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Diagnostic evaluation of patients with nonimmediate cutaneous hypersensitivity reactions to iodinated contrast media

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Keywords
drug provocation test; hypersensitivity; Iodinated contrast media; nonimmediate; skin tests.

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Abstract

Background: Nonimmediate hypersensitivity reactions to iodinated contrast media (CM) are common. Allergological evaluation is necessary to confirm the diagnosis and to find a tolerated alternative. The aim of this study was to establish the role of skin testing and the drug provocation test (DPT) in the diagnosis of nonimmediate reactions to CM.

Methods: Skin intradermal testing and patch testing with delayed readings were carried out with different CM (iobitridol, iomeprol, iodixanol, iohexol, ioversol, iopramide and ioxaglate). Single-blind placebo-controlled DPT was carried out in those cases with a negative skin test. In seven cases, a skin biopsy was obtained from positive skin tests and positive DPT.

Results: Of the 161 subjects evaluated, 34 (21.1%) were skin-test positive, 21 (50%) to Iomeprol, 7 (16.7%) to Iodixanol, 5 (11.9%) to Iobitridol, 4 (9.5%) to Ioxaglate, 3 (7.1%) to Iohexol and 1 (2.4%) to Iopramide. DPT was positive in 44 cases (34.6%) that were skin-test negative, 38 (76%) to Iodixanol, 8 (16%) to Iomeprol and 4 (8%) to Iohexol. Of 78 cases (48.4%) with confirmed hypersensitivity, 34 (43.6%) were identified by skin testing and 44 (56.4%) by DPT. Skin biopsies showed a perivascular mononuclear cell infiltrate, mainly in the dermis, with higher levels of CD4 than CD8 T lymphocytes, with expression of activation markers and skin homing receptors.

Conclusion: Patients with nonimmediate reactions to CM were identified by skin testing in 43.6% and by DPT in 56.4%. The method to confirm the diagnosis differed depending on the CM involved.

Hypersensitivity reactions to iodinated contrast media (CM) can be classified according to the time interval between drug administration and symptom appearance in two groups: immediate reactions, appearing within 1 h after CM administration, and nonimmediate reactions, appearing later than 1 h after CM administration (1). In the last decade, nonimmediate reactions to CM have been increasingly described, with the skin being the organ most frequently involved (1, 2). Reactions may vary from mild to severe, with maculopapular exanthema being the clinical entity most frequently reported, followed by nonimmediate urticaria, whether or not accompanied by angioedema (1, 3, 4). T-cell involvement has been demonstrated with the presence of perivascular dermal infiltrates of T cells in the affected skin lesions and in the positive skin-test sites as well as lymphocyte proliferation tests to the culprit contrast media (5–8).

Several reports have detected positive delayed intradermal tests as well as positive patch tests to undiluted or diluted CM in patients with nonimmediate reactions to CM (9–18), and general guidelines for this procedure have been published (1). A recent multicentre study found that 47% of the patients with nonimmediate reactions to CM were diagnosed by skin testing, although the negative predictive value of skin testing was not assessed (16).

Only a few studies have examined the role of drug provocation tests (DPT) in the diagnosis of patients with

nonimmediate hypersensitivity reactions to CM (9–11, 17). One study evaluating patients with suggestive reactions to CM and skin-test negative in both delayed reading intradermal and patch testing showed that 41.6% of cases developed a positive reaction after DPT (11). It was therefore suggested that DPT should be considered to establish the diagnosis in the case of a negative skin test as well as for choosing an alternative CM in those with a positive skin test.

Given this background, we considered it necessary to establish the role of skin testing and DPTs in the diagnosis of nonimmediate reactions to CM. Accordingly, we evaluated a group of patients with nonimmediate reactions to CM using a well-defined protocol that included skin testing and a DPT.

