUR) do not make different recommendations for different GBCAs. Both societies suggest that alternative tests be considered in patients with previous hypersensitivity reactions to GBCAs. In those for whom contrast-enhanced MRI is deemed necessary for clinical care, corticosteroid premedication should be considered, as should switching to a different GBCA.[8,10] The ESUR also suggests premedication for patients with uncontrolled asthma or atopy requiring medical treatment, even in the absence of prior hypersensitivity to GBCAs. In our practices, we tend to premedicate only those with a previous moderate or severe reaction, to utilize a different GBCA if possible, and to avoid contrast-enhanced MRI altogether in those with a previous severe reaction. No premedication is used for patients with prior reactions to iodinated contrast reactions before administering GBCAs. At our institutions, the standard premedication protocol includes prednisone, 50 mg by mouth, at 13, 7, and 1 hour prior to the examination, and diphenhydramine, 50 mg by mouth, at 1 hour prior to the examination. Regardless of the approach, staff should be trained on how to manage hypersensitivity reactions. Resuscitation equipment should be readily accessible, and patients at risk for hypersensitivity

TABLE 2. Acute Adverse Reactions to GBCAs

	Hypersensitivity	Physiologic
Mild[a]	• Limited urticaria and/or pruritus • Limited cutaneous edema • Limited throat scratchiness • Nasal congestion • Sneezing, conjunctivitis, and rhinorrhea	• Limited nausea and/or vomiting • Transient flushing, warmth, or chills • Headache, dizziness, anxiety, or altered taste • Vasovagal reaction that resolves spontaneously
Moderate[b]	• Diffuse urticaria and/or pruritis • Diffuse erythema with stable vital signs • Facial edema without dyspnea • Throat tightness without hoarseness or dyspnea • Bronchospasm with mild or no hypoxia	• Protracted nausea and/or vomiting • Hypertensive urgency • Isolated chest pain • Vasovagal reaction that responds to treatment
Severe[c]	• Diffuse edema or facial edema with dyspnea • Diffuse erythema with hypotension • Laryngeal edema with stridor or hypoxia • Bronchospasm with significant hypoxia • Anaphylactic shock (hypotension and tachycardia)	• Vasovagal reaction that is resistant to treatment • Arrhythmia • Convulsions or seizures • Hypertensive emergency

[a]Self-limited, uncommonly requiring treatment; do not progress, even without treatment.
[b]More pronounced, commonly requiring treatment; tend to progress without treatment.
[c]Often life-threatening; can result in permanent morbidity or death if not managed appropriately.

reactions should be monitored for at least 1 hour following GBCA injection.

Summary

Immediate adverse reactions to GBCAs are uncommon, and serious adverse reactions are exceedingly rare. Despite over 200 million GBCA administrations, there have been only 614 reports of severe adverse reactions, including only 54 cases of death or permanent disability. The ACR and ESUR recommend consideration of corticosteroid premedication for patients with previous reactions to GBCAs. Pretreatment may result in adverse effects in hospitalized patients or patients with comorbidities. Attempts should be made to avoid contrast-enhanced MRI in those with a previous severe reaction to GBCAs. If contrast-enhanced MRI is deemed clinically necessary in a patient with a previous GBCA-related hypersensitivity reaction, a different GBCA should be selected or, if appropriate, a nongadolinium-based agent such as ferumoxytol can be considered.[24,25] Most importantly, radiology departments should be equipped to identify and treat acute reactions when they arise.

Pregnancy and Lactation

Unique Challenges

Pregnancy and lactation present unique challenges for diagnostic imaging, in light of the radiosensitivity of both the fetus and the maternal breast tissue. Consequently, imaging algorithms in these settings rely heavily on ultrasound and MRI, in order to minimize the risks of exposure to ionizing radiation.[26] Despite the potential for tissue heating secondary to radiofrequency energy deposition, MRI is generally felt to be safe during pregnancy, especially after the first trimester, provided that specific absorption rate (SAR) limits are followed.[27] Importantly, many standard MRI protocols in the general adult patient population call for the administration of GBCAs, which are often essential to the diagnostic utility of these examinations. However, as a result of concerns about potential adverse effects of GBCAs on the developing fetus and infant, many centers restrict the use of GBCAs in expectant and lactating women.[28]

Fetal Uptake and Handling of GBCAs in Pregnancy

Within the placenta, the maternal and fetal blood pools are separated by a thin layer of chorionic trophoblasts, which allow for rapid diffusion of small lipid-soluble molecules.[29] Larger water-soluble molecules, such as iodinated contrast agents and GBCAs, cross the placenta somewhat less readily and appear in the fetal urinary bladder around 11 minutes following maternal intravenous administration.[30] While the kinetics of placental permeability to GBCAs have been studied in detail in mice, higher-order mammalian data are considerably more limited.[31] In primates, the transplacental passage of GBCAs into the fetal circulation was first described in rhesus monkeys and has since been demonstrated clinically in humans.[32]

Once within the fetal circulatory system, GBCAs undergo renal clearance and enter the amniotic fluid via excretion from the urinary bladder, after which fetal swallowing is thought to result in gastrointestinal reabsorption.[33] Corroborating this theory, a study performed in gravid macaques showed the highest amniotic fluid concentration of GBCAs at 19–21 hours after maternal administration

followed by a statistically significant decline at 45 hours.[34] In that study, the liver was the site of second greatest visceral GBCA accumulation (after the kidney), containing 0.0013% of the injected dose per gram of tissue at 45 hours postinjection. In contrast, only 0.00002% of injected GBCA dose was detectable within the fetal brain on a per-gram basis at this same timepoint.

