

BRIEF COMMUNICATION

Diagnosis of immediate hypersensitivity reactions to radiocontrast media

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Keywords

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Abstract

Background: No consensus exists on the diagnostic approach for immediate hypersensitivity reactions (IHR) to radiocontrast media (RCM). We analyzed the diagnostic value of a skin test (ST), drug provocation test (DPT) and basophil activation test (BAT) in patients with symptoms compatible with IHR to RCM.

Methods: Ninety patients with symptoms suggestive of IHR to RCM were evaluated. ST with a panel of RCM was performed, and if negative, DPT was carried out with the culprit RCM. If ST or DPT were positive, tolerance was assessed with an alternative RCM and BAT was carried out with the same panel used for ST.

Results: Eight (8.9%) cases were confirmed as having IHR, 5 (62.5%) by ST and 3 (37.5%) by DPT. Five from those confirmed as IHR (62.5%) had a positive BAT.

Conclusions: Hypersensitivity to RCM was confirmed in 9%, by ST or DPT. BAT proved a valuable method for diagnosis.

Immediate hypersensitivity reactions (IHR) to radiocontrast media (RCM) are those appearing within 1 h after RCM administration (1). Symptoms are usually mild, the skin being the organ most commonly involved (1), although severe anaphylactic reactions can occur (2). Originally, the proposed underlying mechanism of IHR to RCM was the nonspecific release of mast cell mediators (3). However, evidence suggests the existence of a specific IgE-mediated mechanism (3–5), and recently, the basophil activation test (BAT) has been considered useful in the diagnosis (6, 7). The drug provocation test (DPT) has not been routinely recommended because it is not risk free (8), and therefore, the negative predictive value of ST has not been widely established (9). Our aim was to analyze in detail the clinical symptoms and the diagnostic value of skin tests (ST), DPT and BAT in patients with symptoms compatible with IHR to RCM.

Abbreviations

IHR, immediate hypersensitivity reactions; RCM, radiocontrast media; ST, skin tests; IDT, intradermal tests; BAT, basophil activation test; DPT, drug provocation test.

Methods

We studied 90 patients during 2006–2011 because of a history of IHR after RCM administration. IHR severity was classified according to the Ring and Messmer scale (10). We also included 20 patients with good tolerance to RCM as controls, seven of them obtained from the group studied because of a history of a reaction but good tolerance in DPT. ST was carried out as described (1, 4) using the following RCM: iobitridol (Xenetix, Guerbet, Madrid, Spain), iomeprol (Iomeron, Rovi, Madrid, Spain), iodixanol (Visipaque, GE Healthcare Biosciences, Madrid, Spain), iothexol (Omnipaque, GE Healthcare Biosciences, Madrid, Spain), ioversol (Optiray, Covidien, Barcelona, Spain), iopromide (Clarograf, Bayer, Barcelona, Spain) and ioxaglate (Hexabrix, Guerbet, Madrid, Spain). Prick tests were performed using undiluted RCM and IDT using 10-fold dilutions.

In those with a negative ST, a single-blind placebo-controlled DPT was performed with the RCM involved, as described (8). Additionally, in those with a positive ST or DPT, tolerance was assessed with an alternative RCM. This

Table 1 Skin test, DPT and BAT results in patients with confirmed hypersensitivity to RCM (N = 8)

