

Anaphylaxis to Gadobenate Dimeglumine (Multihance®): A Case Report

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Key Words

Gadobenate dimeglumine • Skin testing • Anaphylaxis • Adverse reaction • Multihance®

Abstract

Background: Gadolinium chelates are relatively safe contrast media used in MRI. Immediate severe adverse effects are exceptionally rare and mostly concern mild anaphylactoid reactions. We report a case of anaphylaxis to gadobenate dimeglumine (Gd-BOPTA, Multihance®), a gadolinium-based contrast agent. **Methods:** A 32-year-old female patient with a personal history of multiple sclerosis, while undergoing an MRI scan, developed bronchospasm and acute urticaria with diffuse giant pruritic plaques in the first minute of Gd-BOPTA infusion. The procedure was cancelled and acute treatment of the reaction took place. The patient reported 2 additional MRI scans with definite use of unknown contrast media in the past 2 years without any adverse effect. Blood samples were obtained 2 and 48 h after the reaction for measurement of serum tryptase concentration (Pharmacia Diagnostics, Uppsala, Sweden). Skin prick tests and intradermal tests were performed using 1:1,000, 1:100 and 1:10 dilution of the offending agent and alternative gadolinium-based agents [gadodiamide (Omniscan®) and gadoteric acid (Dotarem®)]. A group of 10 nonatopic individuals who under-

went the same skin testing comprised the control group. **Results:** Tryptase concentration was highly elevated 2 h after the reaction (21 µg/l) compared with that at 48 h (3 µg/l). Skin prick tests in our patient were all negative, while intradermal testing with 0.03 ml of 1:100 and 1:10 preparations of Multihance showed a definite positive wheal-and-flare reaction. Skin tests to the alternative agents showed no response. In the control group, all performed tests were negative. **Conclusion:** We report the first case of an allergic reaction to gadobenate dimeglumine. Besides, skin testing seems to be a precious diagnostic tool which, if positive, strongly suggests a mast cell-mediated underlying mechanism.

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Introduction

Contrast media (CM) represent an essential aid to modern efforts for better internal bodily structures imaging and medical diagnosis. Their prior abilities and safety are reflected on their extended use and variety. Adverse effects related to CM are divided into hypersensitivity and toxic reactions [1]. Immediate hypersensitivity reactions are unusual but when happening are potentially life-threatening and may request urgent management. Iodinated CM are responsible for the vast majority of

such reactions, with a frequency of 0.1–0.4% for ionic and 0.02–0.04% for nonionic agents [1–4].

The importance of magnetic resonance (MR) imaging as a diagnostic imaging modality is reflected in the increasing number of procedures performed annually, as well as the increasing number and variety of MR contrast agents available. Most contrast-enhanced MR procedures worldwide are performed with MR contrast agents based on chelates of the paramagnetic ion gadolinium [5]. Most gadolinium-based agents are similar with regard to their physical properties, mode of action and general safety profiles [6]. However, Multihance® (gadobenate dimeglumine, Gd-BOPTA; Bracco Diagnostics Inc., Princeton, N.J., USA) differs from the others in possessing markedly higher r1 and r2 relaxivity values, thus enhancing the contrast effect in vivo. Besides, as Multihance undergoes limited uptake by normally functioning hepatocytes and biliary excretion, it offers increased delayed liver-lesion contrast [7].

The safety of Multihance has been assessed in more than 3,000 subjects enrolled in clinical trials and in more than 1.5 million patients in postmarketing surveillance [8]. Incidence of reported Multihance-induced immediate hypersensitivity reaction is extremely low [9].

We present a case of a well-documented acute allergic reaction to gadobenate dimeglumine.

Patient

A 32-year-old female patient with a personal history of multiple sclerosis, while undergoing an MRI scan of the central nervous system, suffered acute urticaria with diffuse giant pruritic plaques and shortness of breath in the first minute of CM infusion (Multihance, infusion rate 10 ml/min). The procedure was cancelled and the patient was transferred immediately to the emergency room where clinical examination revealed the following: blood pressure 100/65 mm Hg, heart rate 110 bpm, and expiratory wheezing without abnormal signs or symptoms of the gastrointestinal system. Accordingly, she was treated with intravenous steroids, H1 antihistamines and inhaled salbutamol, and during the first hour symptoms started diminishing until full recovery almost 4 h later.

