

Gadolinium-Based Contrast Agents Associated Adverse Reactions



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KEYWORDS

- Gadolinium-based contrast agents (GBCAs)
- Adverse events
- Acute allergic reactions
- Contrast media

KEY POINTS

- Immediate adverse reactions to gadolinium-based contrast agents (GBCAs) are unintended side effects occurring within 1 hour of contrast agent exposure.
- Immediate adverse reactions can be classified according to their mechanism as physiologic or hypersensitivity (allergiclike and allergic) reactions, and according to their severity, as mild, moderate, or severe.
- The most important risk factor for a GBCA reaction is previous reaction to a contrast media.
- Mild reactions may require nothing more than observation or a dose of antihistamine medication.
- Severe acute reactions need prompt treatment, because most patients recover if treated quickly and appropriately.

INTRODUCTION

All diagnostic radiological practice involves a balancing of the estimated risk of an investigation versus the perceived benefits of the information to be gained from it.¹ Overall, all available contrast materials are well tolerated and safe. However, adverse events and hypersensitivity reactions do still occur in a small percentage of patients.

Gadolinium-based contrast agents (GBCAs) have been used in Magnetic Resonance (MR) imaging since the late 1980s. These agents shorten the T1 relaxation times of surrounding water protons, resulting in marked increase of signal on T1-weighted images. This enhancement is critical in the detection and characterization of several disease processes. Therefore, GBCAs have become an indispensable part of clinical studies of the neural system, vascular system, and for body applications, being routinely used in many

MR protocols, with more than 300 million doses administered worldwide to date.^{2,3}

Several types and classes of GBCAs have been developed for clinical use. After almost 30 years of use, these agents have shown an excellent safety profile, being well tolerated and having a very low incidence of adverse reactions, with reports varying from 0.01% to 2.4%.^{4–8} Overall, this is lower than the incidence of acute adverse reactions associated with low-osmolar nonionic iodinated contrast media used for computed tomography (CT) scans, which is already low (0.2%).⁹ Severe acute reactions are extremely rare, with mortalities ranging from 0.00008% to 0.0019%.^{6,10}

This article discusses GBCAs acute adverse reactions, including pathophysiologic mechanisms, incidence, symptoms, risk factors, treatment strategies, premedication, and the potential use of skin testing.

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GADOLINIUM-BASED CONTRAST AGENT ADMINISTRATION RISKS

GBCA administration carries risks, including nephrogenic systemic fibrosis, gadolinium dechelation and retention in human tissue, and injection site complications, such as extravasation. Interference with laboratory tests has been described, such as pseudohypocalcemia, but these confounding effects have been largely eliminated by improvements to laboratory testing methods and protocols.¹¹

GBCA subcutaneous extravasations are rare. The incidence is lower and symptoms are less severe compared with the iodinated contrast agents used for contrast-enhanced CT scans.¹² Prince and colleagues¹⁰ reported 46 infiltrations in a total of 158,796 gadolinium-based contrast agent-enhanced examinations (3 per 10,000 administrations). Extravasation may be asymptomatic or present with itching, local swelling, and local erythema at the injection site, which resolve spontaneously or with conservative management.¹² Nevertheless, soft tissue edema, inflammation, and necrosis^{10,13} may occur. Tissue damage and necrosis are extremely uncommon after GBCA extravasation, probably mainly reflecting the low volumes of GBCAs that are administered; however, when tissue damage occurs, it tends to be more advanced with agents with higher osmolality.^{12,14}

ADVERSE DRUG REACTIONS: DEFINITION, CLASSIFICATION, AND PATHOPHYSIOLOGIC MECHANISM

Adverse drug reactions are defined as all unintended pharmacologic effects of a drug, excluding therapeutic failures and misadministration.^{15,16} These reactions may be broadly classified as predictable or unpredictable. Predictable reactions are related to the identified pharmacologic effects of a drug, which are generally dose dependent and occur in otherwise normal patients. These effects include side effects, drug overdose, secondary effects, and interactions with other drugs. Unpredictable drug reactions are unrelated to the pharmacologic actions of a drug, may be dose independent, and may be more frequent in individuals with specific susceptibility.¹⁷

