Patterns of Cross-Reactivity in Patients With Immediate Hypersensitivity Reactions to Gadobutrol

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Gadolinium-based contrast agents (GBCAs) are used in contrast-enhanced magnetic resonance imaging (MRI) for diagnosis of inflammation, tumors, and other tissue disorders. GBCAs are classified according to their chemical structure (macrocyclic or linear) and properties. The prevalence of adverse reactions ranges between 0.066% and 1.47% [1]. Immediate hypersensitivity reactions are infrequent and mostly mild, with an incidence of 0.07% in adults and 0.04% in children [2]. Anaphylaxis occurs in 0.01% of cases [3]. Reactions are more frequent for abdominal examinations (0.01%) than for those of the brain (0.005%) and spine (0.003%) and with dimeglumine gadobenate and gadoteridol [2]. The involvement of specific IgE has been suggested, based on positive skin test results in patients who experience anaphylactic reactions [2]. In addition, the cross-reactivity patterns of GBCAs are unclear.

We performed a retrospective analysis of all patients diagnosed with immediate reactions due to GBCAs registered in our database.

Data were retrospectively collected for the period 2014-2019. Patients with symptoms compatible with immediate (1-6 hours) drug hypersensitivity reactions according to international consensus criteria on drug allergy [4] were included. Skin prick tests (SPTs), intradermal tests (IDTs), and drug provocation tests (DPTs) were performed. Reagents included gadobutrol, gadoxetate disodium (GD), and gadoterate meglumine (GM), with undiluted GBCAs used for SPTs and dilutions of 1:100 to 1:10 for IDTs [2,5]. SPTs were negative in all patients. Therefore, positive skin test results were due to IDTs. Patients with negative skin test results underwent DPTs up to a dose suitable for diagnosis. DPTs were performed with the eliciting

GBCA or with an alternative GBCA at the discretion of the attending physicians. Written informed consent was obtained.

Five patients (3 females) fulfilled the selection criteria. The mean age was 50 years (median, 54). The reactions comprised 2 cases of urticaria and 3 of anaphylaxis. Gadobutrol (macrocyclic) was the GBCA involved. Skin test results were positive with gadobutrol in 4 patients and with GM (macrocyclic) in 2. One patient with negative skin test results had a positive DPT result with gadobutrol (Table). Two sensitization patterns were found, namely, positive skin test results with both macrocyclic GBCAs (2 patients) and positive skin test or DPT results exclusively with gadobutrol (3 patients). No patients had positive skin test results with GD (linear). The 2 patients with positive skin test results with both macrocyclic GBCAs did not undergo DPTs owing to severe comorbidities. The 3 patients with a selective response to gadobutrol underwent DPTs with another GBCA. Two of them tolerated GM, the other tolerated GD.

We present 5 patients who experienced immediate reactions to gadobutrol. We found 2 sensitization patterns: selective sensitization to gadobutrol (60%), with tolerance to other GBCAs, and positive skin test results with more than 1 macrocyclic GBCA (40%).

Immediate reactions to GBCAs are infrequent, with isolated case reports or very short series published [1,3,5-10]. Hasdenteufel et al [6] reported 2 anaphylactic shocks with GM. Both patients had positive SPT and IDT results with GM and negative results with 3 linear GBCAs. Galera et al [1] described 2 cases of anaphylaxis, one with gadoteridol and another with gadobenate dimeglumine. In both cases, the skin test results were positive exclusively with the culprit GBCAs. In our study, 4 out of 5 patients had positive skin test results with the culprit GBCA, and 2 had positive skin test results with another macrocyclic agent. In the evaluation of immediate reactions to GBCAs, SPTs are safer but less sensitive than IDTs. Accordingly, none of our patients had positive SPT results with GBCAs. Elsewhere [1,6-8,10,11], positive SPT results were reported with GBCAs, although most cases diagnosed using skin tests were with IDTs. As the sensitivity of skin tests is suboptimal, DPTs are necessary for diagnosis and demonstrate tolerance to other GBCAs. Tomás et al [3] reported 2 cases of hypersensitivity to gadopentetate dimeglumine and gadoteridol, with negative skin test and DPT results for alternative GBCAs. In the first patient, a DPT with gadoteridol was well tolerated. The second patient had reacted to gadoteridol but tolerated gadobenate dimeglumine [3]. Chiriac et al [5] reported data on 27 patients with clinical histories of hypersensitivity to GBCAs of whom 11 tolerated a negative skin-tested GBCA during subsequent MRI scans. Moreno-Escobosa et al [9] reported 1 case of anaphylaxis to gadobutrol, with positive skin test results to all the agents studied (gadobenate dimeglumine, gadodiamide, and GD), except gadoteridol. A challenge test with this agent triggered an immediate reaction.

Cross-reactivity between GBCAs has not been adequately addressed [1-3,7-9,12]. Kolenda et al [7] described 30 patients with immediate reactions to GBCAs, finding cross-reactivity to be more frequent between GM and gadobutrol, both of which are macrocyclic, although they reported 3 patients monosensitized to gadobutrol. Moulin et al [10] reported an anaphylactic reaction to GM with a strongly positive SPT result to gadoterate and negative skin test results to 4 GBCAs (linear and macrocyclic). The authors performed a DPT with gadobenate dimeglumine, which revealed good tolerance. Harr et al [11] reported the first case with positive skin test results 10 years after an anaphylactic reaction to GBCAs in an immunosuppressed patient, illustrating that hypersensitivity with positive IDT and SPT results might persist. These findings agree with the sensitization patterns found in the cases we report, namely, one group with selective responses to gadobutrol and another sensitized to macrocyclic structures. Nonetheless, cross-reactivity between macrocyclic and linear GBCAs and cross-reactivity between linear agents have not been addressed to date. Recently, Mankouri et al [12] found cross-reactivity in 7 of 18 allergic patients (38%). Among the 18 patients in whom both linear and macrocyclic GBCAs were tested (either as culprit agents or alternatives), the cross-reactivity rate was 27.7% between macrocyclic agents, 5.5% between linear agents, and 5.5% between both.

The main limitations of our study are its retrospective nature, which was partially circumvented, since all patients underwent the same protocol, and the small sample size.

Table. Patient Characteristics and Results of the Allergy Study

Sex	Age	Reactions	Positive STs	Positive DPTs	Negative DPTs
Female	51	Anaphylaxis	Gadobutrol/ gadoterate meglumine	Not performed	Not performed
Female	54	Urticaria	Negative STs	Gadobutrol (Mild urticaria)	Gadoterate meglumine
Male	55	Anaphylaxis	Gadobutrol/ Gadoterate meglumine	Not performed	Not performed
Male	55	Urticaria	Gadobutrol	-	Gadoterate meglumine
Female	28	Anaphylaxis	Gadobutrol	-	Gadoxetate disodium

Abbreviations: DPT, drug provocation test; ST, skin test

Additionally, not all GBCAs were tested, and 2 patients did not undergo DPTs owing to comorbidities and the initial reaction.

To conclude, skin tests are useful for diagnosis and for identifying alternative GBCAs by means of DPTs. We believe patients sensitized to the macrocyclic structure should avoid macrocyclic GBCAs. Patients monosensitized to gadobutrol could receive both macrocyclic and linear agents.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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