

Incidence of Immediate Gadolinium Contrast Media Reactions

Martin R. Prince¹
 Honglei Zhang
 Zhitong Zou
 Ronald B. Staron
 Paula W. Brill

Keywords: anaphylactoid reactions, gadobenate dimeglumine, gadodiamide, gadolinium, MRI, nephrogenic systemic fibrosis

DOI:10.2214/AJR.10.4885

Received April 28, 2010; accepted after revision August 2, 2010.

M. R. Prince has patent agreements with Bracco, Bayer, Mallinckrodt, and GE Healthcare.

¹All authors: Department of Radiology, Cornell and Columbia Universities, 416 East 55th Street, New York, NY 10022. Address correspondence to M. R. Prince (map2008@med.cornell.edu).

WEB

This is a Web exclusive article.

AJR 2011; 196:W138–W143

0361–803X/11/1962–W138

© American Roentgen Ray Society

OBJECTIVE. Our objective was to determine the incidence of immediate adverse events for gadolinium-based contrast agents.

MATERIALS AND METHODS. All gadolinium-based contrast agent adverse events reported to radiology quality assurance committees were graded according to American College of Radiology criteria and divided by the total number of injections to determine incidence during the past 10 years. For each event, an age- and examination-matched control patient was identified to compare sex, weight, creatinine, eosinophil count, allergic history and gadolinium-based contrast agent dose differences. The U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) database was analyzed to compare local experience to national trends.

RESULTS. Abdominal MRI had the highest rates of adverse events, 0.013% compared with brain (0.0045%, $p < 0.001$) or spine (0.0034%, $p < 0.001$). Adverse events were more likely in women, with a female to male ratio of 3.3, and in patients with history of prior allergic reactions ($p < 0.001$). Immediate adverse events rates were 0.2, 0.5, 1.2, and 3.3 per 1,000 injections for gadodiamide, gadopentetate dimeglumine, gadobenate dimeglumine, and gadoteridol, respectively. Gadobenate dimeglumine had more severe patient reactions, including three patients who arrested (defined as the patient becoming unresponsive and the code team being called), one of whom died. From 2004 to 2009, the FDA received reports on 40 gadolinium-based contrast agent U.S. deaths unrelated to nephrogenic systemic fibrosis, with an incidence per million doses of 0.15, 0.19, 0.97, 2.7, and 0.7 for gadodiamide, gadoversetamide, gadopentetate dimeglumine, gadobenate dimeglumine, and gadoteridol, respectively.

CONCLUSION. This limited retrospective analysis shows that gadolinium-based contrast agents are very safe, with only rare reports of death, and raises the possibility that non-ionic linear gadolinium-based contrast agents and gadopentetate dimeglumine may have fewer severe immediate adverse events compared with gadobenate dimeglumine.

Since 2007 we have been routinely screening for renal function on all inpatients and outpatients with known renal failure, scheduling MRI on dialysis patients to immediately precede a dialysis appointment, using a maximum of 0.1 mmol/kg in patients with a glomerular filtration rate (GFR) lower than 30 mL/min, and using primarily ionic gadolinium-based contrast agents, gadopentetate dimeglumine and gadobenate dimeglumine, because the latter agent has not been associated with unconfounded cases of nephrogenic systemic fibrosis (NSF) [1, 2]. Although there have been no cases of NSF in our institution since 2006, we have had three arrests related to gadobenate dimeglumine administration; one of these patients died. Abujudeh

et al. [3] have recently reported a higher incidence of adverse events with gadobenate dimeglumine, including one death. While death following injection of gadolinium-based contrast agents has been described in only a few other reports and postmarketing surveillance reviews [4–7], one of our arresting patients died immediately after a power injection of gadobenate dimeglumine for liver MRI. Recent updates to the gadobenate dimeglumine package insert include a more detailed warning on hypersensitivity reactions and a specific contraindication in patients with known allergic reaction to gadolinium (www.multi-hanceusa.com/pdf/updated_PIs_december212009/v2MHP18%205x11-11-09.pdf). Although NSF has heavily influenced our decision-making regarding use of gadolinium-

based contrast agents, we now realize that immediate reactions to gadolinium-based contrast agents are also important. The goals of this article are to systematically explore rates of adverse events for the gadolinium-based contrast agents used at our hospitals during the past 10 years and to assess how our local experience compares to reports made to the U.S. Food and Drug Administration (FDA).