Methods

Patients and controls

A group of patients were evaluated in the Allergy Service of Carlos Haya Hospital because of a clinical history indicative of a nonimmediate hypersensitivity cutaneous reaction after administration of a CM. This was considered when symptoms appearing more than 1 h after CM administration.

The clinical categories included were exanthema and nonimmediate urticaria. The criteria for urticaria were when the manifestations were limited exclusively to the skin and consisted of pruritic, erythematous cutaneous nonpersistent elevations that blanched with pressure at various sites of the body, whether or not associated with angioedema. Maculopapular exanthema was considered to be the presence of small confluent erythematous maculae or papules disseminated over different parts of the body, whether or not followed by desquamation. Patients with severe CM reactions like Stevens–Johnson syndrome, acute generalized pustulosis or drug reaction with eosinophilia and systemic symptoms were not included in this study.

Severity was graded according to Brockow (16) as mild when no treatment was required, moderate when the patient responded to appropriate treatment and no hospitalization was needed, and severe when the reaction required hospitalization.

Patients with at least one skin-test positive to common and prevalent inhalant or food allergens were considered atopics. A group of 25 subjects with good tolerance to CM were included as controls.

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

Skin test

Skin testing was carried out as previously described (1, 16) using the following CM: iobitridol (Xenetix; Guerbet, Madrid, Spain), iomeprol (Iomeron; Rovi, Madrid, Spain), iodixanol (Visipaque; GE Healthcare Biosciences, Madrid, Spain), iohexol (Omnipaque; GE Healthcare Biosciences), ioversol (Optiray; Covidien, Barcelona, Spain), iopramide (Clarograf; Bayer, Barcelona, Spain) and ioxaglate (Hexabrix; Guerbet).

Intradermal tests were performed in the volar forearm using 10-fold diluted and undiluted CM and a patch test with undiluted CM. In the intradermal tests, the wheal area was marked initially and 20 min, 1-, 2- and 3-day after testing. In the immediate reading (20 min), an increase in diameter >3 mm surrounded by erythema was considered positive, and in delayed readings (1- to 3-day), an erythematous induration at the skin-test site was considered positive. Patch tests were removed and read at 48 h with an additional reading at 72 h and considered positive according to the European Society of Contact dermatitis (19).

Drug provocation test

Single-blind placebo-controlled DPT was carried out in those cases with a negative skin test as described by the ENDA group (20). CM was administered intravenously diluted in saline at different doses at 1-h intervals. To control any adverse effect and to avoid severe systemic reactions, this was performed in two runs separated with sufficient time to detect reactions appearing later than 48 h. In the first run, 5, 10 and 15 cc of CM were administered and, if this was well tolerated, 1 week later CM was administered at 20, 30 and 50 cc (cumulative dose = 100 cc).

Skin biopsy

Skin biopsies were obtained with a 6-mm punch from skin-test positive and DPT-positive reactions and were processed as described (21) for haematoxylin–eosin and immunohistochemical staining with the following monoclonal antibodies: CD4, CD69, CD25, Granz-B, and perforin (Novocastra Lab., Newcastle upon Tyne, UK), CD8, and HLA-DR (Dako, Ely, Cambridgeshire, UK) and CLA (BD Pharmingen, San Diego, CA, USA). The binding of these primary antibodies (mouse IgG) was detected using an anti-mouse IgG conjugated to peroxidase-labelled dextran polymer (Zymed Lab., San Francisco, CA, USA) and a 3-3′-diaminobenzidine substrate kit (Sigma, St. Louis, MI, USA).

Statistical studies

Comparisons for qualitative variables were carried out using Chi-squared analysis. All reported P values represent two-tailed tests, with values <0.05 considered statistically significant.

