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Objective evaluation of acute adverse events and image quality of gadolinium-based contrast agents (gadobutrol and gadobenate dimeglumine) by blinded evaluation. Pilot study

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Abstract

Purpose: The purpose was to objectively evaluate a recently FDA-approved gadolinium-based contrast agent (GBCA) in comparison to our standard GBCA for acute adverse events and image quality by blinded evaluation.
Methods: Evaluation was made of a recently FDA-approved GBCA, gadobutrol (Gadavist; Bayer), in comparison to our standard GBCA, gadobenate dimeglumine (MultiHance; Bracco), in an IRB- and HIPAA-compliant study. Both the imaging technologist and patient were not aware of the brand of the GBCA used. A total of 59 magnetic resonance studies were evaluated (59 patients, 31 men, 28 women, age range of 5–85 years, mean age of 52 years). Twenty-nine studies were performed with gadobutrol (22 abdominal and 7 brain studies), and 30 studies were performed with gadobenate dimeglumine (22 abdominal and 8 brain studies). Assessment was made of acute adverse events focusing on objective observations of vomiting, hives, and moderate and severe reactions. Adequacy of enhancement was rated as poor, fair and good by one of two experienced radiologists who were blinded to the type of agent evaluated.
Results: No patient experienced acute adverse events with either agent. The target minor adverse events of vomiting or hives, and moderate and severe reactions were not observed in any patient. Adequacy of enhancement was rated as good for both agents in all patients.
Conclusions: Objective, blinded evaluation is feasible and readily performable for the evaluation of GBCAs. This proof-of-concept study showed that both GBCAs evaluated exhibited consistent good image quality and no noteworthy adverse events.

Keywords: Gadobutrol; Gadobenate dimeglumine; Gadolinium; Adverse reactions; Magnetic resonance imaging; Image quality; GBCA

1. Introduction

Intravenously administered gadolinium-based contrast agents (GBCAs) are an important component of many magnetic resonance (MR) examinations [1–4]. A variety of GBCAs are available in the United States, with more agents also in the process of FDA evaluation [5]. Critical to the decision whether to employ a new contrast agent in an imaging department is how it compares to the currently employed contrast agent [6,7]. The traditional method of evaluating contrast agents is to perform a trial of using the new agent in a predefined number of patients, often based on the number of samples that the local sales representative provides. The technologist, radiologist and often the patient as well are aware that a new agent is being used. This traditional method for evaluating whether an agent should be introduced into an imaging center formulary is fraught with many biases [8,9]. One of the most recognized biases with contrast agent evaluation is termed the Weber effect [10,11], which describes overreporting of adverse events associated with the entry of a new drug to the market. With this effect, the heightened awareness that something new is being evaluated renders technologists and patients more aware of potential adverse events, overreporting them. This effect is well recognized with radiology contrast agents and also has been described as diminishing with time as the technologists begin to become more acclimated to the new agent and more at ease with its use.

To avoid this intense scrutiny centered just on the newly evaluated agent, it is most appropriate to compare the new agent directly with the existing agent in a fashion such that

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the imaging technologist and the patient are unaware of whether anything different from the routine is being employed. It is also critical to create an environment for the patients which is not anxiety provoking by providing calming forewarning messages about the intravenous contrast agent that is about to be administered [12–14]. The most appropriate method to assess a new contrast agent is through scientific methodology in which it is evaluated in a blinded fashion by the individuals involved. This approach has been described in a few reports for iodine-based contrast agents (IBCAs) [15]. To our knowledge, no prior report has described objective blinded evaluation of GBCAs for acute adverse events as a primary end point and image quality. Therefore, the purpose of our pilot study is to evaluate the feasibility and results of a small-scale controlled blinded study comparing a recently FDA-approved GBCA (gadobutrol, Gadavist) to our currently employed agent (gadobenate dimeglumine, MultiHance).