GBCA Safety in Pregnancy

The vast majority of data pertaining to the safety of GBCA administration during pregnancy are derived from animal studies. The package inserts for GBCAs report various fetal toxicities, including growth retardation and congenital anomalies, following extended exposures at doses two to seven times higher than those used in humans for medical imaging.[35] In contrast, other animal studies have failed to demonstrate any appreciable deleterious effects of GBCAs on fetal development. For example, an analysis of viability, morphology, and weight of 739 mouse fetuses found no differences between GBCA-exposed and unexposed animals.[36] Another study reported no teratogenic effects of GBCAs in rabbits and rats,[37] while a primate study found no deficiencies in physical and behavioral development or reproductive performance in the offspring of cynomolgus monkeys exposed to GBCAs.[38]

While no controlled fetal toxicity studies have been conducted in humans, several retrospective observational studies of neonates exposed to GBCAs in utero have been published. One of the earliest case reports of fetal GBCA exposure in humans found no neonatal abnormalities in the infants of two women who underwent contrast-enhanced MRI to diagnose Crohn's disease during pregnancy.[39] Another study of 26 pregnant women who received GBCAs during the first trimester reported no adverse effects on pregnancy or neonatal outcomes.[40] Most recently, a large epidemiological study by Ray et al of over 1.4 million deliveries in the Canadian province of Ontario between 2003 and 2015 found no statistically increased risk of stillbirth/death, NSF-like outcomes, or congenital anomalies among infants exposed to GBCAs during the *first trimester*, compared with their unexposed peers.[41] However, the authors did report statistically increased risks of rheumatologic/inflammatory conditions (adjusted hazard ratio, 1.36; 95% confidence interval [CI], 1.09–1.69) and stillbirth or neonatal death (adjusted relative risk, 3.70; 95% CI, 1.55–8.85) among infants exposed to GBCAs at *any point in utero*, suggesting that exposure during the second two trimesters may carry a greater risk.

Importantly, Ray et al used propensity scores for having an MRI to account for any differences between the mothers of the exposed and unexposed infants.[41] In other words, that study minimized confounders related to the indications for which some women required contrast-enhanced MRI during pregnancy, while other women did not. Therefore, these results imply that the worse outcomes observed among exposed infants were actually related to GBCA exposure rather than differences in maternal health between the exposed and unexposed infant groups. Notably, this study did not account for potential maternal or fetal harm from withholding contrast-enhanced MRIs when such studies would otherwise be indicated. For example, dynamic contrast-enhanced T_1-weighted sequences have proven superior to nonenhanced T_2-weighted sequences for the evaluation of placenta accreta, a condition that can result in poor maternal–fetal outcomes if unrecognized.[42]

Recommendations on Administering GBCAs in Pregnancy

In light of the mixed GBCA safety data in pregnancy, there is considerable variability in practice patterns in this setting. A 2007 survey of academic medical centers revealed that only 57 of 85 institutions (67%) have official departmental policies prohibiting GBCA administration to pregnant women.[28] Among the 33% of centers without such policies, the most common indication for contrast-enhanced MRI in pregnancy was malignancy staging. Various professional societies, including the ACR, ESUR, and American Congress of Obstetricians and Gynecologists (ACOG), have published guidelines regarding the use of GBCAs in pregnancy.[8,10,43] A summary of these guidelines is shown in Table 3. In general, the consensus is that GBCAs can be administered to pregnant patients on a case-by-case basis when the maternal–fetal benefit of a contrast-enhanced MRI is felt to outweigh the potential poorly understood risks of fetal gadolinium exposure.

Infant Uptake and Handling of GBCAs in Lactation

Water-soluble agents generally enter breast milk by binding to milk proteins.[30] Due to their relative lack of affinity for these proteins, GBCAs are not excreted in human breast milk at high levels. Less than 1% of the intravenous dose administered to a nursing mother appears in the breast milk, with less than 1% of the dose present in breast milk subsequently undergoing absorption by the infant gastrointestinal (GI) tract into the bloodstream.[44] Consequently, the effective infant circulatory dose from ingestion of GBCA-containing breast milk is at least 10,000 times less than the intravenous GBCA dose that an infant would typically receive with a contrast-enhanced MRI for a neonatal indication. Once within the infant circulation, the vast majority of gadolinium ions, which remain in chelated form, are excreted from the body, predominantly via the neonatal kidneys in the urine. The amount of unchelated gadolinium reaching the infant's bloodstream is expected to depend on the stability of the gadolinium-chelate complex, which varies from agent to agent, as previously described.

