

CORRESPONDENCE

Combining skin testing and basophil activation testing is useful for evaluation of life-threatening radiocontrast media anaphylaxis

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Editor—Diagnosing life-threatening iodinated radiocontrast media anaphylaxis and identifying safe subsequent radiocontrast media are important for the anaesthetist. Approximately 2–3% of operations involve the use of radiocontrast media.¹ Life-threatening anaphylaxis² to radiocontrast media is estimated to occur in up to four in 10 000 patients.³

Immediate hypersensitivity reactions occur within 1 h of radiocontrast media administration, with 70% occurring within 5 min.⁴ The mechanism of immediate hypersensitivity reaction to radiocontrast media is not fully elucidated.⁴ Many groups hypothesise that detectable sensitisation on *in vivo* and *in vitro* testing may support an immunoglobulin E (IgE)-mediated mechanism for immediate hypersensitivity reaction. By this hypothesis, IgE-mediated mechanisms may account for >50% of life-threatening anaphylaxis, based on positive skin testing.⁵ Drug provocation testing is the gold standard for allergy testing; however, it also cannot prove an IgE-mediated mechanism and may precipitate a life-threatening reaction.⁴ Basophil activation testing is being studied as an alternative diagnostic test to skin testing, as there is minimum risk to the patient, requiring only peripheral blood collection via venepuncture. The performance characteristics of basophil activation testing are unclear, but it may have high specificity.¹ The exact diagnostic value of skin testing and basophil activation testing remains difficult to establish, as it requires comparison to drug provocation testing.

Identification of safe alternatives to radiocontrast media is important. Drug provocation testing is recommended only for skin-test-negative radiocontrast media.⁴ Immunoglobulin E-mediated immediate hypersensitivity reaction may be associated with lower rates of cross-reactivity to other radiocontrast media compared with non-IgE-mediated reactions.⁵ Whilst the prevalence of cross-reactivity amongst radiocontrast media is

uncertain, it does not follow chemical classification. Three groupings (1 [ioxithalamate, iopamidol, iodixanol, iomeprol, ioversol, and iohexol], 2 [iobitridol and ioxaglate], and 3 [amidotrizoate]) have been proposed based on statistical analyses to guide assessment of cross-reactivity.⁶

Our study focuses on the usefulness of combination skin testing and basophil activation testing to diagnose life-threatening radiocontrast media anaphylaxis and plan safe subsequent radiocontrast media administration. The study was reviewed and approved by the local Human Research Ethics Committee (RESP/16/255). Patients with life-threatening radiocontrast media anaphylaxis were sequentially recruited at a tertiary institution in Sydney, Australia, between July 1, 2019 and June 30, 2020. Patients experienced symptoms consistent with life-threatening anaphylaxis within 1 h of radiocontrast media administration. Skin testing results to drugs administered before radiocontrast media administration were all negative. Clinical characteristics and mast cell tryptase levels were collected. Skin testing and basophil activation testing were performed to all radiocontrast media available in our institution: iodixanol (Visipaque™; GE Healthcare Australia Pty Ltd, Sydney, Australia), iohexol (Omnipaque™; GE Healthcare Australia Pty Ltd), iopromide (Ultravist®; Bayer Australia Ltd, Sydney, Australia), meglumine iotroxate (Biliscopin™; Bayer Australia Ltd), and sodium diatrizoate and meglumine amidotrizoate (Urografin®; Bayer Australia Ltd). Skin testing was performed to the European Academy of Allergy and Clinical Immunology guidelines.⁴ Basophil activation testing was performed in line with our protocol⁷ at 1:10 000–1:10 dilutions. Results were expressed as %upregulation above the negative control and stimulation index (SI) for CD63 and CD203c. If skin testing to Urografin was negative, the patient proceeded to single-dose oral sodium diatrizoate 100 mg and meglumine amidotrizoate 660 mg drug

Table 1 Patient characteristics. *CV, cardiovascular (hypotension and tachycardia); G, gastrointestinal (nausea, vomiting, abdominal discomfort, and diarrhoea); R, respiratory (desaturation; symptoms of airway obstruction, including stridor, throat tightness, dysphonia, cough, and wheeze); S, skin (urticaria and angioedema). [†]Skin testing and basophil activation test were performed to iohexol, iodixanol, iopromide, meglumine iotroxate, and sodium diatrizoate and meglumine amidotrizoate for all patients. IHR, immediate hypersensitivity reaction; n/d, not done as patient declined; n/p, not performed; RCM, radiocontrast media; DPT, drug provocation testing.

