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Acute Adverse Events Following Gadolinium-based Contrast Agent Administration: A Single-Center Retrospective Study of 281 945 Injections

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Background: Acute allergic-like and physiologic reactions occur following administration of gadolinium-based contrast agents (GBCAs) for MRI examinations. Because these reactions are uncommon, it is challenging to compare reaction rates between GBCAs and to determine risk factors.

Purpose: To compare reaction rates between the four GBCAs gadodiamide, gadobutrol, gadobenate dimeglumine, and gadoterate meglumine, and to determine potential risk factors for reactions.

Materials and Methods: This retrospective study identified all intravenous GBCA injections for MRI examinations performed at a single institution from June 1, 2009, to May 9, 2017. Reactions were identified by reviewing records from the MRI technologist, MRI nursing staff, radiologist, emergency department, and provider. Reactions were classified as allergic-like or physiologic and as mild, moderate, or severe by using American College of Radiology criteria. GBCA reaction rates and other potential risk factors were examined by using multivariable regression models with generalized estimating equations.

Results: Analysis included a total of 158 100 patients (median age, 55 years [interquartile range, 40–67 years], 51% women) who received a total of 281 945 GBCA injections (140 645 gadodiamide, 94 109 gadobutrol, 39 138 gadobenate, and 8053 gadoterate). At multivariate analysis, gadobenate or gadobutrol had higher rates of allergic-like reactions compared with gadodiamide (gadobenate: odds ratio [OR], 3.9 [95% confidence interval {CI}: 3.0, 5.1]; $P < .001$; gadobutrol: OR, 2.3 [95% CI: 1.8, 2.9]; $P < .001$) or gadoterate (gadobenate: OR, 4.8 [95% CI: 1.0, 23]; $P = .049$; gadobutrol: OR, 2.8 [95% CI: 0.6, 14]; $P = .20$). Physiologic reactions were more frequently observed with gadoterate (OR, 7.7 [95% CI: 2.3, 25; $P = .001$), gadobenate (OR, 1.8 [95% CI: 1.3, 2.5; $P < .001$), and gadobutrol (OR, 1.6 [95% CI: 1.3, 2.1; $P < .001$) administration compared with gadodiamide. Six severe allergic-like reactions (three gadobutrol, three gadobenate) occurred requiring hospitalization. Patient age (P values .025 to $< .001$), sex ($P < .001$), location ($P = .006$), and MRI type ($P = .003$ and $P = .006$) were associated with acute reactions.

Conclusion: Gadobenate and gadobutrol are associated with higher rates of allergic-like reactions compared with gadodiamide or gadoterate, and gadoterate, gadobenate, and gadobutrol are associated with higher rates of physiologic reactions compared with gadodiamide. Patient sex, age, location, and MRI type correlate with acute reaction rates.

Online supplemental material is available for this article.

Gadolinium-based contrast agents (GBCAs) are an integral component of MRI examinations and often provide crucial clinical information not available with an unenhanced MRI or any other imaging modality. Despite a favorable pharmacovigilance risk profile, both allergic-like (hypersensitivity) and physiologic (eg, nausea and vomiting, vasovagal responses, chest pain) acute reactions are known risks of GBCA administration. These acute adverse events are uncommon and most frequently occur within 1 hour of intravenous GBCA administration, with a reported incidence of seven to 240 per 10 000 injections (1). This rarity has made it challenging to compare the rate of reactions between GBCAs and to determine what risk factors are associated with acute reactions. Although the mechanisms of these reactions are still poorly understood, current evidence suggests significant inter- and intraclass differences in GBCAs may exist in the event rates of these reactions (2). These differences suggest that some GBCAs may be preferable in situations in which the risk of allergic acute reaction must be minimized.

The purpose of this large single-center retrospective study was to examine and to compare rates of acute allergic-like and physiologic reactions between four gadolinium-based contrast agents (gadodiamide, gadobutrol, gadobenate dimeglumine, and gadoterate meglumine) and to determine potential risk factors associated with these reactions. For patients receiving a GBCA injection, we hypothesized that reaction rates would be higher for gadobutrol and gadobenate compared with gadodiamide and gadoterate. We also hypothesized that patient age and sex would affect reaction rates.

Abbreviations

CI = confidence interval, GBCA = gadolinium-based contrast agent, OR = odds ratio

Summary

The rate of acute reactions following gadolinium-based contrast agent administration is affected by type of contrast agent used and patient demographics.

