

Reactions to Both Nonionic Iodinated and Gadolinium-Based Contrast Media: Incidence and Clinical Characteristics

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OBJECTIVE. The objective of our study was to assess the incidence rate and clinical characteristics of allergiclike reactions in patients who received both nonionic iodinated contrast medium (ICM) and gadolinium-based contrast medium (GBCM).

MATERIALS AND METHODS. Acute allergiclike reactions in patients who received both ICM and GBCM to nonionic ICM or GBCM injections during a 5-year period were analyzed. Allergy preparation was not administered when patients received a different type of contrast material. Acute allergiclike reactions to both ICM and GBCM were evaluated.

RESULTS. Of 302,858 contrast injections (155,234 ICM and 147,624 GBCM) during a 5-year period, 1006 (752 ICM and 254 GBCM) acute allergiclike contrast reactions were reported. The overall rate of reaction to ICM was 0.48% (95% CI, 0.45–0.52%), and the overall rate of reaction to GBCM was 0.17% (95% CI, 0.15–0.19%). A total of 19,237 patients received at least one ICM injection and one GBCM injection, with a total of 56,310 injections (19,237 initial injections and 37,073 subsequent injections). Nine patients had reactions to both ICM and GBCM with the primary reaction rate of 9/19,237 (incidence rate, 0.047%; 95% CI, 0.044–0.050%), and the secondary reaction rate of 9/37,073 (incidence rate, 0.024%; 95% CI, 0.023–0.026%). All secondary reactions in patients who had a reaction to both ICM and GBCM were mild. None of the patients required medication for the treatment of the secondary reaction.

CONCLUSION. An allergiclike reaction to both nonionic ICM and GBCM was an extremely rare event that presented as a mild acute reaction without significant clinical consequences despite the fact that an allergy preparation was not administered.

Keywords: contrast allergic reactions, gadolinium-based contrast medium, iodinated contrast medium, primary reaction, secondary reaction

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CT and MRI are the mainstays of diagnostic imaging. The use of contrast medium in CT and MRI has increased in different clinical settings because of the higher utilization of these imaging studies [1, 2]. Like all pharmaceutical agents, contrast media can be associated with adverse reactions, resulting in morbidity or mortality in patients who receive these agents.

Acute allergiclike reactions are a known complication of intravascular administration of nonionic iodinated contrast medium (ICM) for CT or gadolinium-based contrast medium (GBCM) for MRI. The clinical manifestations of an acute allergiclike reaction to contrast medium can range from mild symptoms such as urticaria, itching, and sneezing to more severe reactions such as anaphylaxis, cardiac arrest, and death. Although the symptoms of allergiclike reactions can mimic allergic or hypersensitivity reactions, the exact mechanism is believed to be different from

an antigen-antibody interaction in most cases [3]. The severity of subsequent reactions to the same contrast medium is usually the same as that of the first reaction, and no definite antibodies have been found against ICM or GBCM in immunologic studies [4]. Direct membrane effects related to the osmolality or chemical structure of a contrast medium, complement system activation, direct bradykinin formation, or IgE-mediated reactions have been introduced as possible mechanisms of allergiclike reactions to contrast media [5].

A reaction to both ICM and GBCM in the same patient is believed to be a rare event [4]. However, data are limited on the incidence of these reactions. The aim of this study was to assess the incidence rate and clinical characteristics of acute allergiclike reactions to both ICM and GBCM in patients who have received both types of contrast media for imaging studies. This information is essential for assessing risk of a future reaction and the need for premedication before contrast administration.

Materials and Methods

We obtained institutional review board (IRB) approval for this HIPAA-compliant retrospective study. The IRB waived the requirement for informed consent because of the retrospective nature of this study.

