

Anaphylaxis after first exposure to gadoterate meglumine: a case report and literature review

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Clinical Implications

- Gadolinium contrast agents can cause IgE-mediated reactions after first exposure. Intradermal tests seem to have the greatest sensitivity in etiological diagnosis, but it must be properly conducted in patients with suspected anaphylaxis due to gadoterate meglumine.

TO THE EDITOR:

Contrast agents (CoAg) for magnetic resonance imaging (MRI) are widely used because they represent an essential aid for internal bodily structures imaging. Among CoAg for MRI, those based on paramagnetic ion gadolinium are the most frequently used. Gadolinium CoAg consist of complex molecules, resulting in chemical bonds between a gadolinium ion and a chelating agent. The chelating agents prevent the toxicity of gadolinium while maintaining its contrast properties. The different chelating agents give to the molecule a cyclic (gadoterate meglumine, gadoteriol) or linear (gadopentetate dimeglumine, gadobenate dimeglumine, gadodiamide) structure. In particular, gadoterate meglumine (gadolinium-tetraazacyclododecanetetraacetic acid, Gd-DOTA) is a CoAg widely used in MRI for the central nervous system, abdomen, and vessels. It is characterized by a macrocyclic structure with a cavity containing gadolinium ion. The addition of a meglumine molecule to gadoteric acid results in the neutralization of the free carboxylic group.¹

A 78-year-old nonatopic woman on no regular medications and with no history of medication allergy who was affected by hepatic steatosis presented 15 minutes after intravenous infusion of Gd-DOTA (DOTAREM) for an abdominal MRI examination with generalized erythema and itch, dyspnea, nausea, and decrease in blood pressure resulting in a loss of consciousness. Anaphylactic shock was diagnosed, and the patient was treated with intravenous epinephrine, steroids, H1 antihistamines, and fluids with a positive prompt response. The patient had never

previously experienced drug hypersensitivity nor had MRI examination, and she denied the previous use of CoAg.

Six weeks later, we performed the skin tests reported in Table I. The intradermal (ID) test with Gd-DOTA (DOTAREM) diluted 1:100 in saline solution induced an immediate positive reaction with a wheal of 5 mm diameter, surrounded by a slight erythema (Fig 1), associated with generalized erythema interpreted as a systemic reaction to the skin test. Skin tests with meglumine were negative. The ID test with Gd-DOTA 1:100 in 20 healthy subjects was negative. The patient refused further skin tests with other gadolinium-containing CoAg.

Adverse drug reactions induced by gadolinium-containing CoAg are rare: in large cohort studies, incidence ranges from 0.17% to 0.48%, and the incidence of anaphylactic shock ranges from 0.004% to 0.1%.¹⁻³ In these studies, previous allergic reactions to contrast medium were considered a significant risk factor. In the literature, only 6 documented cases of anaphylactic reactions to gadolinium CoAg with positive skin tests are reported (Table II).⁴⁻⁷ Cyclic molecules seem to be more sensitizing: 4 of the 6 reported cases occurred with these molecules, as in our patient.

Skin tests are useful for etiological diagnosis. Among these, the ID test seems to have the greatest sensitivity, followed by the prick test (Table II). Commercial compounds of offending agents can be used, but it is recommended to always use increasing concentrations (from 1:1000), starting with the prick test and then continuing with the ID test. The latter with the undiluted commercial compound should be avoided because of the risk of irritant reactions.⁷ Skin tests are quite safe, even if in our patient we observed a systemic reaction, never previously reported in the literature.

According to the European Academy of Allergy and Clinical Immunology,⁸ the immediate onset of the reaction, the severity of clinical feature, and the positivity of the ID test suggest an IgE-mediated anaphylaxis induced by gadoteric acid. IgE-mediated allergy caused by meglumine is ruled out by negative skin test results. Gadolinium reactions seem to be IgE mediated more often than those induced by other CoAg, such as iodinated contrast media, because gadolinium induces lesser nonspecific histamine release,⁷ despite its hyperosmolarity.¹ Our patient was not previously exposed to gadolinium, as in the majority of cases of anaphylaxis induced by gadolinium CoAg, especially due to cyclic agents (Table II). This phenomenon could be related to a latent sensitization induced by previous exposure to other macrocyclic structures similar to Gd-DOTA (such as macrolide antibiotics) or to other gadolinium sources (magnet manufactures, metallurgical plants, fluorescent lamps, or

TABLE I. Skin test results

Substance tested	Concentration	Patch test (pet)			Prick test (aq)		ID test (aq)	
		20'	D2	D4	20'	D1	20'	D1
Gd-DOTA 370 mg/mL (DOTAREM)	1:1000	—	—	—	—	—	—	—
	1:100	—	—	—	—	—	+++	—
	1:10	—	—	—	—	—	NP	NP
	as is	—	—	—	—	—	NP	NP
Meglumine	0.1%	—	—	—	—	—	—	—

aq, In saline solution; Gd-DOTA, gadoterate meglumine; NP, not performed; pet, in petrolatum.



FIGURE 1. Positive intradermal test (20') to gadoterate meglumine (1:100 in saline solution).

TABLE II. Reported patients with anaphylactic reaction to gadolinium contrast agents

Author, year	Sex, age	Contrast agent (C, L)	Positive skin test	First exposure
Beaudouin et al, 2003 ⁴	F, 33	Gadoterate meglumine (C)	Prick (as is) ID (1:1000)	Yes
Kalogeromitros et al, 2007 ⁵	F, 32	Gadobenate dimeglumine (L)	ID (1:100)	No
Hasdenteufel et al, 2008 ⁶	M, 72	Gadoterate meglumine (C)	Prick (as is) ID (as is)	Yes
	F, 61	Gadoterate meglumine (C)		Yes
Galera et al, 2009 ⁷	M, 66	Gadoteridol (C)	Prick 1/10 ID 1/10	Yes
	M, 66	Gadobenate dimeglumine (L)		Yes

C, Cyclic; ID, intradermal; L, linear.

television sets).⁶ However, other authors described a patient sensitized to gadoteridol but not to gadoterate meglumine, excluding a class allergy, although they concluded that the cross-reactivity hypothesis must not be rejected, but should be further evaluated.⁷ Reactions after first exposure to a drug has already been described also for other agents. For example, it is known that immediate allergy to muscle relaxants occurs after the first exposure to these drugs in 30% of evaluated patients.⁹

In conclusion, gadolinium CoAg can cause anaphylaxis, also after first exposure. These compounds should be carefully used, especially in patients with previous reaction to CoAg. Skin tests are safe and useful to confirm the allergy, and they must be properly conducted in patients with suspected gadolinium CoAg-induced anaphylaxis.

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