Original Article

Skin Testing for Suspected Iodinated Contrast Media Hypersensitivity

Rik Schrijvers, MD, PhD[a,b], Christine Breynaert, MD, PhD[a], Yazid Ahmedali, MD[b], Jean-Luc Bourrain, MD[b], Pascal Demoly, MD, PhD[b,c], and Anca Mirela Chiriac, MD[b] *Leuven, Belgium; and Montpellier and Paris, France*

What is already known about this topic? A subgroup of iodinated contrast medium (ICM) hypersensitivity reactions is immunologically mediated, potentially life threatening, and can be diagnosed using skin testing. Skin testing is preferred early (1-6 months) after the event. However, the negative predictive value of skin testing is insufficiently evaluated.

What does this article add to our knowledge? Skin testing for potential ICM hypersensitivity can identify safe alternative(s) for re-exposure, especially in patients with a history of an immediate hypersensitivity reaction. Reactions on re-exposure are infrequent and mostly milder.

How does this study impact current management guidelines? Our work validates the role of skin testing to identify safe alternatives and offers an allergologist-driven, clinical history-, and skin-test-based approach to guide ICM re-exposure, without the need for provocation testing outside an imaging context.

BACKGROUND: The management of iodinated contrast medium (ICM) hypersensitivity has been a matter of debate. Skin testing to identify a subgroup of ICM allergic patients has been proposed, in addition to complete avoidance, provocation testing, or premedication.

Objective: The objective of this study was to assess the negative predictive value (NPV) of skin testing for ICM.

METHODS: Patients with a hypersensitivity reaction to ICM who underwent skin testing during a 13.5-year period at a single center were evaluated for re-exposure to a negatively skin-tested ICM. Premedication, consisting of second-generation H1-antihistamines twice a day 48 hours before the examination, was advised only for patients with mast cell disorder or chronic urticaria who had negative skin tests.

RESULTS: A total of 597 patients tested for 423 (70.9%) immediate, 118 (19.7%) nonimmediate, and 56 (9.4%) hypersensitivity reactions with undetermined chronology were included. Eighty (13.4%) patients were skin test positive. Re-exposure to ICM occurred in 233 (39.0%) patients and was tolerated in 16 of 17 (94.1%) with at least 1 positive skin test and 201 of 216 (93.1%) with all negative skin tests. Reaction intensity was similar in 4, milder in 10, unknown in 1, and worse in 1 patient although this reaction was deemed to be nonallergic in hindsight. Premedication was administered in 20.7% of patients and associated with more reactions (19.4% vs 5.7%, $P = .01$). The overall NPV of skin testing for ICM was 93.1% (95% confidence interval [CI] 89.1% to 96.0%), and for immediate and nonimmediate hypersensitivity reactions 94.2% (95% CI 89.6% to 97.2%) and 86.1% (95% CI 72.1% to 94.7%), respectively. We cannot exclude some challenges occurred with a different than the initial culprit ICM, possibly overestimating the NPV.

CONCLUSIONS: Skin testing for potential ICM hypersensitivity can identify safe alternative(s) for ICM re-exposure especially in patients with an immediate hypersensitivity reaction and/or skin test-proven ICM drug allergy. Reactions on re-exposure were infrequent, mostly milder, and occurred in some patients despite premedication. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Allergy; Hypersensitivity; Iodinated contrast media; Radiocontrast; Anaphylaxis; Negative predictive value; Skin tests; Drug allergy*

Since their introduction in the 1950s, iodinated contrast media (ICMs) have been among the most commonly prescribed drugs for radiological imaging.[1] Four structurally different groups can be distinguished (ionic or nonionic, monomeric or dimeric).[2]

[a]Laboratory of Clinical Immunology, Department of Microbiology and Clinical Immunology, KU Leuven, Leuven, Belgium
[b]Exploration des Allergies, Département de Pneumologie et Addictologie, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, Montpellier, France
[c]Sorbonne Universités, UPMC Paris 06, UMR-S 1136, IPLESP, Equipe EPAR, Paris, France

