Allergy 2009: 64: 234–241

DOI: 10.1111/j.1398-9995.2008.01832.x

Original article

Skin testing in patients with hypersensitivity reactions to iodinated contrast media – a European multicenter study

Background: Iodinated contrast media cause both immediate and nonimmediate hypersensitivity reactions. The aim of this prospective study was to determine the specificity and sensitivity of skin tests in patients who have experienced such reactions.
Methods: Skin prick, intradermal and patch tests with a series of contrast media were conducted in 220 patients with either immediate or nonimmediate reaction. Positive skin tests were defined according to internationally accepted guidelines. Seventy-one never-exposed subjects and 11 subjects who had tolerated contrast medium exposure, served as negative controls.
Results: Skin test specificity was 96–100%. For tests conducted within the time period from 2 to 6 months after the reaction, up to 50% of immediate reactors and up to 47% of nonimmediate reactors were skin test positive. For immediate reactors, the intradermal tests were the most sensitive, whereas delayed intradermal tests in combination with patch tests were needed for optimal sensitivity in nonimmediate reactors. Contrast medium cross-reactivity was more common in the nonimmediate than in the immediate group. Interestingly, 49% of immediate and 52% of nonimmediate symptoms occurred in previously unexposed patients. Many of these patients were skin test positive, indicating that they were already sensitized at the time of first contrast medium exposure.
Conclusions: These data suggest that at least 50% of hypersensitivity reactions to contrast media are caused by an immunological mechanism. Skin testing appears to be a useful tool for diagnosis of contrast medium allergy and may play an important role in selection of a safe product in previous reactors.

K. Brockow[1], A. Romano[2], W. Aberer[3], A. J. Bircher[4], A. Barbaud[5], P. Bonadonna[6], E. Faria[7], G. Kanny[8], M. Lerch[9], W. J. Pichler[9], J. Ring[1], J. Rodrigues Cernadas[10], E. Tomaz[11], P. Demoly[12], C. Christiansen[13], for the European Network of Drug Allergy and the EAACI interest group on drug hypersensitivity

[1]Department of Dermatology und Allergology Biederstein, Division Environmental Dermatology and Allergology Helmholtz Zentrum München/TUM, Technical University Munich, Munich, Germany; [2]Allergy Unit, C.I. Columbus, Rome and IRCCS Oasi Maria S.S., Troina, Italy; [3]Department of Dermatology, Medical University of Graz, Graz, Austria; [4]Allergy Unit, Department of Dermatology, University Hospital, Basel, Switzerland; [5]Department of Dermatology, University Hospital, Fournier Hospital, Nancy, France; [6]Allergy Unit, Verona Hospital, Verona, Italy; [7]Immunoallergology Department, Coimbra University Hospital, Coimbra, Portugal; [8]Department of Internal Medicine, Clinical Immunology and Allergy, University Hospital, Hospital Central, Nancy, France; [9]Clinic for Rheumatology and Clinical Immunology/Allergology, Inselspital, Bern, Switzerland; [10]Department of Allergy and Clinical Immunology, University Hospital of S. João, Porto, Portugal; [11]Hospital S. Bernardo, Setúbal, Portugal; [12]Exploration des Allergies, Maladies Respiratoires, INSERM, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, Montpellier, France; [13]Research and Development, GE Healthcare, Oslo, Norway

Key words: contrast media; hypersensitivity; skin tests.

Knut Brockow, MD
Department of Dermatology and Allergology
Biederstein
Technische Universität München
Biedersteiner Str. 29
80802 München
Germany

Accepted for publication 20 May 2008

Iodinated contrast media (CM) are highly concentrated solutions of iodinated benzene derivatives, used to enhance X-ray procedures (1). Although these products are regarded as relatively safe, they are known to cause both immediate (≤ 1 h) and nonimmediate (>1 h) hypersensitivity reactions in susceptible individuals (2).

Immediate hypersensitivity reactions to CM are mainly anaphylactic reactions that can be severe or even fatal (3), whereas nonimmediate reactions predominantly manifest themselves as exanthematous skin eruptions occurring hours to days after CM application [reviewed in Ref. (4)]. Even the newer generation CM cause immediate and nonimmediate reactions in about 1–3% of applications (2). These reactions are a serious problem considering that more than 75 million CM-enhanced X-ray procedures are conducted yearly world wide (5).

CM-induced hypersensitivity reactions have traditionally been classified as nonallergic reactions (6), and skin tests have been regarded as inappropriate tools in patients having experienced such reactions. However, during the last few years several investigators have reported positive skin tests in patients with both immediate and nonimmediate hypersensitivity reactions after CM exposure, which indicates that immunological mechanisms may be involved (7–15). The European Network of Drug Allergy (ENDA; the EAACI interest group on drug hypersensitivity) therefore designed a prospective multicenter study to explore the sensitivity and specificity of skin tests in patients who reported typical features of CM hypersensitivity reactions. In this paper we report the results from the first 4 years of study.

