

Contrast Media

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Abbreviation:

LTT = lymphocyte transformation test

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Effective Prophylactic Protocol in Delayed Hypersensitivity to Contrast Media: Report of a Case Involving Lymphocyte Transformation Studies with Different Compounds¹

A patient with maculopapular reactions to iopamidol needed to undergo angiography for a cerebral arteriovenous malformation. In vivo and in vitro tests were performed with ionic and nonionic contrast media, including iopamidol and iobitridol. All results were positive, demonstrating delayed hypersensitivity. The patient received 6- α -methylprednisolone and cyclosporine 1 week before and 2 weeks after four angiograms were obtained with the use of iobitridol, which was well tolerated.

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Reactions occurring more than 1 hour after contrast medium administration—called “late” or “delayed” adverse reactions—have recently attracted attention, possibly as a result of a substantial reduction in the number of immediate reactions that occur with the increased use of nonionic contrast media (1). The most common symptoms of delayed adverse reactions to nonionic contrast media are headaches, dizziness, cutaneous eruptions (rash, urticaria, and erythema), gastrointestinal disturbances (nausea, diarrhea, vomiting, and abdominal pain), and persistent pain at injection sites (2–11). The incidence of delayed skin reactions to nonionic contrast media varies from 0.2% to 17.5% in different studies (2–9,11).

The pathogenic mechanisms of most delayed adverse reactions are unknown. In some cases of maculopapular eruptions, however, a type IV cell-mediated pathogenic mechanism has been demonstrated on the basis of delayed intradermal-test and/or patch-test positivity to the contrast medium (12–16). In two patients, diagnosis was confirmed by means of the positivity of the intravenous challenges with the contrast medium (12,14). Moreover, a patient with ioxaglate-induced hypersensitivity syndrome displayed a delayed positive intradermal test result for several nonionic contrast media, including the one responsible (17). There are also reports of single cases of delayed cutaneous (18) or fixed (19,20) eruptions, in which intradermal and/or patch tests of the agents iotrolan, iopamidol, and iomeprol provoked a delayed positive response when performed where the eruption had originally appeared, while they had no effect on previously unaffected regions. In some studies (14,17,18), biopsy results of positive skin and/or patch tests confirmed a cell-mediated pathogenic mechanism, revealing spongiosis and lymphocytic infiltrates.

Patients with a prior adverse reaction to contrast media—particularly of the anaphylactoid type—are at increased risk on subsequent exposure (21). Pretreatment with corticosteroids and antihistamines have been effective in reducing this risk, particularly in patients who have experienced immediate reactions (22,23). Moreover, corticosteroids, when administered with appropriate lead time

before examinations with contrast medium, appear to confer protection against delayed systemic reactions to ionic and nonionic contrast media (24,25).

In the only patient with a true delayed allergic reaction to iopamidol, however, which was diagnosed on the basis of patch-test positivity, a pretreatment regimen with prednisone (50 mg daily) and cetirizine (20 mg daily), which was started 3 days before the examination, was not effective. In fact, in spite of the prophylactic protocol, he experienced a pruritic, macular exanthema, accompanied by enanthema of the oral mucosa and hoarseness 24 hours after repeat exposure to iopamidol, which was administered for a percutaneous transluminal coronary angioplasty (13).

We present the case of a patient with delayed hypersensitivity to iopamidol who tolerated four subsequent diagnostic procedures with iobitridol, to which he was also positive, with a pretreatment regimen that included 6- α -methylprednisolone and cyclosporine.

I Case Report

We report the following case with institutional review board approval and the patient's informed consent.

A 19-year-old man who had experienced a right frontal cerebral hemorrhage with intraventricular hematoma underwent angiography with 160 mL of iopamidol (Iopamiro 370: 7.55 mg/10 mL of water for injectable solution; Bracco Diagnostics, Seattle, Wash), which showed a cerebral arteriovenous malformation approximately 3 cm in diameter, fed by frontal branches of the anterior and middle cerebral arteries. Three days later, he experienced a diffuse, slight maculopapular rash. The patient had been on the same daily medication (100 mg of phenobarbital [Gardenale; Rhone Poulenc Rorer, Milan, Italy], 150 mg of ranitidine [Ranidil; Menarini Sud, L'Aquila, Italy], and 1.5 mg of dexamethasone [Decadron; Merck Sharp & Dohme, Rome, Italy]) for 4 days, beginning 1 day before angiography. Dexamethasone was discontinued, and intramuscular administration of betamethasone (Bentelan; Glaxo Wellcome, Verona, Italy) was started (4 mg daily); after 3 days, the eruption subsided.