Materials and Methods

Local Adverse Events Rates

During the period from January 1, 2000 to December 31, 2009, five gadolinium-based contrast agents were used: gadopentetate dimeglumine (Magnevist, Bayer HealthCare), gadodiamide (Omniscan, GE Healthcare), gadoteridol (ProHance, Bracco), gadobenate dimeglumine (MultiHance, Bracco) and gadoxetate (Eovist, Bayer HealthCare). Data on all gadolinium-based contrast agent adverse events spontaneously reported by hospital employees were collected by reviewing all available quality assurance (QA) and patient care committee meeting minutes and supporting data at our two major teaching hospitals, which have merged into a single fiscal entity. In these meeting minutes and the hospitals' electronic adverse events reporting database, each adverse event was listed together with the date of occurrence, gadolinium-based contrast agent involved, and any details felt to be relevant by the person reporting the case and supervisor investigating the incident. Each event was graded as mild, moderate, or severe, according to the American College of Radiology (ACR) Criteria [8].

This retrospective review of prospectively acquired QA data was undertaken at the request of the hospital's formulary committee and was exempt from institutional review board (IRB) approval because it was a QA activity. Once a decision to publish this data was made, IRB and conflict-of-interest approval for retrospective review of existing prospectively acquired QA data was granted. No patient consent was required.

Data on the number of cases performed with each contrast agent were obtained from hospital purchasing records, review of billing records, and by examination of MRI scanner log books. Incidence of adverse events was calculated by dividing the number of reported events by the number of administrations for each agent.

To determine if the adverse reactions of the patients having gadolinium-based contrast agent were significantly different from the average patient undergoing MRI enhanced with a gadolinium-based contrast agent, a case control study was performed. For each patient with an adverse event, a control patient was identified by searching the hospitals' picture archiving and communica-

tions system for a patient of the same age undergoing the identical examination on the same day. If no same-day control was identified, the search was gradually expanded until an age- and examination-matched control was found close in time to the adverse reaction patient examination. For all adverse event and control patients, the hospital medical records were searched for sex; weight; inpatient/outpatient status; clinical history, including allergic reactions history; number of prior gadolinium-based contrast agent-enhanced MRI examinations; and number of follow-up examinations. Laboratory data on serum creatinine and eosinophil count were collected, if available, within 6 months of the gadolinium-based contrast agent administration. The significance of differences in these data was evaluated with Student's *t* test for paired data for the continuous variables and chi-square test for categorical variables.

The distribution of examinations among the patients with adverse events was compared with the distribution of examinations actually performed with contrast enhancement based on review of scanner logs and billing records.

National Adverse Events Rates

All spontaneous reports of adverse events to the FDA are entered into an Adverse Event Reporting System (AERS), also known as MedWatch. These tables are created each calendar quarter and are available for public review (www.fda.gov/cder/aers/extract.htm) as zipped Summary Reports of Adverse Events dating back to 2004.

Analysis of FDA Data

An initial analysis was performed by combining the four quarters of 2008 into a single set of tables and uploading them into a relational database (Access 2007, Microsoft). Exploring the data with a variety of queries revealed that reports corresponding to adverse reactions to gadolinium-based contrast agents could be identified with the search terms *Gad*, *Gd*, Magnevist, Omniscan, Prohance, MultiHance, eovist, optimark, MRI, DTPA, GE, Bayer, Berlex, Bracco and Mallinckrodt. Events where a gadolinium-based contrast agent was the "Primary Suspect" for the adverse event were coded as ROLE_COD = PS. Outcomes were coded as death, hospitalization, life-threatening, disability, congenital anomaly, required intervention to prevent permanent impairment, or other. There can be variability in the criteria for determining if an event is life-threatening or requires hospitalization or should be reported to the FDA. Accordingly, we focused on reports with the outcome coded as "death," because death is free of observer bias. Once those optimized search terms were established, a final analysis was performed

by running queries for the entire 6 years of FDA data. Duplicates were eliminated by comparing event date, age, and sex.

NSF cases have been extensively reported elsewhere and were excluded from this analysis. Although there were cases reported from all over the world, only U.S. events were included in the analysis. This was necessary because reliable sales data used to determine the number of injections of each agent were only available for the United States.

