

Should patients with risk factors be tested for hypersensitivity to contrast media: a prospective study

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Received: 30 January 2016 / Accepted: 18 April 2016
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Abstract

Background Previous hypersensitivity reactions to contrast media (CM), atopy, atopic disease, drug allergy, and age (20–29 or >55) are risk factors for CM hypersensitivity reactions. Our aim was to evaluate whether these risk factors should prompt skin testing for diagnosing CM allergy.

Methods The study was conducted among patients referred for allergy testing with CM. Skin tests were performed with non ionic or gadolinium CM, recommended by a radiologist. After completion of tests patients were telephonically queried on their symptoms of reactions.

Results 151 risk patients (53 men, 98 women; mean age 55.2) were included in the study. Only 13 (9 %) had a history of hypersensitivity reaction to CM. Compared with the other patients, atopy was significantly more common in patients with a history of CM hypersensitivity reactions. Female gender and mean age were also higher, but not significant. All of the tests with CMs were negative. Only one patient reported urticaria within 1–2 min after administration of CM (telephonically).

Conclusions Atopy can increase the risk of CM allergy. However, skin tests with CMs may be inefficient, unnecessary, and time-consuming, except in cases with a history of CM allergy. Premedication protocols appear to

be beneficial in patients with a history of CM allergy and cannot be recommended for patients with well-controlled asthma, rhinitis, atopic dermatitis or history of drug allergy.

Keywords Contrast media · Allergy · Radiocontrast media · Skin prick test · Intradermal test

Introduction

With the evolution of iodinated contrast media (CM) from ionic, high-osmolality to non-ionic, low-osmolality, the incidence of hypersensitivity reactions to CM used for computed tomography (CT) and angiography has decreased. It is currently estimated to be between 0.3 and 3 % [1, 2]. The rate of reactions with gadolinium CM used for magnetic resonance (MR) imaging is estimated at 0.07–0.67 % [3, 4]. Although the exact mechanism behind these reactions is unclear, non-immunoglobulin E (IgE) mediated pathways appear to be involved. Hypersensitivity reactions to CM may be due to (1) a direct membrane effect related to the osmolality or chemical structure of the CM (pseudo-allergy); (2) an activation of the complement system; (3) direct bradykinin formation; or (4) an IgE-mediated mechanism [5, 6]. Therefore, hypersensitivity reactions do not require IgE antibodies or prior exposure to CM. Hypersensitivity reactions can be immediate (within 1 h of administration) or non-immediate (more than 1 h after administration). Current evidence suggests that a subset of immediate reactions is likely mediated by IgE and most non-immediate skin reactions are most likely caused by T cells [7–9].

The most common risk factor for hypersensitivity reactions to CM is a previous reaction. Patients with a previous reaction have a 21–60 % risk of a repeat immediate reaction [10–12]. Atopy, history of drug allergy, atopic disease,

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age between 20 and 29 years or more than 55 years may also increase the risk of CM hypersensitivity reactions [12–19]. Beta blockers do not impart a direct risk, but antagonize the effects of epinephrine, which is used for treating hypersensitivity reactions. In addition, the presence of cardiovascular disease (CVD) and asthma is associated with a more serious reaction [18, 20].

Researchers tried to predict CM-induced hypersensitivity reactions by injecting a small amount of CM intravenously before the formal injection. In a study, pretest positive patients showed more hypersensitivity reactions compared to pretest negative group [16]. But another study showed that pretest could not predict the risk of severe reaction [21]. Currently hypersensitivity to CM can be tested with skin prick tests (SPTs), intradermal tests (IDTs), patch tests (PTs), and provocation tests according to the type of reactions [9, 22, 23]. Skin testing with CMs has a high specificity but its role in diagnosing hypersensitivity is limited. The rate of positive results increases with a higher severity of immediate hypersensitivity reaction [17, 23, 24]. Positive results of SPTs are rare but up to 25 % of patients can be diagnosed with early readings of IDTs. Furthermore, if the patients are tested after 2–6 months following the reaction, the positivity rate increases up to 50 % [25]. In a study in which the exact CM agent causing the reaction was known, undiluted CM for IDT was used and showed that the sensitivity of skin tests reached up to 64.7 % [26]. Using delayed IDTs and PTs, up to 60 % of the patients with non-immediate skin reactions to CM can be diagnosed [25]. These are post-event diagnostic skin tests; however, we still have insufficient evidence that these tests have sufficient value in reducing the risk of hypersensitivity reactions to CMs in patients with allergy histories other than CM allergy. Our aim was to evaluate whether these factors indicate an increased risk of developing allergic reactions to CMs, whether testing for these factors is required, and the diagnostic value of performing skin tests with CMs.