Three months later, before angiography for embolization of the malformation with histoacrylic glue (Histoacryl; B. Braun, Milan, Italy), prophylaxis with betamethasone was started (4 mg daily) 2 days before the examination, and io-

pamidol (200 mL) was used again as a contrast medium. Three days after the embolization, the patient developed a generalized maculopapular exanthema with severe itching. The rash resolved completely after 10 days of therapy with intramuscular administration of chlorphenamine (Trimeton; Schering Plough, Milan, Italy) (10 mg twice daily) and oral administration of prednisone (Deltacortene; Bruno Farmaceutici, Rome, Italy) (25 mg twice daily).

There was no personal or family history of allergic diseases.

Because the embolization was not completely successful, the patient had to undergo other diagnostic and therapeutic procedures requiring the use of contrast medium.

One month after the last iopamidol reaction, the patient came to our clinic to be evaluated for a possible allergy to contrast media, and after obtaining his informed consent, the following allergy study was undertaken.

Skin Tests

Prick and intradermal tests were performed with a 1:10 dilution in 0.9% NaCl of a series of ionic (first two) and nonionic (remaining six) contrast media: ioxaglate (Hexabrix 320: 19.65 mg of sodium ioxaglate per 100 mL and 39.3 g of methylglucamine ioxaglate per 100 mL; Guerbet, Aulnay-sous-Bois, France), ioxitalamate (Telebrix 35: 350 mg/mL; Guerbet), iopamidol (Iopamiro 370; Bracco Diagnostics), iomeprol (Iomeron 350: 70 g/200 mL; Bracco Diagnostics), iohexol (Omnipaque 300: 64.7 g/100 mL; Nycomed, Princeton, NJ), iobitridol (Xenetix 300: 65.81 g/100 mL; Guerbet), iopromide (Ultravist 370: 153.772 g/200 mL; Schering, Berlin, Germany), and ioversol (Optiray 320: 678 mg/mL; Mallinckrodt Medical; St Louis, Mo).

All of the above reagents were initially tested on volar forearm skin by means of the prick method, and reactions were considered positive when a wheal larger than 3 mm in diameter was present 20 minutes later. When prick test results were negative, 0.01 mL of the reagent solution was injected intradermally on volar forearm skin. Readings were performed 20 minutes and 24 and 48 hours after injection. Results were considered positive when wheals larger than 5 mm were present. Positive controls for prick and intradermal tests were performed with histamine (at 10 and 1 mg/mL, respectively). Normal saline was used as a negative control. The contrast media

concentrations proved to be nonirritant in a control group of 10 healthy subjects, five of whom had previously tolerated contrast media. Institutional review board approval and informed consent was obtained for these subjects, as well.

Patch Tests

Patch tests were performed with the same series of contrast media by using the undiluted substances. All reagents were applied to uninvolved skin on the interscapular region of the patient's back by using acrylate adhesive strips (Curatest; Lohmann, Neuwied, Germany) with small plates attached for test allergens. Occlusion time was 48 hours. Readings were performed 15 minutes after removal of the strips and 24 hours later, as recommended by Wilkinson et al (26).

Patch tests performed with all the reagents reported above produced negative results in the control group.

Lymphocyte Transformation Test

The lymphocyte transformation test (LTT) was performed according to the Nyfeler and Pichler method (27).

Iopamidol, iohexol, iobitridol, iopromide, and ioversol were added to the medium (RPMI-1640; Sigma-Aldrich, Taufkirchen, Germany) at concentrations ranging from 10 to 150 μ g/mL, while ioxaglate was added at concentrations ranging from 5 to 50 μ g/mL. Tetanus toxoid (Istituto Berna, Barcelona, Spain) was used as a control antigen at a final concentration of 10 limit flocculation per milliliter.

Stimulation indexes were calculated as counts per minute of antigen-containing cultures divided by counts per minute of control cultures (cultures without drugs). A value of more than 2.0 was interpreted as a positive result.

LTT was also performed in five control subjects, three of whom had previously tolerated contrast medium examinations, with negative results.