Market Share Data

Data on the market share of each agent were available from Intercontinental Marketing Services (IMS). These data are based on reports provided directly by companies in the form of liters of gadolinium-based contrast agents sold each year. These data were converted into doses administered by dividing the total volume sold for each agent by 17 mL, our estimate of average dose, which accounts for both standard and high-dose administrations. We also asked each manufacturer the number of doses administered in the United States and worldwide in each year from 2004 to 2009, and these data, when provided, were consistent with IMS data. Finally, these data were shared with Bayer HealthCare, Bracco, GE Healthcare, and Mallinckrodt, with a request to correct any errors. The statistical significance of differences in the rate of death between macrocyclic and linear chelates, between ionic and nonionic linear chelates, and between each of the gadolinium-based contrast agents was compared using Fisher's exact test.

Results

Data on adverse events were available dating back to 2004 in one hospital and dating back to 2000 for the other hospital. During these periods there were a total of 158,796 gadolinium-based contrast agent enhanced examinations using gadodiamide (*n* = 55,703), gadopentetate dimeglumine (*n* = 66,157), gadoteridol (*n* = 3,371), gadobenate dimeglumine (*n* = 33,114) and gadoxetate (*n* = 451). Hospital QA records detailed 140 events related to gadolinium-based contrast agents, including 46 infiltrations (3 per 10,000 injections) and 94 gadolinium-based contrast agent acute adverse reactions (5.9 per 10,000 injections) graded as mild = 74, moderate = 16, and severe = 4, according to ACR criteria. The rate of severe reactions was about 1 in 40,000 injections.

The types of MRI examinations for the patients who had adverse reactions are shown in Table 1 compared with the distribution of all examinations performed with gadolinium-based contrast agent enhance-

TABLE 1: Rate of GBCA Adverse Events by Type of MRI Examination^a

Type of GBCA-Enhanced Examination	No. of Exams	No. of Reactions	Reactions/10,000 Exams
Brain	72,756	33	4.5
Orbit/face/neck	3940	3	7.6
Spine	23,656	8	3.4
Cardiac	7328	4	5.5
Breast	4304	4	9.3
Abdomen	20,992	28	13 ^b
Pelvis	7328	4	5.5
Extremity	4492	4	8.9
MR angiography	14,000	6	4.3
Total	158,796	94	5.9

Note—GBCA = gadolinium-based contrast agent.

^aWhen more than one type of study was performed with a single injection of GBCA, the study was only counted once based on the primary reason for the study.

^bStatistically significantly higher rate of reactions compared with brain at the $p < 0.001$.

ment. Abdomen examinations had more than double the overall rate of reactions (13 vs 5.9 reactions per 10,000 examinations), a figure significantly higher than the rate of gadolinium-based contrast agent adverse reactions for brain and spine MRI ($p < 0.001$). Gadolinium-based contrast agent reactions with abdominal MRI included 26 outpatients and two inpatients. A trend toward a higher rate of adverse events with breast and extremity MRI examinations was not statistically significant.

Compared with age- and examination-matched control patients, there were significantly more women who experienced adverse events (Table 2). The female-to-male ratio for adverse events was 3.3, compared with 1.1 for control patients ($p < 0.001$). Patients who experienced adverse events also had a higher incidence of prior reactions to gadolinium ($p = 0.007$) and more prior al-

lergic events, with 38 of 94 patients having a history of allergy to something, compared with 16 of 94 patients for the control group ($p < 0.001$). No differences between adverse event and control patients were found in weight, serum creatinine, eosinophil count, ratio of inpatients to outpatients, or mean gadolinium-based contrast agent dose.

