

Incidence and Risk Factors for Gadolinium-Based Contrast Agent Immediate Reactions

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Abstract: Since their clinical introduction in 1988, gadolinium-based contrast agents (GBCAs) have demonstrated an excellent safety profile with a reported acute adverse reaction rate ranging from 0.01% to 2%. By comparison, the acute adverse reaction rate of low osmolar nonionic computed tomography contrast agents (CTCs) ranges from 0.7% to 3.1%. Many of the risk factors associated with CTC reactions (drug allergies, asthma, atopy, prior contrast reaction) also point toward an increased incidence of acute adverse events to GBCAs. With CTCs, an increased adverse event rate was associated with ionic preparations and high osmolality. In response to concerns for nephrogenic systemic fibrosis, GBCAs are now selected for their augmented chemical stability. These agents possess some combination of macrocyclic chelates or ionic preparations. With their improved chemical stability, these agents also possess higher osmolality and the increased potential to elicit an acute adverse reaction. In light of these concerns, researchers are now focusing greater efforts on reexamining acute adverse reactions to GBCAs and whether there is an increased association with certain agents. In addition to hypersensitivity reactions, this article will also discuss contrast extravasations, safety of GBCAs for pregnant and nursing patients, and the potential nephrotoxic effects of GBCAs.

Key Words: acute adverse reactions, contrast extravasation, contrast nephrotoxicity, gadolinium-based contrast agents, immunologic mechanism for contrast reaction

(*Top Magn Reson Imaging* 2016;25:257–263)

The Gadolinium (Gd) chelate $[\text{Gd}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$ received FDA approval in 1988 as the first intravenously administered drug to provide contrast-enhanced (CE) magnetic resonance (MR) images. Gd^{3+} is a lanthanide element that demonstrates unique hydrogen proton spin lattice relaxation effects that result in T1 shortening. Free ionic Gd^{3+} is extremely toxic, but the toxicity can be reduced by complexing free Gd^{3+} within a stable organic ligand, referred to as a chelator. The chelator not only prevents the free Gd^{3+} from interacting with surrounding tissue, but it also promotes rapid physiologic excretion, reducing the potential for disassociation from the organic ligand.^{1,2} Currently, there are 9 FDA-approved Gd-based contrast agents (GBCAs). Over the past 25 years, GBCAs have been administered to over 100 million patients and have become a mainstay of advanced diagnostic imaging.³ GBCAs have demonstrated an impressive overall safety profile. In a large study by Bleicher and Kanal⁴ involving 23,553 intravenous administrations of gadobenate dimeglumine, an acute adverse reaction rate of 0.76% was reported with a severe acute reaction rate of only 0.03%.

In recent years, GBCAs have fallen under closer scrutiny. In 2006, an association between certain GBCAs and nephrogenic

systemic fibrosis (NSF) was established for patients with markedly impaired renal function (stage 4 or stage 5 disease^{5,6}). In 2014, reports emerged that linked T1 shortening effects in the globus pallidus and dentate nuclei with repeated prior administrations of GBCAs, independent of renal function.⁷ Additional studies have identified a dose-dependent effect on the T1 shortening, depending upon whether the GBCA contained a linear or macrocyclic chelator.⁸ This increased attention has heightened the importance of reexamining the chemical stability of GBCA and emphasized the importance of using contrast agents with a decreased risk of Gd^{3+} disassociation from the chelate. Such chemically stable GBCAs not only possess some combination of ionic and/or macrocyclic properties but also have higher osmolality. On the basis of our example with computed tomography contrast agents (CTCs), there is a theoretical potential for an increased risk of acute adverse reactions to these chemically more stable GBCAs^{9,10} due to higher osmolality. This review will examine the physiologic basis of adverse reactions to GBCAs, the factors that increase the risk of adverse reactions, and also the types and frequencies of adverse reactions.