Key Points

- At multivariate analysis, patients administered gadobenate or gadobutrol had higher rates of allergic-like reactions compared with patients administered gadodiamide (reactions per 10 000 injections: gadobenate, 33; gadobutrol, 20; gadodiamide, nine) ($P <$ .001) or gadoterate (five reactions per 10 000), versus gadobenate (P = .020) versus gadobutrol (P = .20).
- Physiologic reactions were more frequently observed with gadoterate, gadobenate, and gadobutrol compared with gadodiamide (reactions per 10 000 injections: gadoterate, seven; gadobenate, 18; gadobutrol, 16; gadodiamide, 10) (P = .001 to $P <$ .001).
- Women (allergic-like, $P <$ .001; physiologic, $P <$ .001), patients aged 21–50 years (allergic-like vs age groups of 21–30 years, 31–40 years, and 41–50 years: P = .014, P = .013, and P = .025, respectively; physiologic vs age groups of 0–20 years, 21–30 years, and 41–50 years: P = .007, P = .001, and $P <$ .001, respectively), outpatients (allergic-like, P = .009), and patients undergoing abdomen or pelvis MRI examinations (allergic-like, P = .006) appeared to be at higher risk of an acute reaction and may warrant additional monitoring before and after MRI.

Materials and Methods

Study Design and Clinical Data Retrieval

Study design and implementation of this retrospective study were overseen by our institutional review board and conformed to Health Insurance Portability and Accountability Act guidelines on patient data integrity. At our institution, all new patients are given written consent forms that authorize that their medical records may be used for retrospective research. Clinical data from patients who do not provide research authorization may not be used for research. The need for written informed consent for this study for patients who had provided this research authorization was therefore waived. All clinical data, including MRI examination information, GBCA information, and patient demographics, were automatically extracted from our institutional electronic medical record.

Study Population

Patients were included if they provided research authorization and received an intravenous GBCA injection for a contrast material–enhanced MRI examination from June 1, 2009, to May 9, 2017, at a single-center tertiary-quaternary academic medical facility. Both pediatric (age <18 years) and adult patients were included regardless of examination indication or type in a consecutive manner. Patients were excluded if they did not provide research authorization. Infrequently used GBCA agents (<5000 total doses during our study time frame, representing 1.9% of all injections [5542 of 287 487]), including gadoxetate disodium (Eovist; Bayer Healthcare, Leverkusen, Germany) (n = 2435), gadopentate dimeglumine (Magnevist; Bayer Healthcare) (n = 1704), gadofosveset trisodium (Ablavar; Lantheus Medical Imaging, North Billerica, Mass) (n = 1343), and other GBCAs (n = 60), were excluded from the analysis.

MRI Examination Protocol and GBCA Administration

Contrast-enhanced MRI examinations included in our study were performed with the intravenous agent gadodiamide (Omniscan; GE Healthcare, Chicago, Ill), gadobutrol (Gadavist; Bayer Healthcare), gadobenate dimeglumine (MultiHance; Bracco Diagnostics, Milan, Italy), and gadoterate meglumine (Dotarem; Guerbet, Villepinte, France) at a target bolus dose of 0.1 mmol/kg for both adult and pediatric patients. On January 1, 2015, our institution transitioned from administration of gadodiamide and gadobenate to gadobutrol as our primary contrast agent. Gadoterate utilization, used predominantly for prostate MRI examinations (7810 of 8053, 97%), did not change during this transition. Nursing and technologist assessments, GBCA administration, and surveillance protocols after examination did not change during this transition.

Identification and Classification of Acute Reactions

At our institution, all patients are monitored during and after GBCA-enhanced MRI examinations (30–45 minutes total) to identify and treat GBCA-mediated acute reactions. All identification and classification of acute reactions was performed by one author (J.S.M., a researcher with 7 years of experience) while blinded to GBCA type, MRI examination type, clinical indication, and patient demographics. Reactions were classified into allergic-like or physiologic types and into mild, moderate, and severe categories by using American College of Radiology criteria (1). Reaction details, including time of reaction relative to GBCA administration, symptoms, intervention, and duration of symptoms are documented by MRI technologists and nursing staff and entered into the patient's electronic medical records. Acute reactions were identified by a combination of automated retrieval and manual review of the above MRI technologist and nursing staff notes, radiologist reports, emergency department admission notes related to GBCA reactions, and subsequent provider visit notes related to GBCA reactions. An automated free text search of terms indicative of a reaction (Table E1 [online]) was performed on the above sections of the medical record to identify potential reactions. A manual review of these records was then performed by one author (J.S.M.) for final confirmation. The medical records of all patients with a listed allergy to GBCAs who underwent a GBCA-enhanced MRI examination at our institution were also reviewed to determine if a GBCA reaction occurred following an MRI examination that was performed within or outside of our institution. Reactions that occurred due to MRI examinations performed at outside institutions were not included in the study because there was no way to confirm the type, symptoms, or severity of that reaction or what GBCA was administered to cause the reaction.