Unpredictable drug reactions or hypersensitivity reactions include allergic and nonallergic or allergiclike reactions. By definition, an allergic reaction refers to an antigen-specific, immunologically mediated hypersensitivity reaction to a drug in a susceptible individual. Allergic reactions are subdivided into at least 4 types according to the

Coombs-Gell classification. From those 4 types, immediate allergic reactions (type 1) are immunologic reactions in which the primary feature is immunoglobulin (Ig) E mediated. In contrast, nonallergic or allergiclike reactions are caused by release of mediators from mast cells or basophils through non-IgE-mediated mechanisms.¹⁷ Non-IgE-mediated mechanisms include direct membrane effect, complement activation, and bradykinin generation.¹⁴ Direct effects on the basophil or mast cell membrane are related either to the chemical structure or the osmolality of the contrast material. The anaphylatoxins C3a and C4a complexes produced through the activation of the complement cascade can also activate mast cells. 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.^{14,17,18} The non-IgE-mediated mechanism has been regarded as the primary player in immediate reactions to contrast media. However, it is unclear to what extent each non-IgE-mediated mechanism contributes to GBCA reactions, and the full range of cell types and chemicals involved.

GADOLINIUM-BASED CONTRAST AGENTS ADVERSE REACTIONS

Immediate adverse reactions are defined as unintended side effects occurring within 1 hour of contrast agent exposure. Although more delayed reactions may occur, most anaphylactic reactions develop within 20 minutes after intravenous injection of the contrast agent.

Nonimmediate adverse reactions are reactions occurring 1 hour to 10 days after injection. To our knowledge, nonimmediate hypersensitivity reactions to gadolinium chelates have not been definitively described to date, although the possibility of such a reaction occurring cannot be ruled out¹⁹ and our opinion is that nephrogenic systemic fibrosis (NSF) and the entity gadolinium deposition disease (GDD) may fit into this category. A detailed description and discussion of either NSF or GDD is beyond the scope of this article. Only acute adverse reactions are discussed here.

ACUTE ADVERSE REACTIONS Definition and Incidence

Classification of the contrast media adverse reactions is still controversial, mainly because the exact underlying pathophysiologic mechanism is not completely elucidated.

One possible classification broadly divides acute adverse reactions into type A and B.²⁰ Type A reactions are the most common, predictable, and physiologic, probably related to the pharmacologic properties of the drug. Type B reactions are unpredictable, uncommon, and usually not related to the pharmacologic properties of a drug. As stated before, type B or hypersensitivity immediate acute reactions can be further subdivided into IgE-mediated or non-IgE-mediated processes. It has been estimated that more than 80% of contrast media adverse drug reactions are type A reactions, whereas less than 20% are type B^{20,21} (Fig. 1).

According to the severity, adverse reactions may be classified as mild, moderate, or severe.²² Mild reactions are self-limited, showing no evidence of progression of signs and symptoms. Moderate reactions refer to more pronounced symptoms, which may require medical management and may progress if untreated. Severe reactions are life threatening and may result in permanent morbidity or death. Most patients have reactions shortly after GBCA exposure, while they are still in the radiology department, and 94% to 100% of severe and fatal reactions occur within 20 minutes of the contrast medium injection.²³

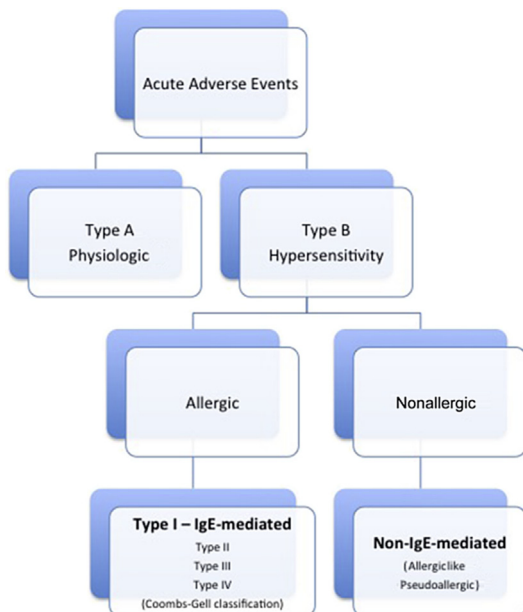


Fig. 1. Classification of acute adverse events into physiologic (type A) and hypersensitivity (type B) reactions. The latter can be further divided into allergic versus nonallergic depending on whether the process is mediated by IgE.