Gadolinium Structure

GBCAs cause T1 shortening through their strong hydrogen proton spin-lattice relaxation effects. In its cation form, gadolinium is extremely toxic, depositing into several different tissue types (liver, lymph nodes, bone, skin) and interfering with Ca^{2+} channels.^{1,11} Free Gd^{3+} can cause damaging effects to the reticuloendothelial system, neural transmission, and blood coagulation, interfering with several key enzymatic pathways (ATPase enzyme, dehydrogenases, kinases, glutathione *S*-transferases, aldolase) through competitive and noncompetitive inhibition of Ca^{2+} binding.¹² The damaging effects of free Gd^{3+} are minimized by confining the lanthanide ion within an organic ligand chelator. The chelator not only minimizes interaction of free Gd^{3+} with soft tissue, but it also promotes rapid excretion that reduces the chance of biotransformation and tissue accumulation. There are 2 major categories of chelate molecular complexes: macrocyclic and linear. Similar to CTCs, the chemical preparation of GBCAs can be either ionic or nonionic. In addition to their T1 shortening effects and biodistribution, these chemical descriptions directly affect the osmolality and viscosity of the contrast agent. Water-soluble GBCAs can distribute into the extracellular space, intracellular space, blood pool, or a specific tissue type. Table 1 contains a listing of the biochemical properties of the FDA-approved GBCAs.^{2,13–17}

The organic ligand chelator binds to the free Gd^{3+} ion with high selectivity and helps prevent disassociation into the circulation. There are several measures of the stability of the GD chelate: (1) thermodynamic stability, (2) conditional stability constant, (3) selectivity constant, and (4) kinetic stability of the complex. The most important of these metrics is the thermodynamic stability that reflects the amount of energy needed for the organic ligand to release the Gd^{3+} . With weak thermodynamic stability, the chelator is more susceptible to release the free Gd^{3+} and to bind to a different cation such as endogenous Zn^{2+} , Cu^{2+} , Fe^{3+} , Mg^{2+} , and Ca^{2+} , a process called transmetallation.¹⁸ The molecular structure of the chelator

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The authors report no conflicts of interest.

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DOI: 10.1097/RMR.000000000000109

TABLE 1. FDA-Approved Gadolinium-Based Contrast Agents

Chemical Name	Commercial Name	Chemical Structure	Osmolality, mOsm/kg	Thermodynamic Stability Constant (log K_{therm})	Excretion Pathway
Gadodiamide	Omniscan® (GE Healthcare, Princeton, NJ, USA)	Linear, nonionic	650	16.8	Renal
Gadoversetamide	OptiMARK® (Mallinckrodt, St Louis, MO)	Linear, nonionic	1110	16.6	Renal
Gadopentetate Dimeglumine	Magnevist® (Bayer Healthcare, Morristown, NJ)	Linear, ionic	1960	22.1	Renal
Gadobenate Dimeglumine	MultiHance® (Bracco Diagnostics Inc., Princeton, NJ)	Linear, ionic	1970	22.6	93% Renal; 3% Hepatobiliary
Gadoxetic Acid	Primovist® (Bayer Schering Pharma AG, Berlin, Germany)	Linear, ionic	688	23.5	50% Renal, 50% Hepatobiliary
Gadofosveset Trisodium	Vasovist® (Bayer Schering Pharma AG, Berlin, Germany)	Linear, ionic	700–950	22.0	91% Renal, 9% Hepatobiliary
Gadoteridol	ProHance® (Bracco Diagnostics Inc., Princeton, NJ)	Macrocyclic, nonionic	630	22.8	Renal
Gadobutrol	Gadovist® (Bayer Schering Pharma AG, Berlin, Germany)	Macrocyclic, nonionic	1603	21.8	Renal
Gadoterate Meglumine	Dotarem® (Guerbet Research, Aulnay Sous Bois, France)	Macrocyclic, Ionic	1350	25.4	Renal