Methods

Patients and negative control subjects

Patients who were referred to the 12 allergy departments of the ENDA CM task force members because of a reported previous hypersensitivity reaction after CM exposure were included in the study. Most cases (95%) were prospectively collected over a 4-year period from January 2003 to December 2006. Eight patients in the immediate group and two patients in the nonimmediate group were tested prior to 2003. The same standardized procedures were used in all patients. Clinical data were recorded using an adaptation of the ENDA drug allergy questionnaire (16). The hypersensitivity reaction was classified as immediate (onset ≤ 1 h after CM administration) or nonimmediate (onset >1 h after CM administration). For immediate reactions the severity scale of Ring and Messmer (17) was used: grade I: generalized cutaneous and/or mucocutaneous symptoms; grade II: mild systemic reactions; grade III: life-threatening systemic reactions; grade IV: cardiac and/or respiratory arrest. In patients with nonimmediate hypersensitivity reactions, the reaction was graded as mild when no treatment was required, moderate when the patient responded readily to appropriate treatment and no hospitalization was needed, and severe when the reaction required hospitalization or was life-threatening.

Seventy-one subjects never exposed to any CM and 11 subjects who had tolerated CM exposure could be recruited on a voluntary basis as negative controls. Before testing, informed consent was obtained from all control subjects for whom the skin tests were not part of the recommended routine allergological workup. The study was approved by regional institutional review boards.

Skin testing

Skin testing was performed with a minimum delay of 1 week and a median delay of 6 months after the CM-induced hypersensitivity reaction. Skin prick tests (SPTs) with undiluted CM were followed by intradermal tests (IDTs) with 10-fold diluted CM and patch tests (PTs) with undiluted CM. SPTs were performed on the volar forearm, and were read after 20 min and on days 2 and 3. The SPT was considered positive if a wheal of ≥ 3 mm in diameter was observed after 20 min (immediate reading) or if an erythematous induration occurred at the skin test site on days 2 or 3 (delayed reading). Intradermal tests were conducted on either the volar forearm or the back. The test solution (0.03–0.05 ml) was injected into the skin to produce a bleb of 4–5 mm in diameter. Readings were conducted after 20 min and on days 1, 2 and 3. The IDT was regarded as positive if the size of the initial wheal had increased by at least 3 mm in diameter and was surrounded by erythema after 20 min (immediate) or if an erythematous induration at the skin test site was present in the delayed readings. Histamine (0.01%) and saline (0.9%) served as positive and negative controls, respectively. Patch tests were conducted with CM soaked on a filter paper in a 12 mm aluminium Finn chamber, fixed with adhesive tape on the back for 2 days. Readings were conducted 15 min after removal of the strips and 24 h later in accordance with the recommendations of the European Society of Contact Dermatitis (18). Patients were instructed to return to the treating physician in case of positive reactions at other time points.

Patients were skin tested with the culprit CM (if known) and as many of the following 13 CM as could be practically handled in the respective allergy centers: The three ionic monomers sodium amidotrizoate, ioxithalamate and iodamide; the ionic dimer ioxaglate; the seven nonionic monomers iohexol, iomeprol, iobitridol, iopamidol, ioversol, iopromide and iopentol; and the two nonionic dimers iodixanol and iotrolan. All solutions had a strength of 300–320 mgI/ml.

All the above listed CM were used for skin testing in 31 or more nonexposed individuals. While iodamide was tested only in 1 CM exposed control, the other 12 CM were tested in 7 or more of the 11 individuals in this group. SPT, IDT and PT with immediate and late readings were conducted, as described above.

A history of a typical drug hypersensitivity reaction after administration of CM was used as a gold standard, and skin test sensitivity was calculated as the percentage of skin test positive among these patients. Skin test specificity was calculated as the percent of negative controls with positive skin test to any of the tested CM, indicating possible irritative skin test reactions.

Statistical methods

Two-sided 95% confidence intervals (CI) for frequencies were based on Kaplan–Meier estimates, using Minitab 12 software. The Fisher exact test was used for statistical comparison between groups. Differences with *P*-values less than 0.05 were considered significant.

Results

Patient characteristics

Table 1 summarizes the information collected from the 220 investigated patients with well-characterized features of either immediate (122 patients) or nonimmediate (98 patients) hypersensitivity reactions after CM administra-

tion. The median age at the time of the diagnostic testing was 54 years (age range 12–83) for patients in the immediate group and 58 years (age range 12–80) for patients in the nonimmediate group.

Significantly more patients reported hypersensitivity reactions after intravenous than after intra-arterial CM administration (98% *vs* 2% respectively). Sixty-two percent of patients in the immediate group and 49% of patients in the nonimmediate group reported a history of allergy. Other drug allergies were said to have affected 28% of the patients with immediate reaction and 29% of those with nonimmediate reaction. None of the patients in either group claimed to suffer from seafood allergy.

