

Letter to the Editor

Analysis of cross-reactivity among radiocontrast media in 97 hypersensitivity reactions

To the Editor:

Radiocontrast media (RCM) are responsible for immediate (likely to be IgE- or complement-mediated) or delayed adverse reactions thought to be due to delayed T-cell-mediated hypersensitivity reactions.^{1,2} RCM are assigned to 4 classes: ionic tri-iodized monomers (IMs), ionic hexa-iodized dimers (IDs), nonionic tri-iodized monomers (NIMs), and nonionic hexa-iodized dimers (NIDs).³ A tri-iodinated benzene ring is shared by all RCM, with 3 iodine atoms covalently bonded and substituted radicals in the other 3 positions of the benzene ring. In patients sensitized to RCM, skin tests may be helpful for identifying nontolerated RCM, and also for finding an alternative tolerated radiocontrast medium.⁴⁻⁶ Mechanisms underlying the cross-reactivities between RCM are not fully understood, but iodine is not the eliciting agent.⁷ We examined the cross-reactivities between RCM in patients with immediate (onset ≤ 1 hour after RCM administration) or delayed (>1 hour after RCM administration) hypersensitivity to RCM, and determined whether they were in accordance with the classical chemical classification.

A retrospective study was performed using data from our computerized database "DIAMM-Allergo" (Laboratory Microsix and University Hospital of Nancy Vandoeuvre-Les-Nancy, France). Patients who had skin tests from 2006 to 2012, with 9 RCM, after a nontolerated injection of radiocontrast medium, followed by a substitution test with another radiocontrast medium, were studied. Skin tests were also performed with RCM excipients (trometamol, edetic acid disodium salt, sodium calcium edetate) and povidone-iodine (10% in water) according to previously published guidelines.^{8,9} Patients were also tested, under hospital surveillance, with a radiocontrast medium to which they had a negative skin test result. Intravenous administration was performed with 1/100 of the dose required for radiological examination (1/100 of the usual volume with an undiluted solution); then, if well tolerated, 1 hour later, an injection with 1/10 of the dose required was given. The challenge was considered negative if no adverse reaction occurred within the next 1 week. A complete dose was delivered only during the next radiological examination.

Patients with at least 1 positive patch test result, skin prick test result, or intradermal test result and/or nontolerated challenge (up to 10-1 of the usual dose) with a different radiocontrast medium than the one involved in the patient's reaction were included. Cross-reactions between RCM were studied by multiple correspondence analysis in terms of immediate reactions, delayed reactions, both immediate and delayed reactions, and challenge reactions.¹⁰

Among 340 patients investigated for adverse reactions to RCM, 97 patients (42 men and 55 women; median age, 63.9 years; range, 24-89 years) were included in the study because they had at least 1 positive skin test result and/or nontolerated challenge of radiocontrast medium (28.5%). The clinical features with immediate reactions were urticaria (8), angioedema (14), anaphylactic shock (2), erythema (7), pruritus (1), vomiting (3), and dyspnea (2). Delayed adverse reactions consisted of maculopapular

TABLE I. Skin tests and challenge results with a radiocontrast medium that had negative skin test results

Test	Immediate reactions (N = 38 of 97)	Delayed reactions (N = 50 of 97)	NR (N = 9 of 97)
Positive patch test results	3 (8)	14 (28)	1 (11)
Positive prick test results			
20 min	0	0	0
24 h	0	3 (6)	0
Positive IDT results			
20 min	24 (63)	6 (12)	4 (44)
24 h	8 (21)	33 (66)	1 (11)
Positive challenges	2 (5)	3 (6)	1 (11)

Patch tests, prick tests, and IDTs: performed with 9 RCM. Challenges were performed with 1 of the 9 RCM that was different from the culprit radiocontrast medium.

IDT, Intradermal test (percentages shown in parentheses); NR, not recorded as to whether reaction was immediate or delayed.

