

Anaphylaxis to Iodinated Contrast Material: Nonallergic Hypersensitivity or IgE-Mediated Allergy?

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OBJECTIVE. Contrast material is generally well tolerated although approximately 1% of patients who receive low-osmolar nonionic contrast material will develop anaphylaxis symptoms. Because most anaphylactic reactions are mild and nonallergic, clinically mimicking immunoglobulin E (IgE)-mediated allergy, diagnostic skin testing has been discussed controversially in the past and prophylactic pretreatment drug regimens are recommended instead. In the past 6 years, all patients with contrast material–induced anaphylaxis have been subjected to allergologic diagnostic procedures to clearly differentiate allergic and nonallergic anaphylaxis. Thus the purpose of our study was to identify and differentiate IgE-mediated allergy and nonallergic contrast material–induced hypersensitivity. Furthermore, the objective of our diagnostic procedures was not only to identify the culprit contrast material but also to find alternative contrast material for future radiologic interventions.

SUBJECTS AND METHODS. We evaluated 96 patients with anaphylaxis symptoms after contrast material application using standardized intradermal skin testing. In patients with positive skin tests, the IgE-mediated allergy was further evaluated with in vitro and challenge tests.

RESULTS. In four patients (suffering from anaphylaxis grades 2 and 3) out of the 96 (4.2%), skin tests and basophil activation tests strongly suggested IgE-mediated allergy to the contrast materials iopromide (two patients), iomeprol, and iopentol. In two patients with allergies to iopromide and iomeprol, alternative nonionic monomer contrast materials were tolerated, as identified in controlled challenge tests with iopamidol and iopromide, respectively.

CONCLUSION. The evaluation of patients with contrast material–induced anaphylaxis (at least those with anaphylaxis $\geq$ grade 2) should always include appropriate skin tests ensuring that patients with an IgE-mediated allergy are not missed. Moreover, allergologic testing may identify a contrast material of the group of nonionic monomers that will be tolerated in future radiologic interventions.

Keywords: adverse reaction, allergy, anaphylaxis, basophil activation test, contrast media, IgE-mediated allergic hypersensitivity, radiocontrast media

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All iodinated contrast materials in current use are chemical modifications of a 2,4,6-tri-iodinated benzene ring with different side chains in the 1, 3, and 5 positions and different numbers of benzene rings. They are classified on the basis of their physical and chemical characteristics including osmolality, ionization in solution, and chemical structure. Currently, four classes of contrast material are commercially available: ionic monomers, nonionic monomers, ionic dimers, and nonionic dimers. Contrast materials are administered mostly in volumes of 50–150 mL; the compounds are rapidly distributed in the body and are recovered mainly unmetabolized in urine within 24 hours. The frequency of mild anaphylactic reactions ranges from 3.8% to

12.7% in patients receiving high-osmolar ionic contrast material and 0.7% to 3.1% in patients receiving low-osmolar nonionic contrast material [1–4]. The risk for serious or severe reactions—that is, anaphylaxis grade 3—has been estimated to be from 0.1% to 0.4% with ionic contrast material and 0.02% to 0.04% with nonionic contrast material [2–5]. Pharmacologic side effects are due to the main properties of contrast material: osmolality, ionicity, and viscosity. The symptoms of these side effects such as vascular pain at the injection site, flushing, nausea, and vomiting cannot always be clearly distinguished from the beginning or low-grade symptoms of anaphylaxis. Objective and clear-cut symptoms of anaphylaxis include urticaria, angioedema, bronchospasm, hypotension, and shock [6].

Anaphylaxis to Iodinated Contrast Material

The symptoms of nonallergic anaphylaxis to contrast material are caused by histamine release from mast cells and basophils either directly by the osmolality effect of the contrast material solution and nonspecific binding of contrast material on membrane receptors or indirectly by complement–kinin activation [7, 8]. On the other hand, evidence for an immunoglobulin E (IgE)-mediated allergic anaphylaxis to contrast material was reported in the literature [9–12]. During the past 6 years, we evaluated all patients who presented with a history of anaphylaxis to contrast material using our standardized allergologic workup. The purpose of our study was to identify and differentiate IgE-mediated allergy and nonallergic contrast material–induced hypersensitivity. Furthermore, the objective of our diagnostic procedures was not only to identify the culprit contrast material but also to find an alternative contrast material for future radiologic interventions.