Statistical Analysis

Statistical analyses were performed by using commercially available JMP software (version 10; SAS Institute, Cary,

NC) or open-source R software (version 3.5.2; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as medians and interquartile range, and categorical variables are presented as percentages. Statistical significance was assigned to differences with a *P* value of ≤ .05.

We estimated logistic regression models to evaluate the impact of GBCA and patient and clinical factors on allergic-like or physiologic reactions. In these models, reaction rate (yes or no) was the dependent variable and GBCA, patient age, sex, location, and MRI examination type were the independent variables. To account for the clustered nature of the data points by patient, we performed logistic regression by using generalized estimating equations. Analyses were performed by using the geeM package in R assuming an exchangeable correlation structure (3,4). Robust sandwich variance estimates were calculated to generate Wald statistics and 95% confidence intervals (CIs).

We examined potential seasonality in acute reactions in the entire study time frame. Negative binomial log-linear segmented regression models were fit to the data for allergic-like reactions and physiologic reactions. Segmented regression models were used to assess for immediate and gradual effects after a point of change or intervention. Autocorrelation factors, partial autocorrelation factors, and periodograms were reviewed to assess for need for model adjustment for autocorrelation and seasonality. Durbin-Watson and Fisher *g* tests were also performed (5). Because of evidence of both annual and nonannual periodicity, physiologic reactions included separate overall and month within year sinusoidal components based on periodogram frequency; regression splines and months as indicator variables were tested as alternative fit options. Model selection was performed by using Bayesian information criterion. Rate ratios and 95% CIs are presented.

We looked for evidence of a Weber effect by examining changes in acute reaction rates in the nine quarters before and after the institutional transition in GBCAs. Negative binomial log-linear segmented regression models were fit to the data for allergic-like reactions and physiologic reactions. Reaction counts were modeled as a function of GBCA change, time, an interaction term between change and time, and additional terms for periodic or seasonal effects, which were dropped from the model if nonsignificant. Model selection was performed by using Bayesian information criterion. Rate ratios and 95% CIs are presented.

Results

Study Population

We administered a total of 281 945 GBCA injections (140 645 gadodiamide [50%], 94 109 gadobutrol [33%], 39 138 gadobenate dimeglumine [14%], and 8053 gadoterate meglumine [2.9%]) in 158 100 patients in the study time frame (Fig 1). Patient demographics and MRI examination details are shown in Table 1. Half of the examinations were performed in women (144 451, 51%), and the median age of included patients was 55 years.

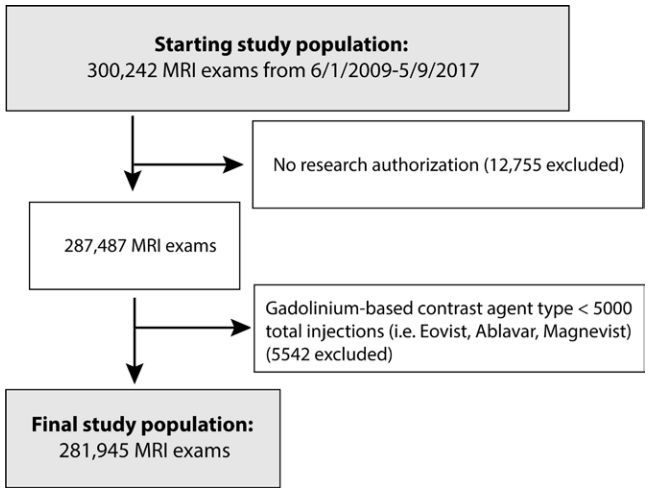

Figure 1: Flowchart shows study population.

Table 1: Study Population and MRI Details

Characteristic	Value
No. of GBCA injections	281 945
No. of patients	158 100
Age (y)*	55 (40–67)
Sex	
Female	144 451 (51)
Male	137 494 (49)
Ethnicity	
White	257 590 (91)
Nonwhite	24 355 (8.6)
GBCA used	
Gadodiamide	140 645 (50)
Gadobutrol	94 109 (33)
Gadobenate dimeglumine	39 138 (14)
Gadoterate meglumine	8053 (2.9)
GBCA dose (mL)*	14 (9–18)
Location at time of MRI†	
Inpatient	21 094 (7.5)
Outpatient	260 404 (92)
Not provided	447 (0.2)
MRI type	
Brain	133 790 (47)
Abdomen and/or pelvis	51 796 (18)
Spine	35 572 (13)
Musculoskeletal	15 518 (5.5)
Prostate	11 355 (4.0)
Breast	9960 (3.5)
Cardiac	8584 (2.9)
Chest	4776 (1.7)
Other†	4036 (1.4)
Multiple types	6858 (2.4)

Note.—Unless otherwise specified, data in parentheses are percentages. GBCA = gadolinium-based contrast agent.