One month later, our subject underwent an immunosuppressive regimen with oral administration of 100 mg of cyclosporine (Sandimmun Neoral; Novartis Farma, Oreggio [Va], Italy) twice daily and intramuscular administration of 40 mg of 6- α -methylprednisolone (Urbason; Aventis Pharma, Lainate [Mi], Italy) daily. The latter drug was chosen because prednisolone and methylprednisolone are widely used in immunosuppressive protocols, such as those administered to kidney graft recipients (28). To assess the regimen's effectiveness, we re-

peated LTT (on the 6th day after the start of therapy) and the intradermal and patch tests (on the 9th day). Therapy lasted 14 days.

I Results

Results of prick and intradermal tests for all the reagents tested were negative at the immediate (20-minute) reading. Intradermal tests produced positive responses for all contrast media (erythematous, indurated wheals larger than 10 mm) at subsequent readings. After 24 hours, maximum diameters of the wheals were 30 mm for iopamidol, 12 mm for iomeprol, 20 mm for iohexol, 15 mm for iopromide, and 15 mm for ioversol. After 48 hours, maximum diameters of the wheals were 13 mm for ioxaglate, 12 mm for ioxitalamate, and 11 mm for iobitridol.

In patch testing, iopamidol and iohexol produced positive reactions (++ out of a possible +++), consisting of indurated, erythematous areas about 15 mm in diameter with vesicles; ioxaglate, ioxitalamate, iomeprol, iobitridol, iopromide, and ioversol produced indurated, erythematous lesions larger than 10 mm in diameter (+). The positive reactions were present at the 48- and 72-hour readings.

LTT responses to four different concentrations of contrast media in the patient are presented in the Table (3rd column). Results were negative (stimulation index ≤ 2.0) for iopromide and ioversol at all the concentrations used, but they were positive for ioxaglate, iopamidol, iohexol, and iobitridol.

Results of patch and intradermal tests performed on the 9th day of immunosuppressive therapy were negative for all the reagents tested.

The Table (4th column) shows LTT responses in the patient on the 6th day of the immunosuppressive protocol. Results were negative for iohexol, iobitridol, iopromide, and ioversol at all the concentrations used, but they were still positive (stimulation index > 2.0) for ioxaglate and iopamidol.

When considering the results of these tests performed before and during the immunosuppressive regimen, iobitridol was selected as the contrast medium, and the immunosuppressive protocol were applied in subsequent contrast media examinations. In particular, the choice of iobitridol was based on the fact that our patient had negative results for both in vivo and in vitro tests for this contrast

LTT Results before and during Immunosuppressive Therapy

Contrast Medium	Concentration ($\mu\text{g/mL}$)	Stimulation Index before Therapy	Stimulation Index during Therapy
ioxaglate	50	0.8	0.5
	25	0.9	0.5
	10	2.9*	1.5
iopamidol	5	2.9*	3.4*
	150	0.6	0.2
	75	2.0	1.0
iohexol	30	0.9	0.7
	10	2.1*	2.5*
	150	0.4	0.3
iobitridol	75	1.2	0.2
	30	3.1*	0.6
	10	1.0	1.0
iopromide	150	0.7	0.4
	75	2.5*	0.2
	30	0.7	0.7
ioversol	10	1.3	0.9
	150	0.4	0.3
	75	0.7	0.5
ioversol	30	1.2	0.9
	10	1.4	0.7
	150	0.7	0.3
	75	0.4	0.3
	30	1.0	0.8
	10	1.0	0.7

* Corresponds to positive results (over cutoff values).

medium. For the same reason, iohexol could have been selected, but iobitridol was more available.

Four months after evaluation, our patient tolerated angiography with a second embolization, which was unsuccessful, as demonstrated by results of an examination performed 1 week later, without adverse reaction to the contrast medium. This embolization produced slight intraparenchymal bleeding, with a generalized seizure. Two months later, the patient underwent craniotomy and arteriovenous malformation extirpation, as well as two follow-up angiography sessions (at 1 week and 2 months after surgery, respectively), which did not provoke adverse cutaneous reactions and demonstrated that the surgery was successful. Doses of contrast medium used for the examinations at 4 months, 6 months, and the two follow-up angiograms were 300, 35, 50, and 50 mL, respectively.