The patient had undergone 2 additional MRI scans with definite use of unknown CM, the former 2 years and the latter 1 year before, without any adverse effect. Besides, she had received iodinated CM twice, 4 and 6 years before, without any adverse effect. Past medical history was negative for atopic disease and bronchial asthma; in addition, she had never experienced any episode of acute urticaria or any drug hypersensitivity reaction before. The patient had a 20 packs/year tobacco usage, but had quit smoking 3 years earlier. She denied use of alcohol or illicit drugs and she did not take any medication for the multiple sclerosis during the 6-month period preceding the reaction.

Materials and Methods

Blood samples were obtained 2 and 48 h after the reaction for measurement of serum tryptase concentration (Unicap; Pharmacia Diagnostics, Uppsala, Sweden).

In vivo diagnostic evaluation of possible reactions to the offending agent and to alternative gadolinium-based agents took place in our facilities 1 month after the incident. We conducted skin prick tests (SPTs) and intradermal (ID) tests to gadobenate dimeglumine (Gd-BOPTA), gadodiamide (Gd-DTPA-BMA) and gadoteric acid (Gd-DOTA), using their commercial compounds Multihance 529 mg/ml, Omniscan® 287 mg/ml (Nycomed Amersham, Princeton, N.J., USA) and Dotarem® 27.93% (Guerbet Laboratories, Paris, France). All cutaneous tests were performed on the volar aspect of the forearms, using the agents at concentrations ranging from 1:1,000 to 1:10 (using 1:1,000, 1:100 and 1:10 dilutions of the agents in 0.9% saline). An interval of 20 min was held between the applications of different increasing concentrations. Histamine phosphate 2.7 mg/dl (Stallergenes, Antony, France) and normal saline served as positive and negative controls, respectively. SPTs to 10⁻¹ concentration (dilutions in 0.9% normal saline) of the 3 agents and the commercial regimens were first performed. If negative, ID testing with 0.04 ml injections of 1:1,000, 1:100 and 1:10 dilutions took place [10]. Reading of tests was taken after 20 min for immediate reaction and after 24 and 72 h for evaluation of nonimmediate (late) reactions. A wheal diameter >3 mm served as criterion of positivity in SPTs, and in ID testing positivity was reached when the size of the initial wheal increased by ≥3 mm in diameter and was associated with a flare [11].

Presence or absence of atopy was estimated by at least 1 positive SPT to 7 common inhalant allergens (*Olea europaea*, Grasses, *Parietaria* sp, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Cladosporium herbarum*, *Alternaria alternata*; all from Stallergenes). SPTs to inhalant allergens were performed 10 days apart from CM testing.

In order to exclude irritant reactions, 10 adult subjects without record of MR procedure before underwent the same skin testing evaluation and served as control group.

Results

Tryptase concentration was highly elevated 2 h after the reaction (21 µg/l) compared with that at 48 h (3 µg/l).

SPTs with the gadolinium-based CM were all negative, with positive controls developing a mean wheal diameter of 7 mm. ID testing in Multihance showed negative response to the 1:1,000 dilution, but developed positive reactions to the 1:100 and 1:10 dilutions with mean wheal diameters of 9 and 13 mm plus pseudopodium, respectively; all the other tests were negative. Additional readings 24 and 72 h later showed no positive response in any of the performed tests. Besides, SPTs to inhalant allergens in our patient were negative, too.

Table 1. Evaluation of ID testing to gadolinium-based CM – 20-min reading

Contrast media	Dilutions		
	1:1,000	1:100	1:10
Multihance (gadobenate dimeglumine)	negative	positive, 9-mm wheal	positive, 13-mm wheal + pseudopodia
Omniscan (gadodiamide)	negative	negative	negative
Dotarem (gadoteric acid)	negative	negative	negative



Fig. 1. Reaction in ID test to 1:100 preparation of gadobenate dimeglumine (Multihance) – 20-min reading.

Figure 1 presents the observed reaction in 10^{-2} Multihance concentration. The 20-min evaluation of ID testing is summarized in table 1.

In the control group, 2 individuals presented skin reactivity in inhalant allergens. Concerning CM testing, no positive SPT or ID reaction was detected; all performed tests were negative.

Discussion

In recent years, a number of excellent review articles have summarized the safety profiles of the currently available MR contrast agents. Multihance, except presenting unique imaging properties, has a safety profile equivalent to the other gadolinium-based agents. We report a well-documented anaphylaxis to Multihance; to our knowledge, no other cases of mast cell-mediated allergic reactions have been reported in the literature. Besides, we have shown the value of skin testing as a diag-

nostic tool for Multihance and 2 alternative agents, based on the absence of irritant reactions in the tested dilutions among our control population.