Subjects and Methods

Terminology

The terminology used to characterize allergic and allergy-like reactions is confusing. The report of the European Academy of Allergology and Clinical Immunology (EAACI) published in 2001 as the official EAACI position statement, “A Revised Nomenclature for Allergy,” has gained substantial international recognition [13]. Hypersensitivity means objectively reproducible symptoms initiated by exposure to a dose tolerated by normal persons. Allergy means hypersensitivity initiated by specific immunological mechanisms. Anaphylaxis is a severe generalized or systemic hypersensitivity reaction. Anaphylaxis is subclassified as allergic anaphylaxis when the reaction is mediated by an immunologic mechanism or nonallergic anaphylaxis due to any nonimmunologic cause (formerly anaphylactoid reaction).

Patients

From 2000 to 2006, all patients referred to our allergy clinic with a history of anaphylaxis to iodinated contrast material were subjected to a standardized skin test. Written informed consent for allergologic workup was obtained. Because determination of potential allergy is part of routine diagnostic practice, further ethical approval was not required. The reported anaphylaxis symptoms were classified according to severity [14] (Table 1). Grade 1 consists of cutaneous symptoms such as urticaria and angioedema; grades 2 and 3 include symptoms of the following organ systems: cardiovascular (hypotension, tachycardia), respiratory (dyspnea, bronchoconstriction), and digestive (vomiting,

abdominal pain, incontinence). Only patients with clearly documented symptoms of at least grade 1 anaphylaxis were evaluated. Pain at the injection site, heat sensation, flushing or erythema, headache, and nausea were considered pharmacologic side effects.

Skin Test

We performed intradermal tests on the volar forearm with iopamidol (Solutrast, Altana), iopromide (Ultravist, Bayer HealthCare), iomeprol (Imeron, Altana), iopentol (Imagopaque, Amersham) and, where necessary, the culprit contrast material. After 20 minutes, the intradermal test was defined as 1 +, positive reaction with a wheal diameter of 3–5 mm; 2 +, positive reaction with a wheal diameter of 6–10 mm; and 3 +, positive reaction with a wheal diameter of 11–15 mm. All tests were performed according to the EAACI recommendations [15]. In individual cases, allergic or nonallergic hypersensitivity to other drugs administered concomitantly with the contrast material and latex allergy (e.g., natural rubber latex from stoppers, tubes, or gloves) that may be responsible for the symptoms as well were excluded using skin and challenge tests.

Tryptase Measurement

Commercially available ImmunoCAP Tryptase (Phadia) was used as an in vitro test for the quantitative measurement of tryptase concentration in human serum [16].

Basophil Activation Test

In cases of positive intradermal skin tests, blood (5 mL) from patients and nonallergic controls was used within 6 hours of blood sampling for the basophil activation test. The basophil activation test, synonymously called “flow-cytometric cellular allergen stimulation test (Flow-CAST),” is based on the in vitro allergen-induced specific activation of basophils [17]. The assay was performed using a kit according to the instructions of the manufacturer. Briefly, leukocytes were stimulated in vitro with contrast material, control antigen (bee and wasp venom), and positive control (activating anti-Fc RI antibody). Because there is little experience with the basophil activation capacity of contrast material,

a broad spectrum of dilutions ranging from 10^{-12} to 1 µg/mL was covered. The cells were double stained with anti-CD63-PE- and anti-IgE-FITC-labeled antibodies. A minimum of 500 basophils (IgE-positive cells) per sample were collected, and activated basophils (CD63 + and IgE ++ double positive cells) were assessed by flow cytometry at 488 nm on a FACS Calibur system using the CellQuest software (Becton, Dickinson Immunocytometry Systems). Drugs usually give lower basophil activation percentages than inhalants, food, or hymenoptera allergens [18, 19]. Therefore, to obtain optimal sensitivity and specificity, a cutoff value of 5% was applied so far as negative control was maximally 2.5%. Therefore, activation of the patients' basophils after stimulation with contrast material was considered positive if data analysis yielded more than 5% activated basophils, provided that the stimulation index (SI), which is the contrast material stimulation divided by the negative control, was equal to or greater than 2 ($SI \geq 2$).