RS is an EAACI research grant awardee, Fundamenteel klinisch mandaat FWO.
Conflicts of interest: C. Breynaert has received research support in the format of a C1 internal grant; and has received travel support for congresses. P. Demoly has received consultancy fees from Stallergenes Greer, ALK, Chiesi, Medarini, and ThermoFisher Scientific; has received research support from AstraZeneca and MEDA/Mylan; and has received lecture fees from ALK and Stallergenes Greer. A. M. Chiriac has received research support from COBIOPHAD (Horizon2020 Project). The rest of the authors declare that they have no relevant conflicts of interest.
Received for publication November 6, 2016; revised September 10, 2017; accepted for publication October 9, 2017.
Available online ■■

Corresponding author: Anca Mirela Chiriac, MD, Allergy Unit, Arnaud de Villeneuve Hospital, University Hospital of Montpellier, 371, Avenue du Doyen Gaston Giraud, Montpellier Cedex 5, Montpellier 34295, France. E-mail: a-chiriac@chu-montpellier.fr.

2213-2198

https://doi.org/10.1016/j.jaip.2017.10.040

Abbreviations used
CI- Confidence interval
DHR- Drug hypersensitivity reaction
ICM- Iodinated contrast medium
IDT- Intradermal test
IHR- Immediate hypersensitivity reaction
IQR- Interquartile range
MPE- Maculopapular exanthema
NIHR- Nonimmediate hypersensitivity reaction
NPV- Negative predictive value
OR- Odds ratio
SPT- Skin prick test
UC- Undetermined chronology

High-osmolarity ionic monomers (amidotrizoate and ioxithalamate) have been abandoned in most countries because of a high frequency of adverse effects[3] and replaced by nonionic monomers (iohexol, iopamidol, ioversol, iopramide, iomeprol, iopentol, and iobitridol), nonionic dimers (iodixanol), or ionic dimers (ioxaglate). ICMs are considered safe drugs, even if adverse reactions are reported in 1%[4-6] to 3%[7] of administrations. This can be attributed to pharmacological toxicity (eg, nephrotoxicity) or hypersensitivity reactions, next to unrelated events.[8] Hypersensitivity reactions can be subdivided into immediate (IHRs, occurring ≤1 hour after administration) and nonimmediate (NIHRs, occurring from >1 hour to several days after administration) hypersensitivity reactions.[9] A minority of IHRs, and typically those with a severe clinical presentation, are considered to be IgE mediated and can be identified using skin testing.[10-14] These reactions are classified as drug allergies.[9] In contrast, non−IgE-mediated IHRs are generally considered to be nonallergic hypersensitivity reactions (formerly coined anaphylactoid reactions), resulting from nonspecific mast cell and/or basophil degranulation.[9] Some NIHRs appear to be T-cell-mediated and can likewise be diagnosed using skin testing.[11-15]

The frequency of IHRs is reported to be 0.7% to 3% in patients receiving nonionic ICMs with severe reactions occurring in 0.02% to 0.04%.[7] Fatality rate (for both ionic and nonionic ICMs) is estimated to be in the range of 1 in 100,000[16] to 1 in 10 million.[3,7] NIHRs are reported to occur in 0.5% to 3% of administrations and may include life-threatening severe NIHRs.[7]

Risk factors for ICM drug hypersensitivity reactions (DHR) are poorly understood and include asthma,[17] a previous severe reaction,[3] and multiple exposures.[5] However, up to 34%[18,19] of reactions to ICMs are reported to occur on the first exposure suggesting a nonallergic nature in a subset of reactions and/or previous exposure to a hitherto unidentified sensitizing agent.

