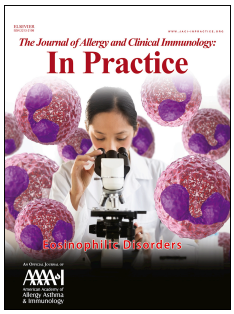
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Hypersensitivity to gadolinium-based contrast agents: a single-center retrospective analysis over 7 years

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Hypersensitivity to gadolinium-based contrast agents: a single-center retrospective analysis over 7 years

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Clinical Implication Box:
13.6% of the patients undergoing skin tests (ST) for a suspicion of gadolinium-based contrast agents (GC) hypersensitivity (HS) reaction were allergic, 95% had immediate HS. Cross-reactivity concerned 38% of ST-positive patients and involved especially macrocyclic GC. Amongst the allergic patients, one third was re-exposed to a ST-negative GC and tolerated it.

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Gadolinium-based contrast agents (GC), used for magnetic resonance imaging (MRI) are classically considered safer with regards to hypersensitivity (HS) reactions than iodinated radiocontrast media (iRCM) [1, 2].

We conducted a retrospective analysis of 132 consecutive patients investigated for suspicions of GC HS (**Repository Text**).

Among the 132 tested patients (83.3% female), 110 (83.3%) had a history of immediate HS (<1h) (**Table 1**). Isolated skin involvement (generalized or localized) was the main clinical presentation reported by half patients (31.1% urticaria and 18.2% maculo-papular exanthema), followed by anaphylaxis (with or without shock in 40.1%). Gadoteric acid was the most frequently reported GC (35.3%), followed by Gadobenic acid (13.5%). Many patients (42.1%) could not identify the culprit GC.

Eighteen patients (13.6%) (**Table 2**) were considered allergic based on positive ST: 17 with immediate and one with non-immediate HS. In the allergic group, ST with the culprit GC was positive in 15 patients (83.3%). In two patients (N°8 and 14), there was a miss-match between the reported GC and the ST-positive ones. Patient N°11 had positive ST, but the culprit GC was unknown. Six patients out of 15 (40%) reacted on their first exposure to GC (information not available for the others), including Patient N°2 for whom the kinetics of tryptase confirmed a mast cell degranulation. Although some differences were identified between the allergic and the non-allergic group (**Table 1**) no risk factor of confirmed allergy was retained after multivariate analysis (data not shown).

Cross-reactivity in ST was revealed in seven of the 18 allergic patients (38%): in four cases to two GC and in three cases to three agents. Overall, amongst the 18 patients in whom both linear and macrocyclic GC were tested (either as culprits or as alternatives), the cross-

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reactivity rate was: between macrocyclic alone 27.7% (5 patients), between linear alone 5.5% (1 patient) and between the two classes 5.5% (1 patient) (**Figure E1**). Gadodiamide was neither involved in any index reaction nor in cross-reactivity, although it was tested in all allergic patients.

One third of the allergic patients underwent another MRI with an alternative ST-negative GC and none experienced another reaction. The information was not available for the rest of the cohort.

As previously described [2-5], GC were mainly elicitors of immediate reactions. Proven allergy concerned 15.4% of immediate reactors and 4.5% of non-immediate reactors. Sex was not a risk factor for confirmed allergy in our series, supporting other studies [2].

Similar to other studies [2], isolated skin involvement was the main clinical presentation. One in ten patients (10.7%) in this population had positive ST. Amongst patients describing anaphylaxis (with or without shock), the positive rate reached 20.7%. Conversely, in the group with positive ST and immediate HS, one third (35%) presented cutaneous symptoms only, and two thirds (65%) anaphylaxis. This is in agreement with the cohort of Clément et al [2] on GC in which the frequency of proven allergy increased with the severity of the reaction. However, in our study, neither anaphylaxis nor anaphylactic were independent risk factors for confirmed allergy, after adjustment for all the other variables.

Of note, one third of allergic patients had no known previous exposure to GC, as previously described [2, 6-7]. It is unknown, at this point, how these patients get sensitized to GC.

In our cohort, diagnosis of GC allergy was based on ST. Tryptase at the time of the reaction was not measured for most patients, no BAT [4] were available, and DPT were performed in selected cases only, unlike other reports [5]. The median time between reaction and test was

7.6 months, which seems as a reasonable delay to allergy work-up for other contrast agents (iRCM) to avoid false-negative results [8].