TABLE 3. Professional Society Guidelines for GBCA Use in Pregnancy and Lactation

	GBCAs in pregnancy	GBCAs in lactation
ACR[10] Year: 2016	"Each case should be reviewed carefully by members of the clinical and radiology service groups, and a GBCA should be administered only when there is a potential significant benefit to the patient or fetus that outweighs the possible but unknown risk of fetal exposure to free gadolinium ions."	"Because of the very small percentage of gadolinium-based contrast medium that is excreted into the breast milk and absorbed by the infant's gut, we believe that the available data suggest that it is safe for the mother and infant to continue breast-feeding after receiving such an agent."
ESUR[8] Year: 2015	"When there is a very strong indication for enhanced MR, the smallest possible dose of one of the most stable gadolinium contrast agents . . . may be given to the pregnant female." "Following administration of gadolinium-based agents to the mother during pregnancy, no neonatal tests are necessary."	"Breast feeding should be avoided for 24 hours after contrast medium if high-risk agents are used."
ACOG[43] Year: 2016	"The use of gadolinium contrast with MRI should be limited; it may be used as a contrast agent in a pregnant woman only if it significantly improves diagnostic performance and is expected to improve fetal or maternal outcome."	"Breastfeeding should not be interrupted after gadolinium administration."

ACOG = American Congress of Obstetricians and Gynecologists; ACR = American College of Radiology; ESUR = European Society of Urogenital Radiology; GBCA = gadolinium-based contrast agent.

GBCA Safety in Lactation

There are no available safety data specifically pertaining to the risks of GBCA ingestion by breast-feeding infants. A thorough literature search reveals no case reports of adverse infant events attributable to GBCA-containing breast milk. In the absence of better information, studies of intravenous GBCA use in the general pediatric population may be useful to discussions between healthcare providers and lactating women about whether to engage in temporary breastfeeding cessation after maternal contrast-enhanced MRIs. For example, gadobenate (MultiHance) has been shown to be safe when administered intravenously to infants and young children and is widely used in this population.[35]

Recommendations on Administering GBCAs in Lactation

The ACR, ESUR, and ACOG have also issued guidelines concerning the use of GBCAs in lactating women.[8,10,43] A summary of these guidelines is shown in Table 3. There is no consensus among these societies, with the ACOG and ACR recommending against temporary cessation of infant breast-feeding following GBCA administration to the mother and the ESUR advising 24 hours of breastfeeding cessation after mothers receive high-risk GBCAs. Overall, the decision about whether to cease breast-feeding for a short period of time after contrast-enhanced MRI may be best made on a case-by-case basis, depending on the specific GBCA administered to the lactating mother.

Summary

Pregnancy and lactation present unique challenges for diagnostic imaging. Maternal imaging algorithms generally rely on ultrasound and MRI, given concerns about radiation exposure to the fetus and to maternal breast tissue. MRI protocols that include GBCAs have the potential for fetal gadolinium exposure via transplacental passage and for infant gadolinium exposure via excretion in the breast milk. In general, the consensus among various professional societies is that GBCAs should be administered to pregnant patients only when the maternal–fetal benefit of a contrast-enhanced MRI is felt to outweigh the potential risks of fetal gadolinium exposure, and temporary cessation of breast-feeding after maternal GBCA administration is not recommended. Regardless, if the decision is made to administer a GBCA to a pregnant or lactating woman, an agent with high thermodynamic stability, given at the lowest dose required for a diagnostic study, is advisable.

Gadolinium Deposition and Toxicity

Gadolinium Deposition

The deposition of gadolinium in human tissues as a result of GBCA use was first described in the context of end-stage

TABLE 4. Professional Society Guidelines for GBCA Use in Patients With Chronic Kidney Disease

	Patients at risk for NSF	High risk agents	Dialysis after GBCA administration
ACR[10] Year: 2016	• On dialysis (any form) • Severe or end-stage CKD (CKD 4 or 5, eGFR less than 30 mL/min/1.73-m^2) without dialysis • eGFR 30-40 mL/min/1.73-m^2 without dialysis[a] • Acute kidney injury	"When GBCA administration is required, agents associated with the greatest apparent NSF-associated risk (Group I agents, [Omniscan, Magnevist, and OptiMARK]) should be avoided."	"...GBCA-enhanced MRI examinations [should] be performed as closely before hemodialysis as is possible..."
ESUR[8] Year: 2013	• Patients with CKD 4 and 5 (GFR < 30 mL/min/1.73-m2) • Patients on dialysis • Patients with acute kidney insufficiency	"Omniscan, Magnevist, and OptiMARK are contraindicated in at risk and should be used with caution in patients with CKD 3 (GFR 30–60 mL/min/1.73-m^2)."	"Extra hemodialysis session to remove [gadolinium-based] contrast medium as soon as possible after it has been administered is recommended."
FDA[99] Year: 2010	"[Patients with] acute kidney injury (AKI) or chronic, severe kidney disease (with a glomerular filtration rate or GFR < 30 mL/min/1.73-m^2)."	"Magnevist, Omniscan, and OptiMARK [...] are contraindicated in these patients".	"For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a GBCA..."