Anaphylaxis is a type of immediate systemic contrast reaction described as a serious, progressive, and potentially life-threatening hypersensitivity reaction with severe multisystem involvement. Diagnosis of anaphylaxis is based on aggregate clinical symptoms following exposure to the provocative agent.^{14,24} It is likely to be diagnosed when all of the following 3 criteria are met: (1) sudden onset and rapid progression of symptoms, (2) life-threatening airway and/or breathing and/or circulation problems, and (3) skin and/or mucosal changes (flushing, urticaria, angioedema).²⁴

Immediate allergic reactions to GBCAs have been reported in up to approximately 0.07% of adults and 0.04% of children. Of these, 74% were graded as mild, 19% as moderate, and 7% as severe,^{7,25,26} and anaphylaxis is very rare (0.001%–0.01%).^{27–29} From 2004 to 2009, a death rate of 0.00008% (40 deaths in 51 million administrations of administered GBCAs) was reported by the United States Food and Drug Administration. Other studies have reported death rates of 0.0007% to 0.0019%.^{6,10} These data suggest that the risk of death associated with GBCAs exposure is extremely low and similar to the risk of death associated with routine daily activities.

Pathophysiology

As mentioned earlier, physiologic reactions are predictable and likely caused by direct toxicity of the administered agent, such as contrast-related hyperosmolality and molecular binding to nonimmunologic receptors.³⁰

In contrast, the exact mechanism of hypersensitivity reactions to GBCA has not been clarified (see earlier). Both involve the release of histamine and other active biological mediators such as serotonin, prostaglandins, bradykinin, leukotrienes, adenosine, and endothelin,³¹ as well as activation and inhibition of several enzyme systems.²⁴ The release of active biological mediators from mast cells and basophils can be IgE mediated or non-IgE mediated. IgE-mediated reactions have been called allergic reactions, whereas the non-IgE-mediated events have been called nonallergic, pseudoallergic, allergiclike, or nonimmunologic reactions.

One typical feature of allergic reactions is the currently accepted theory that the initial exposure to an allergen induces sensitization and only subsequent contact elicits the clinical symptoms. Therefore, clinical symptoms should not occur at the initial exposure. Some investigators argue that this observation supports the nonallergic

nature of GBCA acute adverse events.²⁰ However, positive skin tests in some of the patients who have survived to a severe reaction point to a potential IgE-mediated mechanism, suggesting an allergic mechanism.^{26,29} Research on this topic is still ongoing.

As seen with iodinated contrast agents there is a theoretic potential for an increased risk of acute adverse reactions to the chemically more stable GBCAs^{11,32} because of their higher osmolality.¹⁴ However, small amounts of GBCAs are used for contrast-enhanced MR imaging, and thus the high-osmolality agents do not cause substantial shift of fluids from the intracellular to the extracellular space, which may lead to cell dehydration and an increase in intracellular fluid viscosity precipitating cellular dysfunction.^{24,31,33} However, several studies have been published regarding possible variations in the risk associated with different types of GBCAs according to their specific molecular structures.

Clinical Symptoms

Physiologic reaction symptoms include injection site discomfort (coldness, warmth, or pain), paresthesias, nausea, vomiting, headache, dizziness, myalgia/arthritis, and thrombophlebitis. In children, acute side effects commonly include nausea and vomiting.^{17,34} Under high-stress situations, vagal reactions are common and may be difficult to distinguish from allergic reactions. Vagal reactions are characterized by the combination of prominent sinus bradycardia (pulse rate <60 beats/min), hypotension (systolic pressure <80 mm Hg), pallor, weakness, nausea, vomiting, and diaphoresis.