Materials and methods

Patients

This study was conducted on patients referred to our Immunology and Allergy department by physicians for testing for CM allergy due to a history of adverse reactions to drugs (who gave a reliable history of urticaria/angioedema, nasooocular symptoms, bronchospasm after ingesting drugs) CVD, beta blocker use, atopy, atopic disease, or advanced age. The participants were evaluated using a standard questionnaire for the following: demographic data, history of atopic disease, previous exposure to CM, history of reaction with CM, severity reactions with CM, latent period

from administration to reaction, time interval between reaction and testing, use of beta blockers, CVDs and adverse reactions with NSAIDs or antibiotics. Physical examination and blood analysis were performed. The total IgE levels and eosinophil count were analyzed for each patient.

Immediate CM allergic reactions were assessed using the Ring and Messmer scale for estimating the severity of reaction: [27] grade 1 (generalized cutaneous and/or mucocutaneous symptoms), grade 2 (mild systemic reactions), grade 3 (life-threatening systemic reactions), or grade 4 (cardiac and/or respiratory arrest). Non-immediate reactions were graded using the scales suggested by the European Network of Drug Allergy (ENDA) [28] and European Academy of Allergy and Clinical Immunology (EAACI) interest group on drug hypersensitivity: [10] 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.

Lung function tests were performed in patients with symptoms of airflow limitation or asthma, such as episodic breathlessness, wheezing, cough, and chest tightness after exercise, exposure to airborne allergens or pollutants. An improvement of 12 % and 200 ml in the FEV1 from the prebronchodilator baseline value after inhalation of 400 µg salbutamol was considered to be diagnostic for asthma. Management of asthma was based on the assessment of disease control as stated by the Global Initiative for Asthma (GINA) guidelines [29].

Atopy was defined as a positive skin prick test (SPT) to at least one of the aeroallergens and nutritive allergens (SoluprickSQ, ALK-Abello A/S, Hørsholm, Denmark). Positive histamine and negative saline solution controls were also included in these tests. A 1-mm tip disposable lancet was used to puncture the skin, and a mean wheal diameter of 3 mm or greater than the control solution was considered positive. Medications that could affect the results of these tests were discontinued before the test [28]. None of the patients had urticaria or angioedema in the 2 weeks prior to the test. All asthmatic patients were under control with appropriate treatment. Those patients who were pregnant, breast feeding, had psychosomatic disorders, or who had contraindications to the use of epinephrine were excluded from the study. Informed consent was obtained from all patients. This study was approved by the hospital ethics committee.

Protocol

SPT was performed on the volar forearm with non-ionic CM (iohexol, iopromide, iomeprol, iobitridol, ioversol), or gadolinium CM (gadodiamide, gadoterate meglumine, gadobenate dimeglumine, gadoversetamide, gadobutrol)

recommended by a radiologist. After 20 min of the test, a wheal mean diameter of greater than 3 mm, compared with that of the negative control, was considered positive. IDT was then performed with tenfold diluted CM. It was considered positive if the size of the initial wheal increased by 3 mm or more in diameter after 20 min. In patients with a history of any adverse drug reactions, tests were made 3–6 months after the last reaction. In a patient with a history of hypersensitivity reaction to a CM, the drug which caused the previous reaction was not re-administered and the IDT was performed with 1:1000 diluted CM. Even though the tests were negative in patients with a history of CM hypersensitivity reactions, a premedication protocol was used with 40 mg of methylprednisolone administered 13, 7, and 1 h before injecting CM, and 45.5 mg/2 ml of pheniramine maleate administered 1 h before the injection [12]. In patients with a history of CM-induced non-immediate skin reactions, delayed IDTs and undiluted patch tests were performed and read after 48–72 h. In patients with a history of maculopapular reactions after administration of CM, a graded provocation test was performed depending on the time course of the primary reaction (e.g., one-tenth of the full dose on day 1, one half of the dose on day 2, and the full dose on day 3). After the tests, patients were questioned about their reaction telephonically.