Results

A total of 161 subjects with a history of a nonimmediate reaction imputable to at least one CM were evaluated. One patient who developed Stevens–Johnson syndrome was not included. The median age was 58.5 years (IR: 48.85–66.5) with 82 men (50.9%). According to the information obtained from the clinical history, the CM involved in the reaction were iomeprol in 53 (32.9%), iodixanol in 46 (28.6%),

iohexol in 27 (16.8%), iobitridol in 4 (2.5%), ioversol in 3 (1.9%), iopramide in 3 (1.9%), ioxaglate in 2 (1.2%) and unknown in 23 (14.3%). The examinations carried out were a CT scan in 60 (37.5%), coronary angiography in 51 (31.7%), angioCT in 15 (9.3%), urography in 9 (5.6%) and others in 26 (16.1%). Regarding the time interval between drug administration and development of symptoms, different intervals were considered: 1–6 h (13 cases), 7–12 h (27 cases), 13–24 h (68 cases), 25–48 h (41 cases) and >48 h (12 cases). The median interval between the last reaction occurrence and the study was 3.7 months (IR: 1.37–19.5). According to the clinical history, 108 cases (67.1%) developed symptoms compatible with exanthema and 53 (32.9%) with delayed urticaria. Regarding symptom severity, 16 cases (9.9%) had mild reactions, 143 (88.8%) moderate reactions, and 2 severe reactions (1.2%) consisting of desquamative exanthema. Concerning the number of episodes, 132 cases (82%) had one episode and 29 cases (18%) two episodes. Thirty-seven cases (23%) were atopic, 32 (19.9%) had a confirmed diagnosis of drug allergy (20 to nonsteroidal antiinflammatory drugs, 9 to betalactams and 3 to fluoroquinolones) and 7 (4.3%) had chronic urticaria.

In the total group of cases evaluated ($N = 161$), 34 subjects (21.1%) developed a delayed reading of the intradermal tests positive (13 at 1/10 dilution and 29 undiluted). Of these, 27 were skin-test positive to just one CM, 6 to two CM and 1 to three (Table 1). The immediate reading of the intradermal tests was negative in all cases. The skin test was positive to iomeprol in 21 cases (50%), to iodixanol in 7 (16.7%), to iobitridol in 5 (11.9%), to ioxaglate in 4 (9.5%), to iohexol in 3 (7.1%) and to iopramide in 1 (2.4%). In the 34 cases with a positive intradermal test, 10 also had a positive patch test. No positive patch tests were detected in the patients with negative intradermal results. The skin test was negative in all the controls. In the search for an alternative tolerated CM, in this group of 34 patients with a positive skin test, DPT was carried out selecting a CM with a negative skin test. Eleven (32.3%) cases developed 13 positive DPTs (9 to one CM and 2 to two CM). Nine cases developed a positive DPT to iodixanol and 4 to iohexol (Table 1). Figure 1 shows a positive skin test.

A skin biopsy was taken from seven skin-test positive and DPT-positive patients (cases 5, 19, 30, 36, 55, 88 and 150) (Fig. 2), with similar results in all cases. There was a perivascular mononuclear cell infiltrate, mainly in the dermis, with higher levels of CD4 lymphocytes than CD8 T lymphocytes, with expression of CD25 and a higher expression of HLA-DR and CLA. There were foci of vacuoles containing lymphocytes and in six cases accompanied by a high presence of eosinophils.

In the patients with a negative skin test to all the CM tested ($N = 127$), a DPT was carried out with the CM involved (Fig. 3). DPT was positive in 44 cases (34.6%), 19 to one CM and 3 to two CM. Thirty-eight cases (76%) were positive to iodixanol, 8 (16%) to iomeprol and 4 (8%) to iohexol. The response appeared at 50 cc after the first day evaluation in 69% of the episodes and in 31% the maximum dose (100 cc) in the second day evaluation was needed before symptoms developed. These symptoms were similar to those reported by the patients although with a lower intensity (data not shown). The time interval between drug administration and symptom development was: 1–6 h (13 cases), 7–12 h (27 cases), 13–24 h (68 cases), 25–48 h (41 cases) and >48 h (12 cases). Comparisons of this time interval showed that patients responded faster in the DPT than in the clinical history ($P < 0.001$) (Fig. 4).