Description of molecular structure, preparation, and other chemical properties. Adapted from.^{2,13–17}

largely governs the susceptibility to transmetallation. Numerous studies have established that macrocyclic Gd complexes are far less susceptible to transmetallation than linear Gd complexes. These results correlate to the corresponding thermodynamic stability of the examined GBCAs.^{19–21} In addition, contrast preparations that are ionic demonstrate further enhanced thermodynamic and kinetic stability.²² One measure of assessing stability examines the transmetallation between Zn^{2+} and Gd^{3+} and the resulting zinc chelate that is excreted in the urine. In vivo studies have documented that a nonionic linear chelate such as gadodiamide results in almost 3 times the amount of zincuria in comparison to an ionic linear chelate such as gadopentetate dimeglumine. Additional in vivo studies have shown that ionic macrocyclic chelates such as gadoterate meglumine exerted no change in zinc excretion in comparison to placebo controls.²³

Mechanisms of Contrast Reaction

There are several proposed pathophysiologic mechanisms attributed to the generation of an immediate contrast reaction to intravenous contrast agents. The majority of what is known about this topic originates from experience with CTCs. Immediate contrast reactions can be classified into 2 categories: (1) non-IgE mediated (often referred to as a nonallergic reaction or “pseudo-allergy,”) (2) IgE mediated. Non-IgE mediated mechanisms have accounted for the majority of immediate reactions, seen most frequently in several classes of drugs, including opiates, synthetic ACTH, and several antibiotics (quinolones, pentamidine, vancomycin).²⁴ Traditionally, the non-IgE mediated mechanism has been regarded as the primary player in immediate reactions to contrast media.

The non-IgE description includes 3 different pathways: (1) direct membrane effect, (2) complement activation, and (3) bradykinin generation. For the first pathway, the contrast media exerts a direct membrane effect upon the basophil or mast cell related either to its chemical structure or the osmolality of the contrast material. Experiments have shown an increase in histamine release from rat and human mast cells in addition to basophils when exposed to a higher osmolality CTC in comparison to a lower osmolality agent.^{25,26} Three frequently encountered clinical scenarios support this pathway: (1) immediate contrast reactions in patients without

prior sensitization or exposure to contrast; (2) failure to generate an immediate contrast reaction following exposure to a previously administered CTC agent; and (3) lack of increasing severity of the contrast reaction upon repeat exposure.^{26,27} The second pathway involves activation of the complement system by IgG antigen complexes. In patients with severe immediate reactions, increased levels of C3a and C4a have been identified. These anaphylatoxins can bind to the non-IgE receptors on the mast cell surface and lead to degranulation.²⁴ The third pathway involves direct bradykinin formation.²⁸

Anaphylaxis is a type of immediate contrast reaction described as a serious and potentially life-threatening hypersensitivity reaction that involves severe compromise of the cardiovascular and respiratory systems. Diagnosis of anaphylaxis is based on aggregate clinical symptoms following exposure to the inciting agent. In a large study conducted from 1990 to 2000, 0.5% of all cases of anaphylaxis resulted from radiocontrast media. The risk of fatal anaphylaxis from radiocontrast media is 1 in 100,000.²⁹

For nonimmediate reactions (occurring 1 hour to 10 days after injection), these responses are predominantly T cell mediated. The presentation of a maculopapular skin eruption usually arises 2 to 10 days following the initial exposure and charts a clinical course very similar to nonimmediate reactions to penicillin.²⁷ Given the low-protein binding capacity of most intravenous contrast agents and their inability to function as haptens, researchers previously discounted the ability of contrast agents to activate T cells.²⁶ Recent evidence has clarified an alternative pathway to activate T cells, the p-i concept (pharmacologic interaction of drugs with immune receptors). With this pathway, drugs stimulate T cells through an HLA-restricted pattern.³⁰