ACR = American College of Radiology; ESUR = European Society of Urogenital Radiology; FDA = Food and Drug Administration; GBCA = gadolinium-based contrast agent.
[a]"...patients with eGFR 30 to 40 mL/min/1.73-m^2 should also be considered at risk because eGFRs may fluctuate (e.g., from the 30 to 40 mL/min/1.73-m^2 range one day to below 30 mL/min/1.73-m^2 on another day)."

renal disease patients with NSF, which is discussed in much greater detail in the subsequent section.[4] The presence of gadolinium has since been recognized in tissues other than the skin, even in patients with normal renal function.[45,46] In a 2014 study, Kanda et al reported a significant correlation between the degree of hyperintensity in the dentate nucleus and globus pallidus on unenhanced T_1-weighted images (Fig. 2) and the number of previous GBCA administrations.[47] This finding, which persisted when controlling for patients' renal function, was surprising to many radiologists, as gadolinium deposition had been widely believed to be a problem unique to patients in renal failure. Subsequent cadaver studies confirmed the presence of significant gadolinium in these brain structures.[48] Interestingly, a study of cerebral gadolinium deposition in rats revealed progressive and persistent T_1-hyperintensity in the deep cerebellar nuclei in those repeatedly exposed to the nonionic gadodiamide (Omniscan) but not in those repeatedly exposed to the newer ionic agent gadoterate meglumine (Dotarem).[49] While the administration of any GBCA likely results in at least some degree of gadolinium deposition, the findings of this study suggest that imaging evidence of gadolinium deposition in the brain may become less common in the near future, as the use of GBCAs with more tightly binding chelates becomes more widespread.

Gadolinium deposition has also been shown to occur in organs other than the brain and skin, most notably the bones and liver. In a 2004 prospective study, Gibby et al compared samples of human bone tissue obtained from total hip arthroplasty patients who received GBCAs intravenously 3–8 days prior to surgery with bone tissue from age-matched controls and found significantly higher levels of gadolinium in the bones of patients with presurgical GBCA exposure.[50] Similarly, a retrospective study of 21 pediatric patients who underwent liver biopsy following hematopoietic stem cell transplantation for various indications found a positive correlation between gadolinium deposition in the liver and cumulative GBCA dose from prior MRIs.[51] Interestingly, five of these patients also received deferoxamine, a chelating agent, for concurrent hepatic iron overload. Subsequent biopsies in these five patients showed an average reduction in liver gadolinium of 70.7% (range, 52.1–99.8%); this reduction was not observed in the patients not treated with chelation. These findings suggest that gadolinium deposition from GBCAs is at least partially reversible, although additional studies are needed to determine whether similar results can be achieved prospectively and in organs other than the liver.

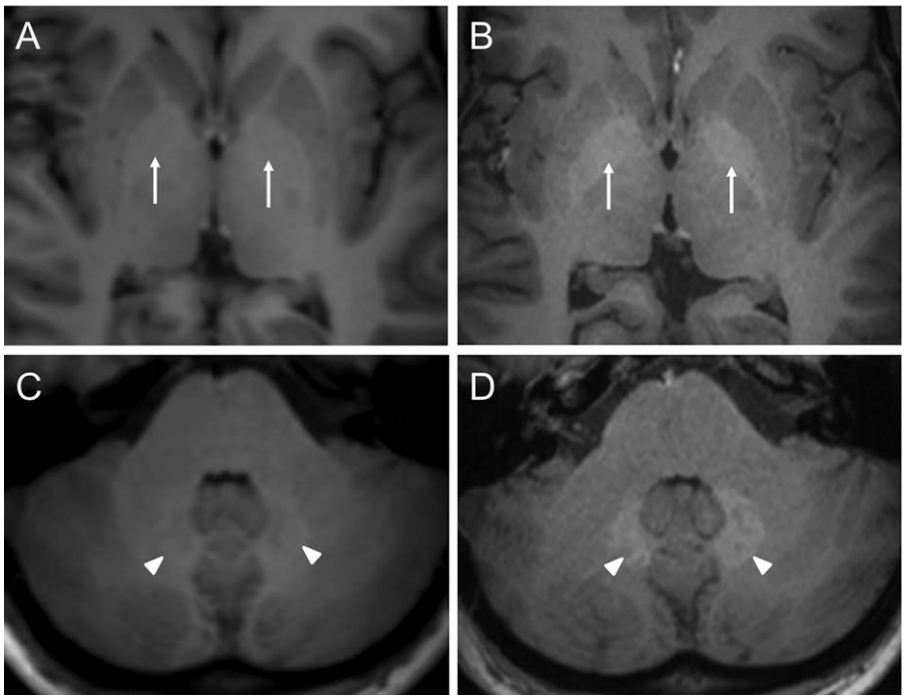

FIGURE 2: Cerebral gadolinium deposition. Transaxial nonenhanced T_1-weighted MR images of the basal ganglia (B) and cerebellum (D) from a patient with numerous prior MRIs performed with GBCAs demonstrate intrinsic T_1-hyperintensity of the globus pallidus (arrows in B) and the dentate nucleus (arrowheads in D) bilaterally. On a brain MRI from several years earlier (A,C), these same structures (globus pallidus: arrows in A; dentate nucleus: arrowheads in C) were not intrinsically T_1-hyperintense. Overall, these findings are consistent with gadolinium deposition from repeated GBCA exposure. The globus pallidus and dentate nucleus are two of the most common sites in the brain to be affected by gadolinium deposition.