* Data are medians, with interquartile range in parentheses.

† Other includes MRI elastogram, interventional MRI, and research MRI.

We performed the majority of MRI examinations in outpatients (260 404, 92%) versus inpatients (21 094, 7.5%). Brain MRI examinations made up approximately half of all examinations performed (133 790, 47%), followed by abdomen and/or pelvis MRI (51 796, 18%) and then spine MRI (35 572, 13%).

Table 2: Acute Reaction Rates Following GBCA Administration

GBCA Used	Total Injections	Mild	Moderate	Severe	Total
All reactions					
Gadodiamide	140 645	196 (14)	70 (5)	0	266 (19)
Gadobutrol	94 109	245 (26)	92 (10)	3 (0)	340 (36)
Gadobenate dimeglumine	39 138	141 (36)	56 (14)	3 (1)	200 (51)
Gadoterate meglumine	8053	9 (11)	1 (1)	0	10 (12)
Allergic-like reaction					
Gadodiamide	140 645	76 (5)	46 (3)	0	122 (9)
Gadobutrol	94 109	107 (11)	75 (8)	3 (0)	185 (20)
Gadobenate dimeglumine	39 138	77 (20)	51 (13)	3 (1)	131 (33)
Gadoterate meglumine	8053	4 (5)	0	0	4 (5)
Physiologic reaction					
Gadodiamide	140 645	120 (9)	24 (2)	0	144 (10)
Gadobutrol	94 109	138 (15)	17 (2)	0	155 (16)
Gadobenate dimeglumine	39 138	64 (16)	5 (1)	0	69 (18)
Gadoterate meglumine	8053	5 (6)	1 (1)	0	6 (7)

Note.—Data in parentheses are number of reactions per 10 000 injections. GBCA = gadolinium-based contrast agent.

Rate and Symptoms of Acute Reactions

Allergic-like reactions occurred at an overall rate of 16 per 10 000 injections (Table 2) (442 of 281 945; reactions per 10 000 injections: gadobenate, 33 [131 of 39 138]; gadobutrol, 20 [185 of 94 109]; gadodiamide, nine [122 of 140 645]; gadoterate, five [four of 8053]). Physiologic reactions occurred at an overall rate of 13 per 10 000 injections (374 of 281 945; reactions per 10 000 injections: gadobenate, 18 [69 of 39 138]; gadobutrol, 16 [155 of 94 109]; gadodiamide, 10 [144 of 140 645]; gadoterate, seven [six of 8053]).

When stratified by severity of reaction, there was a 21 per 10 000 injections rate of mild reactions (591 of 281 945), eight per 10 000 rate of moderate reactions (219 of 281 945), and two per 100 000 rate of severe reactions (six of 281 945). All six severe allergic-like reactions (three gadobutrol, three gadobenate) that occurred during the study time frame required hospitalization. Of note, the severe reactions that occurred following gadobutrol administration were more serious and required longer hospitalizations than did the severe reactions that occurred following gadobenate administration. Two patients who received gadobutrol required subsequent extracorporeal membrane oxygenation support (Table E2 [online]). No deaths related to GBCA administration were noted.

Distribution of the various symptoms associated with allergic-like and physiologic reactions in this cohort are shown in Table 3. The most common symptoms associated with allergic-like reactions were hives and throat symptoms (eg, itchiness, swelling, difficulty swallowing). Rates of hives varied with GBCA (reactions per 10 000 injections: gadobenate, 23 [89 of 39 138]; gadobutrol, 14 [136 of 94 109]; gadodiamide, seven [97 of 140 645]; gadoterate, five [four of 8053]). The most common symptoms associated with physiologic reactions were nausea or vomiting, vasovagal response or dizziness, and flushing or chills. Rates of nausea or vomiting varied with GBCA (reactions per 10 000 injections: gadobenate, 14 [53 of 39 138]; gadobutrol, nine [88 of 94 109]; gadodiamide, five [67 of 140 645]; gadoterate, five [six of 8053]).