2. Materials and methods

This study represented a quality and safety project conducted by our department, which was IRB-compliant and HIPAA-compliant with signature waiver. The study was also approved by the hospital legal department. The vice chair of Quality and Safety for the Department of Radiology charged the chief technologist of MR to provide intravenous GBCAs to the imaging technologist, without informing the latter individual on which agent was being administered. The GBCAs evaluated were a newly FDA-approved macrocyclic agent, gadobutrol (Gadavist; Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ, USA), and the center's standard GBCA agent, gadobenate dimeglumine (MultiHance; Bracco Diagnostics Inc., Princeton, NJ, USA). The vice chair instructed that the agents should be administered randomly to patients who had clinical MR studies ordered of the brain or the abdomen, which represented two of the most frequently requested contrast-enhanced study indications at our center. The chief technologist was also instructed that the imaging technologist should use the same non-stress-provoking contrast agent forewarning to all patients: "shortly you will feel the contrast agent running up your arm, and it may give you a warm sensation throughout your body that won't last long." Once the patient study was finished and the patient was removed from the bore of the magnet, attention was paid to adverse events. The mild adverse events targeted for evaluation were vomiting and hives. Moderate and severe contrast agent adverse events, using the American College of Radiology criteria [16], were also to be recorded. Once this step was complete, the chief technologist inserted the contrast agent brand name in the patient MR study on the imaging console so that it would be correctly registered in our center database.

Thirty vials of gadobutrol (Gadavist, Bayer) were provided by the sales representative of the agent. Following the instructions mentioned above, a total of 60 gadolinium-enhanced MR scans were performed between 04/25/11 and 06/09/11 in 60 patients. In one MR exam with gadobutrol, the patient experienced claustrophobia and could not complete the study, and so this exam was not evaluated. Fifty-nine MR exams were evaluated (59 patients, 31 men, 28 women, age range of 5–85 years, mean age of 52 years). The gadobutrol group was comprised of 29 MR exams (14 men, 15 women, mean age of 53 years, 22 abdominal studies and 7 brain studies). The gadobenate dimeglumine group was comprised of 30 MR exams (17 men, 13 women, mean age of 51, 22 abdominal studies and 8 brain studies). Eight abdominal MR exams (four with gadobutrol and four with gadobenate dimeglumine) were performed with a 3.0-T MR system (Avanto, Siemens Medical Systems, Malvern, PA, USA). All the other exams were performed with a 1.5-T MR system (Avanto, Siemens Medical Systems, Malvern, PA, USA). Both GBCAs were administered intravenously in a power-injected (Medrad, Pittsburgh, PA, USA) bolus at 2 ml/s in all patients followed by a bolus of 20 ml of saline flush. The GBCA was loaded by the chief technologist into the power injector to ensure blinded administration. Gadobutrol was administered at a dose of 0.1 mmol/kg, which is the full dose recommended by the manufacturer. A half-dose of gadobenate dimeglumine was used (0.05 mmol/kg). This dosage is routinely used at our institution, which we based on consistent reports demonstrating that a half-dose of gadobenate dimeglumine generates a similar diagnostic MR examination compared to a full dose (0.1 mmol/kg) [17–19]. This lower dose has been instituted in 2007 as part of an overall strategy to reduce the risk of nephrogenic systemic fibrosis (NSF).

The set of images evaluated in the brain MR exams included axial precontrast and axial, sagittal and coronal postcontrast T1-weighted sequences using three-dimensional gradient-echo technique (3D-GE) with fat saturation. The set of images evaluated in the abdominal MR exams included axial precontrast and postcontrast T1-weighted breath-hold sequences using 3D-GE and fat saturation. Three passes following the GBCA injection were obtained in all abdominal MR studies (hepatic arterial dominant phase, portal venous phase and interstitial phase) [20].

Images were independently and retrospectively evaluated by an experienced neuroradiologist (MC, 15 brain studies, 7 with gadobutrol) and an abdominal radiologist (RCS, 44 abdominal studies, 22 with gadobutrol), each of whom had greater than 20 years of experience with GBCA-enhanced MR study interpretation. A radiologist (not taking part in the image analysis) uploaded randomly the cases on a Picture Archiving Computer System terminal (that is, gadobutrol MR exams were randomly mixed with gadobenate dimeglumine ones) and deleted all the information on the screen. The reviewers did not know the order in which the cases were uploaded and were blinded to the information of which contrast was administered. The blinded readers were instructed to analyze each postcontrast phase in order to subjectively rate the adequacy of overall enhancement as