

Allergic-Like Breakthrough Reactions to Gadolinium Contrast Agents After Corticosteroid and Antihistamine Premedication

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OBJECTIVE. The objective of our study was to determine the number and severity of allergic-like breakthrough reactions to IV gadolinium-containing contrast agents in children and adults after premedication with corticosteroids and antihistamines.

MATERIALS AND METHODS. Contrast material reaction forms from the department of radiology for pediatric (under 19 years old) and adult patients were reviewed for the time period from January 1, 2001, through December 31, 2006. All documented allergic-like reactions to IV gadolinium-containing contrast media after premedication with corticosteroids and antihistamines were identified. Forms were evaluated for reaction manifestations, management, and patient outcome. Our institutional electronic medical record system was accessed for each individual patient to identify pertinent medical history, including demographic information, history of allergic-like reaction to contrast media (gadolinium- or iodine-containing), and additional factors that led to prophylactic premedication.

RESULTS. Eight patients experienced nine allergic-like reactions after the IV administration of gadolinium-containing contrast media despite premedication. A single patient had two breakthrough reactions. Six breakthrough reactions were mild, and three were moderate. No severe or fatal breakthrough reaction occurred. Eight of nine breakthrough reactions occurred in adults. All patients who experienced breakthrough reactions had a history of allergic-like reaction to either gadolinium- or iodine-containing contrast media.

CONCLUSION. Allergic-like reactions to gadolinium-containing contrast media can occur despite premedication with corticosteroids and antihistamines.

Allergic-like reactions to IV iodine-containing contrast agents are known to occur despite premedication with corticosteroids and antihistamines [1, 2]. Such reactions, termed “breakthrough reactions,” have been observed in both adults and children. Although allergic-like reactions to IV gadolinium-containing contrast agents have been previously described [3–15], little is known about the occurrence of allergic-like breakthrough reactions to such agents after corticosteroid and antihistamine premedication.

The purpose of this study was to determine retrospectively the number and severity of allergic-like reactions to IV gadolinium-containing contrast agents that occurred in children and adults after premedication with corticosteroids and antihistamines from January 1, 2001, through December 31, 2006, in our department of radiology. In addition, we sought to identify the factors that led to premedication prophylaxis in these patients who experienced breakthrough reactions.

Materials and Methods

This study was approved by our institutional review board and was HIPAA-compliant. Participant informed consent was not required because this investigation was retrospective.

At our institution, all patients experiencing allergic-like reactions to contrast media within the department of radiology are assessed in person by a radiologist. Following reaction management, the details of the event, including reaction manifestations and medical treatment, are documented by the same radiologist on a standardized contrast material reaction form. This is departmental policy and was in place before and throughout the duration of this investigation.

All pediatric (patients under 19 years old) and adult contrast material reaction forms completed between January 1, 2001, and December 31, 2006, were reviewed to identify all documented allergic-like reactions to IV gadolinium-containing contrast media in patients who had been premedicated with a corticosteroid and antihistamine regimen. Forms were evaluated for specific allergic-like manifestations, contrast agent administered and

Keywords: allergic reaction, antihistamine, contrast agents, contrast reaction, corticosteroid, gadolinium, MRI, premedication

DOI:10.2214/AJR.07.2718

Received June 11, 2007; accepted after revision July 16, 2007.

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AJR 2008; 190:187–190

0361–803X/08/1901–187

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dose (mL), any required medical management, and patient disposition from the department of radiology (e.g., whether the patient was discharged, transferred to the emergency department, or admitted to the hospital).

Our institutional electronic medical record system was accessed for each individual patient to identify relevant medical history, including any allergic-like reaction to gadolinium-containing contrast media, presumed allergic reaction to a substance other than gadolinium-containing contrast media (including iodine-containing contrast media), and documented asthma. Patient demographic information, including age and sex, was also recorded. Finally, patient outcome at the time of discharge from the institution was determined (e.g., whether the patient was released in the state of health as before the breakthrough reaction, experienced breakthrough reaction–related permanent disability, or died).

Each allergic-like breakthrough reaction was categorized as mild, moderate, or severe according to a departmental reaction classification system adapted from the “Categories of Reactions” of the American College of Radiology (ACR) [16]. Mild breakthrough reactions were self-limited, exhibited no significant progression, and required no medical treatment except antihistamine administration for cutaneous reaction manifestations. Moderate breakthrough reactions necessitated medical management other than or in addition to antihistamine

administration or eventual outpatient transfer to the emergency department. A breakthrough reaction was deemed severe if it was life threatening (typically requiring hospital admission of an outpatient or emergency department patient) or fatal.

If a patient experienced more than a single reaction manifestation, the reaction severity was classified according to the most concerning sign or symptom. Adverse events to contrast material administration, such as nausea, vomiting, altered taste, perspiration, warmth, flushing, and anxiety, are considered physiologic side effects in accordance with departmental policy. Such adverse events are generally not regarded to be allergic-like in origin, infrequently require medical management, and rarely necessitate radiologist documentation. Chemotoxic reactions (e.g., nephrogenic systemic fibrosis) and contrast material extravasations after premedication are not allergic-like in origin and were therefore also not included in this investigation.