According to the results obtained, we confirmed hypersensitivity in 78 cases (48.4%), 34 (43.6%) by skin testing and 44 (56.4%) by DPT. The method confirming the diagnosis differed depending on the CM involved. When we considered the two CM most frequently involved in the reaction (iomeprol and iodixanol), the following results were observed: in the 46 cases induced by iodixanol, the diagnosis was confirmed in 16, 6 (37.5%) by means of a positive skin test and 10 (62.5%) by a positive DPT, and in the 53 cases induced by iomeprol, the diagnosis was confirmed in 20, 12 (60%) by a positive skin test and 8 (40%) by a positive DPT. However, these differences were not significant ($P = 0.157$).

Discussion

Nonimmediate cutaneous hypersensitivity reactions to CM include a variety of manifestations, ranging from mild, such as exanthema, to severe, such as Stevens–Johnson or Lyell syndromes, although most reactions reported are from mild to moderate, as occurred in our study group (1, 3, 4). The evaluation of nonimmediate reactions to CM has been gaining attention over recent years (1–4), and for this purpose, a consensus guideline has been produced (1). A number of studies have evaluated the value of skin testing in the diagnosis of nonimmediate reactions to CM, although with variable results (11, 14–17), and only a limited number evaluated the role of DPT (9–11, 18).

In this study, we studied a group of patients with nonimmediate reactions to CM using skin testing and DPT. The inclusion criteria for the study were a consistent history compatible with a nonimmediate reaction with skin involvement after CM administration. The clinical characteristics of these patients were similar to those previously published (11, 15, 17).

We confirmed as allergic nearly 50% of the patients evaluated with an indicative history of a nonimmediate reaction to a CM, a proportion that was higher than found with other drugs such as betalactams (22, 23) or corticosteroids (24). Regarding the diagnostic method that induced a positive response, 43.6% of the cases were skin-test positive, results similar to those recently published in a multicentre study where 47% of the patients with nonimmediate reactions to CM were diagnosed by skin testing (17). Regarding the skin-test protocol, our results agreed with those of other authors (11), confirming that intradermal test sensitivity was higher than patch testing, finding no patient with a negative intradermal skin test and a positive patch test. Intradermal tests were carried out at 1/10 dilution and undiluted, with nearly 70% reacting to the undiluted concentration. Moreover, we found a lack of false positives with both dilutions, with 100% specificity in controls, who all had good tolerance to

Table 1 Skin test and DPT results in skin test positive patients ($N = 34$)