IV Contrast Material Challenge

Two patients with IgE-mediated contrast material allergy were challenged with skin- and basophil activation test–negative contrast material according to our established protocol using standardized doses of contrast material: 0.05, 0.5, 1, 5, 7.5, 10, and 25 mL for a total of 49.05 mL. The general principles of our challenge protocol were as follows: the time interval since the anaphylactic reaction was at least 6 weeks; during the entire challenge procedure, the patient was observed and equipment for emergency treatment was available; the dosage of contrast material increased stepwise to a normal dose with intervals of 30 minutes between the individual doses; there was strict adherence to absolute and relative contraindications for drug challenge tests; and before challenge testing, written informed consent was obtained from each patient.

Results

Patients

Ninety-six patients were evaluated. There were 69 women and 27 men presenting from 2000 to 2006 with anaphylaxis symptoms after injection of iodinated contrast material

TABLE 1: Grading System for Anaphylaxis (modified from [14])

Grade	Symptoms
1 Mild: skin and subcutaneous tissue only	Generalized urticaria, periorbital edema, or angioedema
2 Moderate: features suggesting respiratory, cardiovascular, or gastrointestinal involvement	Dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), tachycardia, chest or throat tightness, or abdominal pain
3 Severe: hypoxia, hypotension, or neurological compromise	Cyanosis, hypotension (systolic blood pressure < 90 mm Hg in adults), confusion, collapse, loss of consciousness, or incontinence

(Table 2). The average age at the time of the anaphylactic reaction to contrast material was 59 years (age range, 23–83 years). Seventeen patients (17.7%) were considered atopic due to a positive skin prick test with aeroallergens or a history of atopic dermatitis, rhinitis, or asthma. The contrast material was administered IV ($n = 74$), intraarterially ($n = 20$), or intracavitarily ($n = 2$) for the following indications: angiography ($n = 25$), urography ($n = 38$), CT ($n = 27$), cholangiography ($n = 4$), and myelography ($n = 2$). In 17.7% of cases, iomeprol was the incriminated contrast material, followed by iopromide (11.5%) and iopamidol (7.3%). Seventy-one patients had experienced contrast material–induced anaphylaxis within 12 months before testing, 19 patients between 1 and 5 years, and six patients between 6 and 10 years before testing. The latency between application of contrast material and onset of symptoms was recorded as virtually immediate ($n = 30$), less than 5 minutes ($n = 29$), 5–10 minutes ($n = 19$), 10–30 minutes ($n = 12$), and 30 minutes to 1 hour ($n = 6$). Fifteen of the 96 patients had experienced a prior adverse reaction to contrast material, and three had received antihistamine or steroid premedication. Episodes of contrast material–induced anaphylaxis included anaphylaxis grade 1 (41.7%), grade 2 (45.8%), and grade 3 (12.5%) (Table 2).

Skin Tests

In 92 patients, the intradermal skin tests with iopamidol, iopromide, iomeprol, iopentol, and the culprit contrast material were completely negative. In four patients, diagnosis of IgE-mediated allergic anaphylaxis was suspected on the basis of positive intradermal skin tests. In Table 3, the contrast material, the application of contrast material, latency, and symptoms are shown for these four patients. Results of intradermal tests are summarized in Table 4.

TABLE 2: Clinical Features of Subjects Studied

No. of Patients	96
Mean age (range) (y)	59 (23–83)
Sex (M/F)	27/69
Patients with atopic disease (%)	17 (17.7)
Anaphylaxis symptoms	
Grade 1 (%)	40 (41.7)
Grade 2 (%)	44 (45.8)
Grade 3 (%)	12 (12.5)

Tryptase Measurement

Raised baseline serum tryptase level (obtained either before the anaphylaxis event or at least 1 day after resolution of the clinical signs) as a symptom of systemic mastocytosis reflects an elevated mast cell burden and constitutes a substantial risk factor for severe or hypotensive anaphylaxis [6, 16]. In the four patients with IgE-mediated allergy to contrast material, tryptase levels (measured at least 6 weeks after the anaphylactic reaction) were within the normal range.

