

Case report

Delayed-type hypersensitivity to a nonionic, radiopaque contrast medium

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Background True allergic reactions to iodinated radiocontrast media are rare, and only a few well-documented cases of delayed-type hypersensitivity reactions caused by contrast media have been described.

Methods We report a 61-year-old patient in whom percutaneous transluminal coronary angioplasty (PTCA) was performed with iopamidol, a nonionic contrast medium. Seven days later, the patient developed generalized maculopapular exanthema. Repeated patch tests with several iodinated agents were performed.

Results A first patch test with iopamidol was positive. Repetition of the patch tests showed positive results to iopamidol as well as to iohexol and ioversol, two other nonionic contrast media, but not to other iodinated substances. Three months later, PTCA was repeated, and iopamidol was used again. Despite premedication, pruritic macular exanthema developed 1 day later. Whether iopamidol or trometamol – an additive substance in the contrast medium – was causative could not be determined, since a third set of patch tests was negative.

Conclusions Delayed-type hypersensitivity reactions to iodinated contrast media are rare. We recommend that patients with delayed exanthematous reactions undergo patch or intradermal tests with different contrast media and their additives, and that readings be performed immediately and later at days 2 and 3.

S. Courvoisier, A. J. Bircher

Allergy Unit, Department of Dermatology, University Hospital, Basel, Switzerland

Key words: cross-reactivity; delayed-type hypersensitivity; iopamidol; late-type reactions; nonionic contrast media; trometamol.

Dr A. J. Bircher
Allergy Unit
Department of Dermatology
University Hospital
Petersgraben 4
CH-4031 Basel
Switzerland

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Adverse reactions after injection of nonionic, iodinated contrast media occur in about 3% of patients (1). Immediate reactions, including urticaria, angioedema, bronchospasm, nausea, and anaphylaxis, have typically a nonimmunologic, so-called pseudoallergic pathogenesis (2). In the radiologic literature also, so-called delayed reactions are well documented (3, 4). Usually, they are defined as occurring 1–24 h after injection (2, 3). The definition refers exclusively to the time delay between the injection of the contrast medium and the appearance of the reaction; there is no correlation with either a pathogenetic mechanism or clinical symptoms. Recently, it was proposed to define “delayed reactions” as the onset of adverse events more than 60 min after administration of the contrast medium (5). To avoid confusion with delayed-type hypersensitivity, we prefer the term

“late reactions”, as proposed by Brockow & Ring (6).

Clinical manifestations include persistent pain at the injection site, gastrointestinal symptoms (nausea, vomiting, abdominal pain), flu-like illness, parotitis, angioedema, dyspnea, flush, fixed drug eruption, maculopapular exanthema, and febrile hypersensitivity syndrome (6–11). The pathogenetic mechanisms of most of these reactions are not known (4, 7). Maculopapular eruptions, however, may be based on cell-mediated delayed-type hypersensitivity reactions.

The incidence of late occurring skin rashes due to a nonionic contrast medium (iopamidol) was 5.5% in a study including 1381 patients (7). No further investigations (especially skin tests) were performed in this series. In the literature, there are only a few well-documented case reports of

Table 1. Results of patch tests

Substance	Concentration	Test 1 (days 2/3) (1 month after first exposure)	Test 2 (days 2/3) (2 months after first exposure)	Test 3 (days 2/3) (6 months after second exposure)
Standard series		-/-	nd	nd
Iodine compounds				
Betadine	As is	+ / +, irr	nd	-/-
Betadine	1:10	-/-	nd	nd
Betadine	1:100	-/-	nd	nd
Lugol's solution (potassium iodide)	10%/5%	nd	+ + / + +, irr	-/-
Tincture of iodine (elementary iodine)	0.5%	nd	nd	-/-
Iodoform (Triiodmethane)	5%	nd	nd	-/-
Ionic contrast medium Sodium amidotrizoate	300 mg/ml	nd	-/-	-/-
Nonionic contrast media				
Iopamidol	612.4 mg/ml	+ / + +, all	+ + / + +, all	-/-
Iohexol	755 mg/ml	nd	+ + / + +, all	nd
Ioversol	636 mg/ml	nd	+ + / + +, all	-/-
Iotrolanum	513 mg/ml	nd	nd	-/-
Ioglicine acid	683 mg/ml	nd	nd	-/-
Trometamol	0.1	nd	nd	-/-

all: allergic reaction; irr: irritative reaction; -: negative reaction; nd: not done.