Only 53 of 108 patients (49%) in the immediate group and 48 of 92 (52%) in the nonimmediate group had a reported history of prior CM exposure. Information about prior CM exposure was available for 23 of the 27 patients with immediate grade III reactions. Only 12 of these patients had previously been exposed to a CM. Of the two patients with grade IV reaction, 1 received a CM for the first time.

For 137 patients, the implicated CM was known. Reactions to nonionic CM were far more frequent than reactions to ionic CM (120 *vs* 15), reflecting their current much greater usage. While there was no significant difference in frequency of immediate reactions to the different nonionic CM, iodixanol caused late reactions significantly more often than the other nonionic products ($P < 0.05$). However, it should be noted that the relative frequency of use of the different nonionic CM in the different centers was unknown.

Table 1. Patient information

	Immediate reactors, *n* (%)	Nonimmediate reactors, *n* (%)
Demographics		
Total number	122	98
Female gender	80 (66)	57 (58)
History of allergy	77 (62)	48 (49)
Asthma bronchiale	19 (16)	9 (9)
Rhinoconjuctivitis	40 (33)	14 (14)
Other drug allergies	34 (28)	28 (29)
Contact allergy	12 (10)	16 (16)
Known prior exposure	53/108 (49)	48/91 (53)
Prior reaction	28/108 (26)	12/91 (13)
Route of administration		
Intravenous	109	87
Intra-arterial	1	3
Other	1	3
Unknown	11	5
Implicated contrast medium		
Iobitridol (nonionic monomer)	5	4
Iohexol (nonionic monomer)	6	5
Iomeprol (nonionic monomer)	17	12
Iopamidol (nonionic monomer)	6	3
Iopentol (nonionic monomer)	1	7
Iopromide (nonionic monomer)	12	8
Ioversol (nonionic monomer)	3	2
Iodixanol (nonionic dimer)	4	26
Ioxithalamate (ionic monomer)	5	4
Amidotrizoate (ionic monomer)	–	1
Ioxaglate (ionic dimer)	4	–
Others	–	5
Unknown	59	24

Clinical characteristics of the reported hypersensitivity reactions

Clinical manifestations. Cutaneous, respiratory, gastrointestinal and cardiovascular organ systems were all frequently involved in the immediate reactions, while skin reactions were the main manifestations of the nonimmediate reactions (Table 2). Immediate skin reactions were urticaria, angioedema and erythema, whereas nonimmediate skin reactions were various types of skin rashes such as macular and maculopapular exanthema, as well as urticaria-like rashes and angioedema. Nausea, vomiting, dyspnoea and hypotension were the main noncutaneous symptoms affecting the immediate reactors.

Severity. The severity of the immediate reactions was grade I in 38 patients (31%), grade II in 55 patients (45%), grade III in 27 (22%) and grade IV in 2 patients (1.6%). Four patients with grade III reaction were known to be premedicated with anti-histamines and/or steroids, but the regimens used were not specified. Medical treatment was reported for 78% of patients. The type of treatment depended on symptoms.

Nonimmediate reactions were mainly mild to moderate skin eruptions (81%) that were often treated with either antihistamines (12%), corticosteroids (31%) or a combination of the two (42%). Hospitalization was reported for two patients. Occasionally, more severe skin eruptions were observed. These were bullous exanthema, flexural exanthema, palpable purpura, purpura/maculopapular eruption combined with eosinophilia, psoriasis-like exanthema, acute generalized exanthematous pustulosis (AGEP) and exfoliative eruption (each type of eruption reported once). Of the three patients with nonimmediate cardiovascular symptoms, only one was known to suffer from cardiovascular disease. She reported bronchospasm and cardio-respiratory arrest 12 h after a computed

Table 2. Clinical manifestations of immediate and nonimmediate hypersensitivity reactions to iodinated contrast media

Symptoms	Immediate (%)	Nonimmediate (%)
Urticaria/urticarial rash	33	19
Angioedema	25	24
Exanthema	12	67
Erythema	11	9
Dyspnea	30	7
Nausea/vomiting	18	6
Hypotension	16	0
Collapse	11	3

tomographic thorax examination. The other two patients reported unspecified collapse after 3 and 24 h, respectively. Only the patient with unspecific collapse after 24 h had a history of previous CM administration.

Repeated reactions. Of the 53 patients in the immediate group who reported prior CM exposure, 28 (53%) had experienced a previous reaction. The symptoms of the reactions were known in 22 cases. The repeated reaction was of the same grade as the previous reaction in 15 and more severe in 7. For six of these seven patients the repeated reaction was of grade III and occurred despite known premedication in four.