Risk Factors for Acute Reactions

Several risk factors were found to be associated with higher rates of allergic-like reactions at multivariate analysis, including GBCA, age, sex, outpatient status, and examination type. Patients administered gadobenate or gadobutrol had higher rates of allergic-like reactions compared with patients administered gadodiamide (gadobenate: odds ratio [OR], 3.9 [95% CI: 3.0, 5.1]; $P < .001$; gadobutrol: OR, 2.3 [95% CI: 1.8, 2.9]; $P < .001$) or gadoterate (gadobenate: OR, 4.8 [95% CI: 1.0, 23]; $P = .049$; gadobutrol: OR, 2.8 [95% CI: 0.6, 14]; $P = .20$) (Table 4). When compared with patients aged 51–60 years, patients in the age groups of 21–30 years, 31–40 years, and 41–50 years had higher reaction rates (OR, 1.6 [95% CI: 1.1, 2.3]; $P = .014$; OR, 1.5 [95% CI: 1.1, 2.1]; $P = .013$; OR, 1.4 [95% CI: 1.0, 1.9]; $P = .025$, respectively). Women had higher rates of allergic-like reactions compared with men (20 per 10 000 injections vs 11 per 10 000; OR, 1.7 [95% CI: 1.4, 2.1]; $P < .001$). Rates of allergic-like reactions were observed approximately twice as frequently in outpatients compared with inpatients (OR, 1.9 [95% CI: 1.2, 3.2]; $P = .009$), and more frequently with abdomen and/or pelvis MRI examinations compared with brain MRI examinations (OR, 1.4 [95% CI: 1.1, 1.8]; $P = .006$).

At multivariate analysis, physiologic reactions were more frequently observed with gadoterate (OR, 7.7 [95% CI: 2.3, 25]; $P = .001$), gadobenate (OR, 1.8 [95% CI: 1.3, 2.5]; $P < .001$), and gadobutrol (OR, 1.6 [95% CI: 1.3, 2.1]; $P < .001$) administration compared with gadodiamide (Table 3). Patients in the age groups of 0–20 years, 21–30 years, and 41–50 years had higher physiologic reaction rates (OR, 1.8 [95% CI: 1.2, 2.7]; $P = .007$; OR, 1.9 [95% CI: 1.3, 2.9]; $P = .001$; OR, 1.9 [95% CI: 1.4, 2.6]; $P < .001$, respectively) than did patients in the age group of 51–60 years. Women had higher physiologic reaction rates compared with men (17 per 10 000 vs 10 per 10 000; OR, 1.6 [95% CI: 1.3, 2.0]; $P < .001$). Physiologic reactions occurred less frequently with prostate MRI examinations (OR, 0.1 [95% CI: 0.0, 0.5]; $P = .003$) when compared with brain MRI examinations.

Table 3: Symptoms of Acute Reactions Based on Type of Contrast Agent

Type of Symptom	Gadodiamide Injections (n = 140 645)	Gadobutrol Injections (n = 94 109)	Gadobenate Dimeglumine Injections (n = 39 138)	Gadoterate Meglumine Injections (n = 8053)
Allergic-like reaction				
Hives	97 (7)	136 (14)	89 (23)	4 (5)
Throat symptoms	23 (2)	31 (3)	17 (4)	0
Wheezing, shortness of breath	10 (1)	19 (2)	11 (3)	0
Edema	3 (0)	13 (1)	10 (3)	0
Nasal or eye symptoms	6 (0)	12 (1)	21 (5)	0
Anaphylaxis	0	3 (1)	3 (1)	0
Physiologic reaction				
Nausea or vomiting	67 (5)	88 (9)	53 (14)	5 (6)
Vasovagal, dizziness	50 (4)	46 (5)	16 (4)	0
Flushing, chills	27 (2)	40 (4)	16 (4)	0
Chest tightness or pain	19 (1)	12 (1)	8 (2)	1 (1)
Headache	8 (1)	7 (1)	1 (0)	0
Unresponsive	0	1 (0)	1 (0)	0
Seizure	1 (0)	0	0	0
Pulmonary edema	0	1 (0)	0	0
Pulseless electrical activity	0	1 (0)	0	0

Note.—Data in parentheses are number of reactions per 10 000 injections.

When examining specific reaction symptoms at multivariate analysis, hives occurred more frequently following gadobenate or gadobutrol administration compared with gadodiamide (gadobenate: OR, 3.4 [95% CI: 2.5, 4.6]; $P < .001$; gadobutrol: OR, 2.1 [95% CI: 1.6, 2.8]; $P < .001$) or compared with gadoterate (gadobenate: OR, 3.5 [95% CI: 0.6, 20]; $P = .16$; gadobutrol: OR, 2.2 [95% CI: 0.4, 12]; $P = .38$). Nausea or vomiting occurred more frequently following gadoterate, gadobenate, or gadobutrol administration compared with gadodiamide (gadoterate: OR, 13 (95% CI: 3.2, 52]; $P < .001$; gadobenate: OR, 3.1 [95% CI: 2.1, 4.7]; $P < .001$; gadobutrol: OR, 2.0 [95% CI: 1.5, 2.8]; $P < .001$).

