

Letter to the Editor

Anaphylactic shock after first exposure to gadoterate meglumine: Two case reports documented by positive allergy assessment

To the Editor:

We report 2 cases of life-threatening anaphylactic reactions to gadoterate meglumine (Gd-DOTA) documented by positive skin test results. Since the first marketing authorization of gadopentetate dimeglumine (Gd-DTPA) in the United States, Europe, and Japan in 1988, gadolinium-based contrast agents have been widely used, and they currently account for approximately 30% of all magnetic resonance imaging (MRI) procedures. Anaphylactic shock induced by gadolinium-containing products is rare: incidence ranges from 0.004% to 0.01%.^{1,2} Gd-DOTA is an ionic cyclic gadolinium-containing product with high osmolality. Systemic anaphylaxis reactions to Gd-DTPA were first described in 1990.³ A patient with history of asthma and anaphylactic shock to iodinated contrast media presented laryngeal and facial edema minutes after intravenous injection of Gd-DTPA. Since this early report, some severe cases of anaphylactoid reactions (grade III to IV) caused by Gd-DTPA⁴ or to Gd-DOTA⁵ have been documented in the literature. A case of allergic anaphylaxis caused by Gd-DOTA documented by positive skin tests and leukocyte histamine release test (LHRT) has been previously reported.⁶

Skin tests were performed in accordance with drug allergy European Network of Drug Allergy/European Academy of Allergology and Clinical Immunology recommendations.⁷ Skin prick tests (SPTs) with undiluted MRI contrast agents were followed by intradermal tests (IDTs) with different concentrations of MRI contrast agents (first a 10⁻³ dilution and then a gradual increase to the undiluted contrast medium). SPTs were performed on the volar forearm, and a diameter greater than 3 mm was considered a positive response for an immediate reading at 15 minutes, with a positive response to codeine phosphate 9% and negative to the control saline. IDTs were performed by intradermally injecting of 0.02 to 0.05 mL, raising a papula of 3 to 4 mm on the back. An increase in wheal diameter of greater than 3 mm is considered a positive response for the immediate reading at 15 minutes. Ten controls who had previously undergone MRI examination with good tolerance and had negative skin tests were included. Additional LHRT was performed for 1 patient. Two other patients who had completely

negative LHRT served as control subjects. Table I summarizes the results of both skin and biological tests.

In case 1, a 61-year-old woman without an allergy history presented generalized erythema and a decrease in blood pressure (80/40 mmHg) within minutes after the first injection of Gd-DOTA while undergoing carotid angiography for acute ischemic stroke. It was the patient's first MRI examination, and the anaphylactic shock was treated with fluids; she did not receive epinephrine. She has had surgery of lumbar disk hernia. Gd-DOTA SPT was negative (280 mg/mL), and IDT was positive (28 mg/mL). SPT and IDT were negative with gadopentetate dimeglumine (Gd-DTPA; Magnevist, Bayer HealthCare Pharmaceuticals, Wayne, NJ), gadobenate dimeglumine (Gd-BOPTA; Multihance, Bracco Diagnostics Inc, Princeton, NJ) and gadodiamide (Gd-DTPA-BMA; Omniscan, GE Healthcare, Princeton, NJ). LHRT was positive for Gd-DOTA, with the maximum histamine release 47.8% (28 mg/mL).

In case 2, a 72-year-old man with no allergy history developed anaphylactic shock (bronchospasm, generalized urticaria, facial angioedema, and collapse) within minutes during a cerebral MRI with Gd-DOTA. The shock was treated with intravenous fluids and intravenous injection of epinephrine and corticosteroids before admission in an intensive care unit. No previous exposure to gadolinium-based agents was documented. SPT was positive with Gd-DOTA at 280 mg/mL, and SPT and IDT with meglumine were negative at 100 mg/mL. IDTs with other gadolinium-based media (Gd-DTPA, Gd-BOPTA, and Gd-DTPA-BMA) were negative.

These case reports demonstrate an immediate reaction to Gd-DOTA documented by skin tests and LHRT. The hypothesis of nonspecific histamine release does not appear to be plausible because controls had negative skin tests. Moreover, the ability of gadolinium-based contrast agents to induce a nonspecific histamine release has been studied on *ex vivo* and *in vivo* models using canine mast cells.⁸ It appears that the Gd-DTPA concentrations able to induce an *in vitro* mast cell degranulation by osmototoxicity are about 100 to 400 times the estimated serum concentrations found in patients after a standard injection of 0.1 to 0.2 mmol/kg Gd-DTPA. IgE-mediated allergy caused by meglumine is ruled out by negative skin tests results with other MRI contrast agents containing meglumine (Gd-DTPA and Gd-BOPTA).

These patients have no allergy background. Interestingly, and as previously described by Rahman et al,⁴ these cases

TABLE I. Results of skin and biological tests

Patient no.	Age (y)	Sex	Gd-DOTA	Gd-DTPA	Gd-BOPTA	Gd-DTPA-BMA
1	61	Female	SPT – IDT + LHRT +	SPT – IDT –	SPT – IDT –	SPT – IDT –
2	72	Male	SPT + IDT not done	SPT – IDT –	SPT – IDT –	SPT – IDT –

of anaphylactic shock to Gd-DOTA occurred on their first exposure to gadolinium-containing products. However, no other previous exposure to gadolinium (ie, in metallurgical plants, magnet manufactures, fluorescent lamps, or television sets) was found in these patients' histories. Reaction after first exposure to a drug has already been described for neuromuscular blockers, for which immediate allergy occurs without previous exposure in about 30% of tested patients.⁹ It could be postulated that a macrocyclic structure similar to Gd-DOTA could have induced a latent sensitization.

Because of the results of the allergy assessment that documented a clear monosensitization to Gd-DOTA for both cases, other tested MRI contrast agents would constitute a valuable alternative for MRI procedures in these patients. However, the predictive value of skin testing could be established only by the further use of these contrast media and demonstration of an acceptable tolerance. This has not been pursued in these patients because of lack of indication for another MRI examination as well as ethical reasons.

These 2 cases of IgE-mediated anaphylaxis to Gd-DOTA underline the importance of an appropriate allergy assessment, principally skin tests, to document the drug's involvement.

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