The incidence of adverse effects is 0.05% for Multihance as for all gadolinium-based agents; most of them are mild and transient. The occurrence rate of serious reactions is 0.01%, mainly referring to dyspnea, nausea, urticaria and hypotension. Reports of so-called anaphylactoid reactions are presented even less often [8, 9]. Accordingly, gadolinium-based agents are thought to be safe and useful alternatives to iodinated CM for numerous procedures such as hysterosalpingography [12] and gadolinium-enhanced MR angiography before endovascular aortic aneurysm repair [13].

Immediate hypersensitivity reactions to CM are at least in part associated with histamine release from basophils and mast cells. Histamine release may be due to (1) a direct cell membrane effect related to the osmolarity of the CM solution or the chemical structure of the CM molecule, (2) an activation of the complement system or (3) an IgE-mediated mechanism. Evidence for an IgE-mediated reaction has mainly been found in the rare cases of severe reaction; almost all references deal with reactions to iodinated CM [1].

According to the European Academy of Allergy and Clinical Immunology (EAACI), the following circumstances must be fulfilled for the proposal of an IgE-mediated hypersensitivity mechanism responsible for any drug reaction [1]: (1) an immediate onset of the reaction, the severity of the adverse event increases the probability of a mechanism involving IgE, (2) prior exposure to CM, (3) positivity of ID tests and (4) no positive reaction to skin tests of a known nonreactive CM. If possible, plasma histamine and tryptase assessment immediately after the AE should be considered. In our case, although we could not identify the specific agents, the patient reported 2 gadolinium-based CM MRI scans before. We believe that without demonstration of serum-specific IgE against Gd-BOPTA, our data strongly suggest the aspect of a mast cell degranulation mechanism rather

than documenting an IgE-underlying mechanism. The presented evidence based on positive SPTs, the intensity and the immediate onset of the reaction, as well as the increased tryptase concentration can be consistent with either an IgE-mediated or a C5a-dependent activation pathway; C5a is a very potent agonist of mast cells and basophils via C5a receptor. So, complement activation cannot be ruled out, although according to the above-mentioned EAACI requirements, an IgE mechanism can be proposed.

The diagnostic value of skin tests for drug hypersensitivity has not been fully evaluated and experience in different centers has rarely been exchanged. Thus, reliable skin procedures for the diagnosis of drug hypersensitivity are generally missing and test concentrations are unknown or poorly validated for most drugs. However, a large study of skin testing in normal patients before iodinated CM administration has shown that 97.6% of subjects do not react to iodinated CM solutions diluted 1:10, indicating that false-positive tests do not exceed 2.5% [14]. In our patient, the typical wheal-and-flare reaction with increasing reactivity from 10^{-2} to 10^{-1} concentration combined with the negative tests in 10 control subjects strongly suggest a mast cell-mediated underlying mechanism. Besides, the strong suggestion that skin tests in gadolinium-based agents are nonirritant, according to the control population results, enhances their clinical utility in selected cases.

Elevated serum levels of histamine and tryptase have been found in some but not all patients with severe or fatal immediate reactions, but not in those with milder symptoms [3]. The peak concentration was observed 15–30 min after the reaction and the elimination half-time in plasma was 90 min to 2 h [15]. Thus, blood sampling

2 h after the onset of symptoms and comparison with new blood sample 48 h after the reaction favors the hypothesis of a true anaphylaxis. In our case, the severity of the reaction was dramatically modified by the immediate stop of infusion and the rigorous and adequate treatment in the emergency department; otherwise the reaction could have had a different, tremendous outcome. Accordingly, the high concentration of tryptase in comparison with the 48-hour measurement may be indicative of a severe reaction that was treated properly.

In the series of Li et al. [16], who recorded a 0.48% incidence of acute adverse reactions to intravenous gadolinium-based CM, 6.7% among the 45 reactors had prior reactions to iodinated CM and 6.7% had prior reactions to a different gadolinium-based CM; our patient did not report such reaction before.

Conclusively, although gadolinium-based CM agents are safe, we found that adverse reactions mediated by mast cell degranulation may occur. The index of suspicion for the occurrence of reactions to gadolinium and the documentation and management of adverse reactions must be as rigorous for Multihance and other MR contrast agents as they already are for reactions associated with iodinated CM. Besides, skin testing may prove a useful diagnostic tool in order to evaluate such reactions and to provide alternative agents that can be safely used in further diagnostic procedures.

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