As stated earlier, allergic and allergiclike reaction symptoms are related to stimulation of histamine and the release of other active biological mediators from mast cells and basophils. Histamine is a vasogenic amine that induces characteristic organ-specific symptoms, including skin flushing, urticaria, pruritus, angioedema, nasal congestion, wheeze, bronchospasm, nausea, vomiting, diarrhea, and hypotension with reflex tachycardia.

By definition, signs and symptoms of a mild reaction include scattered urticaria, which is the most commonly reported adverse reaction, pruritus, rhinorrhea, nausea, brief retching and/or vomiting, diaphoresis, coughing, and dizziness. Moderate reaction has more noticeable symptoms such as persistent vomiting, diffuse urticaria, headache, facial edema, laryngeal edema, mild bronchospasm or dyspnea, palpitations, tachycardia or bradycardia, hypertension, and

abdominal cramps. Severe reactions include life-threatening arrhythmias (ie, ventricular tachycardia), hypotension, evident bronchospasm, laryngeal edema, pulmonary edema, seizures, syncope, and death.²²

The presentation of mild allergic/allergiclike and physiologic reactions may be similar. For example, urticaria may be difficult to distinguish from flushing. Hypotension could present as a manifestation of either anaphylaxis or a vagal episode.^{17,35} However, angioedema and bronchospasm are not vagal responses and indicate an anaphylactic reaction.^{29,36}

RISK FACTORS

The risk factors for reactions to paramagnetic contrast media are very similar to those described for iodinated contrast media. The most convincing risk factor for a contrast allergy is history of a prior reaction. This association strongly points to a mechanism of sensitization and mobilization of IgE antibodies targeted to an intravenous contrast agent.¹⁴ Jung and colleagues⁶ reported a 30% chance of an immediate hypersensitivity reaction in patients who previously experienced hypersensitivity reactions to MR contrast media. Furthermore, the incidence of immediate hypersensitivity reactions increased depending on the number of exposures to GBCA.⁶ In addition, patients who had previous reaction to iodinated contrast agents are also at an increased risk of hypersensitivity reaction to GBCA.^{10,28,37,38}

Female gender and a history of atopy, including rhinitis or asthma, any food allergy, and hypersensitivity reactions to other drugs have also been associated with an increased risk of severe reaction to contrast media.^{6,19} However, minor allergies or well-controlled asthma do not seem to increase the overall risk.^{11,29,39,40}

In a study performed by Dillman and colleagues⁷ in 2007, 52% of the patients with an acute allergiclike reaction to GBCA showed at least 1 risk factor, such as history of previous allergic reaction to contrast media, asthma, and drug allergies. With a history of asthma and drug allergies, a 1.5-fold to 1.9-fold increased risk of an adverse event was reported.^{41,42} This reaction rate is very similar to results with iodinated contrast media.^{14,43}

Despite adverse reaction being described as more common in female patients, severe allergic reactions have been reported as more likely to be fatal in male patients.^{10,29} because the incidence of fatal acute reactions to GBCA is exceedingly low there is currently no definitive evidence of this tendency. Our experience suggests that it may be more common in female patients, who are often

young, with no prior history of reaction. In part this may reflect a delay in diagnosis in this age population because it is not expected. A genetic basis for anaphylaxis reactions may also have a role.

Reactions have been reported more frequently for abdominal explorations (0.01%) than for explorations of the brain (0.005%) or spine (0.003%).¹⁰ This finding may reflect differences in contrast dose or injection rate, but further studies are needed to confirm these findings.

IS THERE VARIATION IN RISK BETWEEN THE DIFFERENT BRANDS OF GADOLINIUM-BASED CONTRAST AGENTS?

The rarity of severe reactions to GBCAs makes it challenging to analyze accurately any differences between the reactions associated with individual GBCAs.