Repeated reactions were less frequent in the nonimmediate group. Of the 48 patients with known prior CM exposure, only 12 (25%) reported a previous reaction which in 3 occurred despite premedication. All patients with nonimmediate repeated reactions experienced the same symptoms on each occasion.

No patients experienced first a nonimmediate reaction and subsequently an immediate reaction or vice versa.

Time to onset of reaction. Time to onset of the reaction was known for 107 patients in the immediate group and for 95 patients in the nonimmediate group. Reaction within 1–5 min after CM injection was recorded in 72 immediate reactors, after 10–15 min in 19, after 20–30 min in 13 and after 45–60 min in 3. For the nonimmediate reactors, the latency was 1–6 h in 18, 7–12 h in 21, 13–24 h in 21, > 1–2 days in 14, > 2–3 days in 9 and > 3 days in 12. As shown in Fig. 1, there was no difference in the delay between CM injection and the onset of symptoms in patients having previous CM exposure or not. There was no tendency that the more severe immediate reactions were reported to occur more rapidly than the less severe reactions.

Skin test results

Immediate reactors. Positive skin tests were observed in 32 of 122 patients with immediate reaction (26%; 95% CI: 18–34%). Only 4 of the 122 patients had positive SPT. Intradermal tests were positive in 30/121 patients (25%) when read after 20 min and in 3/121 patients (2.5%) when read after 10–24 h. One patient with a severe anaphylaxis to an unknown ionic CM 28 years previously, experienced a systemic reaction consisting of urticaria, rhinoconjuntivitis and glottis edema 5 min after an IDT with a nonionic CM, whereas all SPTs had been negative.

Positive immediate IDT to at least one of the tested CM was observed in 3/71 of the unexposed controls, but in none of the 11 CM-exposed controls. Thus, the specificity of the IDT was 96.3% (95% CI: 92–100%).

Each patient was only skin tested on one occasion. The percentage of patients with positive skin tests varied according to the time between reaction and testing (Table 3). While the frequency of positive test results

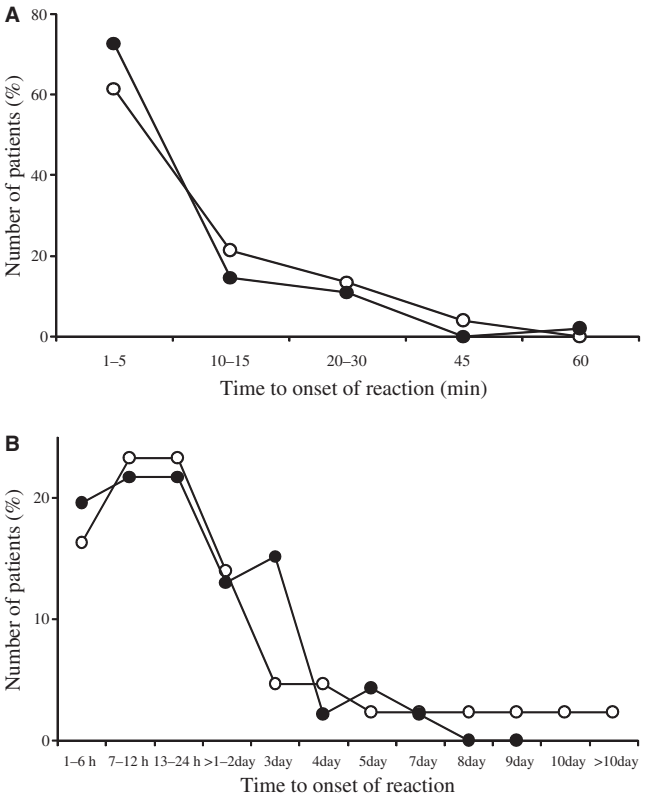

Figure 1. Time to onset of immediate (A) and nonimmediate (B) reactions for patients with (●) or without (○) previous contrast medium exposure.

was 14/28 (50%) in patients tested within 2–6 months, it was only 17/92 (18%) for patients tested at other time points (earlier than 2 months or later than 6 months). This difference was statistically significant ($P = 0.0003$). Interestingly, 43% of the patients with positive skin tests had reacted to a CM on first exposure.

For patients tested within the optimal time period 2–6 months after the reaction, there were no more patients with severe reactions nor patients with a history of allergy in the skin test positive group than in the skin test negative group (data not shown).

The CM that had caused the reaction was known for 28 of the skin test positive patients. Twenty-four of them (86%) tested positive to the implicated CM. Twenty-seven of the 32 skin test positive patients were tested with 4 or more CM. In each case, at least one product was skin test negative. More extensive cross-reactivity testing with 8 or more CM was conducted in 11 patients. The results are shown in Table 4. Six patients were positive to only one product, two patients were positive to two products, while more extensive cross-reactivity was observed in the remaining three patients. Cross-reactivity between ionic and nonionic CM was reported in 4 of the 11 patients.