This study included 151 patients: 53 men and 98 women. All were referred to the allergy clinic because of risk factors for CM allergy. The majority (68.2 %) had never been exposed to CM. Forty-one patients (27 %) had CVD and thirty-nine (26 %) were taking beta blockers. Sixty-three patients (41.7 %) had asthma, 20 (13.2 %) had rhinosinusitis, 6 had atopic dermatitis (4 %), and 17 had chronic urticaria (11 %). According to the patients, 29 (19.2 %) had suffered a reaction to NSAIDs and 74 (49 %) had suffered a reaction to antibiotics (mostly penicillin). A skin prick test with aeroallergens and food allergens was performed on all subjects. In four cases, these tests were not reliable due to dermatographism. The atopy ratio was 37.7 % in the study group. None of the patients were allergic to seafood. The most common food allergy was to peanuts. Although the mean eosinophil count of the patients was within normal limits (2.7 %), the mean total IgE level was raised (243 ± 549.2 IU/ml). The demographic characteristics of patients and their risk factors for CM allergy are shown in Table 1.

Only 13 (9 %) patients had a documented history of adverse events after administration of CM and only three of these were aware of the exact drugs that caused the reactions. These three had a reaction with gadobutrol (Gadovist), iobitridol (Xenetix), and iodixanol (Visipaque). These patients reported the following symptoms during the reaction: shortness of breath (3), rhinitis and/or conjunctivitis (3), urticaria/angioedema (8), near fainting (2), pruritis (1), and palpitations (2). One patient also complained of

Table 1 Baseline characteristics of the study participants

Variables	Total <i>n</i> = 151 (%)
Age (years)	55.21 $\pm$ 14.3
Gender (female/male)	98/53 (64.6–35.1)
Atopy (present/absent)	57/90 (37.7–59.6)
Dermographism = 4	
Atopic diseases	
Allergic rhinitis	20 (13.2)
Chronic urticaria	17 (11.2)
Asthma	63 (41.7)
Atopic Dermatitis	6 (3.9)
Nasal poliposis	6 (3.9)
Food allergy	7 (4.6)
Total IgE	
Mean	243 $\pm$ 549.2
Median (IU/ml)	67.3
Eosinophilia	2.7 $\pm$ 1.91
Venom allergy	6 (3.9)
Cardiovascular diseases	41 (27.1)
Beta Blocker use	39 (25.8)
Previous exposure to contrast media	48 (31.7)
Drug allergies	
NSAID allergy	29 (19.2)
Antibiotic allergy	74 (49)
Other drug allergy	9 (5.9)
Names of contrast media tested	
Iopromide	28 (18.5)
Iohexol	68 (45)
Iomeprol	3 (1.9)
Ioversol	1 (0.6)
Iobitridol	1 (0.6)
Gadoterate	9 (5.9)
Gadobenate Meglumine	10 (6.6)
Gadoversetamide Dimeglumine	8 (5.2)
Gadodiamide	22 (14.5)
Gadobutrol	2 (1.3)

chest pain. Kounis syndrome (allergic myocardial infarction) was suspected in this patient because of ST-segment elevation in D1, AVL, and precordial leads V1–V4. The patient also had a raised CK-MB fraction and troponin T value. However, the coronary angiography performed after 3 days revealed normal coronaries. The patient may have recovered by this time with adrenaline, antihistamines, and corticosteroids. Ten patients had immediate reactions (grade I: 4; grade II: 5; and grade III:1). Three patients had non-immediate reactions; one had a severe maculopapular eruption after 24 h, and two had moderate urticaria after 6–10 h. The characteristics of these reactions are shown in Table 2.

Table 2 Features of previous hypersensitivity reactions to contrast media

	Immediate reaction (<i>n</i> = 10)	Non-immediate reaction (<i>n</i> = 3)
Presence of previous exposure to contrast media	6 (60 %)	1 (33 %)
Contrast media used	1 Gadobutrol Others are unknown	1 Iobitridol 1 Iodixanol Others are unknown
Time interval between reaction and skin test (months)	58	4.8
Severity	Grade 1: 4 Grade 2: 5 Grade 3: 1	Mild: 0 Moderate: 2 Severe: 1
Names of contrast media tested		
Iopromide	2	0
Iohexol	6	2
Gadoterate Meglumine	1	1
Gadobutrol	1	0

Statistical analysis

Numerical results were expressed as mean $\pm$ standard deviation (SD). Nominal variables were expressed as percentage of the patients. A *p* value of less than 0.05 was considered significant. The Statistical Package for Social Sciences (SPSS) for Windows version 14.0 (Chicago, IL, USA) was used to analyze the data.