Effects of Seasonality and Institutional GBCA Transition on Acute Reaction Rates

The median GBCA acute reaction rates per month are shown in Figure E1 (online). There was no indication of significant seasonal effects for allergic-like reactions when assessed with periodogram, autocorrelation factors and partial autocorrelation factors, or Fisher test ($P = .78$). Months as indicator variables were all nonsignificant (jointly and individually) when included in the model and were dropped from the model prior to analysis for institutional transition. There was no evidence of a significant change in allergic-like reaction rates during or after institutional transition (rate ratio, 0.97 [95% CI: 0.65, 1.45]; $P = .90$) (Fig 2). Physiologic reactions showed evidence of seasonality on autocorrelation factors and partial autocorrelation factors and periodogram. After adjustment for overall time, month within year remained significant ($P = .005$), peaking quarterly with the highest median rates occurring in February (23 per 10 000 injections) and August (15 per 10 000 injections). There was also evidence of an increase in reaction rate at the time of transition (rate ratio, 1.87 [95% CI: 1.06, 3.30]; $P = .03$), although no evidence of continued increase after transition (time × change rate ratio, 1.01 [95% CI: 0.98, 1.04]).

Discussion

This single-center retrospective study of 281 945 gadolinium-based contrast agent (GBCA) injections found that allergic-like acute reactions occurred more frequently following gadobutrol or gadobenate dimeglumine administration compared with gadodiamide or gadoterate meglumine administration (gadobenate vs gadodiamide: odds ratio [OR], 3.94 [95% confidence interval {CI}: 3.0, 5.1]; $P < .001$; gadobutrol vs gadodiamide: OR, 2.3 [95% CI: 1.8, 2.9]; $P < .001$; gadobenate vs gadoterate: OR, 4.8 [95% CI: 1.0, 23]; $P = .049$; gadobutrol vs gadoterate: OR, 2.8 [95% CI: 0.6, 14]; $P = .20$). Physiologic reactions occurred more frequently following gadoterate, gadobutrol, or gadobenate administration compared with gadodiamide (gadoterate: OR, 7.7 [95% CI: 2.3, 25]; $P = .001$); gadobenate: OR, 1.8 [95% CI: 1.3, 2.6]; $P < .001$); and gadobutrol: OR, 1.6 [95% CI: 1.3, 2.1; $P < .001$). No severe reactions were documented with gadodiamide or gadoterate administration at our institution over 10 years and 148 698 total injections. We identified several apparent risk factors for acute reactions, including being a woman, ages 21–50 years (compared with older patients), admission status (higher in outpatients compared with inpatients), and imaging location (higher rates with abdomen and/or pelvis MRI examinations compared with brain MRI examinations). We observed a potential seasonality component with physiologic reactions (median rates highest in February [23 per 10 000 injections] and August [15 per 10 000 injections]) but not allergic-like reactions. These results demonstrate that the rate of acute GBCA reactions varies between GBCA type and is associated with specific patient demographics.

Table 4: Risk Factors for Acute Reactions at Multivariate Analysis

Risk Factor	No.	Allergic-like Reactions	*P* Value	Odds Ratio*	Physiologic Reactions	*P* Value	Odds Ratio*
GBCA							
Gadodiamide (reference)	140 645	122 (9)	…	…	144 (10)	…	…
Gadobutrol	94 109	185 (20)	<.001	2.3 (1.8, 2.9)	155 (16)	<.001	1.6 (1.3, 2.1)
Gadobenate dimeglumine	39 138	131 (33)	<.001	3.9 (3.0, 5.1)	69 (18)	<.001	1.8 (1.3, 2.5)
Gadoterate meglumine	8053	4 (5)	0.80	0.8 (0.2, 3.9)	6 (7)	.001	7.7 (2.3, 25)
Age (y)							
0–20	22 185	27 (12)	0.52	0.9 (0.5, 1.4)	39 (18)	.007	1.8 (1.2, 2.7)
21–30	20 775	51 (25)	.014	1.6 (1.1, 2.3)	44 (21)	.001	1.9 (1.3, 2.9)
31–40	29 331	69 (24)	.013	1.5 (1.1, 2.1)	46 (16)	.07	1.4 (1.0, 2.1)
41–50	41 829	89 (21)	.025	1.4 (1.0, 1.9)	86 (21)	<.001	1.9 (1.4, 2.6)
51–60 (reference)	59 725	88 (15)	…	…	62 (10)	…	…
61–70	59 620	67 (11)	0.12	0.8 (0.6, 1.1)	54 (9)	.54	0.9 (0.6, 1.3)
≥71	48 480	51 (11)	.017	0.6 (0.5, 0.9)	43 (9)	.43	0.9 (0.6, 1.3)
Sex							
Female	144 451	296 (20)	<.001	1.7 (1.4, 2.1)	244 (17)	<.001	1.6 (1.3, 2.0)
Male (reference)	137 349	146 (11)	…	…	130 (10)	…	…
Patient location							
Inpatient (reference)	21 094	16 (8)	…	…	17 (8)	…	…
Outpatient	260 404	424 (16)	.009	1.9 (1.2, 3.2)	357 (14)	.07	1.6 (1.0, 2.6)
MRI type							
Brain (reference)	133 790	177 (13)	…	…	166 (12)	…	…
Abdomen and/or pelvis	51 796	116 (22)	.006	1.4 (1.1, 1.8)	91 (18)	.06	1.3 (1.0, 1.7)
Spine	35 572	45 (13)	.93	1.0 (0.7, 1.4)	41 (12)	0.94	1.0 (0.7, 1.4)
Musculoskeletal	15 518	20 (13)	.77	0.9 (0.5, 1.6)	14 (9)	.18	0.7 (0.4, 1.2)
Prostate	11 355	8 (7)	.60	1.4 (0.4, 4.2)	5 (4)	.003	0.1 (0.0, 0.5)
Breast	9960	31 (31)	.96	1.0 (0.7, 1.5)	23 (23)	.53	1.2 (0.7, 1.9)
Cardiac	8284	18 (22)	.10	1.5 (0.9, 2.5)	12 (14)	.49	1.2 (0.7, 2.2)
Chest	4776	13 (27)	.21	1.5 (0.8, 2.7)	5 (10)	.51	0.7 (0.3, 1.8)
Other†	4036	3 (7)	.17	0.5 (0.1, 1.4)	2 (5)	.15	0.4 (0.1, 1.4)
Multiple types	6858	11 (16)	.70	1.1 (0.6, 2.1)	15 (22)	.08	1.6 (1.0, 2.8)