Results

Between January 1, 2001, and December 31, 2006, in our department of radiology, eight patients experienced nine allergic-like reactions to IV gadolinium-containing contrast media despite corticosteroid and antihistamine premedication. A single patient experienced two breakthrough reactions. During the study period, 78,353 gadolinium-containing contrast material injections were per-

formed. The exact number of patients who were premedicated before the IV administration of gadolinium-containing contrast media during the study period is unknown.

Six breakthrough reactions to IV gadolinium-containing contrast media were mild, and three were moderate. Specific reaction manifestations are listed in Table 1. No severe or fatal breakthrough reaction occurred during the study period. Eight (89%) of nine breakthrough reactions occurred in adult patients. Six (75%) of eight patients who experienced breakthrough reactions were female.

Four of nine breakthrough reactions followed the IV administration of gadopentetate dimeglumine (Magnevist, Bayer HealthCare). The exact contrast agent administered was not documented for five breakthrough reactions; however, gadopentetate dimeglumine was the predominant agent used during the study time period at our institution, accounting for greater than 90% of gadolinium-containing contrast material administrations according to department of radiology purchasing records. The mean volume of contrast material administered was not documented for a single patient with a breakthrough reaction who experienced mild symptoms (urticaria). The mean volume of contrast material administered to the other eight patients was 17 mL (range, 13–30 mL).

TABLE 1: Allergic-Like Breakthrough Reactions with Gadolinium-Containing Contrast Material

Sex	Age (y)	Contrast Material (mL)	Severity	Manifestations	Management ^a	Risk Factors ^b
F	15 ^c	13	Mild	Periorbital edema	Observation only	Gadolinium-containing contrast reaction history (urticaria, periorbital edema)
F	43 ^c	14	Mild	Urticaria	Observation only	Gadolinium-containing contrast reaction history (manifestations unknown), penicillin allergy
M	47 ^{d,e}	U	Mild	Urticaria	Diphenhydramine	Gadolinium-containing contrast reaction history (urticaria)
M	48 ^{d,e}	17	Mild	Urticaria	Observation only	Gadolinium-containing contrast reaction history (urticaria)
F	59 ^e	13	Mild	Urticaria	Diphenhydramine	Iodinated contrast reaction history (manifestations unknown), multiple medication allergies (> 3)
F	61 ^e	30	Mild	Urticaria	Observation only	Iodinated contrast reaction history (manifestations unknown)
F	43 ^e	13	Moderate	Difficulty breathing, rash, throat symptoms	Diphenhydramine, epinephrine, transfer to emergency department	Gadolinium-containing contrast reaction history (urticaria)
M	62 ^c	15	Moderate	Difficulty breathing, chest tightness	Albuterol, epinephrine	Gadolinium-containing contrast reaction history (hypotension)
F	67 ^c	20	Moderate	Difficulty breathing	Transfer to emergency department	Iodinated contrast reaction history (urticaria, bronchospasm), asthma, penicillin and sulfa allergies

Note—U = unknown volume.

^aInitiated within the department of radiology.

^bIncludes factor that led to premedication, such as previous gadolinium- or iodine-containing contrast material allergic-like reaction, as well as pertinent medical history that may have contributed to increased risk of reaction.

^cBreakthrough reaction after IV administration of gadopentetate dimeglumine.

^dSame patient (who had a birthday between MRI examinations).

^eBreakthrough reaction for which the specific gadolinium-containing contrast agent administered is unknown.

Breakthrough Reactions to Gadolinium Contrast Agents

Six (67%) of nine reactions occurred in patients with a history of allergic-like reaction to gadolinium-containing contrast material, whereas three (33%) of nine reactions occurred in patients with a history of allergic-like reaction to iodine-containing contrast material and no history of reaction to gadolinium-containing contrast material. Overall, nine (100%) of nine breakthrough reactions occurred in patients with a history of allergic-like contrast material reaction, although three of these reactions occurred in patients who also had histories of asthma or previous allergic reactions to substances other than contrast media. A single patient who experienced a breakthrough reaction had a history of allergic reactions to numerous (five) substances other than contrast media. Another patient who was premedicated because of a history of significant reaction to iodine-containing contrast media had been administered IV gadolinium-containing contrast medium on at least seven previous occasions at our institution without allergic-like reaction. Specific factors associated with each individual breakthrough reaction are listed in Table 1.

Discussion

Allergic-like reactions to IV gadolinium-containing contrast agents, although relatively rare, do occur. At our institution, such reactions occur at a rate of approximately 0.07% [15]. As with iodine-containing contrast media, we have routinely premedicated patients we believe are at an increased risk of having an allergic-like reaction to IV gadolinium-containing contrast media, with the intent of lowering the risk of reaction.