Study Population and Data Collection

In this study, we used data from the ongoing quality assurance process at Northwestern Memorial Hospital which is a large academic institution with both inpatient and outpatient imaging services. The data for all adult patients undergoing contrast-enhanced imaging studies are monitored and recorded prospectively. According to institutional policy, a radiology resident, fellow, or attending radiologist evaluates each patient who has an allergiclike reaction to ICM or GBCM. The severity of the reaction based on the American College of Radiology (ACR) guidelines [4], the treatment course, and possible transfer to the emergency department are determined by the radiologist and documented in the electronic medical record (EMR). A radiology nurse completes a standardized contrast media reaction report form for each patient, and the report is logged in the EMR system. The contrast media reaction report form contains information about the patient's history of contrast reactions, premedication, the type and volume of contrast medium injected, contrast lot number, patient's symptoms and vital signs, the severity of the reaction, the treatments received, patient transfer, and follow-up telephone calls.

All contrast media reaction report forms logged between September 2011 and August 2016 (fiscal years 2012–2016) were reviewed to determine the incidence and type of acute allergiclike reactions to contrast media that occurred during the study period. The total number of contrast injections and the number of contrast injections in patients with at least one ICM injection and one GBCM injection during the study period were extracted. Acute allergiclike reactions to both ICM and GBCM in that period were recorded. EMRs were reviewed to obtain demographic data and relevant medical history.

Contrast Media

For contrast-enhanced CT studies, low-osmolality contrast medium (LOCM) was administered. A single type of LOCM compound was administered IV for all CT examinations (iopamidol 370 mg I/mL [Isovue-370, Bracco Diagnostics]; or iopamidol 300 mg I/mL [Isovue-300, Bracco Diagnostics]). For the MRI studies, different GBCM compounds were used depending on the clinical and diagnostic task. The following GBCM compounds were used: gadobutrol (Gadovist, Bayer HealthCare), gadopentetate dimeglumine (Magnevist, Bayer Health-

Care), gadoxetate disodium (Eovist, Bayer HealthCare), gadobenate dimeglumine (MultiHance, Bracco Diagnostics), and gadofosveset trisodium (Ablavar, Lantheus Medical Imaging).

Acute Adverse Reactions

The severity of the reactions were classified into three categories (i.e., mild, moderate, severe) according to the *ACR Manual on Contrast Media*, version 10.1 [4]. For patients with more than one symptom associated with different levels of severity, the most severe symptoms were used to categorize the severity of the reaction.

Mild acute allergiclike contrast reactions were characterized by the presence of one or more of the following: hives, itching, limited skin edema, nasal congestion, sneezing, conjunctivitis, or throat itching. Moderate allergiclike reactions were characterized by one or more of the following: diffuse urticaria, diffuse erythema, wheezing, or mild bronchospasm. Severe allergiclike reactions were characterized by one or more of the following: profound laryngeal edema, cardiopulmonary arrest, or anaphylactoid shock. Contrast medium extravasation without allergiclike signs or symptoms was not included as an allergiclike contrast reaction in this study.

Primary and secondary reactions were defined as follows: A primary reaction was defined as the original acute allergiclike reaction to ICM or GBCM that occurred earlier in the study period. A secondary reaction was defined as the subsequent acute allergiclike reaction to the other type of contrast medium category (i.e., GBCM or ICM).

Premedication

Our institutional policy does not require premedication of patients who have had a previous reaction to a different type of contrast material. Therefore, patients with a history of a reaction to ICM did not receive allergy preparation before receiving GBCM. Similarly, patients with a history of a reaction to GBCM did not receive premedication for allergy before receiving ICM.

According to our institution's policy, patients with a history of mild reactions to contrast medium can undergo contrast-enhanced studies with a similar type of contrast material only after they receive proper premedication, which is ordered by the referring physician. The standard premedication regimen at our institution, which is in compliance with the ACR recommendations [4], consists of 50 mg of oral prednisone administered 13, 7, and 1 hour before contrast injection as well as 50 mg of diphenhydramine administered 1 hour before contrast injection either by mouth or as an intramuscular injection. If a patient had an acute allergiclike contrast reaction despite receiving the

proper premedication regimen, the allergiclike reaction is considered a breakthrough reaction [6, 7]. Patients with a mild breakthrough reaction are premedicated again for future studies with a similar type of contrast agent. Patients with a history of moderate or severe acute allergiclike reactions to contrast media do not receive a similar type of contrast agent for future studies. For example, patients with moderate to severe reactions to ICM will not receive ICM for future CT examinations.

