Fast gadolinium-based contrast agent challenge test searching for an alternative contrast media

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To the Editor,

Gadolinium-based contrast agents (GBCA) are used in contrast-enhanced magnetic resonance imaging. Hypersensitivity reactions (HSR) to GBCA are scarce, with an incidence of 0.07% and a recurrence rate of 30%, being urticaria the most common presentation (91%), with 0.52/10000 of severe reactions reported[1]. Recommendation of an alternative GBCA without checking tolerance is dangerous, due to high cross-reactivity between them[2]. Moreover, premedication is not enough[1], showing an overall rate of breakthrough reactions of 39%[3].

Allergy studies to achieve a safe recommendation in HSR to GBCA have been performed. Negative predictive value of skin-tests to GBCA has been estimated in 84%[1]. Therefore, more than 10% of patients could react using an alternative negative skin-tested GBCA, and thus, good tolerance to GBCA should be confirmed through a drug challenge-test (DCT)[4]. These tests are usually performed at graded administrations, and with observation periods between doses[1,5]. However, since GBCA is usually given as a bolus during radiologic exams, DCT at slow rates cannot be extrapolated to further administrations. Trying to avoid this limitation, we study the tolerance of an alternative GBCA, by means of a fast DCT, approaching the infusion rates used in clinical practice.

In accordance with the safety warnings to avoid linear GBCA, we have only used the macrocyclic drugs gadobutrol (Gb) and gadoteric acid (Ga). After obtaining signed informed consent from the patients, skin pricktests (SPT) with undiluted macrocyclic GBCA commercial solutions were done. When SPT at 20 min yielded negative results, intradermal tests (IDT) with 1:10 dilutions were performed, with subsequent readings at both 20 min and 24 hours.

A fast DCT with negative skin-tested GBCA was then performed, following our methodology to study HSR to iodinated contrast media, previously described elsewhere[6]. Doses were 0.2 mg/kg for Ga and 0.1 mg/kg for Gb. First, one third of the total dose of Ga was administered at a rate of 120 cc/hour and, immediately after, the remaining 2/3 at 80 cc/hour. In case of Gb, infusion rates were half those of Ga, i.e., 1/3 at 60 cc/hour and 2/3 at 40 cc/hour. Total infusion time was 8 minutes for both of them. Well-tolerated GBCA was finally recommended for subsequent examinations, and its tolerance was recorded if it was used later.

Study results of sixteen patients that were enrolled are summarized in Table 1. They were 12 women and 4 men, with median age of 45.5 years (range 28-73). Adverse reactions to GBCA were immediate in 13 patients (12 urticaria or exanthema, and 1 anaphylaxis), and delayed exanthema in the remaining 3. Gb was involved in 11 reactions, and unknown GBCA in the other 5. Most of the patients (14/16) had been previously exposed to GBCA.

Median delay to perform the allergy study was 10 months (range 2-72 months). All skin-tests were negative,

except in one patient who showed an immediate positive SPT to Gb, which had been the GBCA involved in the adverse reaction. In our study, we have estimated a negative predictive value of skintests to GBCA of 89%. DCT were negative in 14 patients (12 with Ga, and 2 with Gb). Finally, 15 out of 16 patients had an alternative GBCA, avoiding the use of premedication. In fact, tolerance has been confirmed in 7 of them in subsequent examinations.

Safety of our protocol has been confirmed because our 2 positive DCT showed only mild reactions (delayed exanthema and immediate urticarial, both with Ga), and also by including a patient with previous anaphylaxis to GBCA.

Here we present a prospective protocol to identify a safe alternative GBCA, including DCT at high infusion rates. Further studies will be necessary on this item/to check this.

CONCLUSION

Fast drug challenge-tests, approaching usual administration of contrast media in radiological explorations, seems to be both effective and safe in allergy studies of hypersensitivity reactions to gadolinium-based contrast agents

Patient	**Sex**	**Age**	**Medical History**	**GBCA**	**HSR**	**Previous Contact**	**Study delay (months)**	**ST**	**DCT**
1	M	45	Neurological Ds	Gb	Urticaria (IM)	Yes	2	NEG	Ga NEG
2	M	66	Neurological Ds	Gb	Urticaria (IM)	Yes	4	NEG	Ga NEG
3	F	48	Digestive Ds	Unknown	Exanthema (DY)	No	13	NEG	Ga NEG
4	F	66	Neurological Ds	Gb	Exanthema (DY)	Yes	13	NEG	Ga NEG
5	F	38	Neurological Ds	Gb	Urticaria (IM)	Yes	10	NEG	Ga NEG
6	F	50	Neurological Ds	Gb	Urticaria (IM)	Yes	2	NEG	Ga NEG
7	F	47	Urological Ds	Unknown	Urticaria (IM)	Yes	60	NEG	Gb NEG
8	F	40	Digestive Ds	Gb	Urticaria (IM)	Yes	11	NEG	Ga NEG
9	F	44	Neurological Ds	Gb	Urticaria (IM)	Yes	2	NEG	Ga NEG
10	F	35	Neurological Ds	Unknown	Exanthema (DY)	Yes	72	NEG	**Ga POS (DY)** Gb NEG
11	F	53	Bone Ds	Gb	Urticaria (IM)	Yes	20	**Gb POS**	Ga NEG
12	F	28	Neurological Ds	Unknown	Anaphylaxis	Yes	40	NEG	Gb NEG
13	M	46	Hematological Ds	Gb	Urticaria (IM)	Yes	6	NEG	Ga NEG
14	M	41	Neurological Ds	Gb	Urticaria (IM)	No	22	NEG	Ga NEG

Patient	Sex	Age	Medical History	GBCA	HSR	Previous Contact	Study delay (months)	ST	DCT
15	F	44	Neurological Ds	Gb	Urticaria (IM)	Yes	2	NEG	**Ga POS (IM)**
16	F	73	Neurological Ds	Unknown	Urticaria (IM)	Yes	3	NEG	Ga NEG

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Authors' contribution

Francisco Vega conducted the prospective study, participated in all stages of the study and wrote the first draft of the article.

Azahara Lopez-Raigada y M. Victoria Mugica collaborated to perform skin-tests and drug challenge-tests.

Carlos Blanco coordinated the whole study

All authors have been involved in drafting the manuscript or revising it critically for important intellectual content, and also, they have given final approval of the version to be published.

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Conflict of interest

The authors declare that they have no conflicts of interest

Ethical approval

This protocol was approved by the Committee of Research and Ethics "Comité de Ética de La Investigación con Medicamentos del Hospital Universitario de la Princesa" with the approval number 3396.