Risk Factors for Contrast Reactions

The most compelling risk factor for a contrast allergy has always been a history of a prior reaction. This simple association strongly points to a mechanism of sensitization and mobilization of IgE antibodies targeted to an intravenous contrast agent. In the 1970s and 80s, Japan attempted to screen for an IgE-mediated reaction using a small (0.5 to 1 mL) intravenous injection of CTC media, but eventually discarded the idea following concerns of its clinical utility

and some cases of anaphylactic shock.³¹ Following exposure to both ionic and nonionic CTCs, several groups have reported studies of positive skin tests. In 1 recent study of 200 patients with established immediate hypersensitivity to CTCs, 26% of the reactors tested positive to a skin test, while 96.3% of the controls tested negative. Furthermore, for those 28 patients who were tested within 2 to 6 months of their last immediate reaction to CTC, greater than 50% demonstrated a positive skin test.³² In a separate study, several of these patients who reacted to a positive skin test also tested positive to a basophil activation test.³³ Using immunoassays, additional studies have demonstrated evidence of isolating IgE antibodies specific to CTCs following an immediate reaction.³⁴

With all contrast media reactions, risk factors for immediate and nonimmediate reactions include prior contrast reaction, female gender, allergies, cardiac disease, treatment with beta-blockers, and asthma.^{36,36} In a study performed by Dillman et al³⁷ in 2007, 50% of the patients with an acute allergic-like reaction to Gd demonstrated at least 1 risk factor including prior allergic reaction to contrast media, asthma, and drug allergies. In addition, 19% of these patients reported more than 1 risk factor.³⁷ With a history of asthma and drug allergies, a 1.5X to 1.9X increased risk of an adverse event was reported.^{38,39} This reaction rate is very similar to results with CTC.⁴⁰ In patients who demonstrated a prior hypersensitivity reaction to CTC, a 2.3X to 3.7X increased risk of an adverse event was reported.⁴¹ Several investigations have identified an increased risk of a reaction with female patients.^{36,37,42} In one study, the rate of a reaction among women was 0.098% in comparison to 0.058% for men with a *P* value of 0.06.³⁵ For male patients, there is an overall lower incidence but an increased risk for a severe reaction.^{37,42} One of the most concerning risk factors is the increased risk with repeated exposure to GBCAs. In the study by Jung et al,³⁵ a 30% chance of an immediate hypersensitivity reaction upon re-exposure to a GBCAs was reported. Furthermore, the incidence of the reaction rate progressively increased based upon the number of repeated exposures. These results differ from the general reaction rate of 0.079% with a rate of 0.121% per person. In the study by Nelson et al³⁸ of gadopentetate dimeglumine, an 8X increased risk was reported for those patients with a prior reaction to a paramagnetic MR contrast agent. These outcomes compare with the results following re-exposure to CTCs with a 44% reaction rate to ionic iodinated contrast and an 11.2% reaction rate to nonionic iodinated contrast.³⁶ The ACR Committee on Drug and Contrast Media recommends premedication for all patients who have previously demonstrated a moderate to severe acute adverse reaction to GBCAs.⁴³

For nonimmediate reactions, additional risk factors include prior interleukin-2 therapy, serum creatinine greater than 2.0 mg/dL, and prior contact allergy.⁴⁴ Severity of contrast reaction may also be affected by pre-existing conditions such as mastocytosis, viral infections, and autoimmune disease such as systemic lupus erythematosus.^{30,45}

Acute Immediate Contrast Reactions to GBCA

There is a range of clinical presentations to an acute immediate reaction to a contrast agent. As defined by the American College of Radiology (ACR) Manual on Contrast Media version 10.1, the severity of the reaction can be classified as mild, moderate, or severe.⁴³ This categorization covers both iodinated and gadolinium-containing contrast agents. Within each category, the acute adverse reaction can be described as allergic-like or physiologic. Allergic-like adverse reactions can be governed by both IgE-mediated and non-IgE mediated mechanisms as described above. Patients with a prior allergic-like reaction may require premedication before repeat use of the contrast. Physiologic adverse reactions do not represent an immunogenic response and can arise from direct

