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Adverse allergic reactions to linear ionic gadolinium-based contrast agents: experience with 194, 400 injections

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AIM: To report the authors' experience with the administration of four gadolinium-based contrast agents (GBCA; gadopentetate dimeglumine, gadofosveset trisodium, gadoxetate disodium and gadobenate dimeglumine) in a large study population at a single, large academic medical centre.

MATERIALS AND METHODS: The institutional review board approved this retrospective study in which data in the electronic incident reporting system were searched. A total of 194, 400 intravenous administrations of linear ionic GBCAs were assessed for the incidence of adverse reactions and risk factors from 1 January 2007 to 14 January 2014. The severity of reactions (mild, moderate, and severe), patient type (outpatients, inpatients, and emergency), examination type, and treatment options were also investigated.

RESULTS: In total, 204/194400 (0.1%) patients (mean age 45.7 ± 14.9) showed adverse reactions, consisting of 6/746 (0.80%), 10/3200 (0.31%), 14/6236 (0.22%) and 174/184218 (0.09%), for gadofosveset trisodium, gadoxetate disodium, gadobenate dimeglumine, and gadopentetate dimeglumine, respectively. An overall significant difference was found between different GBCAs regarding the total number of reactions ($p < 0.0001$). When comparing the GBCAs together, significant differences were found between gadofosveset trisodium versus gadopentetate dimeglumine ($p < 0.0001$), gadofosveset trisodium versus gadobenate dimeglumine ($p = 0.0051$), gadoxetate disodium versus gadopentetate dimeglumine ($p < 0.0001$) and gadopentetate dimeglumine versus gadobenate dimeglumine ($p = 0.0013$). Rate of reaction was higher in females (F: 146/113187, 0.13%/M: 58/81213, 0.07%; $p < 0.0001$). Rate of reactions was higher in outpatient (180/158885, 0.11%), emergency (10/10413, 0.10%), and inpatients (14/25102, 0.05%), respectively ($p < 0.0001$). Most of the patients had mild symptoms 171/204 (83.8%). Abdomen–pelvis, liver, and thoracic examinations had highest rates of reactions (0.17 versus 0.16 versus 0.15).

CONCLUSION: The overall rate of adverse reaction to GBCAs was 0.1%. The rates of reactions were highest in gadofosveset trisodium with (0.80%), followed by gadoxetate disodium (0.31%), gadobenate dimeglumine (0.22%) and gadopentetate dimeglumine (0.09%).

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Introduction

Several different MRI gadolinium-based contrast agents (GBCAs) are on the market and, whenever there are options, concerns come up as to the most appropriate utilization of the various products. The four primary concerns regarding GBCAs usage are: (1) whether the use of the GBCA is indicated; (2) whether the specific GBCA matches the indication; (c) whether a specific GBCA is cost-effective and adds value; and (d) whether the benefits outweigh the risks.[1–6]

The risks due to GBCA injections include the risk of extravasation,[7] allergic-type adverse reactions,[1–6] nephrotoxicity, and nephrogenic systemic fibrosis (NSF).[8–11] Some of the GBCAs have been available for decades, whereas others have become available only recently; consequently, the risk of adverse reactions associated with the newer gadolinium products is less well understood than that from the older products. In addition, the newer products are recommended for specific indications; thus the frequency of usage is significantly less.[3,12,13]

Several difficulties can be encountered when examining the published literature regarding the adverse rate of GBCAs. Understandably, the older products have extensive data published with large sample sizes, compared with small sample sizes for the newer products. Different institutions reporting on the same product may use different methods and definitions to acquire the data, which would result in variations in their results. Some reports only include data on one or two products. This lack of uniformity in these studies may contribute to the wide range of reported reactions rates (0.07% to 2.4%) in the literature.[1,3–6,14–18]

The aim of this paper is to present data on the frequency of adverse reaction rates in a single, large academic medical centre in a period in which there were 194,400 intravenous administrations of GBCA using four different products: gadopentetate dimeglumine, gadofosveset trisodium, gadoxetate disodium, and gadobenate dimeglumine. Uniform methods of data acquisition and reporting were used throughout the time period of the investigation to investigate the incidence of adverse reactions to each product, the severity of adverse reactions, and to determine potential risk factors.

Materials and methods

The institutional review board for human subject research approved the study and waived informed consent requirements. The study was compliant with the Health Insurance Portability and Accountability Act (HIPAA). There is no pertinent financial disclosure related to this study. This investigation was based on data extracted from the safety reporting system for adverse reactions to GBCA from 1 January 2007 through 14 January 2014.

Gadolinium-based contrast agents

The following GBCAs were used: gadopentetate dimeglumine (Magnevist; Bayer Healthcare, Wayne, NJ, USA), gadofosveset trisodium (Ablavar; Lantheus Medical Imaging, Billerica, MA, USA), gadoxetate disodium (Gd-EOB-DTPA, gadoxetic acid, Eovist, Bayer Healthcare), and gadobenate dimeglumine (Gd-BOPTA, Multihance; Bracco Diagnostics, Princeton, NJ, USA).[19]

Data collection and study population

Data on adverse reactions among patients undergoing MRI examinations at Massachusetts General Hospital were collected as part of routine quality-assurance protocols in the institutional safety reporting system. Variables for contrast medium reaction documentation included in this online safety reporting system were age, gender, patient type (outpatient, inpatient, emergency department), GBCA type, dose, history of previous reaction to GBCA or other types of allergy, premedication with steroids or diphenhydramine (a first-generation antihistamine) in patients with history of adverse reactions, severity of the reaction, symptoms of adverse reaction, interval between injection to the onset of reaction, patient outcome, treatment provided, type of radiology examination, and time of the examination.

Based on departmental guidelines, all patients who undergo gadolinium-enhanced MRI examinations are prospectively evaluated and assessed for symptoms before and immediately after GBCA administration and before discharge from the department by nurses or radiological technologists. Patients with any adverse symptoms are reported to an on-site radiologist, who evaluates and manages the patient's reactions. It is routine practice at Massachusetts General Hospital to record adverse reactions to contrast medium. A standardized departmental contrast medium reaction form is completed in the online safety reporting system and the details of the event are recorded. Institutional review board and HIPAA guidelines were followed for handling all confidential patient information.

Examinations were categorized into six categories: magnetic resonance angiography (MRA); liver; head, neck and spine (HNS); thoracic and cardiac; abdomen and pelvis (ABP); and extremities. This categorization was made based on the methods used in prior published studies[4] and the specific indications for using different GBCAs at Massachusetts General Hospital. At Massachusetts General Hospital, gadoxetate disodium was mostly used for indications of liver disease. Gadofosveset trisodium was mostly used for MRA, and gadobenate dimeglumine and gadopentetate dimeglumine were used for all indications. The rate of adverse events is reported as the number of events per 100 total number of contrast medium administrations for each contrast agent. Reporting the rates of reactions per total number of injections eliminates the chances of bias in reporting the incidence of reactions for various GBCAs with different sample sizes. The standard dose for GBCA is 0.1 mmol/kg. Double or triple doses (0.2–0.3 mmol/kg) were used for MRA. All doses are administered as a bolus, either by hand or by power injection.

Severity of the reactions and time of occurrence

The severity of the adverse reactions was classified into three categories according to the American College of