

Gadoteridol-induced anaphylaxis – not a class allergy

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The use of gadolinium (Gd) agents for contrast-enhanced Magnetic Resonance Imaging (MRI) has increased rapidly. Total adverse reactions range from 0.17% to 2.40%, nausea and vomiting being the most common (1). Severe anaphylactic reactions are very rare and occur in the range of 0.004–0.01% (1), mainly at first exposure. To date, few detailed reports of anaphylactic reactions related to the use of these agents have been published. In the last report (2, 3) the authors described two cases of patients polysensitized to macrocyclic gadolinium agents and postulated that a macrocyclic structure similar to the macrocyclic gadolinium chelate (gadoterate meglumine : Gd-DOTA, DOTA-REM) could be the cause of a latent sensitization. Two new case reports of anaphylactic shock after first exposure to IV administration of gadolinium contrast media are detailed below. These cases do not support the 'polysensitized macrocyclic hypothesis'.

In case 1, a 66-year-old man with no history of allergy was referred as an outpatient for brain MRI. Shortly after an injection of Gadoteridol (Gd-HP-DO3A, PROHANCE), he presented an anaphylactic shock. He was treated with

Polysensitization between gadolinium agents not always found in case of gadolinium anaphylaxis.

IV fluids and injections of adrenaline/epinephrine and corticosteroid before admission to an intensive care unit. Skin tests were performed in accordance to the European Network of Drug Allergy/European Academy of Allergology and Clinical Immunology recommendations. Skin prick tests (SPT) were performed with an undiluted MRI contrast agent and, when negative, were followed by intradermal tests (IDT) in the range of 10^{-3} to the undiluted commercially-available contrast media. SPT were positive with Gadoteridol at undiluted and 10^{-1} concentrations and negative to Gadoterate (Gd-DOTA), Gadopentetate dimeglumine (Gd-DTPA), Gadobenate dimeglumine (Gd-BOPTA) and gadodiamide (Gd-DTPA-BMA). IDT were all positive with Gadoterate (Gd-DOTA), Gadopentetate dimeglumine (Gd-DTPA), Gadobenate dimeglumine (Gd-BOPTA) and gadodiamide (Gd-DTPA-BMA) at the undiluted concentration and all negative at the 10^{-1} concentration. Because all IDT were positive at the undiluted gadolinium contrast media, we performed them on ten exposed controls with no history of reaction to gadolinium: all SPT were negative (even at the undiluted concentrations) and half of them had positive IDT to the undiluted gadolinium agents. We therefore considered the undiluted gadolinium solutions as irritant. So, in case 1, skin tests were positive for Gadoteridol only.

In case 2, a 66-year-old man with a history of previous allergy to kiwi developed an anaphylactic shock 3 min after the second bolus of Gadobenate dimeglumine (Gd-BOPTA - MULTIHANCE) injection for whole-body MRI angiography (a first bolus was injected 15 min before). The patient had beta-blockers for cardiac disease and was successfully resuscitated by continuous IV adrenaline/epinephrine during three hours and a large IV volume expansion in intensive care. SPT were all negative with Gadoteridol (Gd-HP-DO3A), Gadoterate

(Gd-DOTA), Gadopentetate dimeglumine (Gd-DTPA), Gadobenate dimeglumine (Gd-BOPTA) and gadodiamide (Gd-DTPA-BMA). IDT were positive with Gadobenate dimeglumine (Gd-BOPTA) and were all negative with Gadoterate (Gd-DOTA), Gadoteridol (Gd-HP-DO3A), Gadopentetate dimeglumine (Gd-DTPA), and gadodiamide (Gd-DTPA-BMA) at the 10^{-1} concentration. Latex IgE were negative (SPT and CAP-FEIA) (Table 1).

Our observations do not support the findings of the recent study of Hasden-teufel et al. (2, 3). First, we do not agree that the undiluted concentration of gadolinium agents is not an irritant for skin tests concerning both macrocyclic and open chain molecules. The interpretation of skin tests may not therefore be possible using this concentration. One of their two cases showed polysensitization between gadolinium agents based on a positive skin test with the undiluted concentrations. Second, our cases failed to find polysensitization between several gadolinium agents. Concerning the macrocyclic agent involved in case 1: the negativity of our SPT with Gd-DOTA does not enable us to support the possibility of involvement of the macrocyclic structure as postulated by the authors; nevertheless this hypothesis must not be rejected and should always be checked.

Thus, all mild to severe adverse hypersensitivity reactions should be accurately documented with most of the available gadolinium in order to determine cross reactivities. This is all the more important since challenge with another gadolinium agent giving negative skin tests could be performed safely, therefore allowing these patients further MRI explorations if necessary.

This documentation should now be as rigorous as for hypersensitivity reactions associated with iodinated contrast media (4). Moreover these gadolinium reactions may be IgE-mediated more often than with iodinated contrast media because

Table 1. Skin test results

Patient	Test	Macrocyclic molecules		Open-chain molecules		
		Gd-DOTA Gadoterate Dotarem C = 280 mg/ml	Gd-HP-DO3A Gadoteridol Prohance C = 280 mg/ml	Gd-DTPA Gadopentetate dimeglumine Magnevist C = 470 mg/ml	Gd-BOPTA Gadobenate dimeglumine Multihance C = 530 mg/ml	Gd-DTPA-BMA Gadodiamide Omniscan C = 287 mg/ml
Case 1: 66 Male Gd-HP-DO3A	SPT	– (C = undiluted)	+ (C = 10 ⁻¹)	– (C = undiluted)	– (C = undiluted)	– (C = undiluted)
	IDT	– (C = 10 ⁻¹)	Not done	– (C = 10 ⁻¹)	– (C = 10 ⁻¹)	– (C = 10 ⁻¹)
		+ (C = undiluted)		+ (C = undiluted)	+ (C = undiluted)	+ (C = undiluted)
Case 2: 66 Male Gd-BOPTA	SPT	– (C = undiluted)	– (C = undiluted)	– (C = undiluted)	– (C = undiluted)	– (C = undiluted)
	IDT	– (C = 10 ⁻¹)	– (C = 10 ⁻¹)	– (C = 10 ⁻¹)	+ (C = 10 ⁻¹)	– (C = 10 ⁻¹)

C, concentration.

gadolinium would lead to lesser nonspecific histamine release caused by hyperosmolarity.

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