Certain GBCA agents (gadobenate dimeglumine and gadoteridol) have been reported to be more likely to induce reactions than others.^{6,22,27,44}

In a large retrospective study of 53 institutions, Murphy and colleagues⁴⁵ identified differences in reaction rates between 3 different contrast agents: gadodiamide (linear nonionic), gadopentetate dimeglumine (linear ionic), and gadoteridol (macrocylic nonionic). For gadoteridol, there was an overall adverse reaction rate of 0.406% with a severe allergiclike reaction rate of 0.017% compared with gadodiamide (0.031% and 0%) and gadopentetate dimeglumine (0.066% and 0.001%).

In 2011, Prince and colleagues¹⁰ performed a retrospective study of 158,796 administrations and reported on the number of adverse events per 1000 injections of 4 different types of GBCAs: (1) gadopentetate dimeglumine (0.5 per 1000 injections); (2) gadodiamide (0.2 per 1000 injections); (3) gadoteridol (3.3 per 1000 injections); (4) gadobenate dimeglumine (1.2 per 1000 injections). For the adverse event rate ($P < .05$) and numbers of cardiac arrests/deaths ($P < .001$), a statistically significant difference was identified between gadobenate dimeglumine versus both gadopentetate dimeglumine and gadodiamide.

In a recent retrospective study performed by Jung and colleagues,⁶ 6 different contrast agents were evaluated over a 7-year period. 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%). There was no significant difference in the incidence of reactions according to the molecular structure of the contrast agents or the ionicity.

Among the linear agents, ionic agents had a higher incidence of immediate hypersensitivity reactions (0.085%) than nonionic ones (0.013%), with a P value of .0004, but the presence or absence of ionicity did not affect the incidence rate among the macrocyclic agents. Among the 6 evaluated agents gadobenate dimeglumine had the highest rate of immediate hypersensitivity reactions.⁶ Several other studies have documented a higher acute adverse reactions with gadobenate dimeglumine, including Bleicher and Kanal⁴⁶ (0.76%), Abujudeh and colleagues⁴⁷ (0.28%), and Herborn and colleagues⁴⁸ (1.2%). Recently, Fakhran and colleagues⁴⁹ published a study involving 132,252 doses of gadobenate dimeglumine over a period of 7.5 years in which the risk was lower; only 236 reactions (0.18%) were observed. The reaction rates were higher in the initial years of the study, tapering to a lower baseline rate, comparable with those reported for other GBCAs, which was maintained over more than 5 years.

A common observation that has been recognized for many years with iodinated contrast and now with GBCAs is that the reported incidence of reaction rates is greater in the first year of a study, and tends to decline to the lower baseline rate when studies continue on over more than 5 years. This phenomenon is called the Weber effect.⁵⁰ The Weber effect defines the over-reporting of adverse events related to the entry of a new drug to the market. For a period of 6 months there is characteristically an increased number of reported adverse events, after which the number returns to baseline. Although the precise mechanism is not well understood, the effect seems related to there being a heightened awareness among the persons administering the contrast agent that something new is being evaluated. For this reason, a true comparative evaluation of the adverse reactions of any new GBCA should ideally be performed with the MR imaging technologist, the patient, and the interpreting radiologist all being blinded to the contrast agent used. Furthermore, the evaluation of contrast agents may be biased by the Lalli effect,^{51,52} which is the induction of an increased number of adverse events in patients who sense the anxiety of the health care professional. To counter this, the advice to the technologists administering new contrast agents is to actively try not to transfer any stress to the patient. These factors are especially important because macrocyclic GBCAs are increasingly being adopted because of the perception of the NSF association with linear agents and the apparently lesser tissue retention with macrocyclic agents.