Basophil Activation Test

In three patients with IgE-mediated contrast material allergy, significant activation of basophils with different contrast material was seen (Table 4). The basophil activation test yielded maximally 15% activated basophils at

1 $\mu\text{g/mL}$, whereas activation of basophils was not induced at very low concentrations of contrast material (10^{-10} to 10^{-12} $\mu\text{g/mL}$). In contrast, in contrast material–stimulated samples of the controls, basophil activation was negative with all contrast material concentrations—that is, 1% to 2% activated basophils at 1 $\mu\text{g/mL}$. Stimulation with control antigen (bee and wasp venom) was also negative in two patients, and positive controls with activating anti-Fc ϵ RI antibody yielded basophil activation between 40% and 60% in patients and controls. As a further internal control, in patient number 2, positive skin test results with wasp venom correlated with the basophil activation test findings (bee venom, negative; wasp venom, positive). Because of the wasp venom allergy, this patient is being treated with immunotherapy.

TABLE 3: Clinical History of Four Patients with Allergic Anaphylaxis to Contrast Material

History	Patient No. 1	Patient No. 2	Patient No. 3	Patient No. 4
Contrast material	Iomeprol ^a	Iopentol ^b	Iopromide ^c	Iopromide ^c
Iodine strength	300 mg I/mL	300 mg I/mL	300 mg I/mL	300 mg I/mL
Application	IV for CT	IV for urography	IV for urography	IV for urography
Latency (min)	5	1	10	15
Anaphylaxis	Grade 2	Grade 3	Grade 2	Grade 2

^aImeron 300, Altana.

^bImagopaque 300, Amersham.

^cUltravist 300, Bayer HealthCare.

TABLE 4: Test Results for Four Patients with IgE-Mediated Contrast Material Allergy

Test	Patient No. 1	Patient No. 2	Patient No. 3	Patient No. 4
Intradermal test				
Iopamidol, 61.2 mg/mL	–	–	–	–
Iopromide, 62.3 mg/mL	–	–	1+	3+
Iomeprol, 61.2 mg/mL	2+	2+	2+	1+
Iopentol, 65.8 mg/mL	ND	3+	–	ND
Basophil activation test				
Iopamidol	–	–	ND	–
Iopromide	–	–	ND	+
Iomeprol	+	+	ND	+
Iopentol	ND	+	ND	ND
Challenge test				
Iopamidol	ND	ND	ND	–
Iopromide	–	ND	ND	ND

Note—Quantification of positive intradermal tests as described in Subjects and Methods section of text. Basophil activation test after stimulation with contrast material was considered positive if the stimulation index was ≥ 2 as described in the Subjects and Methods section of the text. Plus sign (+) indicates positive result, minus sign (–) indicates negative result, ND indicates not done.

IV Contrast Material Challenge

Despite knowledge of the IgE-mediated iomeprol-allergy of patient number 1, the radiologist administered 50 mL of iomeprol (Imeron 300) IV in the course of a CT examination. Despite premedication with 16 mg dimethindene 1 hour prior and 750 mg prednisolone 12 hours before contrast material administration, the patient again developed within 5 minutes grade 2 anaphylaxis symptoms. In contrast, no systemic or cutaneous reactions occurred during controlled IV challenge with negatively tested iopamidol (Solutrast 300) and iopromide (Ultravist 300) in the two patients (numbers 4 and 1) with IgE-mediated allergy against iopromide and iomeprol, respectively (Table 4). After the controlled challenge test, CT with contrast material was again indicated in patient number 1, and the patient tolerated iopromide (Ultravist 300) without application of premedication at a dosage of 75 mL.

Discussion

Contrast material reactions range from a mild inconvenience, such as heat sensation associated with nausea, to a life-threatening emergency. Anaphylaxis, characterized by generalized urticaria, acute bronchospasm, and profound hypotension, is a serious, potentially life-threatening, reaction that may occur within minutes of administration of contrast material independent of the injection site [7, 20]. In more than 90% of cases, the direct release of histamine and other mediators is responsible for the anaphylaxis symptoms after application of contrast material. However, according to skin tests and basophil activation tests, an IgE-mediated contrast material allergy was identified in four of 96 examined patients, supporting the literature that genuine IgE-mediated allergic anaphylaxis to contrast material is rare but may arise.

The occurrence of IgE-mediated contrast material allergy has been repeatedly questioned in the literature [21, 22]. In a review for the American Academy of Family Physicians, it is stated that anaphylactic contrast material reactions are not true allergic reactions because they occur in patients who have not been exposed to contrast material previously and IgE antibodies have not been shown [23]. An article investigating breakthrough adverse reactions to low-osmolar contrast material despite steroid premedication questioned the possibility of an IgE-mediated pathogenesis as well [24]. Further investigations by an allergologist to identify

IgE-mediated allergy are not mentioned in these publications. As a consequence, patients at particularly high risk for severe contrast material-induced anaphylaxis despite premedication remain undiscovered.