Statistical Analysis

Descriptive statistics were used for summarizing the data. Quantitative variables were presented as mean $\pm$ SD or as median and range depending on the distribution of the data. The distribution of quantitative data was assessed using Kolmogorov-Smirnov test. For categorical data, frequency (percentage) and the 95% CI were used. The incidence of reactions was calculated by dividing the number of contrast media reaction events to ICM or GBCM by the total number of ICM or GBCM injections performed during the study period, respectively. The Fisher exact test was used to compare the proportions. For comparison of the reaction severity and imaging service setting between reactions to both ICM and GBCM and the overall reaction, the chi-square test with the Yates correction was used. Relative risk (RR) with the corresponding 95% CI was used to measure the difference between incidence rates. A p value of ≤ 0.05 was considered as a statistically significant difference. SPSS software (version 23, IBM) and MedCalc software (version 13.3.3.0, MedCalc Software) were used for statistical analyses.

Results

Acute Allergiclike Reactions to Contrast Media

During a 5-year period, 302,858 contrast injections (155,234 ICM and 147,624 GBCM) were performed in our institution. A total of 1006 (752 ICM and 254 GBCM) acute contrast media reaction events in 939 individual patients were reported. The overall incidence rates of reaction to ICM and GBCM were 0.48% (95% CI, 0.45–0.52%) and 0.17% (95% CI, 0.15–0.19%), respectively. Of 1006 acute allergiclike contrast reactions during the study, 917 (91.1%) were mild, 79 (7.9%) were moderate, and 10 (1%) were severe. Most of the reactions (889/1006, 88.4%) were observed in outpatient imaging services.

Fifty-seven of 939 patients with acute reactions (6.1%) had more than one event of an allergiclike reaction. A total of 19,237 patients received at least one ICM injection and one GBCM injection, with a total of 56,310 injections (19,237 initial injections and 37,073

Reactions to ICM and GBCM

TABLE 1: Clinical Characteristics of the Nine Patients With Allergiclike Reactions to Both Nonionic Iodinated Contrast Medium (ICM) and Gadolinium-Based Contrast Medium (GBCM) and Details About the Primary and Secondary Reactions

Patient		Time Interval ^a	Primary Reaction						Secondary Reaction					
No.	Sex		Age (y)	Type of Contrast Medium	Contrast Medium	Reaction Severity	PM	Type of Facility	Age (y)	Type of Contrast Medium	Contrast Medium	Reaction Severity	PM	Type of Facility
1	F	64 d	64	ICM	Iopamidol 300	Moderate ^b	N	OP	64	GBCM	Gadobutrol	Mild	N	OP
2	M	17 d	61	ICM	Iopamidol 370	Moderate ^c	N	OP	61	GBCM	Gadobutrol	Mild	N	OP
3	F	252 d	57	ICM	Iopamidol 370	Mild	N	OP	57	GBCM	Gadobutrol	Mild	N	OP
4	M	6 h	42	ICM	Iopamidol 370	Mild	N	OP	42	GBCM	Gadobutrol	Mild	N	IP
5	F	183 d	86	ICM	Iopamidol 370	Mild	N	OP	86	GBCM	Gadobenate dimeglumine	Mild	N	OP
6	M	26 d	38	ICM	Iopamidol 370	Mild	N	OP	38	GBCM	Gadobutrol	Mild	N	OP
7	F	45 d	41	ICM	Iopamidol 300	Mild	Y	OP	41	GBCM	Gadoxetic acid	Mild	N	OP
8	F	74 d	53	GBCM	Gadobenate dimeglumine	Mild	N	OP	53	ICM	Iopamidol 370	Mild	Y	OP
9	F	706 d	56	GBCM	Gadopentetate dimeglumine	Mild	N	OP	58	ICM	Iopamidol 370	Mild	Y	OP

Note—PM = premedication, N = no, OP = outpatient, IP = inpatient, Y = yes.