The *ACR Manual on Contrast Media*, 5th ed., indicates that premedication with corticosteroids and antihistamines before the IV administration of gadolinium-containing contrast agents may be particularly useful in patients with a history of moderate to severe reactions to contrast media; however, this publication also acknowledges the “absence of any widely accepted policy for dealing with patients with prior contrast reactions (especially to gadolinium-based compounds)” [16]. At our institution, premedication is suggested per departmental guidelines before the IV administration of gadolinium-containing contrast agents for patients with a history of allergic-like reaction (of any severity) to gadolinium-containing contrast material, significant or multiple (usually four or more) allergic (or allergic-like) reactions to substances other than gadolinium-containing contrast

material (including iodine-containing contrast materials, medications, and foods), and documented asthma when attacks have been recent or severe.

Although there is no evidence to our knowledge within the literature to support premedication as a prophylactic measure before IV gadolinium-containing contrast material administration to prevent allergic-like reactions, premedication protocols [16–20] similar to those described for iodine-containing contrast media are usually used. All patients in this series who had allergic-like breakthrough reactions were pretreated with corticosteroids and antihistamines. The regimens are shown in Table 2 [16]. These protocols are identical to that prescribed at our institution for patients who require premedication before undergoing a radiologic examination using iodine-containing contrast agents.

The majority of allergic-like breakthrough reactions to gadolinium-containing contrast agents in our study were mild, results similar to those reported in a previous study assessing breakthrough reactions in patients who received corticosteroid premedication before IV low-osmolality iodine-containing contrast media administration [1]. However, three moderate reactions did occur in our study. These patients were treated in the following manner: one received epinephrine and albuterol and was then discharged, another received diphenhydramine and epinephrine and was then transferred to the emergency department for additional care, and the third was transferred to the emergency department without any medication administration within the department of radiology. Therefore, breakthrough reactions do occur that necessitate medical management or transfer to the emergency department. Consequently, radiologists should be prepared to handle such events. Although no severe or fatal breakthrough reaction was documented in our study, such an occurrence is possible.

Six of the eight patients who experienced allergic breakthrough reactions were female. The reason for this apparent sex difference is uncertain; however, slightly more females (53%) than males (47%) were examined using contrast-enhanced MRI at our institution during the study period. It is possible that females more frequently experience allergic-like reactions to gadolinium-containing contrast agents than do males or that the premedication regimen used in this study is less effective when administered to females;

however, the exact reason for this sex difference is unknown.

Freed et al. [1] compared a group of patients who experienced breakthrough reactions to low-osmolality iodine-containing contrast materials despite corticosteroid premedication with a control group of patients who had a history of adverse reactions to contrast media but no breakthrough reactions after administration of low-osmolality contrast media and premedication with corticosteroids. In their study, only a history of seafood allergy or hay fever was statistically more likely to be identified in the breakthrough group than in the control group. No patient who experienced a breakthrough reaction in our investigation had a history of seafood allergy or hay fever documented within our institutional electronic medical record. It is uncertain why particular premedicated patients experience breakthrough reactions and others do not. Although premedication regimens do likely reduce the risk of allergic-like reactions to IV contrast agents, they do not totally eliminate such reactions [17–20].

There are several limitations to this retrospective investigation. First, it is possible that one or more breakthrough reactions were not appropriately documented according to department of radiology policy and thus were missed. Second, it is possible that presumed breakthrough reactions were not directly contrast material-related; however, we believe this is very unlikely. Third, it is possible that patients were noncompliant with the prescribed premedication regimen. Premedicated patients at our institution are questioned about compliance before contrast material administration, however. Fourth, only allergic-like breakthrough reactions that occurred while the patient was physically located within the department of radiology were included in this study. It is possible that a patient could have experienced a delayed allergic-like breakthrough reaction to a gadolinium-containing contrast agent after leaving the department. Finally, we cannot determine the frequency of breakthrough reactions to IV gadolinium-containing contrast agents because we do not know the exact number of patients who were premedicated and did not experience breakthrough reactions during the study period.

In conclusion, allergic-like reactions related to IV gadolinium-containing contrast media occur despite premedication with corticosteroids and antihistamines. Such occurrences in our study were typically mild or moderate; no

TABLE 2: Institutional Pediatric and Adult Oral Premedication Regimens Before Administration of IV Contrast Media

Drug	Timing	Pediatric Dosage	Adult Dosage
Prednisone	13, 7, and 1 h before contrast-enhanced imaging	0.5–0.7 mg/kg orally (up to 50 mg)	50 mg orally
Diphenhydramine	1 h before contrast-enhanced imaging	1.25 mg/kg orally (up to 50 mg)	50 mg orally

Note—Adapted with permission from [16]. IV administration (substituting an equivalent dose of hydrocortisone for prednisone) can be used for patients who cannot ingest medication orally.

severe or fatal breakthrough reaction was documented during the study period. Breakthrough reactions can occur in the setting of previous allergic-like reaction to either IV gadolinium- or iodine-containing contrast media. A prospective study to evaluate the frequency of allergic-like breakthrough reaction after premedication in the setting of IV gadolinium-containing contrast agents could be beneficial.

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