The IgE mechanism could explain the high risk of recurrence of the reaction and the ineffectiveness of premedication in some patients [12, 24, 25]. Our study and investigations including the basophil activation test confirmed that IgE-mediated anaphylaxis is rare but may be one of the possible mechanisms. If clear-cut symptoms of anaphylaxis evolve during or minutes after injection of contrast material, an allergologic examination should be performed. Especially after anaphylaxis of at least grade 2, skin tests are indicated to identify patients suffering from IgE-mediated contrast material allergy. For use as skin tests, intradermal tests with a 10% dilution of the contrast material are particularly suitable. After several improvements, the basophil activation test has become a robust and reliable test for *in vitro* investigations of IgE-mediated allergy [17]. However, each allergen has to be assessed to determine its optimal concentration and the threshold for positivity [26].

After diagnosis of an IgE-mediated allergy to one or more contrast material, the question of possible cross-reactivity among other contrast material arises. Only a very small number of patients with anaphylaxis have a positive skin test for the administered contrast material [11, 12]. Because the contrast material concentrations used for skin tests and basophil activation tests have been constantly negative in most patients and in control subjects, the positive predictive value is likely to be high, whereas the negative predictive value is uncertain. Consequently, careful controlled challenge testing may be attempted to verify negative *in vivo* and *in vitro* test results. The majority of patients refuse challenge tests. The reasons are fear of anaphylaxis and no current need for contrast media.

Future administration of contrast material in a patient is certainly facilitated by prior allergologic testing and issued allergologic documents mentioning the causal contrast material and alternative tolerated contrast material. Comparison of the chemical structures of contrast material does not give a clue of potential cross-reactivity in individual patients: one of our patients (patient number 4) has an iopromide–iomeprol allergy and tolerates iopamidol, whereas patient number 1 has an iomeprol allergy and tolerates iopromide.

For patients with undiagnosed previous anaphylaxis to contrast material (i.e., allergologic testing not performed yet), imaging procedures that do not require the administration of iodinated contrast material should be considered or a contrast material of another class should preferentially be used [27].

The use of steroids and antihistamines to prevent contrast material-induced anaphylaxis has been recommended by several authors but has not gained wide acceptance [28–30]. Data supporting the usefulness of premedication in patients with a history of allergic anaphylaxis are lacking and physicians who are dealing with these patients should therefore not rely on the efficacy of premedication [31]. Accordingly, one of our patients (patient number 1) with known iomeprol allergy developed grade 2 anaphylaxis after reexposure to iomeprol despite premedication. It is therefore important that physicians using contrast material routinely should be trained to recognize and treat anaphylaxis early and appropriately [32, 33].

Naturally, after anaphylaxis in temporal relationship to the application of contrast material, other causes for the symptoms always have to be considered [6]. During radiographic investigations, the patient may have contact with natural rubber latex. Non-steroidal antiinflammatory drugs, β -blockers, or angiotensin-converting enzyme inhibitors can trigger symptoms of anaphylaxis, IgE-mediated allergy against β -lactam antibiotics is overestimated but nevertheless relatively frequent. Finally, contrast material injections are capable of precipitating symptoms of occult mastocytosis. Besides exact and careful clinical history, certain laboratory tests (i.e., tryptase measurement, IgE specific for natural latex or penicillins), skin tests, and drug challenge tests help to clarify the diagnosis. Contrast material reactions are frequently falsely considered as an allergy to iodine because contrast materials are iodine based. However, neither contrast material-induced anaphylaxis correlated to IgE-mediated iodine allergy [34] nor allergic contact dermatitis due to iodine-containing antibacterial preparations should be considered evidence of IgE-mediated contrast material allergy [35].

In conclusion, IgE-mediated anaphylaxis is rare but may be one of the possible mechanisms of severe adverse reactions to contrast material. To identify these patients, at least all patients with a history of anaphylaxis symptoms of grade 2 or 3 should be subjected

to an allergologic workup. Skin testing (and basophil activation testing, if available) with a panel of different contrast materials appears to be useful for confirming the presence of an IgE-mediated allergy and for identifying alternative contrast material that can be used safely.

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