Note.—Multivariate analysis included gadolinium-based contrast agent (GBCA), age, sex, location, and MRI type as variables. Unless otherwise specified, data in parentheses are number of reactions per 10 000 injections.

* Data in parentheses are 95% confidence intervals.

† Other includes MRI elastogram, interventional MRI, and research MRI.

During our study time frame, our institution transitioned from gadodiamide and gadobenate to gadobutrol as the primary imaging agent. It is therefore possible that gadobutrol reaction rates may have been artificially elevated due to the Weber effect (6), defined as heightened vigilance and increased reporting of adverse events in the first 2 years following introduction of a drug. We could not fully assess this effect because our data only extended out to just over 2 years following this transition. However, several findings argue against our data being confounded by the Weber effect. First, we observed that acute reaction rates slowly and steadily increased in the nine quarters following the transition to gadobutrol, with rates in the final three quarters slightly higher than in the first three quarters following transition, instead of a rapid increase and subsequent decrease over this time frame characteristic of the Weber effect (7). Second, severe acute reactions following gadobutrol administration that required acute life-saving medical intervention such as those described above are not, by definition, a manifestation of the Weber effect. Finally, our findings of higher rates of acute reactions with gadobutrol compared with gadodiamide and gadoterate corroborate other study findings (2).

Our study found a higher rate of acute allergic-like reactions with the linear ionic GBCA gadobenate and the macrocyclic nonionic GBCA gadobutrol compared with the linear nonionic GBCA gadodiamide and the macrocyclic ionic GBCA gadoterate. Our findings corroborate the recently published meta-analysis of nine independent GBCA allergic-like reaction studies and 716 978 cumulative doses by Behzadi et al (2). We found that women are at greater risk of an acute reaction, which also corroborates prior studies (7–11). Davenport et al (7) likewise noted higher reaction rates in patients aged 18–65 years compared with older and younger patients. Okigawa et al (12) also reported higher rates in patients up to age 50 years compared with older patients. Higher rates of acute reactions had been previously