Regarding serious adverse reactions, a study by de Kerviler⁵³ found an incidence of 2.3 serious

cases per 100,000 patients exposed to gadoterate meglumine. This incidence rate is lower than the reported serious reaction rates of 9.8 per 100,000 administrations with gadobenate dimeglumine,⁵⁴ 1.7 to 3.0 per 100,000 administrations with gadopentetate dimeglumine,^{42,55–57} and 5.6 per 100,000 administrations with gadobutrol.⁵⁸ Concerning pediatric populations, the GARDIAN (Gadovist in Routine Diagnostic MRI – Administration in Non-selected Patients) study included 1142 children (aged <18 years) who received gadobutrol at a mean dose of 0.13 (range, 0.04–0.50) mmol/kg body weight and found that gadobutrol was well tolerated, with low rates of acute adverse reactions (0.5%) and no severe adverse reactions.⁵⁹

Some of these studies suggest that there may be fewer acute adverse reactions with nonionic GBCAs versus their ionic equivalents, as observed with iodinated contrast agents.^{14,60} However, because these studies are not controlled and not blinded, the authors are hesitant to endorse these findings as definitive. In general, it seems that there may be only a slight difference in the incidence of acute adverse reactions between distinct GBCAs despite several studies having shown a trend.

To reduce bias, the assessment of the risk of acute adverse reactions should not rely on the marketing departments of companies sponsoring the trial but on phase III trial data and on postmarket data that have been analyzed scientifically to establish adverse event profiles. Meta-analysis of noncontrolled studies may be intrinsically unreliable. Valid evaluation of GBCA safety should thus ideally be performed in prospective randomized controlled trials, with an unbiased distribution of possible confounding factors. However, in practice, the use of prospective study designs involving parallel groups of appropriate power involves an enormous number of patients and is very expensive. Thus, because large numbers of controlled blinded studies have not been conducted to compare the various agents, the authors do not consider that the current evidence is definitive to consider any GBCA more or less likely to cause acute reactions.

TREATMENT

Mild reactions, which are the most frequent, are usually self-limited and do not need treatment. However, they may represent the first signs and symptoms of a more severe reaction and those patients should be observed closely for systemic symptoms, and the intravenous access should be maintained.

Severe acute reactions, which are rare and have the potential to be life threatening, need prompt

treatment, because most patients recover if treated quickly and appropriately.²⁴

Management approaches for acute adverse reactions after administration of all imaging contrast agents, not only GBCAs but also ultrasonography contrast media and iodinated contrast agents, are essentially the same, and standardized approaches for all contrast agents should be trained in all medical centers that use imaging contrast agents. The first-line management should be standardized and straightforward so that it can readily be performed by radiologists, who do not have the experience of repetitive management of severely ill patients; whereas it makes sense that more intensive management, including administration of second-line drugs, should be handled by the resuscitation team,²⁴ who have experience with management of acutely ill patients and therefore are less likely to make errors.

Important first-line management includes maintaining a patent airway, oxygen supplementation, administration of intravascular physiologic fluids, and measuring the blood pressure and heart rate.²⁴

If bronchospasm is accelerating or severe, or if upper airway edema (including laryngospasm) is present, epinephrine should be injected promptly. Epinephrine must be administered with care to patients who have cardiac disease or those who are taking β -blockers, such as atenolol, propranolol, metoprolol, and nadolol, because the unopposed alpha effects of epinephrine in these patients may cause severe hypertension or angina.²⁹ In pregnant patients, ephedrine is a possible option.²⁴ The correct dose of epinephrine depends on the route of administration, with the concentration at 1:1000 for intramuscular and at 1:10,000 for intravenous administration. The current guidelines recommend the initial use of intramuscular epinephrine/adrenaline and avoidance of intravenous bolus.²⁴ In a recent study, Campbell and colleagues⁶¹ concluded that the risk of overdose and adverse cardiovascular events is significantly higher with intravenous bolus epinephrine administration and the analyzed data supported the safety of intramuscular epinephrine. A standard dose of 0.5 mg in adults, 0.3 mg in children between 6 and 12 years old, and 0.15 mg in patients less than 6 years of age is suggested.⁶² If there is no improvement in the patient's condition, the intramuscular adrenaline dose can be repeated at about 5-minute intervals by a radiologist if the resuscitation team has not arrived.²⁴ However, extreme caution is recommended beyond 1 repeat administration.