All three arrests occurred immediately after gadobenate dimeglumine injection. The case ending in death was a 59-year-old male outpatient with cirrhosis who was on the liver transplant waiting list. He had a remote history of gastrointestinal bleeding and was undergoing liver MRI for tumor surveillance. A hepatologist's note 2 weeks before this MRI described the cirrhosis as "well-compensated." Immediately after power injection of 20 mL gadobenate dimeglumine, the patient was noted to be red, dyspneic, and unable to cooperate with

breath-holding. He then became unresponsive and could not be revived by the code team. The second arrest was a 65-year-old male outpatient with meningioma. Immediately after injection of 18 mL gadobenate dimeglumine, the patient was initially itchy and shaking, and then became unresponsive. The study was aborted, and a code was called. The code team arrest note described wide complex tachycardia (120 beats per minute), hypotension (60/30 mm Hg), and dyspnea (30 breaths per minute). The patient was intubated and responded to intravenous dopamine, normal saline, D50, calcium chloride, and lidocaine. After transferring to the emergency department and later to the coronary care unit, the patient stabilized, was extubated, and was discharged home 2 days later. The third arrest was a 60-year-old male inpatient undergoing pelvic MRI after incomplete resection of a bladder tumor. During injection of gadobenate dimeglumine, the patient squeezed the emergency panic ball and was immediately removed from the scanner, aborting the study. Initially, the patient complained of a metallic taste and then became unresponsive with tachycardia (150 beats per minute), hypotension (70/40 mm Hg), and cyanosis (O_2 saturation = 70%). The code team successfully revived the patient with epinephrine, IV fluids, diphenhydramine, solumedrol, and oxygen. The patient was transferred to the surgical ICU, where he was stabilized, and ultimately underwent bladder resection, with discharge home 3 weeks later.

One severe reaction to gadoteridol was a near arrest in a 9-year-old boy, an outpatient who was having a brain MRI with anesthesiologist-monitored sedation to follow up on white matter changes versus diffuse tumor incidentally discovered on a prior MRI after a fall from the jungle gym. Immediately upon injection of 10 mL gadoteridol, the sedated boy became combative, with urticaria, wheezing, and desaturation (oxygen saturation in the 80s) occurring. MRI was terminated, and the patient was immediately transferred to the pediatric anesthesia care unit across the hallway, where he responded to epinephrine, albuterol, diphenhydramine, and decadron. After stabilizing and recovering from anesthesia, the patient was discharged home.

One patient had transient bradycardia and loss of P waves after bolus injection of gadopentetate dimeglumine and saline flush via a central line directly into the right atrium. This can be a normal physiologic response and has been described in animals [9]. No treatment was required.

TABLE 2: Comparison of Adverse Event Patients with Age- and Examination-Matched Controls

	Adverse Event Patients (n = 94)	Controls (n = 94)	p
Sex (f/m)	72/22 = 3.3	49/45 = 1.1	<0.001 (w/Yates correction)
Weight (lbs)	157 ± 37	163 ± 42	0.6
Creatinine (mg/dL)	0.89 ± 0.31	0.97 ± 0.05	0.4
Mean Gd dose (mL)	17.0 ± 7.8	18.4 ± 9.3	0.24
Asthma	8	2	0.1
Prior Gd exposure	51	48	0.8
Prior Gd reaction	8	0	0.007 (Fisher's exact)
Prior allergic event	38	16	<0.001
Inpatient	6	8	0.8
Steroid pretreatment	4	0	0.1

Notes—Gd = gadolinium, f = female, m = male.

Immediate Gadolinium Contrast Media Reactions

TABLE 3: Rate of Adverse Events by Type of Gadolinium Chelate^a

GBCA	No. of Injections	Mild Adverse Event	Moderate Adverse Event	Severe Adverse Event	All Events ^a	Events per 1,000 Injections ^a	Arrest, Death
Gadoteridol	3371	8	2	1	11	3.3	0
Gadobenate ^b	33,114	31	7	3	41	1.2 ^d	3 ^c
Gadopentetate ^f	66,157	26	6	0	32	0.5	0
Gadodiamide	55,703	8	1	0	9	0.2	0
Total	158,796	73 ^e	16	4	93 ^e	0.6	3

^aExcluding infiltrations; each patient is counted once, regardless of the number of symptoms.

^bAlso known as gadobenate dimeglumine.

^cSignificantly higher than gadodiamide and gadopentetate dimeglumine with $p < 0.05$.

^dSignificantly higher than gadodiamide and gadopentetate dimeglumine with $p < 0.001$.

^eExcluding one gadoxetate adverse event.

^fAlso known as gadopentetate dimeglumine.