TABLE 2. Classification System of Acute Adverse Reaction to Contrast Media

	Allergic-like	Physiologic
Mild	Patchy urticaria Subcutaneous edema Conjunctivitis/rhinorrhea	Transient nausea Flushing/chills Headache/anxiety Mild hypertension Transient vasovagal reaction
Moderate	Diffuse urticaria Facial edema without dyspnea Throat tightness without dyspnea Bronchospasm	Protracted nausea/vomiting Hypertensive urgency Chest pain Vasovagal reaction necessitating treatment
Severe	Facial edema with dyspnea Diffuse erythema with hypotension Laryngeal edema ± stridor/hypoxia Bronchospasm with pronounced hypoxia Anaphylactic shock	Vasovagal reaction unresponsive to treatment Hypertensive emergency Arrhythmia Seizures

Adapted from table in reference.⁴³

chemotoxicity of the contrast agent or a physiologic response to the change in vascular volume if the contrast agent possesses high osmolality.⁴⁶ In contrast to allergic-like adverse reactions, physiologic adverse reactions do not respond to pre-treatment with corticosteroids. Table 2 details the categories of acute reaction.⁴³ For CTCs, 70% of the immediate adverse reactions occur within 5 minutes after injection with 96% of severe reactions declaring themselves within 20 minutes.³² Seventy percent of immediate contrast reactions are limited to pruritus and mild urticaria.³⁶ Only 0.01% to 0.04% of intravenous administrations of radiocontrast media result in severe immediate reactions.

With GBCAs, there is a low incidence of acute immediate contrast reactions. As with CTCs, adverse events following GBCA injection are categorized into 3 types: (1) acute hypersensitivity reactions; (2) toxic reactions (previously discussed with the effects of the disassociated free Gd³⁺; and (3) physiologic (examples detailed in Table 1 include vasovagal reaction and nausea/vomiting).³⁵ Immediate hypersensitivity reactions occurring within 1 hour of injection are governed by the same immunologic discussion detailed earlier for CTCs. Early studies evaluated adverse events with gadopentetate dimeglumine and reported an incidence rate of 1% to 2%. These early studies included presentations such as nausea, emesis, warmth, and pain at the injection site. Early on, the rate of severe reactions was identified as more indicative of the overall GBCA safety profile. In these early studies with gadopentetate dimeglumine, a severe reaction rate of 0.0003% was reported.^{39,47} In 1996, Murphy et al⁴⁸ published a retrospective study examining 21,000 patients who received gadopentetate dimeglumine, gadodiamide, or gadoteridol between January 1990 and October 1994. There was an overall adverse reaction rate of 0.17% with a severe reaction rate of 0.01%.⁴⁸ In 2001, Cochran et al⁴⁹ published a retrospective study with 28,340 administrations of unidentified GBCAs with an adverse reaction rate of 0.06%. In 2006, Knopp et al⁵⁰ evaluated the manufacturer's database of over 45 million administrations of gadopentetate dimeglumine and reported an adverse event rate of 0.01%, with 9.3% of those immediate reactions classified as serious acute. In 2008, Bleicher and Kanal⁴ reported on a prospective study involving

23,553 doses of gadobenate dimeglumine administered over a 13-month period with a total adverse reaction rate of 0.76% with 0.03% eliciting a severe reaction in accordance with the ACR guidelines. In 2009, Hunt et al⁵¹ performed a retrospective study of 158,439 administered doses of GBCAs with an adverse event rate of 0.04%. As this discussion illustrates, there is significant variability in how these investigations were performed (prospective, retrospective, institutional data, corporate data) with even greater variability in what was considered an adverse event. Ultimately, the take-home message focuses upon the overall excellent safety profile of GBCAs with an acute adverse event rate lower than low-osmolar nonionic CTC.

