Patterns of Cross-Reactivity in Patients with Immediate Hypersensitivity Reactions to Gadobrutol

Gallardo-Higueras A[1], Moreno EM[1,2,3,4], Muñoz-Bellido FJ[1,2,3], Laffond E[1,2,3], Gracia-Bara MT[1,2], Macias EM[1,2,3], Campanon MV[1], de Arriba S[1,2,3], Martin C[1], Sobrino M[1], Davila I[1,2,3,4]

[1]Allergy Service, University Hospital of Salamanca, Salamanca, Spain
[2]IBSAL (Institute for Biomedical Research of Salamanca), Salamanca, Spain
[3]Department of Biomedical and Diagnostic Sciences, Salamanca Medical School, University of Salamanca, Salamanca, Spain
[4]RETIC Asma, Reacciones adversas y Alérgicas (ARADYAL), Instituto de Salud Carlos III, Madrid, Spain

Corresponding:
Esther Moreno
Allergy Service. University Hospital of Salamanca.
Paseo San Vicente 58-182
37007 Salamanca, Spain
E-mail: emrodilla@usal.es

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Gadolinium-based contrast agents (GBCAs) are used in contrast-enhanced magnetic resonance imaging (MRI) in diagnosing inflammation, tumors, or other tissue disorders. GBCAs classify according to chemical structure (macrocyclic or linear) and properties. Adverse reactions prevalence range 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 (0.01%) than for brain (0.005%) and spine (0.003%) explorations and with dimeglumine gadobenate and gadoteridol [2]. The involvement of specific IgE has been suggested, based on positive skin test results (STs) in patients with anaphylactic reactions [2]. In addition, cross-reactivity patterns GBCAs are unclear.

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

Between 2014-2019, data were retrospectively collected from our database. Patients with symptoms compatible with immediate (1-6 hours) drug hypersensitivity reactions according to the International Consensus criteria on drug allergy [4] were included. Skin prick tests (SPTs), intradermal tests (IDTs), and drug provocation tests (DPTs) were

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performed. Reagents included gadobutrol, gadoxetate disodium (GD), and gadoterate meglumine (GM), using undiluted GBCAs for SPTs and dilutions of 1:100 to 1:10 for IDTs [2,5]. SPTs were negative in all patients. Therefore, STs positive results were due to IDTs. Patients with negative STs underwent DPTs up to a dose suitable for diagnosis. DPTs were performed with the eliciting GBCA or with an alternative GBCA, as considered by the attending physicians. Written informed consent was obtained.

Five patients (3 females) fulfilled the selection criteria. The mean age was 50 years (median 54). Reactions were two urticarias and three anaphylaxis. Gadobutrol (macrocyclic) was the GBCA involved. STs were positive with gadobutrol in 4 patients and with GM (macrocyclic) in 2 of them. One patient with negative STs had a positive DPT with gadobutrol (*Table 1*). Two different sensitization patterns were found: two patients had positive STs with both macrocyclic GBCAs, and three patients had positive STs or DPTs exclusively with gadobutrol. No patients had positive STs with GD (linear). The two patients with positive STs with both macrocyclic GBCAs did not undergo DPTs due to severe comorbidities. The three 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 with immediate reactions with gadobutrol. We found two sensitization patterns: selective sensitization to gadobutrol (60%), with tolerance to other GBCAs, and positive STs with more than one macrocyclic GBCA (40%).

GBCA immediate reactions are infrequent, with isolated case reports or very short

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series published [1,3,5-10]. Hasdenteufel et al. [8] reported two anaphylactic shocks with GM. Both patients, had positive SPTs and IDTs with GM and negative with three linear GBCAs. Galera et al. [1] described two anaphylaxis, one with gadoteridol and another with gadobenate dimeglumine. In both cases, STs were positive exclusively with the culprit GBCAs. In our study, 4 out of 5 patients had positive STs with the culprit GBCA, and two of them positive STs with another macrocyclic agent. In the evaluation of immediate reactions to GBCAs, SPTs are safer but lower sensitive than IDTs. Accordingly, none of our patients had positive SPTs with GBCAs. Other reported cases [1,7,8,9,10,11] had positive SPTs with GBCAs. Nonetheless, most cases diagnosed by STs, are by IDTs. Nevertheless, as skin tests' sensitivity is suboptimal, DPTs are necessary for diagnosis and demonstrate tolerance to other GBCAs. Tomás et al. [3] described two cases of hypersensitivity to gadopentetate dimeglumine and gadoteridol, with negative STs and DPTs with alternative GBCAs. In the first patient, a DPT with gadoteridol was performed, being well-tolerated. The second case was due to gadoteridol and tolerated gadobenate dimeglumine [3]. Chiriac et al. [5] presented 27 patients with clinical histories of hypersensitivity to GBCAs, of which 11 tolerated a negative skin-tested GBCA during ulterior MRI explorations. Moreno-Escobosa et al [6] published one anaphylaxis with gadobutrol with positive STs to all studied agents (gadobenate dimeglumine, gadodiamide, and GD), except gadoteridol. A challenge test with this agent triggered an immediate reaction.

Cross-reactivity among GBCAs has not been adequately addressed [1,2,3,6,7,8,12]. Kolenda et al. [7] described 30 patients with immediate reactions to GBCAs, finding

cross-reactivities more frequent between GM and gadobutrol, both macrocyclic, although they described three patients monosensitized to gadobutrol. Moulin et al. [10] reported an anaphylactic reaction to GM with a strongly positive SPT with gadoterate and negative STs to four GBCAs, linear and macrocyclic. They performed a DPT with gadobenate dimeglumine with good tolerance. Harr et al. [12] reported the first case with positive STs 10 years after an anaphylactic reaction to GBCAs in an immunosuppressed patient, illustrating that hypersensitivity with positive IDT and SPT might persist. These cases agree with the sensitization patterns found in our patients: a group with selective responses to gadobutrol and a group sensitized to macrocyclic structures. Nonetheless, the cross-reactivity between macrocyclic and linear GBCAs has not been elucidated to date, and cross-reactivity between linear agents has not been addressed. Recently, Mankouri et al. [12], found cross-reactivity in seven of 18 allergic patients (38%). Overall, amongst 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.

Our study's main limitations are its retrospective nature, partially circumvented since all patients underwent the same protocol, and the small sample size. Additionally, not all GBCAs were tested, and there were two patients in whom DPTs were not performed due to comorbidities and initial reaction.

To conclude, STs are useful for diagnosing and alternative GBCA searching using 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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Table 1. Characteristics of the patients 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

STs: Skin tests. DPTs: Drug provocation tests.