Nonimmediate reactors. Delayed skin tests were positive in 37 of 98 nonimmediate reactors (38%; 95% CI:

Table 3. Effect of time period between reaction and skin testing on frequency of positive tests in patients with reported prior immediate and nonimmediate hypersensitivity reaction, respectively

	Immediate reaction		Nonimmediate reaction	
Time from reaction to skin testing	Patients tested	Positive cases (%)	Patients tested	Positive cases (%)
1 week to 1.5 months	18	3 (17)	19	9 (47)
2 months	8	3 (38)	20	7 (35)
3 months	7	5 (71)	11	9 (82)
4–6 months	13	6 (46)	12	5 (42)
7–12 months	8	2 (25)	10	2 (20)
>1–3 years	14	4 (29)	7	2 (29)
>3 years	52	8 (15)	18	4 (22)
Unknown	1	1 (50)	1	–

Table 4. Results from cross-reactivity testing of patients with previous immediate hypersensitivity reactions after contrast medium exposure*

Test	Patient number										
Substance	1	2	3	4	5	6	7	8	9	10	11
Nonionic											
Iodixanol	x	x	x	x	x	x			x	x	x
Iohexol	x	x	x	x	x	x	x		x	x	x
Iopentol	x	x	x		x		x	x	x		
Ioversol	x	x	x	x	x	x	x	x	x	x	
Iomeprol	x	x	x	x	x	x	x	x	x	x	x
Iopamidol	x	x	x	x	x	x	x	x	x	x	x
Iopromide	x	x	x	x	x	x	x	x	x	x	
Iobitridol	x	x	x	x	x		x	x	x	x	x
Iotrolan	x	x	x		x				x	x	
Ionic											
Ioxaglate	x	x	x	x	x	x	x	x	x	x	x
Ioxithalamate	x	x	x		x	x		x	x	x	x
Amidotrizoate				x	x	x	x	x	x	x	x
Iodamide				x							

*The contrast media used for skin tested are marked x and the contrast media that caused the hypersensitivity reactions are highlighted with borders (the implicated contrast medium was unknown for patient 4). The shaded boxes indicate those contrast media that gave positive skin tests.

28–47%). Delayed SPTs were only positive in 3 of the 98 reactors. Thirty-one patients (32%) had positive delayed IDTs that became positive on day 1 in 9 patients, on day 2 in 16 patients and on day 3 in the remaining 6 patients. Patch tests were conducted in 79 patients and 22 (28%) tested positive: 3 were positive on day 2 only, 10 required readings on day 3 to detect all positive reactions and 1 tested positive only on day 3. Nine patients were delayed IDT positive but PT negative, while seven patients were delayed IDT negative but PT positive. Two patients with angioedema 12–14 h after CM exposure were SPT and IDT positive only at the 20 min reading. None of the 82 negative controls had a positive delayed skin test.

While 47% (29/62) of patients were skin test positive when tested within the first 6 months after reactions, only 22% (8/36) were positive when tested at later time points ($P = 0.02$) (Table 3). Interestingly, 33% of patients with positive delayed skin tests had reacted on their first exposure to a CM.

Patients in the delayed skin test positive group differed from those in the skin test negative group with regard to the clinical manifestations of the delayed skin reaction. For those tested within the first 6 months after reaction, there was a significantly higher number of patients with maculopapular exanthema and a significantly lower number of patients with urticaria-like exanthema in the skin test positive group (19/29 *vs* 12/33; $P = 0.04$ and 1/29 *vs* 10/33; $P = 0.007$, respectively).

Thirty-three of the skin test positive patients were skin tested with the CM that had caused the nonimmediate hypersensitivity reaction. Twenty-eight (85%) tested positive to the culprit CM. Thirty-three of the 37 delayed skin test positive patients were tested with four or more products. Only 1 patient reacted to all CM used for testing (four CM in this case). Twenty-five of the 37 delayed skin test positive patients were tested with at least 8 CM (Table 5). Cross-reactivity was especially pronounced among the CM of very similar chemical structure such as iodixanol, iohexol, iopentol, iomeprol and ioversol.

Discussion

Despite the introduction of nonionic, low-osmolar CM, hypersensitivity reactions still occur in a significant proportion of patients, and life-threatening anaphylactic reactions are still a major concern both for the radiologists and the patients involved. It is therefore important to establish whether skin testing is useful in this setting. In this first European multicenter skin test study, involving experts in the field of CM hypersensitivity (7–13, 19), 220 patients with either previous immediate ($n = 122$) or nonimmediate ($n = 98$) hypersensitivity reactions were recruited. It was shown that up to about 50% of patients in both groups could be diagnosed by standardized skin tests, if testing was conducted within 2–6 months after the reaction. This is in accordance with the results reported by the French CIRTACI group (14). At later time points, the frequency of positive tests decreased significantly, especially for patients in the immediate group. This could be due to loss of sensitization over time as reported for other drug allergies (20) or a decreased reliability of the patient's history.