In two cases there were notes attributing reactions to gadopentetate dimeglumine that contradicted other notes indicating use of other agents. Examination of hospital purchasing data helped determine that the notes attributing these reactions to gadopentetate dimeglumine were erroneous, because gadopentetate dimeglumine had not been available at the hospital at the time those examinations had taken place. In addition, the notes had been written by internists (not radiologists) who were unlikely to be familiar with the type of gadolinium-based contrast agents used in radiology. These observations suggest that errors by nonradiology personnel involving the type of gadolinium-based contrast agents used are more likely to result in erroneous attribution of reactions to gadopentetate dimeglumine than to other agents and are consistent with other reports in the literature [10].

Comparison of Local Adverse Event Rates

Reaction rates for each gadolinium-based contrast agent are listed in Table 3. Gadoteridol had the highest rate of adverse events reported

by our hospital personnel, 3.3 per 1,000 injections. However, like gadodiamide and gadopentetate dimeglumine, gadoteridol had no arrests or deaths. Gadobenate dimeglumine had the highest rate of arrests involving activation of the code team, ~1 in 10,000 injections, which was significantly higher than the zero rate for gadodiamide and gadopentetate dimeglumine ($p < 0.0001$). Overall, ionic linear gadolinium-based contrast agents had a significantly higher rate of adverse events compared with nonionic linear gadolinium-based contrast agents ($p < 0.0001$).

FDA AERS Database

From 2004 to 2009 there were a total of 40 deaths reported to the FDA attributed to gadolinium-based contrast agents (excluding NSF) and occurring in the United States (Table 4). Overall the death rate from adverse reactions to gadolinium-based contrast agents reported to the FDA was less than 1 in a million (40 deaths/51 million gadolinium-based contrast agent administrations). The limited information about these deaths in the MedWatch database coded in Preferred Terms suggested that

they were mostly, if not all, allergic, anaphylaxis, anaphylactoid, hypersensitivity-type reactions. The patients' age at the time of these gadolinium-based contrast agent deaths ranged from 9 months to 89 years (mean, 60 years). Interestingly, the male:female ratio was 27:10 for the 37 deaths for which sex was reported. After correcting for market share, the rate of death reported for gadobenate dimeglumine was 18 times higher than that reported for gadodiamide ($p < 0.0001$). The death rate from adverse events for ionic linear agents was seven times higher than the rate of death from nonionic linear agents ($p < 0.0001$), which mirrors the well-known experience with iodinated contrast media [11]. The number of injections of gadoteridol, the only macrocyclic agent available in the United States, was too small to make statistically meaningful comparisons, but a trend toward four times as many deaths as those associated with nonionic linear agents was noted.

Discussion

Safety of gadolinium-based contrast agents has been of increased interest since discovery

TABLE 4: Adverse Events in U.S. Reported to Food and Drug Administration from 2004 to 2009 (Excluding Nephrogenic Systemic Fibrosis)

Type of Chelate	GBCA Name	Doses in Millions	Excluding NSF (i.e., anaphylaxis)			
			Events ^a	Events ^a /Million	Deaths	Deaths/Million
Nonionic linear	Gadodiamide	13.5	63	4.7	2	0.15
	Gadoversetamide	5.4	45	8.3	1	0.19
	Gadopentetate dimeglumine	26	1616	62	25	0.97
Ionic linear	Gadoxetate	—	14	—	0	—
	Gadobenate	3.4	1097	322	9	2.7
Macrocyclic	Gadoteridol	2.8	139	49	2	0.70
Unspecified	Unspecified		75		1	
Total	51	3049	60	40	0.9	

^aIncludes events with outcomes coded as death, life-threatening, disability, hospitalized, congenital, intervention required, and other. GBCA = gadolinium-based contrast agent. Dash (—) indicates not available.