Unlike the study by Clément et al, where patients were included prospectively, many patients (42.2%) in our series could not indicate the culprit GC. Two patients were positive to a different GC than the one they reported a reaction to. This kind of miss-match has already been reported for iRCM [8] and misreporting the wrong GC as being the culprit is likely. This can be explained by a recall bias, or patients might have been misinformed at the time of their reaction, therefore, testing a battery GC (and not just the one pointed as culprit), especially when anaphylaxis is reported, is preferable.

Gadoteric acid was the most frequently GC reported by patients, followed by gadobenic acid. Recently, due to concerns about their involvement in brain tissue deposition, linear GC have been removed from the market. There was a tendency towards macrocyclic GC being more of a risk factor than the linear GC compared to unknown GC, but when we analyzed patients with known culprit GC only (data not shown) there was no difference between macrocyclic and linear GC, possibly because of the small sample. In a recent study (without allergy work-up) including only gadodiamide, gadobutrol, gadobenic acid and gadoteric acid, “allergic-like” reactions were more frequent with gadobenic acid and gadobutrol, respectively linear and macrocyclic GC [9].

Cross-reactivity in ST was demonstrated in one third of the allergic patients. There was more cross-reactivity among the macrocyclic GCs, as first hypothesized by Hasdenteufel [6]. More importantly, cross-reactivities between cyclic and linear GCs were found, as described by others [2,4]. Since cross-reactivity between GC is still unclear because of scarce available

78 data (compared to iRCM) [2,4-5], it is compulsory to perform ST with other GC to find
79 alternative agents.
80
81 None of the six allergic patients who underwent another MRI with an alternative GC that
82 showed negative ST experienced another reaction, confirming the reassuring negative
83 predictive value of GC ST [3], although on a small sample.
84 The negative predictive value of GC ST appears very high, but investigations on larger patient
85 cohorts are required. Like for iRCM, DPT with a with ST-negative GC should not be
86 performed for every patient but can be discussed on a case-by-case basis.
87 In this retrospective and monocentric analysis, allergy to GC was confirmed in 13.6% of
88 referred cases. In one third of allergic patients, the index clinical history had been benign and
89 limited to the skin.

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References

1-Behzadi AH, Zhao Y, Farooq Z, Prince MR. Immediate allergic reactions to gadolinium-based contrast agents: a systematic review and meta-analysis. Radiology. 2018;286:471-82.

2-Clément O, Dewachter P, Mouton-Faivre C, Nevoret C, Guilloux L, Bloch Morot E, et al. Immediate Hypersensitivity to Contrast Agents: The French 5-year CIRTACI Study EClinicalMedicine 2018,1:51–61.

3-Chiriac AM, Audurier Y, Bousquet PJ, Demoly P. Clinical value of negative skin tests to gadolinium contrast agents. Allergy 2011;66:1494-1511.

4-Kolenda C, Dubost R, Hacard F, Mullet C, Le Quang D, Garnier L, et al. Evaluation of basophil activation test in the management of immediate hypersensitivity reactions to gadolinium-based contrast agents: a five-year experience. J Allergy Clin Immunol Pract 2017;5(3):846–849.

5-Seta V, Gaouar H, Badaoui A, Francès C, Barbaud A, Soria A. Low-dose provocation and skin tests in patients with hypersensitivity to gadolinium-based contrast agents. Clin Exp Allergy. 2019;49:724–28.

6-Hasdenteufel F, Luyasu S, Renaudin JM, Paquay JL, Carbutti G, Beaudouin E, et al. Anaphylactic shock after first exposure to a macrocyclic gadolinium chelate: A few comments - Reply. J Allergy Clin Immunol 2008;122:216-17.

7-Galera C, Pur Ozygit L, Cavigioli S, Bousquet PJ, Demoly P. Gadoteridol-induced anaphylaxis not a class allergy. Allergy 2010;65:130-39.

8- Brockow K, Romano A, Aberer W, Bircher AJ, Barbaud A, Bonadonna P, et al. European Network of Drug Allergy and the EAACI interest group on drug hypersensitivity. Skin testing in patients with hypersensitivity reactions to iodinated contrast media - a European multicenter study. Allergy 2009;64:234-41.

9-McDonald JS, Hunt CH, Kolbe AB, Schmitz JJ, Hartman RP, Maddox DE, et al. Acute Adverse Events Following Gadolinium-based Contrast Agent Administration: A Single-Center Retrospective Study of 281 945 Injections. Radiology. 2019;292:620-27.