The specificities of our delayed IDT and PT were both 100%. Our immediate IDT had a specificity of 96.3%, which is slightly lower than the 97.6% reported by Guillen Toledo and Guido Bayardo (21) in their large study in 178 439 patients.

For unknown reasons, almost all hypersensitivity reactions occurred after intravenous administration of CM. The reported time interval between CM exposure and reaction was within 15 min in the majority of patients with immediate reactions, which is in accordance with previous

Table 5. Results from cross-reactivity testing of patients with previous nonimmediate hypersensitivity reactions after contrast medium exposure*

Test Substances	Patient number																								
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Nonionic																									
Iodixanol	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Iohexol	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Iopentol	x	x	x	x	x				x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Ioversol	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x
Iomeprol	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Iopamidol	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Iopromide	x	x		x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Iobitridol	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Iotrolan	x	x	x	x	x				x	x	x			x	x	x	x	x	x	x					
Ionic																									
Ioxaglate	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ioxithalamate	x	x	x	x	x				x	x	x		x	x	x	x	x	x	x	x					
Amidotrizoate		x	x			x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x

*The contrast media used for skin tested are marked x, and the contrast media that caused the hypersensitivity reactions are highlighted with borders. (The implicated contrast medium was unknown for patients 6 and 17 or not used for skin testing in patients 11 and 16.) The shaded boxes indicate those contrast media that were skin test positive.

observations (22). Most patients reported that the nonimmediate symptoms appeared within 48 h, which is somewhat faster than observed by others (23). Seventy-six percent of the immediate reactors reported a grade I or II reaction. The main clinical features of the immediate reactions were urticaria, angioedema, dyspnoea and hypotension, sometimes accompanied by nausea and vomiting. There was no tendency for patients with grade III or IV reactions to have an increased frequency of positive skin tests compared to those with grade I or II reactions.

The nonimmediate reactions were mainly mild to moderate exanthematous skin eruptions as have been reported by other investigators (23). Skin tests were most often positive in patients with maculopapular eruptions, and were very seldom positive in patients with nonimmediate urticaria-like rashes. The same observation has been made for other drug allergies (25).

Immediate reactors were only rarely SPT positive. Intradermal tests with reading after 20 min are the tests of highest value for this group of patients. At present we recommend the use of CM (300–320 mgI/ml) diluted 10-fold in sterile saline, since this concentration has been shown to give a low frequency of false positive reactions and since the irritant potential of undiluted CM remains to be explored. In patients with a history of previous anaphylaxis, SPTs with undiluted CM and reading after 20 min may be conducted before performing IDTs, although we have shown in this study that such testing may give a false sense of security. A panel of several different CM should be tested in an attempt to find a skin test negative product, which *might* be tolerated in future X-ray examinations.

In nonimmediate reactors, both delayed IDTs and PTs were frequently positive. Since some patients tested positive with only one of these tests, we recommend the use of both tests in parallel to enhance test sensitivity. Patch tests should be conducted with undiluted CM. We recommend 10-fold diluted products also when performing delayed IDTs, since the rate of false positive tests with undiluted CM is currently unknown. The CM used for testing need to be carefully chosen because cross-reactivity between different products is rather common in this group of reactors. Ioxaglate, iopamidol, iopromide and iobitridol showed limited cross-reactivity with iodixanol, iohexol, iopentol, ioversol and iomeprol while frequent cross-reactivities were observed among products of the latter group.

The fact that up to 47–50% of patients had positive skin tests when tested 2–6 months after the reaction, indicates that a significant fraction of the CM-induced immediate and nonimmediate hypersensitivity reactions are immunologic reactions, involving CM-reactive IgE antibodies and CM-reactive T cells, respectively. In nonimmediate reactions the involvement of T cells has been proven by the generation of CM-specific T-cell clones (TCC) (26). The implication of CM-specific IgE in immediate reactions is more controversial. It has been argued that the CM reactions are nonallergic reactions since patients can react to a CM on first exposure and the reaction does not always recur. However, the positive immediate skin tests reported by several investigators, the detection of CM-specific IgE antibodies in sera from immediate reactors to ionic CM (27, 28) as well as the recently reported positive basophil activation test in three immediate reactors with positive IDT to the implicated nonionic CM (29), all support an IgE-mediated mechanism.

More than 30% of the skin test positive patients had been administered a CM for the first time. This lack of a clear sensitization phase is similar to the situation described in anaphylaxis to muscle relaxants (30), and indicates that these previously nonexposed patients may have already been sensitized. The chemical structure(s) responsible for the sensitization remains unknown. The

different patterns of CM cross-reactivity shown in this study, indicate that several chemical entities may be involved.