Patient	Age	Sex	Reaction	Contrast media	Skin-test positive	Drug provocation test
5	21	M	Exanthema	Iodixanol	Iomeprol (ID, 1/10)	**Iodixanol (+)**
6	54	F	Exanhema	Iomeprol	Iomeprol (ID, 1/10) Iopramide (ID, 1/1)	Iohexol (−)
9	33	M	Exanthema	Iodixanol	Iodixanol (ID, 1/10) Iohexol (ID, 1/1)	Iomeprol (−)
12	49	M	Urticaria	Iomeprol	Iomeprol (ID, 1/1) Ioxaglate (ID, 1/1)	Iohexol (−)
14	65	M	Exanthema	Ioxaglate	Ioxaglate (ID, 1/1)	Iomeprol (−)
19	72	F	Exanthema	Iomeprol	Iomeprol (ID, 1/10)	**Iodixanol (+)** Ioxaglate (−)
23	48	M	Exanthema	UK	Iobitridol (ID, 1/10)	Iomeprol (−)
27	59	F	Exanhema	UK	Iodixanol (ID, 1/1)	Iomeprol (−)
30	66	F	Exanthema	Ioxaglate	Iomeprol (ID, 1/1) Ioxaglate (ID, 1/1)	**Iodixanol (+)** Iobitridol (−)
31	71	M	Exanthema	Iomeprol	Iomeprol (ID, 1/10)	Iodixanol (−)
36	49	M	Urticaria	Iomeprol	Iomeprol (ID, 1/10)	**Iodixanol (+)** **Iohexol (+)** Iobitridol (−)
39	69	F	Urticaria	Iomeprol	Iomeprol (ID, 1/10)	**Iodixanol (+)** Iohexol (−)
48	62	F	Exanthema	Iobitridol	Iobitridol (ID, 1/1)	Iomeprol (−)
51	67	M	Exanhema	Iodixanol	Iodixanol (ID, 1/10) Iohexol (ID, 1/1)	Iomeprol (−)
55	72	M	Exanthema	UK	Iomeprol (ID, 1/1)	**Iodixanol (+)** **Iohexol (+)** Iobitridol (−)
60	60	F	Urticaria	Iodixanol	Iodixanol (ID, 1/1) Iohexol (ID, 1/1) Iomeprol (ID, 1/10)	Iobitridol (−)
68	68	F	Exanthema	UK	Iomeprol (ID, 1/10) Iobitridol (ID, 1/1)	Iodixanol (−)
72	56	M	Urticaria	UK	Iomeprol (ID, 1/1)	Iodixanol (−)
76	71	M	Exanthema	Iomeprol	Iomeprol (ID, 1/10)	Iobitridol (−)
77	39	M	Exanthema	UK	Iodixanol (ID, 1/1)	Iobitridol (−)
82	49	F	Urticaria	Iomeprol	Iomeprol (ID, 1/1)	Iobitridol (−)
88	68	F	Exanthema	Iomeprol	Iomeprol (ID, 1/1)	**Iohexol (+)**
95	62	M	Exanhema	Iomeprol	Iomeprol (ID, 1/1)	Iohexol (−)
97	54	F	Exanthema	Iodixanol	Iodixanol (ID, 1/1)	Iobitridol (−)
109	33	M	Urticaria	Iohexol	Iobitridol (ID, 1/1)	Iomeprol (−)
111	70	9	Urticaria	Iomeprol	Iomeprol (ID, 1/1)	Iodixanol (−)
120	69	M	Exanthema	Iohexol	Iobitridol (ID, 1/1)	Iomeprol (−)
123	45	F	Exanhema	Iohexol	Iohexol (ID, 1/10)	Iomeprol (−)
128	65	F	Exanthema	UK	Iomeprol (ID, 1/1)	Iobitridol (−)
134	31	M	Exanhema	Iohexol	Iomeprol (ID, 1/1)	**Iodixanol (+)**
141	65	F	Exanthema	Iodixanol	Iomeprol (ID, 1/1)	**Iodixanol (+)**
150	45	F	Urticaria	Iohexol	Iodixanol (ID, 1/10)	**Iohexol (+)** Iomeprol (−)
158	66	M	Exanthema	Iomeprol	Iomeprol (ID, 1/1)	Iodixanol (−)
160	71	M	Exanthema	UK	Ioxaglate (ID, 1/1)	**Iodixanol (+)**

UK, unknown.
Bold data indicate positive provocation test.

CM. Thus, the undiluted concentration needs to be used in the event that the 1/10 dilution is negative in patients with nonimmediate hypersensitivity reactions. In our patients, the procedure was safe and elicited no systemic response with intradermal testing, contrary to what has been published previously (11).