As with CTCs, the risk of an adverse event in the pediatric population following GBCA administration is lower than adults. In the study by Dillman et al³⁷ of gadopentetate dimeglumine, gadodiamide, and gadobenate dimeglumine, there was an acute allergic-like reaction rate in adults of 0.07% versus 0.04% in children. For CTCs administered to a pediatric population, there were allergic-like reaction rates of 0.4% for ionic iodinated contrast and 0.18% for nonionic iodinated contrast.^{52,53}

Several studies have investigated the death rate associated with GBCA. For all GBCAs, there has been an average of seven hypersensitivity reaction deaths reported per year over a 6-year period.⁴² From 2004 to 2009, a death rate of 0.00008% (40 deaths in 51 administrations of administered GBCA) was reported by the United States Food and Drug Administration. Other studies have reported death rates of 0.0007% to 0.0019%.^{35,42} These data confirm that deaths related to GBCAs are extremely rare and have the same associated risk as routine daily activities such as running or jogging (<http://www.besthealthdegrees.com/health-risks/>).

As our selection of GBCAs changes, an examination of the hypersensitivity reaction rate for individual contrast agents assumes greater importance. With the increased discussion of NSF prevention beginning in 2006, medical institutions are selecting chemically more stable GBCAs that are macrocyclic, ionic, or a combination of the two. As early as 1999 in a large retrospective study of 53 centers, Murphy et al⁵⁴ identified differences in reaction rates between 3 different contrast agents: gadodiamide (linear nonionic), gadopentetate dimeglumine (linear ionic), and gadoteridol (macrocyclic nonionic). For gadoteridol, there was an overall adverse reaction rate of 0.406% with a severe allergic-like reaction rate of 0.017% in comparison to gadodiamide (0.031% and 0%) and gadopentetate dimeglumine (0.066% and 0.001%).⁵⁴ In the study by Jung et al,³⁵ six different contrast agents were evaluated in a retrospective study from August 2004 to July 2010. The following immediate hypersensitivity reaction rates were reported: (1) gadoxetic acid disodium (0.116%); (2) gadobutrol (0.099%); (3) gadoteridol (0.080%); (4) gadopentetate dimeglumine (0.061%); (5) gadodiamide (0.013%); (6) gadobenate dimeglumine (0.22%).³⁵ There were no statistically significant differences between the reaction rate of the macrocyclic agents and the linear agents or between the ionic agents and the nonionic agents.

When linear agents were examined in the study by Jung et al,³⁵ there was a statistically significant difference between the ionic (0.085%) and nonionic agents (0.013%) with a *P* value of 0.0004, but no such difference in ionicity was revealed for the macrocyclic agents. Several studies have documented a higher acute adverse reactions with gadobenate dimeglumine, including Bleicher and Kanal (0.76%),⁴ Sherlock et al⁵⁵ (9.1%; a much broader definition of an adverse event was employed including nonallergic and allergic-like reactions), Abujudeh et al (0.28%),⁵⁶ and Herborn et al⁵⁷ (1.2%). In 2011, Prince et al⁴² performed a retrospective study of 158,796 administrations and reported on the number of adverse events per 1000 injections of four different types of GBCAs: (1) gadopentetate dimeglumine (0.5); (2) gadodiamide (0.2); (3) gadoteridol (3.3); and

(4) gadobenate dimeglumine (1.2). For the adverse event rate (*P* < 0.05) and numbers of cardiac arrests/deaths (*P* < 0.001), a statistically significant difference was identified between gadobenate dimeglumine versus both gadopentetate dimeglumine and gadodiamide. Similar to the results by Jung et al,⁴² there was a higher adverse event rate for the ionic linear agents in comparison to the nonionic linear agents (*P* < 0.0001). These data suggest that there may be a lower acute adverse with nonionic GBCAs versus their ionic counterparts. This suggestion mirrors the experience with ionic versus nonionic CTCs.⁵⁶ The ionic GBCAs are higher osmolality preparations that can interact directly with the mast cell and basophil, resulting in degranulation as discussed earlier.^{25,26} For gadopentetate dimeglumine, the manufacturer insert specifically contraindicates its use for those patients with risk factors for hypersensitivity reactions (asthma, allergies, prior reaction to GBCA or CTC agent) (http://imaging.bracco.com/sites/braccoimaging.com/files/technical_sheet_pdf/MultiHance%20Prescribing%20Information.pdf). Some discussion has questioned whether macrocyclic agents may possess higher immunogenicity. This inquiry still remains largely unanswered and requires further investigation.^{42,58}