Most adverse effects result from intravascular administration, although case reports of extravascular administration, including oral administration, associated with severe or life-threatening reactions have been reported.[1,20,21]

Currently, in patients with a possible DHR, multiple strategies exist including avoidance of all ICMs, premedication on readministration[8] although controversial, or, as recommended by the international consensus on drug allergy,[9] a drug allergy workup to identify a potential drug allergy and cross-reacting drugs.[7,9,11] However, whether the latter approach using skin testing alone can also propose safe alternatives remains uncertain. Only few small series evaluated the negative predictive value (NPV) of skin testing in both IHRs[12,14,22-25] and NIHRs.[12,15,24,26-28] A recent meta-analysis[29] indicated that in patients with an initial IHR, 6 of 116 (7.1%, 95% confidence interval [CI] 3.6% to 13.6%) patients did not tolerate re-exposure with a negatively skin-tested ICM, with most reactions being similar or milder and without premedication use in most studies.[12,14,23,25] In NIHRs, a pooled 66 of 209 (34.5%, 95% CI 18.7% to 54.8%) re-exposed patients reacted,[29] suggesting a lower NPV of skin testing in NIHRs compared with IHRs. However, large uniform data series are lacking and multiple strategies exist including provocation testing in the absence of radiological examination. In this work, 597 patients evaluated with skin testing for a suspected ICM-mediated IHR or NIHR, the largest cohort to date, are presented.

METHODS

All patients referred to the Allergy Department of the University Hospital of Montpellier, France, from February 2001 to September 2014, with a compatible clinical history of an ICM-mediated DHR, were included. Patient data were stored in the Drug Allergy and Hypersensitivity Database, a case-control cohort. Clinical data were registered using the European Network of Drug Allergy (ENDA) drug allergy questionnaire before performing skin tests.[9] DHR were classified as IHRs (occurring ≤1 hour after ICM administration) and NIHRs (occurring >1 hour to 7 days after ICM exposure).[8] The Ring and Messmer[30] classification was used to classify the severity of IHRs. Patients presenting with isolated loss of consciousness were scored as grade 3 anaphylaxis, and those with isolated bronchospasm or malaise were considered as a separate group. Severe NIHRs were identified separately.[8]

Skin testing was typically performed with a set of 10 ICMs (amidotrizoate, ioxitalamate, iopamidol, iohexol, ioversol, iopromide, iomeprol, iobitridol, iodixanol, and ioxaglate) for optimal evaluation of potential cross-creativity, identification of alternatives, and to increase the likelihood of testing the culprit ICM in case this ICM was unknown, as previously described.[12] In 193 patients, less than 10 ICMs were evaluated (in 47 patients only 1; in 65, 2-5; and in 70, 6-9 ICMs were tested). Briefly, skin prick tests (SPT) were performed with the undiluted commercially available solution, and in case of negativity, they were followed by intradermal tests (IDT). Evaluation for IHRs was performed 20 minutes after IDT at a 1:10 dilution, and for NIHRs or undetermined chronology (UC), delayed reading of SPT and IDT was performed. A subset of patients with an NIHR underwent IDT with the undiluted solution for optimal sensitivity (41/92 patients before September 2012, after which this was systematically performed in 25/25 patients in accordance with Torres et al[15]). Immediate-reading SPT was considered positive if, after 15 minutes, the size of the wheal was at least 3 mm in diameter with surrounding erythema; for IDT, positivity was considered when the size of the initial wheal after injection of 0.05 mL increased by at least 3 mm in diameter with surrounding erythema after 20 minutes.[9] Delayed reading of SPT and IDT was performed according to the international guidelines of the European Society of Contact Dermatitis.[31] Patients left the department with the instruction that in the absence of radiological alternatives, a negatively skin-tested ICM could be used, that the predictive value of skin testing was uncertain, and the proximity of an anesthesiologist or physician accredited for advanced life support was recommended in case of an initial IHR.[32] Re-exposure to any ICM was counteradvised in patients with a severe NIHR, regardless