Results

All of the tests for CM allergy were negative or non-ionic CM (28 iopromide, 68 iohexol, 3 iomeprol, 1 ioversol, 1 iobitridol) and gadolinium CM (9 gadoterate meglumine, 10 gadobenate dimeglumine, 8 gadoversetamide, 22 gadodiamide, 1 gadobutrol). Late reading IDTs and patch tests were negative in three patients with a history of non-immediate reactions. Provocation test with gadoterate meglumine was performed in one patient with a history of serious severe maculopapular eruption after administration of iobitridol. The result of the provocation test was negative.

After the tests patients were asked about their symptoms over the telephone: eleven patients (7.2 %) could not be reached and four gave up the process (CT, angiography or MR imaging) required for CM. Two patients reported palpitations during CM administration, but their vital and cutaneous signs were normal, which suggests that these were not allergic reactions. Only one patient reported urticaria within 1–2 min after administration of CM, and another had shortness of breath, dizziness, and a burning sensation in the throat after 1–2 min. For these two patients, the tests were repeated after 6 weeks with iopromide and gadodiamide, which caused the initial reaction, and other alternatives (first with iohexol, iomeprol, ioversol, iobitridol;

second with gadoterate meglumine, gadobenate dimeglumine, gadoversetamide, gadobutrol). All tests were negative. The first of these patients did not have atopy, atopic diseases, or a history of drug allergy. However, he did have chronic urticaria. The second patient had atopic dermatitis, asthma, and a history of metamizole allergy. Because of the doubtful nature of the reaction, a provocation test was performed with a placebo in the second patient. Similar complaints (shortness of breath, dizziness, and burning sensation in throat) were reported. The physical examination, oxygen saturation, and vital signs remained normal, and the spirometric values did not change. Further provocation tests were refused by the patient.

The risk factors for CM allergy (only age, sex and atopy; because of small number of patients) in those (tested, phoned, contacted and CM administered; *n* = 134) with and without a history of CM allergy are shown in Table 3.

Nevertheless, the sensitivity of the skin tests for CM hypersensitivity was not clear because those cases with a history of CM allergy (13 patients) were offered a standard premedication protocol. Among those patients who were contacted by telephone, who were administered CM and who did not have a history of CM allergy (total of 121 patients), one (0.8 %) of them developed a reaction, although tests were negative before and after the reaction.

Discussion

Testing for CM allergy in this study showed negative results, which suggests that CM allergy testing is unjustified in patients with the aforementioned risk factors. Patients with a history of CM drug allergy form an exception. In a study based on 1048 patients, 5.8 % had a history of hypersensitivity reaction to CM. Screening for hypersensitivity before the

Table 3 Evaluation of risk factors in patients with and without history of contrast media allergy

		History of allergy to contrast media		<i>p</i> ^a
		<i>n</i> (%)		
		Positive	Negative	
<i>n</i>		13	121	
Sex (male: female)		4:9	44:77	0.88
Rate of atopy		6 (46.15)	45 (37.19)	0.016*
Mean ± SD (median)				<i>p</i> ^b
Age	60.38 ± 12.50 (62)	54.42 ± 13.65 (56)		0.098