TABLE II. RCM were assigned to groups A, B, and C

Group A	Group B	Group C
Ioxitalamate (IM)	Iobitridol (NIM)	Amidotrizoate (IM)
Iopamidol (NIM)	Ioxaglate (ID)	
Iodixanol (NID)		
Iomeprol (NIM)		
Ioversol (NIM)		
Iohexol (NIM)		

exanthema (44), generalized erythema (3), drug reaction with eosinophilia and systemic symptoms syndrome (1), acute generalized exanthematic pustulosis (1), and pruritus (1). Seven patients had unspecified adverse reactions. The most frequently used RCM were iodixanol (n = 33; 34%), iobitridol (n = 15), and iomeprol (n = 14). The responsible radiocontrast medium was unknown in 10 cases, and 22 of the 97 patients (23%) had a reaction to radiocontrast medium after their first exposure.

Skin test results are summarized in Table I. We found only 3 patients (6%) with positive prick test results, whereas 33 patients (66%) had positive intradermal test results at 24 hours in the delayed reaction group. Four patients had positive skin test results to 1 excipient; excipients did not appear to be responsible for the RCM reaction because injection of at least 1 radiocontrast medium containing these excipients was well tolerated. Patch tests with povidone-iodine were positive in 5 of 87 patients. Two patients were sensitized to povidone-iodine and RCM. We observed cross-reactions between RCM in 65 of 97 patients (67%), with more than 1 RCM giving positive skin test results or positive skin test result and positive challenge (see Fig E1 in this article's Online Repository at www.jacionline.org). Cross-reactions occurred between IMs in 2 cases, between NIMs in 93 cases, between ID and IM in 1 case, between NIMs and IMs in 38 cases, between NIMs and IDs in 29 cases, between NIDs and IMs in 9 cases, between IDs and NIDs in 13 cases, and between NIMs in 65 cases (see Fig E2 in this article's Online Repository at www.jacionline.org). Multiple correspondence analyses identified 3 subgroups of RCM (Table II; see Fig E3 in

this article's Online Repository at www.jacionline.org) in which cross-reactions were frequent: group A (iodixanol, iopamidol, iomeprol, iohexol, ioversol, and ioxitalamate), the members of which share 2 identical *N*-(2,3-dihydroxypropyl) carbamoyl side chains (except for ioxitalamate); group B (ioxaglate and iobitridol; we could not establish a chemical link between these 2 RCM); and group C with an isolated radiocontrast medium (amidotrizoate). This classification is based primarily on the scarcity of RCM cross-reactivity among these 3 groups and the frequency of cross-reactivity between RCM within groups A and B. The results were statistically significant among patients belonging to the "delayed" subgroup but less robust for those in the "immediate reactions" group.

To assess more quantitatively the preceding findings, we conducted a logistic regression within the groups for immediate and delayed reactions separately. This allowed us to express the "risk" of positive cross-reactions among the RCM. For delayed reactions, and using a positive reaction to iomeprol as reference, the "risk" of a positive cross-reaction was 19.8 for iodixanol and 33.5 for ioversol. For ioxaglate and iobitridol, the risk was 3. For immediate reactions, taking iopremol as reference, the risk of a positive cross-reaction was 4.6 for amidotrizoate and 10.5 for ioxitalamate. The risk was between 9 and 10 for ioversol, ioxaglate, and iodixanol, using a positive reaction to iopamidol as reference. Other products could not be tested because positive reactions were too rare.