I Discussion

A number of reports (12–16) have shown that maculopapular rashes occurring after contrast media administration often represent type-IV (cell-mediated) hypersensitivity, which is associated with patch-test and/or delayed (ie, more than 6 hours after administration) intradermal-test positivity for the responsible contrast

medium. In some studies (12,14), challenges with the suspect contrast medium induced delayed-onset skin rashes, confirming the diagnosis. Our patient had experienced two maculopapular rashes after iopamidol administration. Results of in vivo and in vitro studies showed that these were cell-mediated reactions. When considering these two reactive episodes, the second of which occurred despite a prophylactic regimen, we did not repeat angiography in our patient by using the same contrast medium. Moreover, experience regarding delayed reactions to aminopenicillins suggests that patch-test positivity, together with delayed intradermal-test positivity, is an indicator of delayed hypersensitivity (29,30). In a previous study (29), all 16 patients who displayed this pattern of positivity and agreed to undergo challenges with the responsible aminopenicillins reacted positively.

Our patient also showed positive responses to different ionic and nonionic contrast media to which he had never been exposed. Some of these agents, such as iohexol and ioversol, share common benzole—NR—CO—R side-chain structures with iopamidol, which may explain such cross reactivity. Other investigators (13,14,17) have used a series of different contrast media when administering skin tests to patients who had experienced maculopapular rashes, re-

porting positive results with structurally related compounds.

According to Brasch (31), reactivity to structurally unrelated compounds may be explained by the fact that our patient could have been sensitized with halogenated benzene ring derivatives (the class of compounds to which most water-soluble contrast media belong), which are found in food additives, pesticides, and herbicides.

However, there are reports (16,18–20) of patients with delayed cutaneous reactions to contrast media who displayed late positive intradermal-test and/or patch-test responses only to the offending drug.

Although there was a previous attempt (13), to our knowledge this is the first time that a pretreatment regimen has been effective in preventing delayed hypersensitivity reactions to subsequent administrations of a contrast medium to which the patient was positive.

Our protocol differs from common pretreatment regimens, including corticosteroids, not only because cyclosporine is used, but also because of the length and timing.

Cyclosporine is an important immunosuppressive agent in current clinical use. It is a cyclic peptide that is a natural metabolite in a species of fungus. The major action of cyclosporine on T cells is inhibiting transcription of certain genes, most notably the IL-2 gene, blocking the IL-2-dependent growth and differentiation of T cells (32).

In our case, performing skin and patch tests with contrast media during immunosuppressive therapy proved to be a useful indicator of subsequent contrast media tolerability.

As far as LTT is concerned, this test is thought to demonstrate sensitization of T-lymphocytes by provoking a proliferation of drug-specific T cells (27). Some authors (33,34) have obtained positive LTT results in patients with allergy-like reactions to ionic contrast media. Girard and Gamba (33), who had positive responses in 40 of 54 patients, believe that a positive LTT result may represent an alarm signal with regard to further investigations with contrast media. However, little attention has been paid to the use of this test for screening possible immune reactions to nonionic contrast media (1). On the basis of data in the literature, LTT has been used for only two patients who had experienced exanthematous eruptions after administration of nonionic contrast medium (13,16). Brockow et al (16) performed LTT, with negative re-

sults, in a patient 1 year after an adverse reaction to iopentol. In one patient, a toxic reaction to the lymphocytes was observed with all contrast media used, including the one responsible—iopamidol (13).

We used ioxaglate at concentrations ranging from 5 to 50 $\mu\text{g/mL}$, because at concentrations higher than 50 $\mu\text{g/mL}$, the response decreased. This phenomenon, observed in the control group, may be due to a toxic effect.

Before the pretreatment regimen, our patient showed positive LTT responses to the responsible contrast medium, as well as to other compounds. Findings at LTT did not confirm positive results of *in vivo* tests with iopromide and ioversol. A discrepancy between *in vivo* and *in vitro* results has been observed by others (27), although in their experience, the sensitivity of LTT was higher than that of skin tests. This discrepancy could be due to the different antigen concentrations used.

Positive LTT results for iopamidol and ioxaglate during the immunosuppressive regimen could be explained by the fact that LTT was performed on the 6th day of therapy, earlier than the skin and patch tests were performed. As observed with intradermal and patch tests, however, repeating LTT during the immunosuppressive regimen proved to be a useful indicator of tolerability of iobitridol, the contrast medium used to acquire the four subsequent angiograms.

Although this prophylactic protocol was applied only in one patient, its effectiveness in four different administrations of contrast media suggests that it should be useful in similar cases.

When considering that our prophylactic protocol is actually one of immunosuppressive therapy, in case of surgical intervention, it is advisable to add antibiotic prophylaxis (eg, cotrimoxazole) for preventing infections, as has successfully occurred in kidney graft recipients treated with cyclosporine (28).

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