**P* < 0.05^a Fisher's exact test^b Mann Whitney *U* test

administration of CMs showed only two positive responses. One of these responses was immediate (0.09 %) and the other was delayed (0.09 %). Testing for CM allergy is, therefore, not recommended as a screening tool. In comparison, our study had fewer patients but all of them had at least one risk factor for CM allergy, e.g., 63 patients had asthma, 20 had A. rhinitis, and 17 had urticaria. But only 8.7 % (91 patients) of the patients in the study by Kim et al. [23] had allergic diseases such as asthma, rhinitis, atopic dermatitis, or food allergy. Moreover, they show that in patients with a history of CM allergy, a positivity test for allergy correlated with more severe hypersensitivity reactions [23]. In our study of the 13 patients with a history of CM allergy most of the reactions were mild (only one patient grade III immediate; one patient severe non-immediate), and the tests were negative. In addition because the time interval between the reaction and the test was more than 6 months, there was an increased likelihood for the test to be negative and only three patients were aware of the exact drug that caused the reaction. These patients did not accept to undergo skin tests for the drugs in question. Only in one patient (grade 1) who did not have a history of CM allergy but reacted, skin tests on the drug in question, and four alternatives, were negative. Depending on the cross reactions between non-ionic CMs, positive alternative tests are described to be positive up to 41.7 % in the study conducted by Ahn et al. [26]. But in our study some of the patient's history was almost 10–20 years ago, and reactions history may have been due to ionic CMs rather than non-ionic CMs, probably so cross reaction can not be occurred. Overall, it appears that skin tests for CM allergy are inefficient, unnecessary, and time-consuming in patients with risk factors, or those with a history of mild reactions with CMs.

When we compare patients who had a history of CM allergy with the other patients, those with a history of CM allergy had higher rates of atopy. Our study supports the findings from previous studies that atopy is associated with

an increased risk of hypersensitivity reactions to CM [14, 15, 17, 18]. More patients with a history of CM allergy were also older (mean age 60.38 $\pm$ 12.50) compared with the other patients (mean age 54.42 $\pm$ 13.65), but not significant. This is in contrast with other studies that showed that CM hypersensitivity reactions were most common in the age of 20–29 [14, 15].

Premedication is recommended in patients with a history of adverse reactions to CM. Guidelines of the European society of Urogenital Radiology suggest considering premedication in patients with a history of moderate or severe reactions [30]. Conversely, the American College of Radiology guidelines do not include the degree of reaction as a criterion for premedication [31]. The College suggests premedication, in patients with a history of asthma or allergies requiring treatment. In our study only one patient with mild persistent asthma who had also CM allergy history was premedicated. We did not premedicate other 62 asthmatic patients. When they were classified based on the GINA guidelines, [32] only three patients severe persistent (FEV1 <60 %) and six patients have moderate persistent asthma (FEV1 = 80–60 %), others are mild persistent or intermittent asthma. Patients received control-based treatment according to the recent update of the GINA guidelines [29]: tests were performed after good asthma control was achieved. Before the CM injection no patient had uncontrolled asthma. Our approach appears to be consistent with the findings of Liccardi et al. [33] who showed that prophylactic therapy should be prescribed according to degree of asthma control as assessed by clinical/functional parameters and in well-controlled asthmatics no premedication is required. For the rest in a review asthmatic patients were addressed based on a lot of work and recommendations from companies. Premedia is not recommended in asthmatics prior to injection of CM (grade C) but for uncontrolled asthma, if possible delaying the injection is recommended (expert opinion) [34]. Also we did not premedicate allergies

requiring treatment; only one patient with chronic urticaria experienced a non-severe reaction, which suggests that pre-medication should not be performed in patients with atopic diseases such as well controlled asthma, allergic rhinitis, or atopic dermatitis and history of drug allergy.

Previous studies have shown that premedication could prevent only hypersensitivity reactions with ionic CM, but could not reduce the risk of hypersensitivity reactions with non-ionic CM [12]. However, a recent study, based on 30 patients, premedicated patients with a history of an immediate hypersensitivity reaction with non-ionic CM and only five had reactions in spite of premedication (breakthrough reactions) [35]. In our study, none of the 13 patients with CM allergy history had symptoms of breakthrough reactions, after non-ionic CM was administered with suggested premedication protocol.

Conclusion

Atopy is associated with an increased risk of CM allergy. But skin tests to rule out allergy to CMs in patients with risk factors are not required. Testing for allergy to CM should only be performed in patients with a history of moderate or severe CM allergy in 2–6 months. Even with negative results on these tests, premedication protocol appears to be beneficial in patients with a history of CM allergy. Conversely, the premedication protocol does not appear to be necessary in patients with well controlled asthma, rhinitis, atopic dermatitis or history of drug allergy. Comparative studies with a large sample size are needed to determine the risk factors for CM allergy and indications of referral of patients to the immunology and allergy clinics to test for CM hypersensitivity.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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