The respiratory component of an adverse reaction requires high-rate (10–12 L/min) oxygen via a

partial nonbreathing mask. Hypotension resulting from an anaphylactic reaction should be treated with intravenous iso-osmolar fluid (ie, normal saline or Ringer lactate solution) in large volumes but administered with careful monitoring to avoid fluid overloading, especially in patients with cardiac disease. High-dose intravenous corticosteroids may be used in the second-line treatment and standard doses can be efficient in reducing delayed recurrent symptoms, which may be seen as long as 48 hours after the initial event, because it takes 6 hours before corticosteroids are entirely active.^{24,29} H₂ antihistamines and H₂ receptor blockers may be used primarily to reduce skin reaction-related symptoms.²⁴

Recent studies have found that many radiologists are not well prepared or confident in handling these incidents, particularly the rare severe reactions.^{63,64} Therefore, it is crucial to train radiologists to be familiar with methods for evaluation and treatment of reactions, indications for medications, types of medications, and doses.

PREVENTION

For all patients, the risk of a physiologic reaction to GBCA seems to be reduced by having a calm, relaxing atmosphere and experienced personnel who are used to working with the contrast media being used. This approach is the most obvious, and least costly, strategy and should be emphasized at all centers.

In contrast with allergic adverse reactions, physiologic adverse reactions do not respond to pretreatment.

Premedication has been considered for patients who had previous immediate hypersensitivity reactions to any type of contrast media. When there is no adequate imaging alternative (ie, contrast material for a particular examination is deemed necessary) the American College of Radiology Committee on Drug and Contrast Media recommends premedication for all patients who have previously shown a moderate to severe acute adverse reaction to GBCAs.²²

Premedication regimens include the use of systemic corticosteroids at scheduled intervals before the planned study. This prophylaxis usually consists of a 12-hour or 13-hour multidose regimen with or without antihistamines before the contrast-enhanced study.⁶⁵ Recently, premedication has been questioned because it does not guarantee complete suppression of all possible contrast-related reactions, which means that acute adverse reactions, including anaphylaxis, may occur despite premedication.²⁰ Dillman and colleagues⁷ concluded that although

premedication could reduce the risk of breakthrough reactions, allergiclike reactions to GBCA might occur despite premedication with corticosteroids and antihistamines. Moreover, pretreatment drugs can induce adverse drug reactions. Despite their efficacy to suppress contrast media adverse events, both drugs are able to provoke adverse reactions such as cutaneous eruptions and anaphylactic reaction.^{20,66–70} The authors are dubious about the value of pretreatment with the drugs currently used and without more selected identification of patients at risk, which may require genetic testing in the future. More specific and targeted drugs to the exact mechanisms of reaction would probably also be important for future development to make pretreatment more clearly beneficial.

For patients with a history of previous reaction to GBCA, every effort should be made to identify the offending agent and to select an alternative agent for further imaging studies. The extent of cross-reactivity between gadolinium chelates is still unclear.^{71–73} However, it seems to be minimal between macrocyclic and linear agents.¹⁹ Using a GBCA different from the one that caused a reaction is likely to be more important than premedication in mitigating risk.

Skin testing for GBCA hypersensitivity has been encouraged for all patients with a history of life-threatening reaction to contrast media if the patient requires subsequent use of GBCA despite a historical adverse drug reaction.¹⁷ It may allow for a safe choice of the GBCA and preclude the need for steroid pretreatment. More evidence that this works is required before advocating this approach.

SUMMARY

GBCAs are extraordinarily safe. Physiologic predictable self-limited reactions are by far the most common adverse events, and in general do not need treatment. Allergic and allergiclike immediate reactions are extremely rare and death is even rarer; however, vigilant awareness of severe adverse reactions is essential. Radiologists should be prepared to identify and treat hypersensitivity reactions when they occur. The main risk factor is a previous adverse reaction to a GBCA. Hence a simple first strategy is to use a different agent, from another class, if there has been a prior moderate or severe reaction. Female gender, a history of rhinitis or asthma, food allergy, and hypersensitivity reactions to other drugs are also recognized risk factors. Premedication with steroids and antihistamine for high-risk patients may have some benefit but it is likely of limited value, especially

with severe reactions, and breakthrough reactions may still occur.

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