Pat	Symptoms	Interval (days)	RCM	Skin test	DPT (TCD)	BAT (SI)
1	Anaphylaxis	37	Iodixanol	Iodixanol (+) lobitridol (-) lomeprol (-) lohexol (+) loversol (-) lopromide (-) loxaglate (-)	lomeprol (-)(100)	Iodixanol (+)(3.27) lohexol (+)(2.89) lomeprol (-)(1.05) lobitridol (-)(0.56)
2	Anaphylaxis	95	UK	Iodixanol (+) ohexol (+) lomeprol (+) lohexol (-) loversol (-) lopromide (-) loxaglate (-)	lobitridol (+)(5)	Iodixanol (+)(2.75) lohexol (+)(8.16) lomeprol (+)(10.05) lobitridol (-)(1.23)
3	Anaphylaxis	82	lomeprol	Iodixanol (-) lobitridol (-) lomeprol (+)	Iodixanol (+)(50) lobitridol (-)(100)	lomeprol (+)(4.92) Iodixanol (-)(0.97) lohexol (-)(1.21) lobitridol (-)(1.08)
4	Urticaria	49	Iodixanol	Iodixanol (+) lobitridol (-) lomeprol (-) lohexol (+) loversol (-) lopromide (-) loxaglate (-)	lomeprol(-)(100)	Iodixanol (+)(2.71) lohexol (+)(3.07) lomeprol (-)(0.23) lobitridol (-)(0.95)
5	Urticaria	315	lohexol	Iodixanol (-) lobitridol (-) lomeprol (-) lohexol (+) loversol (-) lopromide (-) loxaglate (-)	lomeprol (-)(100)	Iodixanol (-)(1.31) lohexol (-)(1.07) lomeprol (-)(0.32) lobitridol (-)(1.01)
6	Anaphylaxis	365	Iodixanol	Iodixanol (-) lobitridol (-) lomeprol (-) lohexol (-) loversol (-) lopromide (-) loxaglate (-)	Iodixanol (+)(20) lobitridol (-)(100)	Iodixanol (-)(0.32) lohexol (-)(0.81) lomeprol (-)(0.23) lobitridol (-)(1.16)
7	Urticaria	91	lomeprol	Iodixanol (-) lobitridol (-) lomeprol (-) lohexol (-) loversol (-) lopromide (-) loxaglate (-)	lomeprol (+)(100) lohexol (-)(100)	Iodixanol (-)(1.45) lohexol (-)(1.09) lomeprol (-)(0.72) lobitridol (-)(1.26)
8	Urticaria	287	UK	Iodixanol (-) lobitridol (-) lomeprol (-) lohexol (-) loversol (-) lopromide (-) loxaglate (-)	Iodixanol (+)(20) lohexol (+)(20) lomeprol (+)(50) lobitridol (-)(100)	Iodixanol (+)(3.22) lohexol (+)(3.57) lomeprol (-)(0.58) lobitridol (-)(0.37)

Pat, patient; Interval, time interval between reaction and the study; UK, unknown; TCD, total cumulative dose in cc; SI, stimulation index.

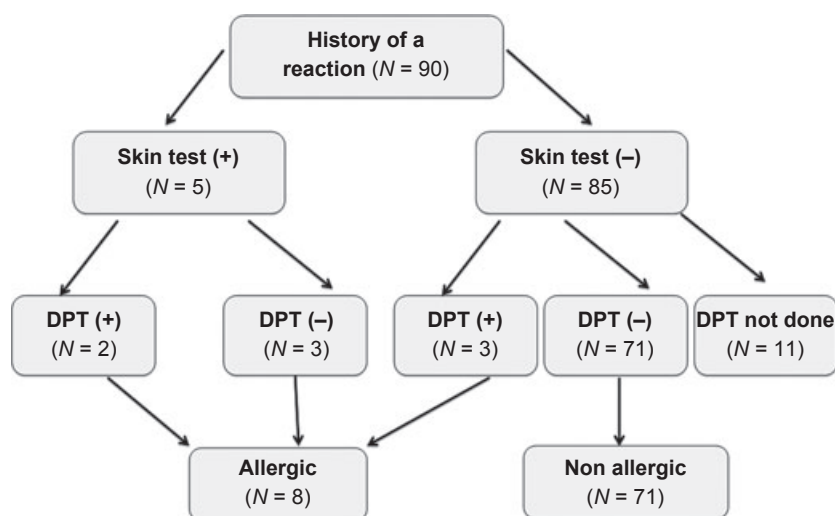


Figure 1 Patients evaluated and methods to confirm the diagnosis.

was administered intravenously in saline at 45-min intervals using 5 cc, 15 cc, 30 cc and 50 cc (cumulative dose = 100 cc).

In patients with a positive ST and/or DPT and in controls, BAT was performed (11) with iohexol (3; 0.3 mg/ml), iodixanol (3; 0.3 mg/ml), iomeprol (3.5; 0.35 mg/ml) and ioxaglate (5.8; 0.58 mg/ml). These concentrations were chosen based on dose–response curves and cytotoxicity studies.