The percentage of cases in our study group in which the CM was not identified was 14.3%, a lower figure than found

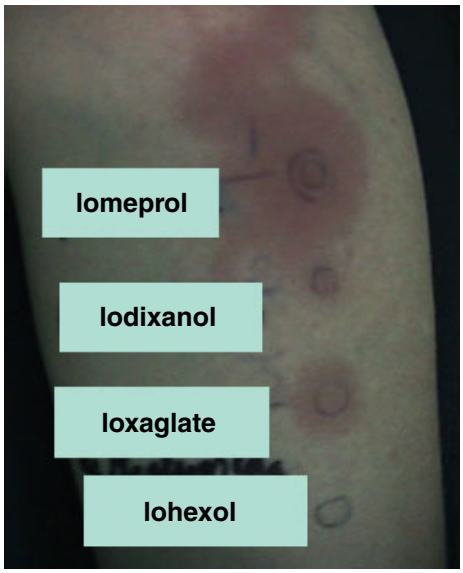

Figure 1 Results of intradermal skin tests at the delayed reading after 48 h with positive reactions to iomeprol and ioxaglate in patient 30.

in a previous multicentre study (16). This is probably due to the short time interval between the reaction and the study (<4 months); these short periods are more appropriate to obtain detailed clinical information than longer intervals (e.g. many years after the episode in many occasions).

Our data confirm that skin-test sensitivity with CM is insufficient, even using maximal concentrations, and that more than half of the cases needed a DPT to be diagnosed. Moreover, in the group of patients with a positive skin test, tolerance could not be guaranteed to an alternative CM from a negative skin test, as DPT was positive in 32.3% of cases.

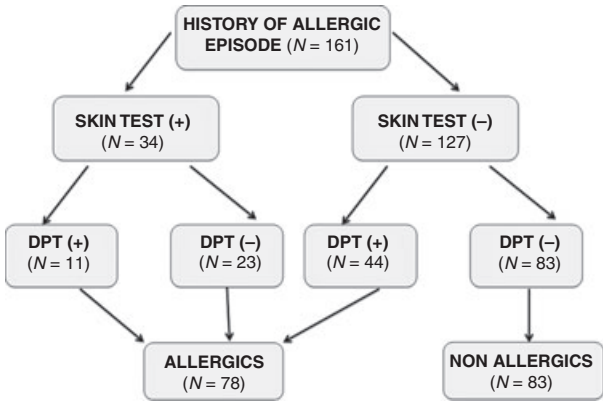

Figure 3 Patients evaluated and methods confirming the diagnosis.

Our data are in agreement with those published by Barbaud, who found that the DPT was positive in 41.7% of patients with nonimmediate reactions to CM and negative skin tests (11), though the results differ from another study showing a high negative predictive value with skin testing (18). However, in this latter study, of the 29 patients evaluated, just four cases were nonimmediate reactions.

Analysis of the time interval between drug administration and symptom development showed that patients reacted sooner when they had a positive DPT compared with the time to symptom appearance reported in their clinical history. One explanation may be that the patients were monitored during the DPT, and therefore, symptoms were detected earlier because of the more precise monitoring of the response. This time interval in DPT is similar to that described for nonimmediate reactions to betalactams (25). Furthermore, the time interval to symptom development reported in the clinical history was also quite similar to that reported by others (16, 17). The analysis of the skin biopsies