of its association with NSF. Although NSF has been virtually eliminated by preventive measures, immediate, allergic-type hypersensitivity reactions remain a real, albeit rare, gadolinium-based contrast agent safety issue. Data from our hospitals showing a rate of serious reactions of about 1 in 40,000 injections are similar to the rate of 1 in 10,000 reported by Murphy et al. [6], who were primarily using a linear ionic gadolinium-based contrast agent [6] and 1 in 20,000 reported by Dillman et al. [12] from the same institution. Dillman et al. also noted a trend toward more reactions in women, as well as greater risk in patients with histories of allergic reaction. Our rate of AEs with gadobenate dimeglumine is similar to a retrospective multicenter analysis of 38,568 doses that resulted in 11 serious reactions [13] and also to a prospective study in which 23,553 doses caused 22 reactions serious enough to require treatment (including eight hospital or ICU admissions) [14]. A review of 79 gadobenate dimeglumine clinical trials, which included comparisons with other gadolinium-based contrast agents but did not show differences in adverse event rates, involved only 3,942 administrations, considerably fewer than the 158,796 patients in this study [15]. The overall rate of gadolinium-based contrast agent deaths reported to the FDA Medwatch database is less than 1 in a million (40 deaths in 51 million administrations), similar to the risk of death from a chest radiograph, drinking one half liter of wine, smoking 1.4 cigarettes (tobaccodocuments.org/lor/03732381-2387.html), or traveling 86 miles by car (www-nrd.nhtsa.dot.gov/Pubs/811291.PDF). Thus, gadolinium-based contrast agents can continue to be considered very safe, with death following gadolinium-based contrast agent administration being extremely rare.

The data from our hospitals and from the FDA suggest the possibility of a lower adverse event rate for nonionic gadolinium-based contrast agents compared with ionic linear or macrocyclic gadolinium-based contrast agents. Although these retrospectively reviewed data based on the vagaries of employee reporting cannot be considered proof, the higher adverse event rates for ionic agents compared with nonionic contrast agents is consistent with the well-established experience of iodinated contrast agents [11], including a prior review of data reported to the FDA [16]. Higher adverse events rates for macrocyclic and ionic gadolinium-based contrast agents were also observed by Mur-

phy et al. [17] in a survey of 105 MRI facilities that encompassed nearly 800,000 gadolinium-based contrast agent administrations. The higher rates may be partly due to the inherently lower osmolality of nonionic agents, which reduces osmo-toxicity, one of the causes of mast cell degranulation [18, 19].

Because the total number of hypersensitivity reaction deaths (~7 per year in the United States for all gadolinium-based contrast agents) far exceeds the number of deaths caused by NSF (near zero now that NSF has been nearly eliminated), allergic reaction risk should be considered in maximizing contrast agent safety. For patients with a GFR lower than 30 mL/min or for patients who are on dialysis, it may make sense to choose a gadolinium-based contrast agent primarily to avoid NSF. Macrocyclic agents, as well as gadofosveset trisodium, gadoxetate disodium, or gadobenate dimeglumine, may be good choices for these patients, because the theoretic benefits of higher stability and higher relaxivity may create diagnostic images with lower doses, as well as partial hepatobiliary excretion. However, if the GFR is higher than 30 mL/min, then the choice of gadolinium-based contrast agents should consider hypersensitivity reaction risks with greater weight than risk of NSF. In the outpatient setting, where NSF is rare [20], and code teams are not conveniently available, allergic reaction risk should be considered with greater weight. Extra care should be taken with patients who have a history of allergic reactions, especially if the allergy is to gadolinium or benzyl alcohol, in which case gadobenate dimeglumine is contraindicated. Patients undergoing abdominal MRI may also be considered at higher risk of immediate adverse reaction to gadolinium-based contrast agents, although our higher rate of reactions in abdominal MRI may have been related to greater use of gadobenate dimeglumine in these patients compared with its use in other types of examinations. Although women had a higher rate of acute adverse events overall, FDA data suggest that men have a higher death rate from acute adverse events.

Most hypersensitivity reactions resolve spontaneously with no permanent effects. The chance of a reaction progressing to death is at least partially related to the skill of the individual monitoring for contrast reactions. Discriminating anaphylaxis from minor vasovagal events, panic attacks, and other transient responses requires constant vigilance of the MRI team. Another important factor may be the use of power injection, which contrib-

uted to the outpatient death at our institution. Hand injection forces the nurse, technologist, or physician to be standing next to the patient during injection, thereby increasing the opportunity for early recognition of the signs of a potentially fatal reaction. Early recognition can facilitate early intervention, which is critical to stop the accelerating cascade of events occurring in anaphylaxis. In our fatal case with power injection of 20 mL gadobenate dimeglumine for liver MRI, neither the technologist nor the nurse was in the scanner room. The patient's evolving contrast reaction was not recognized until after many failed attempts at breath-holding, which had been successful prior to the gadobenate dimeglumine injection.