^aBetween primary reaction and secondary reaction.

^bBronchospasm.

^cGeneral edema.

subsequent injections) during the study period. Nine patients (six women and three men; mean age, 55.7 years; age range, 38–86 years) had reactions to both ICM and GBCM with a primary reaction rate of 9/19,237 (incidence rate, 0.047%; 95% CI, 0.044–0.050%) and a secondary reaction rate of 9/37,073 (incidence rate, 0.024%; 95% CI, 0.023–0.026%). The incidence rate of a reaction to both ICM and GBCM was significantly lower than that of the individual risk of a reaction to ICM (RR, 0.05; 95% CI, 0.03–0.10; $p < 0.0001$) or to GBCM (RR, 0.14; 95% CI, 0.07–0.27; $p < 0.0001$). The clinical characteristics of the patients with allergiclike reactions to both ICM and GBCM and the details of reactions are summarized in Table 1.

Primary Reactions in Patients With a Secondary Reaction

A primary reaction was observed after the administration of ICM in seven of nine (78%) patients and after administration of GBCM in two of nine (22%) patients. The two patients who showed a primary reaction to GBCM had a history of a mild allergiclike reaction to ICM but had not received premedication before GBCM injection. One patient showed a breakthrough reaction to ICM after receiving GBCM despite receiving premedication for a prior mild reaction to ICM. The majority of the primary reactions (7/9, 78%) were mild. All primary reactions in pa-

tients who later had a secondary reaction occurred in outpatient imaging facilities.

Secondary Reactions

The time interval between the primary and secondary reactions ranged from 6 hours to 706 days with the median of 64 days. The secondary reactions were observed after the administration of iopamidol in two patients or GBCM in seven patients (Table 1). Two patients showed breakthrough cross-reactions to ICM despite receiving standard premedication for prior allergic reactions to ICM. All secondary reactions were mild in severity regardless of the severity of the prior reactions, and all resolved without medications. None of the patients required transfer to the emergency department or hospitalization for secondary reactions.

Reaction Severity

The incidence rates of mild, moderate, and severe reactions are summarized in Table 2. Of 752 overall reactions to ICM, 684 were mild, 59 were moderate, and nine were severe reactions. The severity of the reactions to GBCM was mild in 233, moderate in 20, and severe in one reported incident. The overall risk of a mild reaction to ICM was 0.44% (684/155,234), and the overall risk of a mild reaction to GBCM was 0.02% (233/147,624). The risks of moderate and severe reactions were 0.04% and 0.006% for ICM and 0.01% and 0.0007% for GBCM, respectively. All secondary reactions were mild in severity. There was no statistically significant difference in the frequency of mild reactions between the secondary reactions and the overall reactions ($p = 0.76$).

TABLE 2: Incidence Rates of Mild, Moderate, and Severe Reactions to Nonionic Iodinated Contrast Medium (ICM) and Gadolinium-Based Contrast Medium (GBCM)

Type of Contrast Medium	No. of Contrast Injections	Severity of the Reaction		
		Mild	Moderate	Severe
ICM	155,234	684 (0.44)	59 (0.04)	9 (0.006)
GBCM	147,624	233 (0.02)	20 (0.01)	1 (0.0007)
Overall reactions (ICM and GBCM)	302,858	917 (0.3)	79 (0.03)	10 (0.003)
Primary reactions	19,237	7 (0.04)	2 (0.01)	0
Secondary reactions	37,073	9 (0.02)	0	0

Note—Data are presented as frequency (incidence rate [%]).