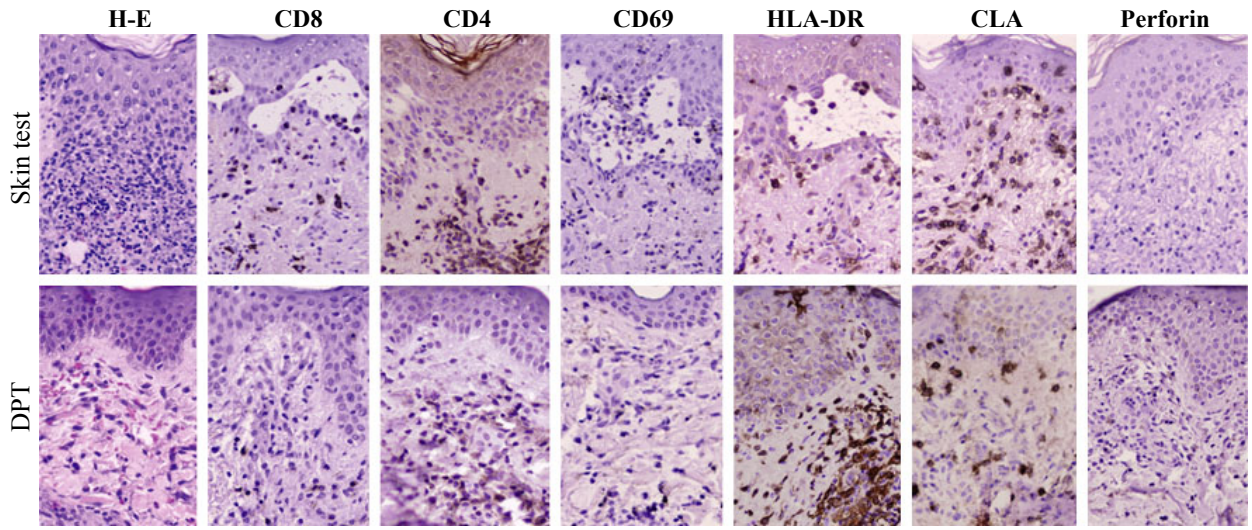

Figure 2 Haematoxylin–eosin and immunohistochemical analysis of different markers, CD4, CD8, CD69, HLA-DR, CLA and perforin, in skin biopsies obtained from the iomeprol-positive skin test and the DPT positive to iodixanol from patient 30.

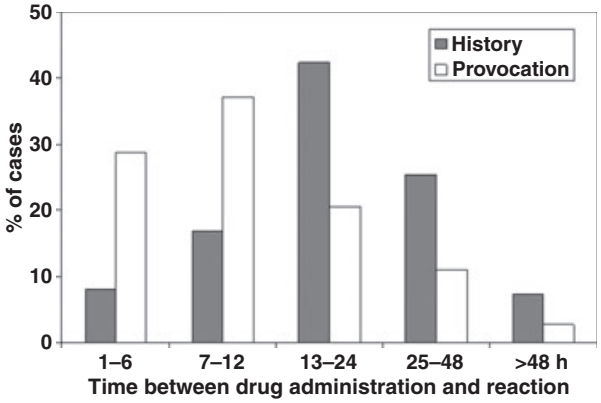

Figure 4 Time elapsed in hours between drug administration and development of the reaction in the history and after DPT in all 55 patients with a positive DPT.

obtained from positive intradermal skin tests and DPTs showed similar results, supporting a T-cell involvement in these reactions, as reported by others (5–8).

In our study, in agreement with others (11, 16), the two CM most frequently involved were iodixanol and iomeprol. We also detected differences in skin-test sensitivity depending on the CM involved, with iomeprol being more likely to induce skin-test positivity, whereas for iodixanol, a DPT was mostly needed to show a positive response, although these differences were not significant and a larger series of cases is needed to confirm the significance of this observation. For iodixanol, though, the skin test appears to be unreliable to predict tolerance. Similar data have been reported by Barbaud (11, 17). The reason for these differences is at present unknown.

Regarding cross-reactivity, the most frequent association detected was iodixanol and its monomer iohexol in six cases: by skin tests in 3, DPT in 2 and skin test plus DPT in one. Cross-reactivity between iodixanol and iohexol has also been described by others (16, 17).

We conclude that skin-test sensitivity is not sufficient and that in more than 50% of cases, a DPT is also needed to establish the diagnosis. Thus, if a radiological examination with CM is needed, the presence of a skin-test negative is not sufficient for recommending a safe alternative.

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Conflict of interest

None of the authors has any conflict of interest. None received money for this study. Research is part of their daily activities. All authors had full access to all the data (including statistical reports) and can take responsibility for the integrity of the data and the accuracy of the data analysis. The study was funded by the FIS-Thematic Networks and Co-operative Research Centres: RIRAAF (RD07/0064).

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