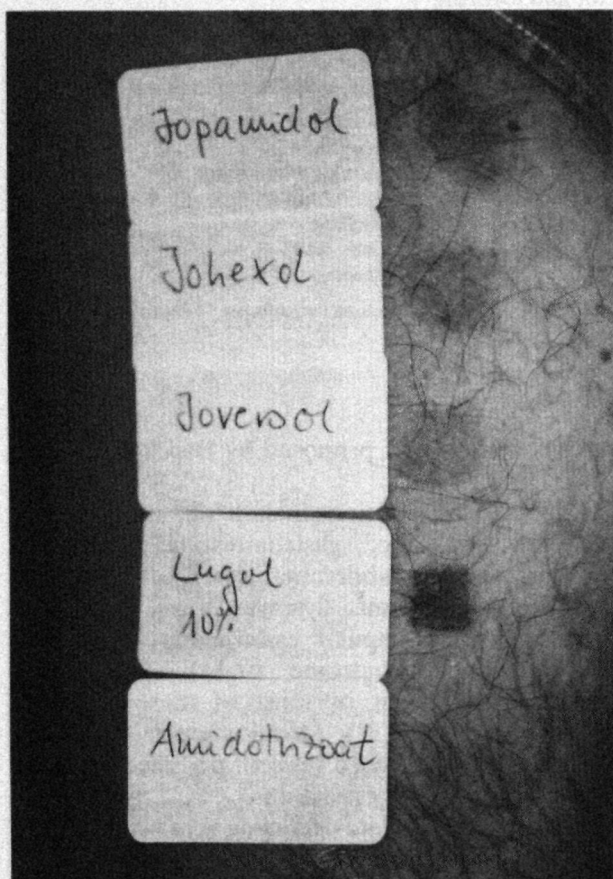


Fig. 1. Positive allergic patch tests to three nonionic contrast media at day 3. Potassium iodide was tested in irritant concentration (10%). Labels top to bottom: iopamidol, iohexol, ioversol, Lugol's solution, sodium amidotrizoate.

delayed-type hypersensitivity reactions to contrast media with positive delayed skin tests (9, 10) (Brockow, personal communication).

We present a patient who developed first maculopapular and then, upon re-exposure, macular exanthema after percutaneous transluminal coronary angioplasty (PTCA) with iopamidol (Iopamiro 370[®]), a nonionic, iodinated contrast medium. Patch tests with iopamidol were twice positive.

Case report

A 61-year-old man was hospitalized because of myocardial infarction. PTCA was performed. Iopamidol (Iopamiro 370), a nonionic product, was used as contrast medium. Seven days later, the patient developed generalized exanthema with severe itching. Two days later, he presented to our outpatient clinic. On examination, there was generalized confluent maculopapular exanthema mainly on the trunk. The face and the mucosae were not involved. The patient had been on the same medication (acetylsalicylic acid 100 mg q.d. and bisoprolol 10 mg q.d.) for 5 weeks. There were no infectious diseases in the recent past. His history showed neither preceding contrast media exposure nor earlier allergic reactions to iodine or drugs, and there was no history of atopy. Under treatment with corticosteroids and antihistaminics, the exanthema resolved without sequelae.

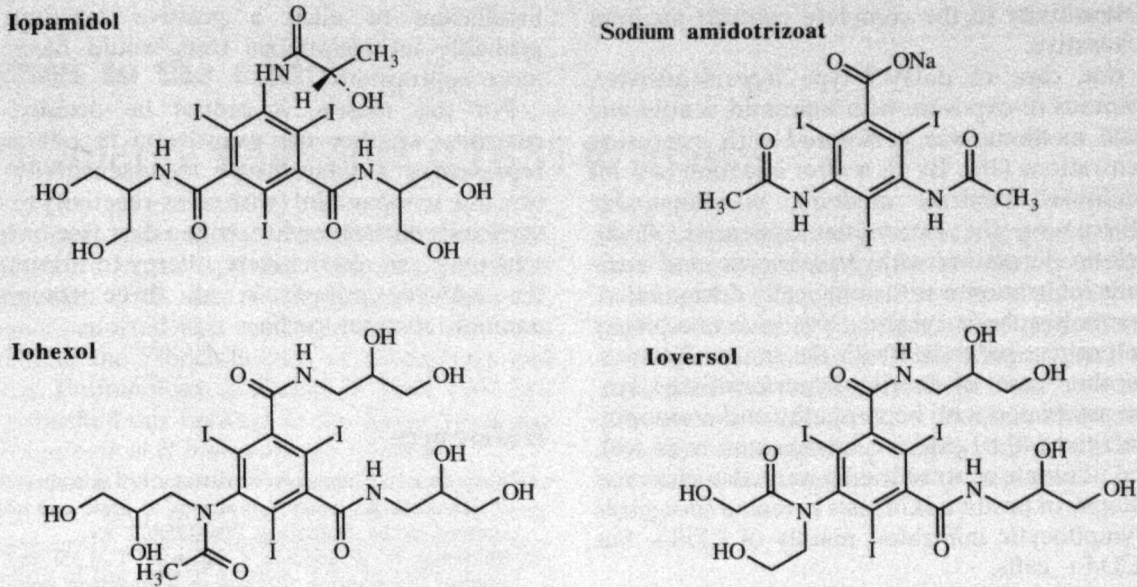


Fig. 2. Chemical structures of three cross-reacting nonionic contrast media and ionic substance sodium amidotrizoate.