Some patients are believed to be at higher risk of hypersensitivity reactions due to asthma, multiple allergies, multiple prior exposures to gadolinium-based contrast agents (which may cause sensitization), or a history of reaction to a gadolinium-based contrast agent or iodinated contrast. For any patient with a history of prior reaction to a gadolinium-based contrast agent, every effort should be made to identify the specific gadolinium-based contrast agent so that a different gadolinium-based contrast agent can be used if it is required again. It has even been proposed that skin prick tests in such patients might identify those gadolinium-based contrast agents that are best tolerated [21–24], although note that gadobenate dimeglumine is specifically contraindicated in these patients according to the package insert (www.multi-hanceusa.com/pdf/updated_PIS_december212009/v2MH-PI8%205x11-11-09.pdf). Patients who are hyperallergenic or allergic to iodinated contrast agents may also be at increased risk of hypersensitivity reaction to gadolinium-based contrast agents. Finally, patients with tenuous health who may not survive anaphylactic shock could also be considered for a gadolinium-based contrast agent with a low adverse event rate.

There are several limitations to this study. The FDA AERS database may not consistently capture gadolinium-based contrast agent adverse events, although the reporting of all such events is the policy at our hospitals. However, by focusing on deaths and looking at the AERS database covering the entire U.S. population, any such biases may average out. If deaths were not reported to the FDA, however, the death rate from hypersensitivity reactions would be greater than indicated in these results. Another potential

bias is that new contrast agents, such as gadobenate dimeglumine (FDA-approved in 2004), may have greater reporting of adverse events due to the Weber effect [25]. This bias may be offset by the bias related to the time interval between adverse events and reporting to the FDA, a situation that would tend to cause gadolinium-based contrast agents in use before 2004 to have many more reported events in 2004. Yet another bias for any new agent is that there will be few patients who received the agent more than once, a situation that will reduce the number of reactions requiring sensitization unless there are alternative sensitization pathways. Yet another bias is that gadobenate dimeglumine has been used at lower doses than the other agents.

An additional limitation to our study is that delayed reactions were not included in this analysis. NSF is an example of a delayed reaction. We are not aware of any cases of NSF developing since we changed our protocol to using primarily ionic linear agents (gadopentetate dimeglumine and gadobenate dimeglumine) at no more than 0.1 mmol/kg, or macrocyclic gadolinium-based contrast agents for doses greater than 0.1 mmol/kg. We are aware of at least one case of a delayed hypersensitivity reaction (not included in this study) in an MRI QA testing volunteer subject. The volunteer was initially symptom-free after receiving 20 mL gadobenate dimeglumine but developed hives 1 hour after returning to work. These resolved spontaneously without sequelae, but the event raises the issue of what is actually happening in patients after they leave the MRI facility.

Although gadolinium-based contrast agents are extremely safe, death from hypersensitivity reactions and debilitating fibrosis are possible. These can be minimized by the skill and vigilance of the radiologist and MRI team.

Acknowledgments

Susan Lu is gratefully acknowledged for assistance with access to the MedWatch database. IMS Incorporated is gratefully acknowledged for providing access to market share data. Paul Christos is gratefully acknowledged for assistance with statistical analysis.