In accordance with previous studies, we observed frequent cross-reactions between RCM (67%) in terms of both immediate and delayed reactions.^{4,6,7,9,11} This study of cross-reactivity between RCM, the largest of its kind to date, demonstrates that frequent cross-reactions between RCM do not follow the current chemical classification. Thus, to explain cross-reactivities, we propose a classification of RCM subgroups A, B, and C according to our clinical results. We suggest challenging sensitized patients with radiocontrast medium from a different subgroup than that of the offending radiocontrast medium (Table II). The frequency of cross-reactions between RCM belonging to the same subgroup is higher than between RCM of the different subgroups A, B, and C. Two previous studies reported frequent cross-reactions (17.5% [n = 34] to 27% [n = 22]) between iodixanol and iohexol (group A),^{4,6} iohexol being the monomer of iodixanol. Hasdenteufel et al¹¹ reported that only 2 of 22 patients sensitized to iodixanol (group A) showed cross-reaction with iobitridol (group B); these data are limited because iobitridol was the only radiocontrast medium used to challenge most of the patients. Regarding the absence of cross-reactivity between RCM and iodized antiseptics, our results are in accordance with previous studies demonstrating that RCM molecules, rather than iodine, are most likely the eliciting compounds.^{4,7} Excipients do not seem to be responsible for RCM hypersensitivity. In studying RCM chemical structures, similar physicochemical characteristics were observed among RCM of group A, except for ioxitalamate, because all shared 2 identical *N*-(2,3-dihydroxypropyl) carbamoyl side chains, which might be an antigenic determinant. Iobitridol does not belong to group A; it has a methyl group on its side chain

[*N*-methyl-(2,3-dihydroxypropyl) carbamoyl], which could change its molecular conformation.

Reactions to RCM frequently occur on first exposure. The percentage of patients unexposed previously to a radiocontrast medium (49.5%; 99 of 200) was also high in a European retrospective multicenter study,⁹ suggesting previous sensitization through an unknown molecule. Cross-reactions among RCM do not follow the current chemical classification. Reactivity to RCM might be induced by earlier exposure to molecules containing carbamoyl side chains, which is found in other molecules such as buzepide metiodure and cefuroxime.

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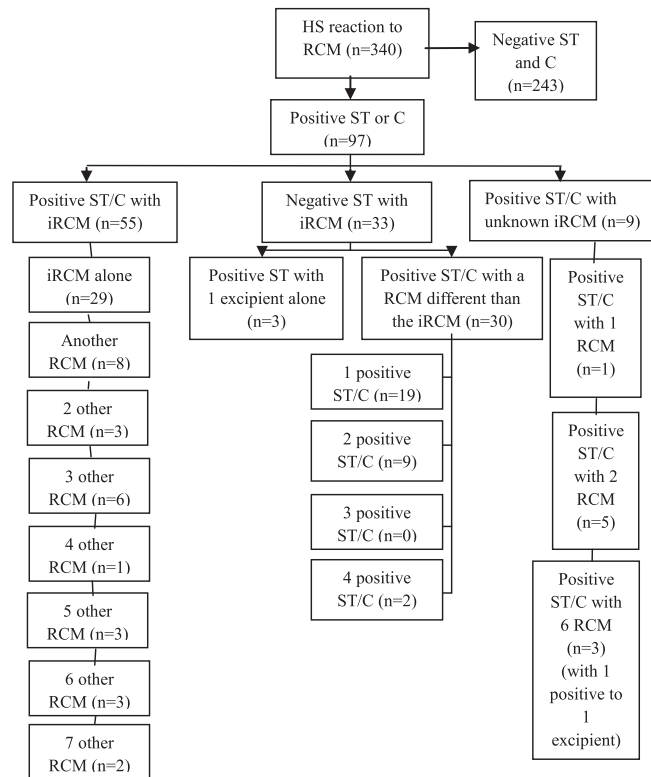


FIG E1. General framework of the study. C, Challenge; HS, hypersensitivity; iRCM, initial radiocontrast media; ST, skin test.