Three months later, PTCA had to be repeated. Despite the confirmation that the patient was sensitized to several nonionic contrast media, iopamidol was used again by the cardiologist. Three days before the examination, premedication with prednisone 50 mg q.d. and cetirizine (Zyrtec®) 2 × 10 mg q.d. was started. Nevertheless, 1 day after PTCA, generalized, confluent macular exanthema, accompanied by severe itching, enanthema of the oral mucosa, and hoarseness, developed. The treatment with prednisone and cetirizine was continued in the same doses, and the symptoms cleared within a few days without sequelae.

Material and methods

Patch tests were performed three times, 1 and 2 months after the first exposure and 6 months after the second exposure. The reason for the third patch tests was an additive substance (trometamol, also called trometamine) found in all three nonionic contrast media to which reactions had been positive in the second skin test series. The substances used in the different patch tests are shown in Table 1. The lymphocyte transformation test was performed with iodine, three nonionic media (iopamidol, ioversol, and iohexol), and sodium amidotrizoate, an ionic contrast medium, 1 month after the first exposure.

Results

In the first patch test, the patient had a positive allergic reaction to iopamidol, an irritative reaction

to Betadine® (polyvidone iodine) 1:1, and no reaction to Betadine 1:10 and 1:100 and our standard series. In the second patch test, we observed allergic reactions to iopamidol, ioversol, and iohexol; an irritative reaction to Lugol's solution (potassium iodide); and no reaction to sodium amidotrizoate (Fig. 1). Three exposed controls had negative patch tests to the contrast agents. The third patch test was negative to all agents tested. The lymphocyte transformation test revealed a toxic reaction to the lymphocytes with all tested substances. For safety and ethical reasons, another re-exposure to any of the earlier positive contrast media was not performed. The patient received an allergy "passport" documenting delayed-type hypersensitivity to the three positive nonionic contrast media.

Discussion

Our patient twice developed exanthema after exposure to iopamidol, a nonionic, iodinated contrast medium. The second time, exanthema appeared despite premedication with prednisone and cetirizine. Other causes of maculopapular skin rashes with predominance of the trunk, such as medicaments or infections, were ruled out by the patient's history. The time between injection of the contrast medium and onset of the rash was 7 days for the first and 1 day for the second episode, indicating induction of hypersensitivity after the first exposure. Iodine as a possible allergen was ruled out by negative patch tests to iodine-containing derivatives. Those facts support the hypothesis that an allergic reaction in the form of delayed-type

hypersensitivity to the complete contrast medium was causative.

In one case of delayed-type hypersensitivity, intravenous re-exposure with iopromid, a nonionic contrast medium, was performed with increasing concentrations (10). By 18 h after injection of 5 ml of undiluted contrast medium, maculopapular exanthema on the extremities appeared. Acute spongiotic dermatitis with lymphocytic and eosinophilic infiltration was histologically documented. The same histologic evidence was seen in a biopsy of the positive patch test with the same substance. In another case of febrile hypersensitivity syndrome associated with hepatopathy and eosinophilia, delayed (48 h) positive intradermal tests with several nonionic contrast media were also observed (9). Biopsy of positive skin tests revealed spongiosis and lymphocytic infiltrates, mainly of CD8+ but also CD4+ cells.

We twice observed positive patch tests to iopamidol. Two other nonionic contrast media (iohexol and ioversol), to which the patient had never been exposed, were also positive in the patch tests. That may be interpreted as cross-reactivity of structurally related contrast media (Fig. 2). Cross-reactivity between ionic contrast media has already been proposed (12). Other authors have also shown positive patch tests and positive intracutaneous tests after 24 and 48 h with more than one nonionic contrast medium in the same patient (9) (Brockow, personal communication). These results support the possibility of cross-reactivity. However, in all three nonionic contrast media used for patch tests in our patient, trometamol (tromethamine, trimethylol aminomethane) was present as additive. Trometamol is an alkalizer and emulsifier used in drugs and cosmetics and might provoke contact dermatitis (13). However, so far, no documented cases have been reported.

Surprisingly, there were no positive reactions to the third set of patch tests. Probably the interval of 6 months between the last exposure and the third tests was too long, and spontaneous decrease of hypersensitivity may have taken place, as is known from other types of allergic drug reactions such as those to penicillins. At that time point, the penetration from patch tests may have been

insufficient to elicit a positive reaction, and probably intracutaneous tests would have been more appropriate.

For this reason, it cannot be decided with certainty whether the exanthema in our patient represented a delayed-type hypersensitivity reaction due to iopamidol (with cross-reactivity to other nonionic contrast media), with a decrease or loss of sensitivity, or, alternatively, allergy to trometamol, the additive present in all three commercial nonionic contrast media.

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