Risk factors for immediate adverse events to Gadolinium-based Contrast Agents (GBCA)

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Target audience: Health care professionals utilizing Gadolinium-based contrast agents to enhance MR exams.

Purpose: To enhance gadolinium safety by identifying risk factors for immediate adverse reactions to Gadolinium based contrast agents (GBCA).

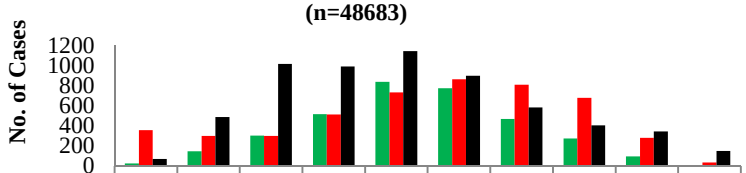
Methods: The U.S. Food and Drug Administration Adverse Event reporting system (FAERS) database was reviewed from 2004 to March 2012 using relational database software. All adverse events in which a Magnetic Resonance Imaging (MRI) contrast agent was the primary suspect drug were identified. Then, they were divided into 2 groups: GBCA and non-GBCA. Reporter country was reviewed to include only those cases occurring in the United States (U.S.). Nephrogenic Systemic Fibrosis (NSF) cases were excluded. The remaining adverse events coded as occurring in the U.S. were analyzed according to age, gender, weight, outcomes and Food and Drug Administration (FDA) report date.

Results: From January 2004 through March 2012, 7777 events were reported to the FDA coded with an MR contrast agent as the primary cause including 9 ferumoxide cases and 7768 cases due to GBCA, 6501 reported as occurring in the US. After excluding 1664 cases of Nephrogenic Systemic Fibrosis (NSF), 4837 U.S. adverse events were available for analysis. Data on age was available in 3444 cases, showing a mean age = 48 years (range: < 1 year to 90 years). The peak age incidence was between 20-60 years **(Figure 1)**. Compared to the age distribution of Gadolinium-enhanced MR exams at our Hospitals, there was a 3-fold increase in adverse reaction rate in the 5th decade compared to the 9th decade ($p<0.0001$) and a 25-fold increase compared to the 1st decade ($p<0.0001$). Data on gender was available in 4126 cases, with a male:female ratio of 0.51 (male=1396, female=2730); however, gender distribution varied according to outcome **(Table 1)**. Interestingly, males had nearly twice the death rate of females even though they had fewer reported reactions ($p<0.0001$). Data on weight was available in 1955 cases, ranging from less than 1 kg to 229 kg. Most patients were in the 60-89 kg range (n=1128). There were 4648 cases with FDA report date **(Figure 2)**.

The 20 most common reactions were urticaria (n=1020), nausea (n=981), vomiting (n=855), pruritus (n=633), respiratory problems (n=628), pain (n=544), oedema/swelling (n=506), throat symptoms (n=448), hypersensitivity (n=386), nasal symptoms (n=345), flushing (n=335), anaphylaxis (n=316), erythema (n=314), rash (n=290), abnormal feeling (n=207), altered mental status (n=205), dizziness (n=190), asthenia (n=147), abnormal sensation (n=138), and gastrointestinal symptoms (n=127). Based on the American College of Radiology (ACR) criteria [1], reactions were divided into 2 groups: *Allergic-like reactions* such as urticaria (21%), pruritus (13%), followed by oedema/swelling (10%), throat symptoms (9%), hypersensitivity (8%) and nasal symptoms (7%), and *Not-allergic-like reactions* such as nausea and retching (20%), vomiting (17%), and flushing (7%). A total of 209 cases had reported injection-site-related reactions, accounting for less than 5% of all cases with different types of reactions coded as pain, extravasation, swelling, erythema, irritation and/or pruritus.

Figure 1.

Comparison between age distribution of U.S. FDA cases (n=3455) and Gadolinium-enhanced exams performed at our Hospitals (n=48683)



Age (years)	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
U.S. FDA	25	146	303	517	836	773	469	274	96	5
Our hospitals/10	355.9	299.8	298.5	512.5	732.2	862.5	807.3	678.3	278.9	33.4
Ratio	70	487	1015	991	1142	896	581	404	344	150

Figure 2.

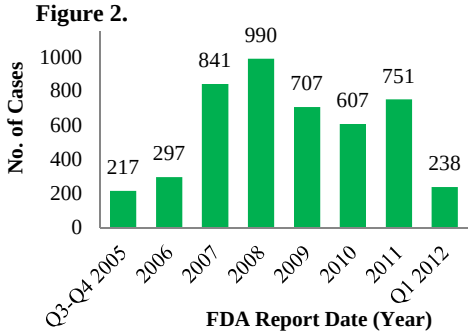


Table 1.

Outcome	Cases	M:F ratio
Death	65	1.9
Required intervention to prevent permanent damage/impairment	72	1.4
Disability	58	1
Life-threatening event	224	0.7
Hospitalization	545	0.6
Other	1122	0.5

Discussion/Conclusion: Analysis of immediate adverse GBCA reactions reported to the FDA shows that Gadolinium is extraordinarily safe. Peak age incidence was between 20-60 years. Babies and elderly had a substantially reduced adverse event rate possibly reflecting a less active immune system or reporting bias. There was an overall female predominance for immediate reactions, but more males had lethal reactions. Of all immediate adverse reactions, urticaria was the most common symptom, similarly to the results of a previous study [2].

References:

[1] American College of Radiology *Manual on contrast media: version 8.* Reston, VA: American College of Radiology, 2012.
[2] Jung JW, Kang HR, Kim M et al. Immediate Hypersensitivity Reaction to Gadolinium-based MR Contrast Media. *Radiology* 2012; 264:2 414-422.
[3] Prince MR, Zhang H, Zou Z et al. Incidence of immediate gadolinium contrast media reactions. *AJR Am J Roentgenol* 2011;196(2):W138–W143.