Discussion

ICM and GBCM are commonly used in diagnostic imaging. These contrast media are generally considered extremely safe, but adverse reactions after the administration of contrast medium are still a challenge in clinical practice. Different risk factors for acute adverse reactions to contrast medium have been established such as a history of a previous acute reaction to the contrast medium, uncontrolled asthma, or allergies necessitating medical treatment [7]. The risk of developing repeat or breakthrough reactions in patients with a history of an allergiclike reaction to the identical contrast medium has been evaluated in several studies [6, 8]. Although studies in the literature have assessed the frequency or possible risk factors for a reaction to ICM [9–16] or GBCM [7, 17–21], there is no evidence in the literature to determine whether previous reactions to each type of contrast medium can alter the risk of a reaction to another type of a chemically distinct contrast medium in subsequent imaging studies. The requirement for premedication in patients undergoing MRI who have had a prior reaction to ICM, or those undergoing CT scan with a prior reaction to GBCM, is also not well studied. There are contradictory recommendations in the literature to date regarding the need for premedication [22–24].

We designed this large-scale study to assess the frequency and clinical characteristics of allergiclike reactions to both ICM and GBCM used for contrast-enhanced CT or MRI studies. Our study of more than 300,000 contrast injections during a 5-year period showed that out of more than 37,000 subsequent contrast injections in patients who received both ICM and GBCM, only nine patients (0.024%) showed reactions to both contrast media. Furthermore, none of the secondary reactions was moderate or severe. Our results suggest that allergiclike reactions to both ICM and GBCM are rare and are more likely to present as mild reactions. These events resolved spontaneously without medical therapy (Table 1).

We calculated the incidence rate of reactions to both ICM and GBCM using the total number of contrast injections in patients who had received both types of contrast media during the study period on a per-injection basis. Previous studies have shown that each injection of contrast medium can pose an independent risk of an allergiclike reaction. In one study, allergiclike reactions to GBCM were seen in 34% of patients who previously had received the agent without allergiclike reactions

[21]. Analysis based on the number of patients who received both types of contrast media on a per-patient basis can result in overestimation of the risk of a secondary reaction.

The overall rate of reaction to ICM (0.48%) and the overall rate of reaction to GBCM (0.17%) in our study were similar to those reported in the literature for low-osmolality ICM (0.2–0.7%) [3, 4, 25–27] and GBCM (0.02–4%) [4, 21, 28]. The incidence rates of a severe reaction to ICM (0.006%) and GBCM (0.0007%) are also within the lower limits of the range that are reported in the literature [25]. Although different rates of adverse reactions have been reported among different GBCM compounds, acute adverse reactions are generally rare regardless of the type of the compound [19, 29].

ICM and GBCM are chemically distinct compounds. Because of their structural differences, cross-reaction between ICM and GBCM would not be expected [4]. The observed incidence rate of reactions to both ICM and GBCM in our study was significantly lower than the individual risks of developing acute allergiclike reaction to either ICM or GBCM. Therefore, in any patient with a history of a reaction to ICM or GBCM, the risk of developing a secondary reaction to injection of the other type of contrast medium is statistically lower than the risk in patients without a history of a contrast reaction.

All secondary reactions observed in our study were mild in severity. The distribution of the severity of the secondary reactions was similar to that of the overall acute allergiclike contrast reactions in our institution (Table 2) and is consistent with the existing evidence [21] showing that most contrast reactions are mild. The extremely low incidence rate, along with mild severity, also support that special precautions may not be required when a patient with a history of a contrast reaction receives other types of contrast medium.

Our study had limitations. Despite a large dataset of contrast injections, the number of allergiclike reaction events to both ICM and GBCM was extremely low, which limited our ability to evaluate the possible underlying cause of reactions to both ICM and GBCM. Moreover, our study is based on the imaging studies performed in imaging facilities of a single large academic institution. A multiinstitutional study may overcome this type of sampling bias. Because of the small number of GBCM injections used in our institution, accurate evaluation of risk factors for each

of these contrast agents was not possible. We did not exclude these agents from our study to avoid selection bias.

In conclusion, allergiclike reactions to both nonionic ICM and GBCM were found to be extremely rare and presented as a mild acute reaction without significant clinical consequences. The use of allergy premedication in patients who have had a prior reaction to ICM or GBCM may not be warranted if they receive GBCM or ICM, respectively.

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