Study limitations. Testing of drug hypersensitivity reactions is traditionally hampered by a multitude of test methods that differ from one center to the next (31). In this study, skin test procedures and interpretation of test results were harmonized, a common skin test protocol was used, and typical cutaneous drug hypersensitivity reactions were defined by pictures. However, the study was driven by enthusiasm and not by funding and thus, some limitations remained:

1. A history of a hypersensitivity reaction to a CM and lack of any other obvious triggers was used as a gold standard. Skin test sensitivity was calculated as the percentage of skin test positive among these patients. A recruitment bias, e.g. by missing patients with milder reactions, is possible and without results from provocation testing, the skin test sensitivity cannot be determined with certainty. A significant underestimate is likely as has been shown for other drug allergies (32). In patients with negative skin tests, lack of test sensitivity, wrong classification as presumed CM hypersensitivity or loss of immunological memory may be considered. The negative predictive value of skin tests has yet to be determined. Safe re-administration of a skin test negative CM has so far only been published for five patients with previous life-threatening immediate reactions (15, 33, 34) and for nine patients with nonimmediate skin eruptions (8). The next task for the study group is therefore to validate the skin test results by collecting data from planned or accidental re-exposure.
2. The number of controls tested depended on possibilities in each center. Ideally, these controls should have been exposed to a CM within the last 6 months without clinical signs of hypersensitivity reaction. However, such controls were difficult to recruit in the allergy centers. Therefore most of the negative controls were healthy subjects never exposed to CM or subjects exposed to a CM a long time ago.
3. Not all centers had the capacity to skin test patients with all the 13 listed CM. Therefore the number of selected CM varied between different centers and sometimes from one patient to the next. It was stated in the protocol that skin tests should be done at least with the culprit CM when known and with a panel of four CM representing the four different classes (ionic and nonionic monomers and ionic and nonionic dimers). Most centers complied with this requirement.
4. Since the patients are seldom informed about the specific CM used during their X-ray examinations, the culprit CM could not be identified in 83 of the 200 cases collected. This means that the responsible compound may not have been tested, again resulting in an underestimation of test sensitivity.
5. In the study, a time interval between reaction and testing of 4–8 weeks was encouraged, but also other time points were accepted, resulting in a wide range of time intervals. The conclusion that the optimal time interval for skin testing may be between 2 and 6 months is based on cross-sectional data only and has not yet been proven by longitudinal data.

Conclusions

This multicenter study is the largest study to date that has investigated the usefulness of skin tests in patients with immediate and nonimmediate hypersensitivity reactions to CM. The data presented suggest that at least 50% of the hypersensitivity reactions to CM are caused by an immunological mechanism. We emphasize that a hypersensitivity reaction on first exposure to a CM does not rule out an immune mediated reaction, as we have shown that a considerable fraction of the patients with such reactions were in fact skin test positive. Skin testing seems to be a useful tool for diagnosis of CM allergy and may play an important role in selection of a safe product in previous reactors. The specificity of our skin tests is as high as 96–100%, but further studies are required to establish their negative predictive value.

References

1. Christiansen C. Hypersensitivity reactions to iodinated contrast media – an update. In: Pichler WJ, editor. Drug hypersensitivity. Basel: Karger, 2007: 140–148.
2. Brockow K. Contrast media hypersensitivity – scope of the problem. Toxicology 2005;**209**:189–192.
3. Kaufman DW, on behalf of The International Collaborative Study of Severe Anaphylaxis. Risk of anaphylaxis in a hospital population in relation to the use of various drugs: an international study. Pharmacoepidemiol Drug Saf 2003;**12**:195–202.
4. Böhn I, Schild HH. A practical guide to diagnose lesser-known immediate and delayed contrast media-induced adverse cutaneous reactions. Eur Radiol 2006; **16**:1570–1579.
5. Christiansen C. X-ray contrast media – an overview. Toxicology 2005; **209**: 185–187.
6. Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy 2001;**56**: 813–824.