Gadolinium Toxicity

The vast majority of data pertaining to potential toxicity of GBCAs derive from in vivo animal studies and in vitro human studies. The toxicity of lanthanides, the class of heavy metals to which gadolinium belongs, is established in mammals. As early as 1961, the chronic oral ingestion of gadolinium chloride and samarium chloride by rats was reported to cause liver damage, skin ulceration, and eventually cardiopulmonary collapse.[52] Subsequent studies have described nephrotoxicity in pigs (intra-arterial injection), neutropenia and hepatotoxicity in mice (intravenous injection), and neurotoxicity in rats (intracerebroventricular injection).[53] In humans, there have been case reports of GBCA-induced recurrent pancreatitis and GBCA-induced renal failure from acute tubular necrosis.[53]

Numerous mechanisms for gadolinium toxicity have been proposed, primarily based on the results of in vitro studies of human and rodent cells. For example, gadolinium ions are similar to calcium ions in terms of ionic radius and electrochemical properties.[53] Accordingly, gadolinium ions have been shown to block the T-type calcium channels present in smooth muscle, skeletal muscle, and neurons, potentially inhibiting action potential propagation in these cells.[53] Gadolinium ions have also been shown to induce elevated levels of reactive oxygen species and trigger apoptosis in rat cortical neurons, suggesting an alternate pathway for neurotoxicity.[53] Other potential mechanisms by which gadolinium may cause tissue toxicity, including the induction of cytokine release by macrophages and the activation of fibroblasts, are discussed in detail in the subsequent section on NSF.

While the development of NSF has been linked to the deposition of gadolinium in the skin of affected end-stage renal patients, low levels of gadolinium skin deposition have also been described in two patients with normal renal function and no clinical evidence of NSF.[54] This observation indicates that the mere presence of gadolinium complexes in tissue is not sufficient to induce the NSF clinical phenotype and also suggests a degree of dose dependence. Furthermore, the gadolinium deposition observed in other tissues, such as the brain and bone, has not been associated with any definite histopathologic effects, raising the possibility of variability in local responses to gadolinium among organ systems.[55] To this point, the FDA recently announced that it will initiate a thorough study of the mechanism of gadolinium retention in the brain to determine whether there are any potential adverse health effects.

Beyond the ample evidence of an association between gadolinium deposition and NSF, there have also been reports of potential links between GBCAs and the development of various clinical symptoms. In a 2016 paper, Semelka et al proposed the term *gadolinium deposition disease* (GDD) to refer to a symptomatic disease process observed in individuals with normal renal function that arises within 2 months of GBCA administration and has no

other alternate etiologic explanation.[45] Their survey of members of online gadolinium toxicity support groups found that the most common manifestations of GDD include central or peripheral pain (98%), altered mentation (69%), headache (67%), bone pain (62%), and skin thickening (52%).[56] Of the 42 study subjects, 41 (98%) were found to have persistent gadolinium in urine samples obtained 1 month after GBCA administration. Importantly, this study lacked a control group and relied on patient self-reporting, both of which were significant limitations. Furthermore, these results have not yet been independently verified by other authors. Larger controlled studies are needed to evaluate possible associations between GBCA exposures and specific clinical symptoms.

Environmental and Public Health Implications

In developed countries, most excreted human wastes, such as gadolinium-containing urine, are transported via sewers to waste water treatment plants. The decontamination processes used by the vast majority of these facilities are ineffective at removing gadolinium.[57] Consequently, the effluents from these treatment plants, which communicate with various aquatic systems, result in the transfer of gadolinium (in both chelated and unchelated forms) to surface and ground waters and subsequently to tap water.[58] Since 1988, when GBCAs first entered clinical use, there has been a sharp rise in gadolinium levels in bodies of water downstream from large western cities. For example, one study of drinking water in Berlin, Germany, reported gadolinium levels up to 17.6 mg/L, greater than 32 times the natural background level.[59] Gadolinium in drinking water can be absorbed at low levels via the gut, conceivably resulting in tissue deposition (and its possible associated toxicities) with chronic exposure. Importantly, newer water treatment processes that involve reverse osmosis membranes have been shown to be 99.85% effective at removing gadolinium contaminants from waste water.[60] Such systems may prove integral to mitigating the potential adverse public health effects of rising gadolinium levels in water supplies. Importantly, gadolinium is also used in various manufacturing processes, so the relative contributions of medical and industrial sources to rising gadolinium water levels are not known.

Recommendations

At present, there have been no specific recommendations from the various professional societies pertaining to the issue of gadolinium deposition. Until more is known about the potential for tissue gadolinium to induce various toxicities, radiologists should attempt to answer clinical questions without GBCAs whenever feasible. For example, noncontrast MR angiography techniques may be adequate for diagnosing various vascular conditions that are typically imaged with GBCAs. When GBCAs are deemed clinically necessary, radiologists and technologists should work together to administer the lowest possible dose that still results in diagnostic-quality images. Finally, when clinically appropriate, ordering physicians should consider lengthening the intervals between follow-up studies to reduce the cumulative effects of repeated gadolinium exposure.

Summary

The deposition of gadolinium in human tissues as a result of GBCA use was first described in the skin of end-stage renal disease patients with NSF and has since been shown to occur in other sites, including the brain, bones, and liver. Numerous mechanisms of gadolinium toxicity have been proposed, including calcium channel inhibition, production of reactive oxygen species, and induction of apoptosis. The mere presence of excess gadolinium in human tissues does not appear to be sufficient to induce particular clinical phenotypes, suggesting a degree of dose dependence and variations in local tissue responses among organ systems. There are no studies definitively linking tissue gadolinium to the development of particular clinical entities other than NSF.