Pts	Amid	Ioxi	Ioxa	Iopa	Iohe	Iome	Iove	Iobi	Iodi
1			IDT(IR)		IDT(IR)			X	
5						IDT(DR)		X	IDT(DR)
6				IDT(DR)				X	
7			Pt					X	Pt
8		IDT(DR)		IDT(DR)	IDT(DR)			X	IDT(DR)
9			IDT(IR)	IDT(IR)				IDT(IR)	X
10			IDT(IR)					X	
11	IDT(IR)							X	
13			IDT(DR)					X	
14			IDT(DR)	X(IR)				X	
15				X	IDR(DR)				IDT(DR)
16	X		IDT(DR)	IDT(DR)	Pt	Pt		Pt	
18			Pt	X					
19			IDT(DR)					X	IDT(DR)
27	IDT(DR)	IDT(DR)		IDT(DR)	IDT(DR)			X	
30			IDT(DR)	IDT(DR)				X	
32				IDT(IR)		IDT(IR)		X	
34				IDT(IR)			X	IDT(IR)	
35		IDT(IR)						X	
36			IDT(IR)				X		
37			Pt	Pt			X		
38				IDT(IR)		IDT(IR)	X		
39							X	IDT(DR)	IDT(DR)
41							X	IDT(DR)	
42			IDT(IR)	IDT(IR)	IDT(IR)	IDT(IR)	IDT(IR)	IDT(IR)	X
44			X				IDT(DR)	IDT(DR)	
46			IDT(IR)	IDT(IR)		X		IDT(IR)	IDT(IR)
48					IDT(IR)	IDT(IR)	IDT(IR)		X
49			IDT(DR)					IDT(DR)	X
50							IDT(DR)	X	

FIG E2. Analysis of cross-reactivity between RCM. *Amid*, Amidotrizoate; *dark gray box*, positive rechallenge; *DR*, delayed skin test reaction; *IDT*, positive intradermal test; *Iobi*, iobitridol; *Iodi*, iodixanol; *Iohe*, iohexol; *Iome*, iomeprol; *Iopa*, iopamidol; *Iove*, ioversol; *Ioxa*, ioxaglate; *Ioxi*, ioxitalamate; *IR*, immediate skin test reaction; *light gray box*, initial RCM (iRCM); *pt*, positive prick test; *Pt*, positive patch test; *Pts*, patients; X, RCM rechallenge.

Pts	Amid	Ioxi	Ioxa	Iopa	Iohe	Iome	Iove	Iobi	Iodi
51			IDT(DR)					X	
52		X					IDT(IR)	IDT(IR)	
53			X(IR)	X				IDT(IR)	
54		X	IDT(DR)	IDT(DR)	IDT(DR)		IDT(DT)	IDT(DT)	IDT(DT)
55		Pt	X	Pt- IDT(DR)	Pt-pt- IDT(DR)	Pt		Pt-pt- IDT(DR)	Pt- IDT(DR)
56					IDT(DR)	IDT(DR)	IDT(DR)	X	IDT(DR)
58			IDT(IR)	IDT(IR)				X	
59					IDT(IR)			IDT(IR)	X
61					IDT(IR)		X	IDT(IR)	
63	IDT(IR)	IDT(IR)				IDT(IR)			X
65		IDT(IR)						X	
66			IDT(IR)					X	
67		X	IDT(DR)		IDT(DR)	IDT(DR)	IDT(DR)	IDT(DR)	IDT(DR)
68				IDT(IR)	X		IDT(IR)		
69				IDT(IR)	X			IDT(IR)	IDT(IR)
70					IDT(DR)			X	
72					IDT(DR)			X	
74		Pt		Pt	Pt	Pt	Pt	X	Pt
75							Pt		
77								X(DR)	
78							Pt	X	X(DR)
79			Pt						X
80			Pt					X	
81			X		IDT(DR)	IDT(DR)	Pt		IDT(DR)
83		Pt		Pt	Pt	Pt	Pt	X	Pt
84		X	IDT(IR)	IDT(IR)				X	
85			X	IDT(DR)	IDT(DR)	IDT(DR)			IDT(DR)
88	X							X(IR)	X(IR)
89	X	Pt	X(DR)	Pt	Pt	Pt	IDT(DR)	Pt	Pt
90		IDT(IR)		IDT(IR)	IDT(IR)	IDT(IR)			X
91			X	IDT(IR)					IDT(IR)
93					Pt	Pt	Pt	X	Pt
94	X	Pt	Pt	IDT(DR)	Pt- IDT(DR)	Pt	Pt	Pt- IDT(DR)	Pt
96			IDT(DR)	IDT(DR)	IDT(DR)	IDT(DR)	IDT(DR)	X	IDT(DR)
97			IDT(IR)			X			

FIG E2. (Continued).