The study was approved by the relevant institutional review boards, and informed consent was obtained from the patients and controls.

Results

The median age of the subjects evaluated was 54.50 ± 27 years; 63 (60%) were women. The RCM involved in the reaction was iomeprol in 26 cases (28.89%), iodixanol in 19 (21.11%), iohexol in 11 (12.22%), iopromide in 9 (10.00%) and unknown in 25 (27.78%). The median time interval between the last reaction and the study was 720 ± 6882.5 days. According to the clinical history, most cases developed reactions with skin involvement (65.65% urticaria/angioedema and 30% generalized erythema), and only 4.44% had airway or cardiovascular involvement. Regarding symptom severity, 69 cases (76.71%) had grade I reactions, 18 (20%) grade II and 3 (3.33%) grade III. No patients had grade IV reactions.

Five subjects (5.56%) had a positive ST: three by prick test (one to iodixanol, one to iomeprol and one to iohexol) and five by IDT (four to iohexol, three iodixanol and two to iomeprol). The ST was negative in all the controls. In the ST-positive patients, DPT was performed with an alternative RCM, being positive in 2 (40%): one to iobitridol and one to iodixanol (Fig. 1).

In cases with a negative ST to all RCM tested ($N = 74$), DPT was carried out with the culprit RCM if known, being positive in 3 (4.05%): one to iodixanol, one to iomeprol and

one to iodixanol, iohexol plus iomeprol. Finally, 11 patients with a negative ST refused to undergo a DPT (Fig. 1). BAT was carried out in the eight cases confirmed as having hypersensitivity, being positive in 5 (62.50%) (Table 1). BAT was negative in all controls.

Those with confirmed hypersensitivity to RCM ($N = 8$) showed a higher grade of severity of the reaction compared to those with good tolerance ($N = 71$). Both groups were similar in age, gender, RCM involved, time interval between reaction and the study, type of examination and number of episodes. No statistical comparison could be made because of the low number of cases in the hypersensitivity group.

Discussion

Of the patients evaluated with a history of IHR to RCM, we finally confirmed fewer than 10% as having hypersensitivity, 62.5% by ST and 37.5% by DPT. In our study, ST positivity was lower than previously reported (73%) (6), possibly due to the presence of false-positive results when ST is performed with pure RCM solutions (2–4, 9, 12). Additionally, in a European multicentre study (4), IDT positivity was higher (26%), possibly due to the higher percentage of patients with severe reactions (2) and the shorter time interval between the reaction and the evaluation (13) as compared to our study.

In the group of patients with positive ST, DPT to an alternative RCM was positive in 40% of cases, indicating that DPT is a necessary and safe method for diagnosing IHR to RCM. These results contrast with a previous report showing a negative predictive value of ST of 96% (9), probably because in this study no DPT with the culprit RCM was carried out.

BAT was positive in 62.5% of cases confirmed as having hypersensitivity, showing a good correlation with the ST and DPT results, thus indicating that BAT may be a useful method for confirming the diagnosis, especially in severe

cases. Moreover, ST and BAT positivity indicate that an IgE mechanism may be involved in some IHR to RCM, mainly the severe reactions (3, 12).

Finally, the RCM most frequently involved were iodixanol and iomeprol, which have a high degree of cross-reactivity (4, 14). We also observed that iodixanol and its monomer iohexol were more likely to induce ST positivity (4, 15).

In summary, we showed that fewer than 10% of cases evaluated after having an immediate reaction after RCM administration were finally confirmed as having hypersensitivity, with both ST and DPT necessary to confirm the diagnosis. In addition, the BAT proved a promising

method for diagnosis that may complement the *in vivo* tests.

Conflicts of interest

None of the authors has any conflict of interest, nor have they received any money for the present study. Research is part of their daily activities. All the authors had full access to all the data and can take responsibility for the integrity of the data and the accuracy of the data analysis. The study was funded by FIS-Thematic Networks and Co-operative Research Centres (RIRAAF/RD07/0064 and RD12/0013).

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