

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 osmotoxicity 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 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

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 –	SPT –	SPT –	SPT –
			IDT +	IDT –	IDT –	IDT –
			LHRT +			
2	72	Male	SPT +	SPT –	SPT –	SPT –
			IDT not done	IDT –	IDT –	IDT –

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.

Frédéric Hasdenteufel, PharmD^a
Samuel Luyasu, MD^b
Jean-Marie Renaudin, MD^a
Jean-Louis Paquay, MD^b
Giuseppe Carbutti, MD^b
Etienne Beaudouin, MD^a
Denise Anne Moneret-Vautrin, MD^a
Gisèle Kanny, MD, PhD^a

From ^aEquipe d'accueil 3999, Allergy Diseases: Diagnosis and Therapeutics, Department of Internal Medicine, Clinical Immunology and Allergology, University Hospital of Nancy, Nancy, France; and ^bthe Department of Internal Medicine and Intensive Care, Clinic of South Luxembourg, Arlon, Belgium. E-mail: frederic.hasdenteufel@wanadoo.fr.

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REFERENCES

- Herborn CU, Honold E, Wolf M, Kemper J, Kinner S, Adam G, et al. Clinical safety and diagnostic value of the gadolinium chelate gadoterate meglumine (Gd-DOTA). *Invest Radiol* 2007;42:58-62.
- Li A, Wong CS, Wong MK, Lee CM, Au Yeung MC. Acute adverse reactions to magnetic resonance contrast media: gadolinium chelates. *Br J Radiol* 2006;79:368-71.
- Weiss KL. Severe anaphylactoid reaction after i.v. Gd-DTPA. *Magn Reson Imaging* 1990;8:817-8.
- Rahman SL, Harbinson M, Mohiaddin R, Pennell DJ. Acute allergic reaction upon first exposure to gadolinium-DTPA: a case report. *J Cardiovasc Magn Reson* 2005;7:849-51.
- Meuli RA, Maeder P. Life-threatening anaphylactoid reaction after iv injection of gadoterate meglumine. *Am J Roentgenol* 1996;166:729.
- Beaudouin E, Kanny G, Blanloeil Y, Guilloux L, Renaudin JM, Moneret-Vautrin DA. Anaphylactic shock induced by gadoterate meglumine (DOTAREM). *Allerg Immunol (Paris)* 2003;35:382-5.
- Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002;57:45-51.
- Baxter AB, Lazarus SC, Brasch RC. In vitro histamine release induced by magnetic resonance imaging and iodinated contrast media. *Invest Radiol* 1993;28:308-12.
- Moneret-Vautrin DA, Laxenaire MC. The risk of allergy related to general anesthesia. *Clin Exp Allergy* 1993;23:629-33.

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Non-IgE-mediated chronic allergic skin inflammation revealed with rBet v 1 fragments

To the Editor:

Atopic dermatitis (AD) is a chronic inflammatory skin disorder affecting about 3% to 10% of patients with IgE-mediated allergies.¹ The cardinal features of AD are eczematous and erythematous skin lesions, which are characterized by spongiosis, epidermal hyperplasia, and perivascular infiltrates consisting of T cells, monocytes, macrophages, and antigen-presenting cells. AD thus resembles many features of delayed-type hypersensitivity. The symptoms of AD are triggered in the vast majority of patients with AD by exogenous exposure

to allergens (ie, extrinsic AD), among them food and aeroallergens.² External application of allergens to the skin by means of atopy patch tests (APTs) can also be used to elicit the characteristic eczematous skin lesions in patients with AD for diagnostic purposes.²

The contribution of IgE-mediated versus non-IgE-mediated mechanisms to chronic inflammation in patients with AD is a matter of discussion. Evidence for an important role of IgE-mediated mechanisms comes from the following findings. Patients with AD with high levels of IgE express higher levels of FcεRI on monocytes and dendritic cells, and it has been demonstrated *in vitro* that IgE-facilitated antigen presentation activates allergen-specific T cells more efficiently than allergen presentation through non-IgE-mediated mechanisms.³ Furthermore, there are reports that certain patients with AD benefit from treatment with anti-human IgE antibodies.⁴ On the other hand, skin manifestations in patients with AD can be improved by using therapy strategies targeting T cells in a relatively selective manner.⁵ In fact, there is also evidence for non-IgE-mediated inflammation in other chronic manifestations of allergy, such as asthma.⁶

To study the contribution of IgE-mediated versus non-IgE-mediated mechanisms in chronic allergic skin inflammation, we used a purified IgE-reactive major allergen (ie, the birch pollen allergen Bet v 1 [molecular weight, 17.4 kDa])⁷ and 2 non-IgE-reactive hypoallergenic fragments thereof (F1: amino acids 1-74 [molecular weight, 8 kDa]; F2: amino acids 75-160 [molecular weight, 9.4 kDa]),⁸ which together comprise the full T-cell epitope repertoire of the Bet v 1 allergen but lack IgE reactivity and allergenic activity (ie, basophil activation and induction of immediate-type skin reactions) for APTs in patients with AD. We performed skin prick tests and APTs in 5 patients with AD and birch pollen allergy, a patient with birch pollen allergy without skin manifestations, an allergic person without birch pollen allergy, and 2 non-allergic individuals using rBet v 1 or a mix of the 2 rBet v 1 fragments (F1: amino acids 1-74; F2: amino acids 75-160).

The demographic, clinical, and serologic characterization of the individuals is summarized in Table I. IgE reactivity to rBet v 1 and rBet v 1 fragments (F1 and F2) was tested in a non-denaturing dot-blot assay⁸ and showed that each of the 6 patients with birch pollen allergy (patients A-F) contained rBet v 1-specific IgE (Fig 1 and Table I: 13->100 kUA/L), but none of them contained IgE specific for the Bet v 1 fragments F1 and F2 (Fig 1 and Table I).

Skin prick testing performed on the backs of the patients confirmed the results of the dot-blot experiments because each of the 6 patients with birch pollen allergy but none of the individuals without birch pollen allergy showed immediate-type skin reactivity to rBet v 1 (20 and 40 μg/mL) after 20 minutes (Table I and Fig E1 in the Online Repository at www.jacionline.org). None of the 6 patients with birch pollen allergy had immediate-type skin reactions to equimolar mixes of the rBet v 1 fragments, which was in agreement with the negative result from the IgE dot-blot experiment (Table I and see Fig E1). In parallel to skin prick tests, APTs were performed with aluminum cups (Finn Chambers on Scanpor, Large, Epitest Ltd Oy, Tuusula, Finland) containing 160 μg of rBet v 1 or a mix containing 80 μg of each rBet v 1 fragment, as previously described.⁹ When the APT result was read and photo documented after 48 hours, we found that rBet v 1 induced a positive eczematous reaction of varying intensity in each of the patients with birch pollen allergy and AD (subjects A-E)