7. Romano A, Artesani MC, Andriolo M, Viola M, Pettinato R, Vecchioli-Scaldazza A. Effective prophylactic protocol in delayed hypersensitivity to contrast media: report of a case involving lymphocyte transformation studies with different compounds. Radiology 2002;**225**:466–470.
8. Vernassiere C, Trechot P, Commun N, Schmutz J-L, Barbaud A. Low negative predictive value of skin tests in investigating delayed reactions to radio-contrast media. Contact Dermatitis 2004; **50**:359–366.
9. Kanny G, Pichler W, Morisset M, Franck P, Marie B, Kohler C et al. T cell-mediated reactions to iodinated contrast media: evaluation by skin and lymphocyte activation tests. J Allergy Clin Immunol 2005;**115**:179–185.
10. Christiansen C, Dreborg S, Pichler WJ, Ekeli H. Macular exanthema appearing 5 days after X-ray contrast medium administration. Eur Radiol 2002; **12**(Suppl 4):S94–97.
11. Brockow K, Kiehn M, Kleinheinz A, Vieluf D, Ring J. Positive skin tests in late reactions to radiographic contrast media. Allerg Immunol (Paris) 1999; **31**:49–51.
12. Arnold AW, Häusermann P, Bach S, Bircher AJ. Recurrent flexural exanthema (SDRIF or baboon syndrome) after administration of two different iodinated radio contrast media. Dermatology 2007;**214**:89–93.
13. Kvedariene V, Martins P, Rouanet L, Demoly P. Diagnosis of iodinated contrast media hypersensitivity: results of a 6-year period. Clin Exp Allergy 2006; **36**:1072–1077.
14. Laroche D, Dewachter P, Mouton-Faivre C, Clément O. Immediate reactions following ICM injection: results of a 3-year prospective multicenter survey. Contrast Med Mol Imaging 2006;**1**:81.
15. Valfrey J, Newinger G, Arbogast R, Pauli G. Anaphylactic shock with ioxaglate during coronary angiography: Two cases. Rev Fr Allergol Immunol Clin 2002;**42**:157–162.
16. Demoly P, Kropf R, Bircher A, Pichler WJ. Drug hypersensitivity: questionnaire. Allergy 1999;**54**:999–1003.
17. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet 1977;**1**:466–469.
18. Barbaud A, Goncalo M, Bruynzeel D, Bircher A. Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. Contact Dermatitis 2001;**45**:321–328.
19. Wyatt JP. Patients' knowledge about their drug allergies. J Accid Emerg Med 1996;**13**:114–115.
20. Brockow K, Christiansen C, Kanny G, Clement O, Barbaud A, Bircher A et al. Management of hypersensitivity reactions to iodinated contrast media. Allergy 2005;**60**:150–158.
21. Blanca M, Torres MJ, García JJ, Romano A, Mayorga C, de Ramon E et al. Natural evolution of skin test sensitivity in patients allergic to beta-lactam antibiotics. J Allergy Clin Immunol 1999;**103**:918–924.
22. Guillen Toledo J, Guido Bayardo R. Anamnesis and skin test to prevent fatal reactions to iodinated contrast media. Rev Alerg Mex 2000;**47**:22–25.
23. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. Radiology 1990; **175**: 621–628.
24. Hosoya T, Yamaguchi K, Akutsu T, Mitsuhashi Y, Kondo S, Sugai Y et al. Delayed adverse reactions to iodinated contrast media and their risk factors. Radiat Med 2000;**18**:39–45.
25. Romano A, Quarantino D, Di Fonso M, Papa G, Venuti A, Gasbarrini G. A diagnostic protocol for evaluating non-immediate reactions to aminopenicillins. J Allergy Clin Immunol 1999;**103**:1186–1190.
26. Lerch M, Keller M, Britchgi M, Kanny G, Tache V, Schmid DA et al. Cross-reactivity patterns of T cells specific for iodinated contrast media. J Allergy Clin Immunol 2007;**119**:1529–1536.
27. Laroche D, Aimone-Gastin I, Dubois F, Huet H, Gérard P, Vergnaud M-C et al. Mechanisms of severe, immediate reactions to iodinated contrast material. Radiology 1998;**209**:183–190.
28. Mita H, Tadokoro K, Akiyama K. Detection of IgE antibody to a radiocontrast medium. Allergy 1998; **53**:1133–1140.
29. Trcka J, Schmidt C, Seitz CS, Bröcker E-B, Gross GE, Trautmann A. Anaphylaxis to iodinated contrast material: nonallergic hypersensitivity or IgE-mediated allergy? Am J Radiol 2008; **190**:666–670.
30. Mertes PM, Laxenaire MC, Lienhart A, Aberer W, Ring J, Pichler WJ et al. Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. J Investig Allergol Clin Immunol 2005;**15**:91–101.
31. Gomes ER, Pichler WJ, Demoly P, Aberer W, Frew AJ, deWeck A. The drug ambassador project. The diversity of diagnostic procedures for drug allergy around Europe. Allergy Clin Immunol Int J World Allergy Org 2005;**17**:1–10.
32. Messaad D, Sahla H, Benahmed S, Godard P, Bousquet J, Demoly P. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. Ann Intern Med 2004;**140**:1001–1006.
33. Kanny G, Maria Y, Mentre B, Moneret-Vautrin DA. Case report: recurrent anaphylactic shock to radiographic contrast media. Evidence supporting an exceptional IgE-mediated reaction. Allerg Immunol (Paris) 1993;**25**:425–430.
34. Dewachter P, Mouton-Faivre C, Felden F. Allergy and contrast media. Allergy 2001;**6**:250–251.