Contrast Extravasations

GBCA contrast extravasations are relatively rare. In the study by Prince et al,⁴² extravasation occurred in 3 out of 10000 administrations. Clinical presentation following extravasation includes soft tissue edema, inflammation, and potentially necrosis.^{2,42} Tissue damage is extremely uncommon with the low volumes of GBCAs that are administered; however, when tissue damage occurs, it tends to be more advanced with agents with higher osmolality. In the study by Runge et al,⁵⁹ they examined the effects of extravasation of gadopentetate dimeglumine, gadodiamide, gadoteridol, and gadoversetamide into the subcutaneous tissue of a mouse model. There was a statistically significant difference in the amount of inflammation and necrosis caused by gadopentetate dimeglumine versus gadodiamide and gadoteridol. Gadopentetate dimeglumine has greater than twice the osmolality of the other two nonionic agents. When assessing for edema, inflammation, and necrosis, no statistically significant difference was detected between gadodiamide and gadoteridol versus the saline placebo.⁵⁹

Safety of Gadolinium in Pregnancy and Lactation

GBCAs can cross the placenta and be excreted by the fetal kidneys into the amniotic fluid. GBCAs are regarded as Pregnancy Category C drugs. More centers are now considering the use of GBCAs in pregnant patients, but it remains a selective evaluation with detailed consideration of risks and benefits. For nursing mothers, animal experiments have demonstrated that a minute amount of drug (less than 0.5%) can be transferred from the milk to the neonate. It is recommended that breast feeding be discontinued for 24 hours following GBCA administration.^{2,60}

Nephrotoxicity of Gadolinium-Based Contrast Agents

The nephrotoxic effects of CTCs have been well documented. Following the administration of CTCs, the incidence of contrast-induced nephropathy (CIN) ranges from 0.15% to 2% for all involved studies, including CT, arteriograms, and intravenous pyelography.^{36,61,62} The incidence increases with risk factors such as renal insufficiency, multiple myeloma, advanced age, dehydration, hypertension, and multiple myeloma. For those patients affected by CIN, 5% to 10% will never regain baseline renal function.⁶³ The largest contributing mechanism for the nephrotoxicity of CTC focuses upon the generation of free radicals secondary to the hyperosmolar stress from the contrast agent. This free radical production is further

promoted by the acidic urine. These free radicals lead to renal tubular damage, leading to an increase in albumin in addition to cytoplasmic and brush border enzymes excreted into the urine. Light microscopy and electron microscopy have documented vacuolization of the proximal convoluted tubules, providing convincing evidence of the resulting renal tubular damage.^{64,65}

All of the GBCAs possess an osmolality that is equal or greater than the low osmolar or iso-osmolar CTCs; therefore, GBCAs may have the theoretical potential for kidney damage. Animal studies have documented some nephrotoxic effect to GBCAs at high concentrations. In the study by Thomsen et al,⁶⁶ high doses of gadodiamide and gadopentetate dimeglumine (4.59 mmol/kg) were administered to rats. Following exposure to GBCAs, the rats demonstrated a 2X to 5X increase in urine albumin along with a significant increase in urine enzymes in comparison to a saline control.⁶⁶