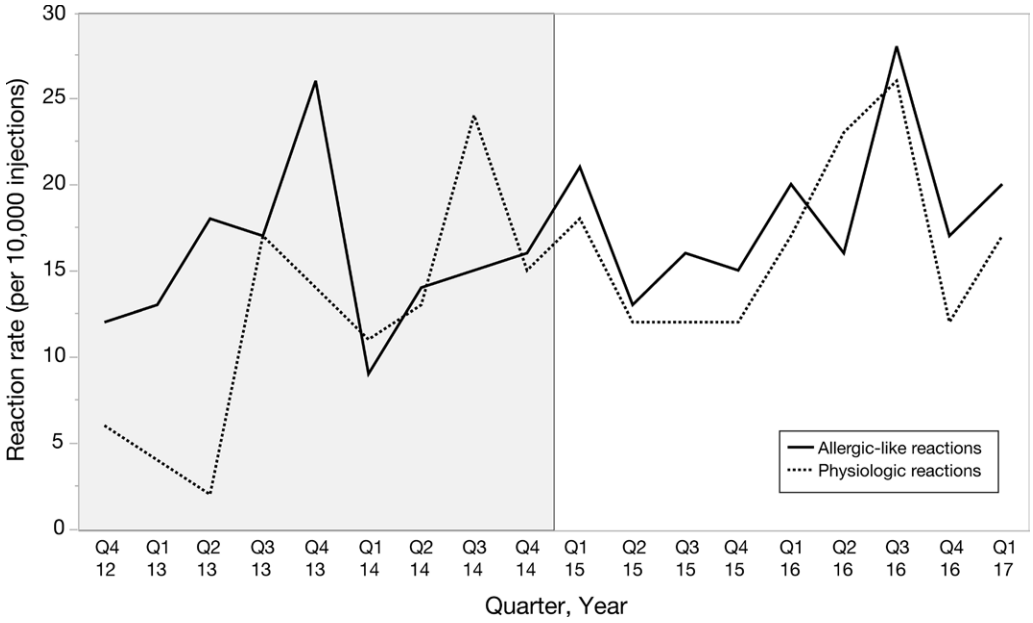

Figure 2: Graph shows no evidence of Weber effect following institutional transition from gadodiamide and gadobenate dimeglumine to gadobutrol. Time frames before (nine quarters [Q], 18 months) and after (nine quarters, 18 months) transition are shown in gray and white, respectively. Quarterly rate of acute reactions are shown in solid (allergic-like reactions) and dotted (physiologic reactions) lines.

observed following abdomen and breast MRI examinations (8,11). Aran et al (8) also reported higher reaction rates in outpatients compared with inpatients. Rates of acute allergic-like reactions in inpatients may be lower because of a decreased ability to report reactions in those patients (ie, intubated) or because inpatients may be more likely to be on steroids, reducing the likelihood of an allergic-like reaction. Our study found a much higher overall rate of acute reactions compared with a prior study that examined GBCA-enhanced MRI examinations at our institution from 2002 to 2006 (29 per 10 000 injections vs four per 10 000) (13), possibly because of changes in specific GBCAs used and reaction reporting protocols (written vs electronic) between the two study time frames.

Our study expands on these prior studies in several ways. First, to our knowledge, this is the largest single-center study of GBCA acute reactions to date. The single-center nature of our study strengthens data validity as variables such as nursing and MRI technologist protocols for monitoring, as well as identifying, treating, and documenting GBCA reactions, were standardized during our study time frame. This standardization eliminated confounding bias as an explanation of the differences in reaction rates between GBCAs. Our study design afforded an opportunity for a more direct comparison of these GBCAs in contrast to multicenter studies using different GBCAs with different institutional policies regarding GBCA reaction identification and documentation. Second, our study used multivariate analysis to examine the simultaneous effects of GBCA, patient demographics, and MRI examination type on acute reactions. Finally, to our knowledge, our study is the first to examine and refute the potential seasonality of acute reactions.

Our study had several limitations. First, our study was retrospective in nature and we were limited to acute reactions documented in the medical record. Acute reactions not recorded in any section of the medical chart would not have been included. However, we believe such occurrences are rare and unlikely to affect our conclusions. Second, our institutional policy was to monitor for acute reactions in the 30 to 45 minutes following GBCA injection. Acute reactions that occurred after dismissal, particularly mild reactions, would not have been captured unless they were later documented by a medical provider. Third, our study was underpowered to compare gadoterate (8053 injections) to certain other GBCAs (gadoterate vs gadodiamide, assuming α = .05 and 14% power to compare allergic-like reactions and 8.5% power to compare physiologic reactions) and to compare especially rare severe acute reactions between GBCAs (ie, gadodiamide vs gadobutrol: 55% power; gadodiamide vs gadobenate: 76% power). Fourth, gadoterate utilization was largely limited to prostate MRI examinations at our institution, potentially affecting a comparison of reaction rates between GBCAs. We attempted to minimize this difference in utilization through a multivariate analysis. Fifth, this was a single-center study and our findings may be different than studies of other medical centers that used different GBCAs and protocols for identifying and documenting acute reactions. Sixth, our negative findings for a Weber effect may have been confounded by other temporal changes at our institution, including other procedural changes. Finally, some acute reactions, particularly physiologic reactions, may have been attributable to non-GBCA causes. This limitation may have resulted in an overestimation of the reaction rate and is inherent to all acute reaction studies.

In conclusion, gadobenate dimeglumine and gadobutrol are associated with higher rates of allergic-like reactions compared with gadodiamide and gadoterate meglumine, and gadoterate, gadobenate, and gadobutrol are associated with higher rates of physiologic reactions compared with gadodiamide. Patient sex, age, location, and MRI type correlate with acute reaction rates. Additional studies and meta-analyses are necessary to confirm and expand on these findings.

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