Nephrogenic Systemic Fibrosis

Clinical and Pathologic Characteristics

The condition now known as NSF was first termed nephrogenic fibrosing dermopathy,[61,62] a presumed idiopathic disease that affected patients with end-stage renal disease. This pathologic entity was later renamed nephrogenic systemic fibrosis following the identification of deep tissue and visceral involvement.[63] NSF is exceedingly rare; fewer than 1000 confirmed cases have been described in the literature despite over 200 million GBCA administrations, although additional cases may be underrecognized or underreported.[64] Few cases have occurred since 2009, reflecting the change in practice patterns in 2006–2007 brought on by FDA recommendations.[65] Indeed, a review of PubMed publications and Google searches in the U.S. demonstrates a waning interest from the scientific community and public since 2010 (Fig. 3). However, NSF remains an important diagnosis in light of its marked clinical morbidity, which can range from mild and reversible to progressive and fatal.[66]

Clinically, patients present with skin thickening and fibrotic changes, predominantly affecting the extremities but with variable involvement of the trunk.[67] Joint contractures and loss of mobility are relatively common features and important causes of disability. Less commonly, fibrotic changes of the skeletal muscles, liver, lungs, and heart can occur.[63] In a series of patients on dialysis, the cutaneous changes of NSF have been shown to confer a 4-fold increase in mortality, compared with dialysis patients without NSF.[67] No effective treatment has been identified for NSF, although improvements in renal function and transplantation have been associated with more benign clinical courses and symptomatic improvements.[66,68]

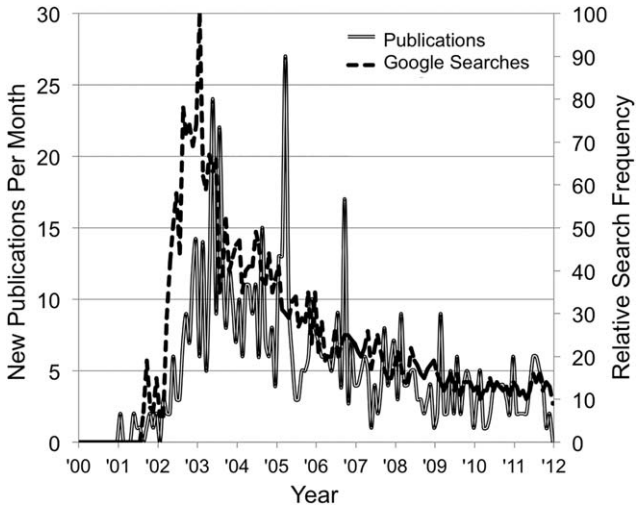

FIGURE 3: Trends in public and scientific interest in NSF. The number of new publications per month in the PubMed database serves as a metric of interest in NSF among members of the scientific community, while relative search frequency on Google serves as a proxy for interest in NSF among members of the general public. Interest in NSF rose rapidly in the early 2000s, as the disease entity initially became recognized, and remained high through 2007, as its etiology and risk factors were quickly identified. Since 2007, interest has progressively waned. As screening for renal insufficiency before GBCA administration became a widespread practice in the late 2000s, the number of new NSF cases has dropped precipitously.

Histopatholgically, NSF is characterized by increased dermal cellularity, the presence of CD34 + fibrocytes, cutaneous mucin deposition, and osseous metaplasia.[69] Gadolinium can be detected in skin biopsy specimens in nearly all patients diagnosed with NSF; however, it can also be detected in patients without NSF (albeit at lower levels), so its presence is not specific for the diagnosis.[70] The Girardi scoring system, which was created by the NSF registry in New Haven, CT, to aid in the diagnosis of NSF, takes into account both clinical and histopathologic features.[69] Notably, the presence of renal disease is a near-absolute requirement for the diagnosis, as no cases of NSF have been reported in the literature in patients with eGFRs greater than 60 mL/min/1.73-m^2. Most patients present with NSF within 6 months of GBCA exposure, and the vast majority present within 2 years.[66,70] Rarely, a considerable temporal delay may occur, with some patients presenting with NSF as many as 10 years after GBCA exposure.[71–73] It may be difficult to attribute individual NSF cases to the administration of a specific GBCA, as many patients with NSF received multiple different GBCAs prior to diagnosis. Nevertheless, our understanding of the pathophysiology of NSF continues to grow through systematic case reviews, animal experiments, and prospective trials.

Pathophysiology

The elimination half-life of GBCA, typically less than 2 hours in patients with preserved renal function, can be prolonged by an order of magnitude in patients with renal insufficiency. The increased physiologic half-life of GBCAs and relatively high circulating concentrations of zinc in the setting of renal insufficiency result in the displacement of gadolinium ions from their chelating ligands, resulting in the formation of gadolinium-phosphate complexes that precipitate in tissues. These complexes are engulfed by local macrophages that secrete TGF-β1, a cytokine that may serve to recruit fibroblasts and induce a fibrotic response.[74,75] The mobilization of catalytic iron is also purported to play a role in NSF.[76]

As previously discussed, the avidity of gadolinium ion binding by the chelating ligand varies widely among GBCAs. As would be expected, there is a strong inverse relationship ($r = –0.88$, $P < 0.05$) between the stability of this gadolinium chelate and the incidence of GBCA-specific NSF cases (Table 1). Accordingly, approximately 70% of single agent NSF cases occurred with gadodiamide (Omniscan, linear nonionic), 25% with gadopentetate (Magnevist, linear ionic), and 4.8% with gadoversetamide (OptiMARK, linear nonionic). As a result, Omniscan, Magnevist, and OptiMARK are now considered by the FDA to be contraindicated in patients with eGFRs <30 mL/min/1.73-m^2. To date, there has been only one potentially unconfounded case of NSF attributed to gadoterate (Dotarem, macrocyclic ionic), in a patient who received an unknown GBCA 9 years prior to the NSF diagnosis.[77] There have also been two unconfounded cases attributed to gadoteridol (ProHance, macrocyclic nonionic) and two unconfounded cases attributed to gadobutrol (Gadavist, macrocyclic nonionic).[78]