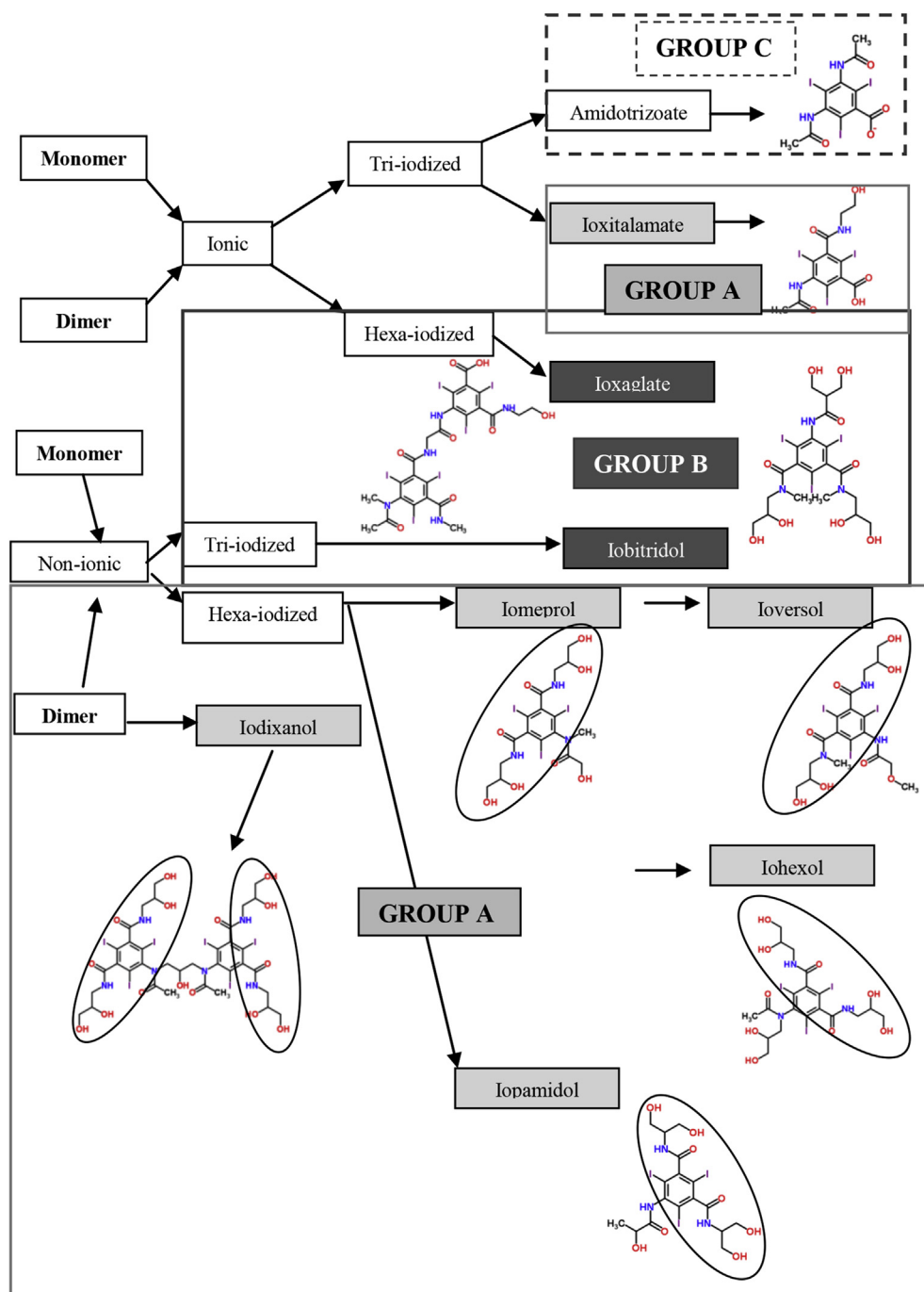


FIG E3. Classification based on radiocontrast media cross-reactivity and their chemical structures.