Incidence of Immediate Gadolinium Contrast Media Reactions

M. R. Prince[1,2], H. Zhang[1], Z. Zou[1], R. B. Staron[2], and P. W. Brill[1]
[1]Radiology, Weill Cornell Medical College, New York, NY, United States, [2]Radiology, Columbia College of Physicians and Surgeons, New York, NY, United States

Objectives: Safety of gadolinium based contrast agents (GBCA) has been of increased interest since discovery of its association with nephrogenic systemic fibrosis (NSF). Although NSF has been virtually eliminated by preventive measures, immediate, allergic type hypersensitivity reactions remain a real, albeit rare GBCA safety issue. The purpose of this study was to systematically explore rates of adverse events for the GBCA used at our hospitals over the past 10 years and to assess how our local experience compares to reports made to the US FDA.

Methods: *Local Adverse Events:* Data on all GBCA adverse events reported by hospital employees were collected and graded as mild, moderate or severe according to the ACR criteria. Data on the total number of injections with each contrast agent was obtained to calculate the incidence. A case control study was performed by identifying a control patient of the same age undergoing the identical exam on or close to the date of each event. The significance of differences in gender, weight, inpatient/outpatient status, clinical history and lab data was evaluated with Students t-test and chi-squared test. The distribution of exam types among the adverse event patients was compared to the distribution of exams actually performed based upon review of scanner logs and billing records.
Analysis of FDA Data: All adverse events reported to the FDA are entered into an Adverse Event Reporting System (AERS). Reports corresponding to adverse reactions to GBCA were identified with the search terms: *Gad*, *Gd*, Magnevist, Omniscan, Prohance, Multihance, eovist, optimark, MRI, DTPA, GE, Bayer, Berlex, Bracco and Mallinckrodt. Events where GBCA was the Primary Suspect for the adverse event were coded as ROLE_COD = PS. Outcomes coded as death were searched by running queries over the entire 6 years of FDA data (2004-2009). NSF cases and non-US events were excluded.
Market Share Data: Data on the market share of each agent were available from Intercontinental Marketing Services (IMS) in the form of liters of GBCA sold each year and were converted into doses administered by dividing the total volume sold by 17 mL. Then the companies were contacted 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 GBCA 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. Hospital quality assurance records detailed 140 events related to GBCA including 46 infiltrations (3 per 10,000 injections) and 94 GBCA acute adverse reactions (5.9 per 10,000 injections). Rate of adverse events for each type of GBCA is listed in Table 1. Severe reactions occurred in 1/40,000 injections. Gadoteridol had the highest rate of adverse events, 3.3/1000 injections, but no arrests/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 GBCA had a significantly higher rate of AE compared to nonionic linear GBCA ($p < 0.0001$).

Table 1. Rate of GBCA adverse events by type* of gadolinium chelate.

GBCA	# of injections	Mild AE	Moderate AE	Severe AE	All events*	Events*/1,000injections	Arrest/Death
Gadoteridol	3371	8	2	1	11	3.3	0
Gadobenate**	33,114	31	7	3	41	1.2****	3***
Gadopentetate♣	66,157	26	6	0	32	0.5	0
Gadodiamide	55,703	8	1	0	9	0.2	0
total	158,796	73*****	16	4	93*****	0.6	3

* Excluding infiltrations and each patient is counted once regardless of the number of symptoms' ** also known as gadobenate dimeglumine
*** significantly higher than gadodiamide and gadopentetate dimeglumine with $p < 0.05$; **** significantly higher than gadodiamide and gadopentetate dimeglumine with $p < 0.001$; ***** Excluding 1 gadoxetate adverse event; ♣ also known as gadopentetate dimeglumine or Gd:DTPA

Abdomen examinations had more than double the overall rate of reactions (13 vs 5.9 reactions per 10,000 exams) and was statistically significantly higher than the rate of GBCA AE for brain and spine MRI ($p < 0.001$). Compared to age/exam matched control patients, there were significantly more female patients with AE (F: M = 3.3) compared to 1.1 for control patients ($p < 0.001$). Adverse event patients also had a higher incidence of prior reactions to GBCA ($p = 0.007$) and more prior allergic events with 38/94 having a history of allergy compared to 16/94 for the controls ($p < 0.001$). All 3 arrests (patient becoming unresponsive and the code team called) occurred immediately following gadobenate dimeglumine injection.
FDA AERS Database: From 2004 to 2009 there were a total of 40 deaths in the US reported to the FDA attributed to GBCA (excluding NSF). The death rate from adverse reactions to GBCA reported to the FDA was less than 1 in a million (40 deaths/51 million GBCA administrations). The patient age at the time of these GBCA deaths ranged from 9 months to 89 years (mean = 60 years) and interestingly the male:female ratio was 27:10 for the 37 deaths where gender was reported. After correcting for market share, there was an 18 times higher rate of death reported for gadobenate dimeglumine compared to gadodiamide ($p < 0.0001$). There was a 7-fold higher rate of death from adverse events for ionic linear agents compared to non-ionic linear agents ($p < 0.0001$) which mirrors the well-known experience with iodinated contrast.

Discussion: Data from our hospitals showed a rate of serious reactions of about 1/40,000 injections, similar to the rates reported by Murphy et al and Dillman et al. Dillman also noted a trend toward more reactions in female patients as well as greater risk in patients with an allergic reaction history. The overall rate of GBCA death reported to the FDA Medwatch database was less than 1 in a million (40 deaths in 51 million administrations), similar to the risk of death from traveling 86 miles by car. These data from our hospitals and from the FDA suggest the possibility of a lower adverse event rate for nonionic GBCA compared to ionic linear or macrocyclic GBCA. This may be partly due to the inherently lower osmolarity of nonionic agents which reduces osmo-toxicity, one of the causes of mast cell degranulation. Since the total number of hypersensitivity reaction deaths (~ 7 per year in US for all GBCA) 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. Although GBCA is 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.