
Paramagnetic Contrast Media: Hypersensitivity and Cross-Reactivity

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Gadolinium-based contrast media have been used for 25 years for contrast-enhanced magnetic resonance imaging (MRI) because of their safety and low rates of adverse effects (0.3%) [1]. The incidence of immediate hypersensitivity reactions to magnetic resonance contrast media is 0.079% in adults and 0.04% in children [2]. Reactions have been reported more frequently for abdominal explorations (0.01%) than for explorations of the brain (0.005%) and spine (0.003%). The most common reaction is urticaria (50%-90% of cases), while anaphylaxis has an incidence of 0.004% to 0.01%. These contrast media can be classified based on their net charge as ionic or nonionic and on their structure as linear or macrocyclic [1,2].

A 45-year-old man diagnosed with astrocytoma was sent to our Allergy Unit because he developed facial edema, generalized erythema, dyspnea, rhinitis, and edema in his hands and feet 5 minutes after starting an infusion with gadobutrol. The infusion was stopped immediately, and he was treated with parenteral methylprednisolone and dexchlorpheniramine. He had received this contrast media previously without adverse reactions. An allergy study was programmed once informed consent was obtained. Since the patient did not wish to undergo tests involving gadobutrol, we carried out prick and intradermal tests with other gadolinium-based contrast media (Table). The patient had to receive a gadolinium contrast media for disease control; therefore, we proposed a challenge test with gadoteridol, because the results of the prick and intradermal tests were negative and positive with other agents. Twenty-five minutes after administration, the patient began to experience facial erythema, palmar pruritus, tinnitus, urticaria on his arms and knees, and mild dyspnea. He was treated immediately with parenteral epinephrine, methylprednisolone, and dexchlorpheniramine.

Hypersensitivity reactions with gadolinium-based contrast agents are very rare, with very few cases reported in the literature. In 2007, Kalogeromitros et al [3] reported a case of anaphylaxis after infusion of gadobenate with a positive intradermal test result. Hasdenteufel et al [4] reported 2 cases of anaphylactic shock with positive results in skin tests with

Table. Results of the Allergy Work-up

Commercial Name	Agent	Chemical Structure	Prick Test (Undiluted)	Intradermal Test (1/10)
MultiHance	Gadobenate	Linear ionic chelate	Negative	Positive
Omniscan	Gadodiamide	Linear nonionic chelate	Negative	Positive
Dotarem	Gadoterate	Macrocyclic ionic chelate	Negative	Positive
ProHance	Gadoteridol	Macrocyclic nonionic chelate	Negative	Negative

gadopentetate in 2008. In 2010, Galera et al [5] reported 2 cases of anaphylactic shock following the administration of gadoteridol and gadobenate, respectively. In both patients, intradermal tests were positive to the contrast media involved and negative to the remaining agents studied. In 2012, Tomás et al [6] reported a case of urticaria in a 17-year-old girl and a generalized rash in a 4-year-old girl after exposure to gadopentetate and gadoteridol, respectively. Skin test results were negative in the first case, and a challenge with gadoteridol yielded a negative result. In the second case, prick tests were negative for all the agents tested and intradermal tests were positive for gadoteridol, gadobutrol, and gadoxetate and negative for gadopentetate and gadobenate. The result of the challenge test with gadobenate was negative. In 2015, Takahashi et al [7] reported a case of fatal anaphylaxis associated with the use of gadoteridol. Autopsy revealed widespread skin rash and severe laryngeal edema, which are typical findings of anaphylaxis, in addition to a very high concentration of serum trypsinase.

Gadobutrol, the gadolinium-based contrast medium responsible for the initial symptoms in the present case, is included in the macrocyclic nonionic group. As skin tests were positive for linear chain agents and although gadoteridol was a macrocyclic agent, the negative results in the prick and intradermal tests led us to perform a challenge test with this agent, as indicated in the report by Tomás et al [6]. Although the skin test results were negative in the present case (as with Tomás et al), the challenge test result—surprisingly—was positive, ie, the patient developed an anaphylactic reaction. According to the study published by Chiriac et al [8] in 2011, the negative predictive value of gadolinium skin tests was excellent and although the data reported are based on a small sample and the severity of the initial reactions was mild, we thought that the patient would tolerate this contrast medium. The negative skin test results with gadoteridol did not allow us to rule out the possible involvement of the macrocyclic structure as being responsible for the reaction with gadoteridol, because the patient had a positive skin test result to gadoterate, another macrocyclic chelate, as reported by Galera et al [5]. Furthermore, Ideé and Corot [9] reported that gadoteridol and gadoterate are both tetra-aza macrocyclic ligands that differ in the presence of an isopropanol moiety in the case of gadoteridol. Therefore, we believe that the skin test results could be related to this difference in structure. We put forward the hypothesis that another common epitope is present in all the gadolinium contrast media tested in the present study and that this may have been responsible for the positive skin test results to linear and macrocyclic agents. Various studies have

suggested the role of transmetallation and competition between Gd^{3+} with Ca^{2+} for cellular processes. Gd^{3+} is very similar to Ca^{2+} in size, thus resulting in competition with Ca^{2+} in cellular and biochemical processes. It is capable of inhibiting voltage-gated calcium channels [10]. Although the immediate reaction suggests an IgE-mediated mechanism, another explanation could be that gadoteridol had led to cellular degranulation with release of a mediator that had been able to produce an anaphylactoid reaction in the present case.

In conclusion, we present a case of anaphylaxis to gadobutrol. Given that a gadolinium-based contrast medium was an essential part of the patient's management, an allergy work-up was performed with other available contrast media. Skin test results were positive to all the agents studied except gadoteridol. A challenge test with this agent yielded a positive result, and the patient experienced an immediate reaction; however, we were unable to demonstrate an IgE-mediated pathway. We think that there may be cross-reactivity between macrocyclic agents and between linear and macrocyclic contrast media, although the few published reports do not address this issue. Therefore, more studies are necessary to assess cross-reactivity. We considered that the challenge test must be performed using an alternative gadolinium-based contrast medium that yielded a negative skin test result because of the possibility of false-negative results and the implication of other immunologic and nonimmunologic reactions.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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