Table 1. Summary table of patients included in the study with comparison of patients with positive and negative skin tests.

	Total N=132 (%)	**Positive test N=18 (%)**	**Negative test N=114 (%)**	***p***
Female	110 (83.3)	14 (77.8)	96 (84.2)	0.50
Median age at the time of reaction (range; yr)	49 (1-82)	51.5 (15-72)	48 (1-82)	0.21
Median time between reaction and test (range; yr)	0.63 (0.08-27)	0.25 (0.08-5.83)	0.75 (0.08-27)	***0.02***
Type of reaction				0.17
Immediate	110 (83.3)	17 (94.4)	93 (81.6)	
Delalyed	22 (16.7)	1 (5.6)	21 (18.4)	
Symptoms				
Urticaria	41 (31.1)	6 (33.3)	35 (30.7)	0.82
Maculopapular exanthema	24 (18.2)	1 (5.6)	23 (20.2)	0.14
Anaphylaxis	38 (28.7)	5 (27.8)	33 (28.9)	0.65
Anaphylactic shock	15 (11.4)	6 (33.3)	9 (7.8)	***0.02***
Isolated bronchospasm	6 (4.5)	0	6 (5.3)	0.32
Others **§**	7 (5.3)	0	7 (6.1)	0.28
Unknown	1 (0.8)	0	1 (0.9)	0.69
Culprit GC	**N=133 (%)** †	**N=18 (%)**	**N=115 (%)** †	
GDTA (Dotarem™)	47 (35.3)	7 (38.9)	40 (34.8)	0.74
GB (Gadovist™)	7 (5.2)	4 (22.2)	3 (2.6)	***0.001***
GT (ProHance™)	3 (2.2)	2 (11.1)	1 (0.9)	***0.01***
GDBA (MultiHance™)	18 (13.5)	4 (22.2)	14 (12.2)	0.25
Gadodiamide (Omniscan™)	2 (1.5)	0	2 (1.7)	0.57
Unknown	56 (42.1)	1 (5.5)	55 (47.8)	***0.001***
Culprit GC				
Macrocyclic	57 (42.9)	13 (72.2)	44 (38.3)	0.07
Linear	20 (15.0)	4 (22.2)	16 (13.9)	0.36
Unknown	56 (42.1)	1 (5.6)	55 (47.8)	***0.001***

Abbreviations: GB: Gadobutrol; **GC:** Gadolinium-based contrast agent; **GT:** Gadoteridol; **GDBA:** Gadobenic acid; **GDTA:** Gadoteric acid; **ICM:** Iodinated contrast agent, **N:** Number; **Yr:** years.

† Total number including patient with suspected hypersensitivity to 2 GC

§ Including isolated eczema, erythroderma, thrill, fever, tightness and discomfort

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Table 2. Summary data of patients with positive skin tests.

	Patient number																	
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9‡**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17‡**	**18‡**
Patient summary																		
Age at reaction	68y	49y	51y	54y	66y	25y	71y	52y	54y	46y	51y	70y	45y	72y	15y	47y	72y	42y
Sex	F	F	F	F	F	F	F	F	M	F	M	M	F	M	F	F	F	F
Previous exposure to GC	NA	No	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	NA	NA	Yes	No	No	Yes	Yes
Delay between reaction and test (Mo)	1	1.5	72	1	6	3	2	9	3.6	2	7.2	3	72	6	13	12	1	12
Type of reaction	I	I	I	I	I	I	I	I	I	I	I	I	I	NI	I	I	I	I
Symptoms	GU, Ao, h, T, Dia, V, Mal	GU, h, T	GU, P, h	GU	MPE, P	GU, Cj, T	Ex, D, N	GU, Ao	U	GU, N	GU, D, Mal	D, h	Ao	MPE	Ao, P	LU, Ao, D, C, Cj	GU	GU, D, V, Mal
Symptom class	Shock	Shock	Shock	Cut	Cut	Ana	Ana	Cut	Cut	Ana	Shock	Shock	Cut	Cut	Cut	Ana	Cut	Shock
GC used for ST †																		
GDTA (Dotarem™)	+ *	-	-	-	+ *	-	+ *	- *	+ *	+ *	-	-	-	-	-	-	-	+ *
GB (Gadovist™)	ND	ND	ND	ND	ND	ND	+	-	ND	ND	-	-	+ *	- *	+ *	-	+ *	+
GT (ProHance™)	ND	ND	+ *	-	+	-	+	-	-	-	-	ND	+	+	+	+ *	-	+
GDPT (Magnevist™)	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	ND	ND	ND
GDBA (MultiHance™)	-	+ *	-	+ *	-	+ *	-	+	-	-	+	+ *	-	-	-	-	-	-
Gadodiamide (Omniscan™)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Negative predictive value of ST																		
Re-exposure to GC on radiologic examination	No	Yes	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No
GC used	-	GDTA	-	-	-	-	-	-	Gadodiamide	GB	GDTA	GDTA	-	-	-	GDTA	-	-
Reaction	-	No	-	-	-	-	-	-	No	No	No	No	-	-	-	No	-	-