Another GBCA-specific factor that may influence the incidence of NSF is its route of excretion. The majority of GBCAs are excreted only via the kidneys. In contrast, gadobenate (MultiHance) and gadoxetate (Eovist) undergo significant degrees of hepatobiliary excretion, ranging from 3–50% of administered doses in patients with normal renal function.[79] The proportions excreted by the liver are likely much higher in the setting of renal insufficiency.[80] To date, there have been only two reported unconfounded cases of NSF with either of these agents despite a total of over six million administrations.[77]

Updates on Epidemiology

The Food and Drug Administration Adverse Event Reporting System (FDA-AERS) includes 1603 cases of NSF as of the end of 2013.[81] Notably, some of these cases may not be unique, and some lack complete clinical information. Spinazzi et al reviewed 815 distinct cases of NSF from 200 articles in the peer-reviewed literature from 2000 through December 2012, with the onset of the latest case occurring in 2009.[64] Using the same PubMed search terms as these authors, specifically "nephrogenic systemic fibrosis," "nephrogenic fibrosing dermopathy," "scleromyxedema-like," and "scleroderma and gadolinium," we identified 205

articles published since December 2012. Our review of these articles yielded a total of 76 NSF cases in six articles not captured by Spinazzi et al.[71,73,82–85] Two cases involved patients with delayed presentations of NSF, occurring 8 and 10 years after GBCA exposure, respectively.[71,73] The remainder of the cases involved onset of NSF prior to 2011. Overall, few (if any) cases of NSF are felt to have resulted from a GBCA administration after 2010.

While NSF occurs in patients of all ages (range 8–87 years), the greatest incidence of NSF has been observed in patients aged 51–60 years, even though the frequency of GBCA use in patients with eGFRs <30 mL/min/1.73-m^2 is highest among patients aged 71–80 years.[64,86] Men and women are similarly affected.[64] NSF has occurred in patients from 28 different countries and a variety of ethnic backgrounds. The greatest number of cases has been reported in the U.S. (73%), likely reflecting a combination of more frequent GBCA use, higher GBCA doses, and higher levels of reporting.[30]

No cases of NSF have been described in patients without significant renal disease. Of the NSF patients whose renal status was reported in the literature, the majority of cases (88%) occurred in patients with stage 5 chronic kidney disease (CKD; eGFR <15 mL/min/1.73-m^2); 10% occurred in patients with acute renal failure; and 2% occurred in patients with stage 4 CKD (eGFR of 15-29 mL/min/1.73-m^2), with only a single case reported in a patient with stage 3 CKD (eGFR of 30–59 mL/min/1.73-m^2).[64] The estimated incidence of NSF among patients with acute or chronic renal failure receiving GBCAs is 1.6% (range 0–18%).[86] This risk is likely substantially lower for the GBCAs associated with the fewest cases of NSF.

NSF also occurs more frequently in patients with hyperphosphatemia, acidosis, or proinflammatory states at the time of GBCA administration.[66,86] This observation suggests a physiologic environment that promotes dissociation of gadolinium ions from their chelating ligands. Patients with advanced CKD who undergo dialysis soon after GBCA administration appear to have a decreased incidence of NSF, likely reflecting the partial dialyzability of GBCAs and possibly also the ability of dialysis to correct the underlying metabolic disturbances that promote GBCA dissociation.[87] The stability of individual GBCAs seems to influence the likelihood of developing NSF, as previously described. Higher GBCA doses, such as those initially used for MR angiography with gadodiamide (Omniscan), are also associated with an increased risk of NSF, and the vast majority of patients diagnosed with NSF received a dose that was greater than the now standard doses for these agents.[66,86] In contrast to CKD, chronic liver disease does not appear to predispose patients to NSF, as formerly thought.[86,88]

Strategies to Minimize Risk

Changes in practice patterns, such as routine screening for renal insufficiency, withholding GBCAs in patients in advanced CKD, and a widespread shift away from the high-risk GBCAs (ie, gadopentetate [Magnevist], gadodiamide [Omniscan], and gadoversetamide [OptiMARK]) have almost completely eliminated new cases of NSF. At least six prospective trials involving more than 2200 patients have been conducted to assess the risk of NSF in patients with renal impairment receiving GBCAs.[21,89–93] Nearly half of the patients in these trials had eGFRs <30 mL/min/1.73-m^2, and one study included 268 patients on dialysis.[89] These studies tested all GBCAs except the three agents (ie, the high-risk agents listed above) with the strongest associations with NSF. No cases of NSF were reported in any of these trials.