At the FDA-approved dosing for clinically recommended on-label use, GBCAs are administered intravenously at low doses (<0.2 mmol/kg) that significantly minimizes the osmotic load and potential for nephrotoxicity. When given in these low doses to patients with normal renal function and renal insufficiency, extensive investigation has documented the safety profile of GBCAs with no measurable impact on renal function. For patients with normal renal function, there are no cases of CIN within the published literature.^{39,67} In 2005, Hoffmann et al⁶⁸ evaluated the renal performance of patients following administration of gadopentetate dimeglumine at a mean dose of 0.14 mmol/kg. In the 181 patients with normal renal function, there was no significant change in the serum creatinine or GFR. In the 198 patients with renal insufficiency, there was a statistically significant decrease in the serum creatinine and an increase in the GFR.⁶⁸ In 2006, Zhang et al⁶⁹ performed a retrospective study of magnetic resonance imaging (MRI) examinations performed from 1993 to 2004 with gadodiamide and gadopentetate dimeglumine. For the 2788 studies performed, there were no cases of a documented increase in serum creatinine or CIN. Furthermore, in the 254 administrations of gadopentetate dimeglumine in patients with renal insufficiency, the serum creatinine decreased from an average of 3.62 to 3.49 mg/dL. In those patients who received gadodiamide, there was no change in serum creatinine levels.⁶⁹ When administered at low doses and intravenously, these studies provide convincing evidence of GBCA safety. Furthermore, in comparison to similar studies with CTCs, these investigations conclude that GBCAs are considered safe alternatives to CTCs in patients with impaired renal function.

Although the safety of GBCAs at clinically recommended doses of less than 0.2 mmol/kg has been well documented, several studies have questioned the safety of GBCAs when administered for off-label applications. Such examples of off-label use include high-dose administration for digital subtraction angiography, intra-arterial administration, and substitutes for iodinated contrast for CT imaging. In vitro and animal studies show that at doses needed to achieve equivalent x-ray attenuation, GBCAs demonstrate equivalent and even greater nephrotoxicity than CTCs.⁷⁰ In a 2007 in vitro study by Heinrich et al,⁷¹ gadopentetate dimeglumine and gadobenate dimeglumine demonstrated more pronounced toxic effects upon cultured renal tubular cells than equimolar concentrations of iomeprol. With these applications, clinical studies have documented increased concerns for nephrotoxic effects in patients with known renal insufficiency. In a randomized study of 21 patients with renal insufficiency receiving intra-arterial injections of iohexol and high-dose gadobutrol for DSA, the incidence of CIN was equivalent for both groups of patients.⁷² In a retrospective study of patients with renal insufficiency undergoing cardiac catheterization, there was a significantly higher incidence of CIN in those patients who received a mixture of iodinated contrast with high-dose GBCA versus those who received

only iodinated contrast.⁷³ When equal x-ray attenuating doses are used, several researchers have concluded that GBCAs pose a far greater nephrotoxic effect in patients with impaired renal function than low osmolar iodinated contrast media. In order to achieve equivalent x-ray attenuation, a large osmotic load of GBCAs must be administered that is 2X to 7X more hypertonic than plasma and has the potential for 6X to 25X more acute toxicity than low osmolar iodinated contrast.⁷⁰ In conclusion, most authorities recommend that GBCAs not be used intra-arterially or at doses higher than 0.2 mmol/kg, particularly in patients with renal insufficiency with a creatinine clearance less than 60 mL/min/1.73 m².^{1,70}

CONCLUSION

Overall, acute adverse rates with GBCAs are extremely low with an incidence ranging from 0.01% to 2%. Severe acute reactions are even less prevalent with a mortality rate of 1 in a million. Although there may be some minor increased rate of acute adverse events with higher osmolality and ionic preparations, the overall rate of adverse reactions remains quite low, and no significant difference in acute adverse reactions have been documented to date with the more stable, macrocyclic GBCAs. Identification of potential risk factors (such as clinical history of prior contrast reactions) remains the most reliable method for risk stratification, allowing implementation of patient monitoring and treatment strategies (such as premedication) for at-risk patients.

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