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"**+**": Skin prick test positive with the tested GC, "**-**" Skin prick test negative with the tested GC, "*****"culprit GC. The culprit GC was unknown for patient 11 and there was a miss-match between the GC reported by the patients 8 and 14 and the one positive in ST. For patient 11, the culprit GC was unknown.

‡ Considered positive based on clinical history and response in ST with erythema (patient 9: 30mm for GDTA and GDPT, 34 mm for GDBA; patient 17: 18mm for GB; patient 18: 38mm for GDTA, 12 mm for GB and GT). The tryptase level during the reaction was measured only in patient 1 and 2 and was increased in both (41µg/L and 27.9 µg/L respectively, basal tryptase available only for patient 2 and <1 µg/L)

† Gadobutrol was tested in 56 patients and was negative in 51 patients (91.1%), gadoteric acid in 129 patients and was negative in 123 of them (95.4%), gadopentic acid in 105 patients and was negative in 103 patients (98.1%), gadobenic acid in 125 patients and was negative in 118 of them (94.4%), gadoteridol in 112 patients and was negative in 104 patients (92.9%) and gadodiamide was tested in 124 patients, but negative in all.

Abbreviations: Ana: Anaphylaxis **Ao:** Angiodema, **C:** Cough, **Cj:** Conjunctivitis, **Cut:** Cutaneous, **D:** Dyspnea, **Dia:** Diarrhea, **Ex:** Exanthema, **F:** Female, **GB:** Gadobutrol, **GC:** Gadolinium-based contrast agents, **GT:** Gadoteridol, **GU:** Generalized urticaria, **GDBA:** Gadobenic acid, **GDPT:** Gadopentetate dimeglumine, **GDTA:** Gadoteric acid, **h:** Hypotension, **I:** Immediate, **LU:** Localized urticaria, **M:** Male, **Mal:** Malaise, **Mo**: Month, **MPE:** Maculopapular exanthema, **N:** Nausea, **NA:** Not available, **ND:** Not Done, **NI:** Non-immediate, **P:** Pruritus, **ST**: Skin tests, **T:** Tachycardia, **V:** Vomiting, **Y:** Years

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Figure E1.

		MACROCYCLE GC			LINEAR GC		
		GDTA	GB	GT	GDPT	GDBA	Gadodiamide
MACROCYCLE GC	GDTA	X	2/2 (100%)	3/5 (60%)	1/5 (20%)	1/6 (16.6%)	0/6
	GB	0/3	X	2/3 (66.6%)	0/2	0/3	0/3
	GT	0/2	0/1	X	0/1	0/2	0/2
LINEAR GC	GDPT	0/0	0/0	0/0	X	0/0	0/0
	GDBA	0/4	0/1	0/2	1/4 (25%)	X	0/4
	Gadodiamide	0/0	0/0	0/0	0/0	0/0	X

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Legend figure E1: Cross-reactivity patterns for seven patients with at least two positive skin tests to GC ¶

¶ The rate of cross reactivity was calculated using the ratio of patients positives in ST for this alternative on the number of patients tested.

The GC responsible for the reaction are listed vertically, while GC tested for cross-reactivity are listed horizontally. Patient 8 and 14 were excluded from the analysis because of the mismatch between the culprit GC and the positivity found in ST.

Abbreviations: GB: Gadobutrol; **GC:** Gadolinium-based contrast agent, **GT:** Gadoteridol; **GDBA:** Gadobenic acid; **GDPT:** Gadopentetate dimeglumine, **GDTA:** Gadoteric acid, **ST:** Skin tests.

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