References

1. Kanal E, Broome DR, Martin DR, Thomsen HS. Response to the FDA's May 23, 2007, nephrogenic

- systemic fibrosis update. *Radiology* 2008; 246:11–14. [E-pub ahead of print 2007 Sept 12]
2. Tsushima Y, Takahashi-Taketomi A, Endo K. Nephrogenic systemic fibrosis in Japan: advisability of keeping the administered dose as low as possible. *Radiology* 2008; 247:915–916
3. Abujudeh HH, Kosaraju VK, Kaewlai R. Acute adverse reactions to gadopentetate dimeglumine and gadobenate dimeglumine: experience with 32,659 injections. *AJR* 2010; 194:430–434
4. Jordan RM, Mintz RD. Fatal reaction to gadopentetate dimeglumine. *AJR* 1995; 164:743–744
5. Knopp MV, Balzer T, Esser M, Kashanian FK, Paul P, Niendorf HP. Assessment of utilization and pharmacovigilance based on spontaneous adverse event reporting of gadopentetate dimeglumine as a magnetic resonance contrast agent after 45 million administrations and 15 years of clinical use. *Invest Radiol* 2006; 41:491–499
6. Murphy KJ, Brunberg JA, Cohan RH. Adverse reactions to gadolinium contrast media: a review of 36 cases. *AJR* 1996; 167:847–849
7. Runge VM, Bradley WG, Brant-Zawadzki MN, et al. Clinical safety and efficacy of gadoteridol: a study in 411 patients with suspected intracranial and spinal disease. *Radiology* 1991; 181:701–709
8. Cohan RH, Jafri S, Choyke P, et al. *Manual on contrast media: version 7*. Reston, VA: American College of Radiology, 2010
9. Muhler A, Saeed M, Brasch RC, Higgins CB. Amelioration of cardiodepressive effects of gadopentetate dimeglumine with addition of ionic calcium. *Radiology* 1992; 184:159–164
10. Grobner T. Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant* 2006; 21:1104–1108 [Erratum in: *Nephrol Dial Transplant*. 2006; 21:1745] [Comment in: *Nephrol Dial Transplant* 2006; 21:3604; author reply 3604–3605; 2006; 21:3344]
11. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. *Radiology* 1990; 175:621–628
12. Dillman JR, Ellis JH, Cohan RH, Strouse PJ, Jan SC. Frequency and severity of acute allergic-like reactions to gadolinium-containing i.v. contrast media in children and adults. *AJR* 2007; 189:1533–1538
13. Herborn CU, Jager-Booth I, Lodemann KP, Spinazzi A, Goyen M. Multicenter analysis of tolerance and clinical safety of the extracellular MR contrast agent gadobenate dimeglumine (Multi-

- Hance). *Rofo* 2009; 181:652–657
14. Bleicher AG, Kanal E. Assessment of adverse reaction rates to a newly approved MRI contrast agent: review of 23,553 administrations of gadobenate dimeglumine. *AJR* 2008; 191:W307–W311
15. Shellock FG, Parker JR, Venetianer C, Pirovano G, Spinazzi A. Safety of gadobenate dimeglumine (MultiHance): summary of findings from clinical studies and postmarketing surveillance. *Invest Radiol* 2006; 41:500–509
16. Lasser EC, Lyon SG, Berry CC. Reports on contrast media reactions: analysis of data from reports to the U.S. Food and Drug Administration. *Radiology* 1997; 203:605–610
17. Murphy KP, Szopinski KT, Cohan RH, Mermilod B, Ellis JH. Occurrence of adverse reactions to gadolinium-based contrast material and management of patients at increased risk: a survey of the American Society of Neuroradiology Fellowship Directors. *Acad Radiol* 1999; 6:656–664
18. Baxter AB, Lazarus SC, Brasch RC. In vitro histamine release induced by magnetic resonance imaging and iodinated contrast media. *Invest Radiol* 1993; 28:308–312
19. Moloney ED, Griffin S, Burke CM, Poulter LW, O'Sullivan S. Release of inflammatory mediators from eosinophils following a hyperosmolar stimulus. *Respir Med* 2003; 97:928–932
20. Sadowski EA, Bennett LK, Chan MR, et al. Nephrogenic systemic fibrosis: risk factors and incidence estimation. *Radiology* 2007; 243:148–157
21. Beaudouin E, Kanny G, Blanloeil Y, Guilloux L, Renaudin JM, Moneret-Vautrin DA. Anaphylactic shock induced by gadoterate meglumine (DOTAREM). *Eur Ann Allergy Clin Immunol* 2003; 35: 382–385
22. Hasdenteufel F, Luyasu S, Renaudin JM, et al. Anaphylactic shock after first exposure to gadoterate meglumine: two case reports documented by positive allergy assessment. *J Allergy Clin Immunol* 2008; 121:527–528
23. Kalogeromitros DC, Makris MP, Aggelides XS, et al. Anaphylaxis to gadobenate dimeglumine (MultiHance): a case report. *Int Arch Allergy Immunol* 2007; 144:150–154
24. Laroche D. Immediate reactions to contrast media: mediator release and value of diagnostic testing. *Toxicology* 2005; 209:193–194
25. Weber JCP. Epidemiology of adverse reactions to nonsteroidal anti-inflammatory drugs. In: Rainsford KD, Velo GD, eds. *Side-effects of anti-inflammatory drugs, advances in inflammation research*. New York: Raven Press, 1984