Various strategies exist for avoiding GBCAs in patients at risk of NSF. Noncontrast MRI, CT, or ultrasound can in some cases provide similar information to contrast-enhanced MR sequences.[94] Nongadolinium-based contrast agents have also been explored. Superparamagnetic iron oxides, especially ferumoxytol, show particular promise in this setting.[24] Attempts have also been made to minimize gadolinium exposure by reducing GBCA doses while using 3T magnets to preserve diagnostic image quality.[95] Alternatively, several authors have proposed using gadobenate (MultiHance) at 25–50% of the prescribed dose, as this agent exhibits a favorable safety profile and provides excellent image quality even at lower doses, given its high degree of T_1-relaxivity and protein-binding characteristics.[96,97]

Recommendations

The ESUR, ACR, and FDA all have distinct sets of recommendations (Table 4) for the three GBCAs associated with the highest risk of NSF: gadopentetate (Magnevist), gadodiamide (Omniscan), and gadoversetamide (OptiMARK).[10,98,99] All three groups consider these agents to be contraindicated in patients with CKD stage 4–5 or acute renal failure. Furthermore, the ACR recommends against use of these particular GBCAs in patients with eGFRs of 30–40 mL/min/1.73-m^2, as renal function can fluctuate from day to day.

Beyond these specific high-risk agents, the ESUR, ACR, and FDA all recommend (Table 4) that the remaining GBCAs be used with caution in patients with eGFRs <30 mL/min/1.73-m^2 (or 40 mL/min/1.73-m^2 for the ACR). The ESUR further stratifies the GBCAs into intermediate and lowest risk agents; however, its recommendations do not differ between these two groups. The ACR and ESUR recommend the lowest possible gadolinium dose to achieve a diagnostic study and advise that multiple doses not be administered within a 7-day period. The ESUR promotes an additional 50% dose reduction with gadobenate

(MultiHance) and a reduced dose of gadoxetate (Eovist), provided that diagnostic results can be achieved. Additionally, the ACR recommends that patients already on dialysis undergo a dialysis session shortly after completion of an examination with GBCAs, while the ESUR does not. The ACR also directs clinicians and radiologists to consider contrast-enhanced CT instead of contrast-enhanced MRI in patients on dialysis. Most importantly, the ACR and ESUR recommend that a contrast-enhanced MRI never be withheld if absolutely necessary for clinical management, regardless of renal function.

All three organizations advise that patients planning to receive GBCAs undergo screening for CKD and acute renal failure. Per their guidelines, renal function screening by questionnaire is generally acceptable and patients need not have a recent eGFR unless they are older than 60 years, have a history of renal disease, or have hypertension or diabetes. The ESUR also mandates the checking of eGFR prior to administering any of the three high-risk GBCAs. For all inpatients, the ACR recommends that a serum creatinine (Cr) be obtained for eGFR calculation within 2 days of GBCA administration due to the risk of abrupt changes in renal function during hospitalization. In practice, there are various approaches to renal function screening. At one of our two institutions, we uniformly employ point-of-care Cr testing unless a recent serum Cr value is available for eGFR calculation. In contrast, at the other institution, serum Cr is checked only in patients meeting at least one of the following criteria:

1) age $\geq$60 years;
2) receiving potentially nephrotoxic chemotherapy;
3) history of CKD, partial or complete nephrectomy, or renal transplant;
4) recognized downward trend in eGFR.

Notably, several large centers perform GBCA-enhanced MRIs on patients with end-stage renal disease, as long as dialysis is performed immediately following the completion of imaging. Although there are no prospective data to support the theoretical benefits of prompt dialysis after GBCA administration in such patients, we employ this practice whenever possible, given its low risks.

Summary

NSF is a rare but important entity, the recognition of which has had a profound impact on the use of GBCAs in MRI. Resulting from dissociation of the gadolinium-chelate complex and subsequent tissue gadolinium deposition, NSF occurs almost exclusively in patients with significant renal impairment who have previously received a high-risk GBCA. Routine screening for renal insufficiency, limiting the use GBCAs in patients with stage 4–5 CKD or acute renal failure, and widespread switching to low-risk GBCAs have virtually eliminated new cases of NSF. Prospective trials investigating high-stability agents at lower doses, with special focus on those with hepatobiliary excretion, may establish the safety of these GBCAs in patients with even advanced renal disease.

Conclusion

Immediate adverse reactions to GBCAs are uncommon and typically mild. Contrast-enhanced MRI should be avoided in patients with previous severe reactions to GBCAs, as well as in all patients for whom a noncontrast examination would likely be adequate to answer the clinical question at hand. Radiology departments should be equipped to identify and treat hypersensitivity reactions when they arise. Pregnancy and lactation present unique challenges for contrast-enhanced MRI, as the effects of GBCAs on the fetus and nursing infant are unknown. Given this uncertainty, decisions regarding GBCA administration to pregnant patients should be made on a case-by-case basis after a thorough consideration of the maternal–fetal risks and benefits. Temporary cessation of breast-feeding after maternal GBCA administration is generally not advised, given the low levels at which GBCAs are excreted in breast milk. GBCA-related toxicities are thought to arise from the deposition of gadolinium ions in various tissues. Toxicities appear to vary in degree among different GBCAs, depending on the strength of the bond between the gadolinium ion and its chelating ligand. Deposition of gadolinium in various organs, including the brain, liver, and bone, has been demonstrated but has not yet been definitively linked to any adverse effects. Consequently, there are no firm recommendations to limit GBCA administration due to concerns about general tissue deposition. In contrast, an etiologic role of gadolinium in NSF is established. With the implementation of screening for renal insufficiency and the widespread adoption of GBCAs with lower tendencies for dissociation of the gadolinium-chelate complex, new cases of NSF have been almost completely eliminated since 2010.

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