Patient	Sex (M/F)	Age (yr)	Time from reaction (days)	Contrast agent administered	Symptoms* of IHR	Time after i.v. contrast to anaphylaxis (min)	Grade of anaphylaxis	Asthma (yes/no)	Atopy (yes/no)	Severe cardiovascular disease (yes/no)	Previous RCM exposure (yes/no)	Previous RCM reaction (yes/no)	Other drug allergy (yes/no)
1	F	37	105	Iohexol	CV, G, S	<5	3	No	No	No	Yes	Yes (flushing)	Yes
2	F	61	242	Iohexol	CV, R, S	<5	3	Yes	Yes	No	No	No	Yes
3	F	69	50	Iohexol	R, S	<5	3	No	Yes	Yes	No	No	No
4	M	44	455	Iohexol	CV, R	<20	3	No	No	Yes	No	No	No
5	F	75	371	Iohexol	CV, R	<5	3	No	Yes	No	Yes	Yes (vomiting)	No
6	M	83	1706	Iopromide	CV, R	<20	4	No	No	Yes	Yes	No	No
7	F	74	404	Iopromide	CV, S	<20	3	No	No	No	No	No	No
8	M	40	376	Amidotrizoate	CV, S	<5	3	No	No	No	No	No	No

Patient	Tryptase, significant rise and fall (yes/no)	Skin testing [†]					Basophil activation test [†]					DPT or therapeutic administration				
		Iohexol	Iodixanol	Iopromide	Meglumine iotroxate	Meglumine amidotrizoate	Iohexol	Iodixanol	Iopromide	Meglumine iotroxate	Meglumine amidotrizoate	Iohexol	Iodixanol	Iopromide	Meglumine iotroxate	Meglumine amidotrizoate
1	Yes	+	–	–	–	–	–	–	–	–	+	Culprit	Pass	n/p	n/p	Pass
2	Yes	+	–	–	–	–	–	–	–	–	–	Culprit	Pass	Pass	n/p	Pass
3	No	–	–	–	–	–	+	+	+	+	–	Culprit	n/d	n/d	n/d	Pass
4	Yes	+	+	–	–	–	+	+	+	+	+	Culprit	n/p	n/d	n/d	n/d
5	Yes	+	–	–	–	–	+	–	–	+	+	Culprit	n/p	n/p	n/p	Pass
6	Yes	–	–	–	–	–	–	–	–	–	–	Pass	n/p	Culprit	n/p	Pass
7	n/p	–	–	–	–	–	–	–	+	+	+	Pass	n/p	Culprit	n/p	Pass
8	Yes	–	–	–	–	+	–	–	–	–	+	Pass	n/p	n/p	n/p	Culprit

provocation testing (Gastrografin® 100 ml; Bayer Australia Ltd) with no premedication. Patients proceeded to routine radiocontrast media administration for contrast radiography, or 0.5 ml kg⁻¹ single-dose i.v. radiocontrast media challenge, with alternative skin-test-negative radiocontrast media suitable for future needs. No premedication was administered. Drug provocation testing was performed to determine safe alternative radiocontrast media and confirm the negative predictive value of skin testing and basophil activation testing.

Eight patients with life-threatening anaphylaxis were identified, five with iohexol anaphylaxis (62.5%), two with iopromide anaphylaxis (25%), and one with amidotrizoate anaphylaxis (12.5%). Patient characteristics and results of skin testing, basophil activation testing, and radiocontrast media administration are shown in [Table 1](#).

Radiocontrast media anaphylaxis occurred for five patients (62.5%) on first exposure. All patients developed exposure within 20 min of administration. Significant change in mast cell tryptase consistent with anaphylaxis was detected in six patients (75%). There were no tryptase results available for one patient (12.5%). Skin testing was positive in five patients to the culprit radiocontrast media (62.5%); all had significant tryptase change. Using standard cut-offs for basophil activation testing of 5% and 10% upregulation for CD63 and CD203c, respectively,^{7,8} and an SI >2.0, there were four false positives to sodium diatrizoate and meglumine amidotrizoate, and one false positive to iohexol based on results of drug provocation testing to Gastrografin and Omnipaque. Adjusting cut-offs to 10% and 15% reduced false positives to two for sodium diatrizoate and meglumine amidotrizoate and zero for iohexol. Basophil activation testing was positive to the culprit radiocontrast media in five patients (62.5%); two were skin-test negative to the culprit radiocontrast media. A set of eight control patients who tolerated radiocontrast media demonstrated no reactivity on basophil activation testing. There were no patterns of cross-reactivity identifiable on skin testing or basophil activation testing. There was significant lack of agreement between skin testing and basophil activation testing for all radiocontrast media ($P < 0.05$) (McNemar's test). Five of five patients who consented to i.v. administration tolerated at least one alternative skin-test-negative radiocontrast media.

We present a series of eight patients with life-threatening radiocontrast media anaphylaxis. The main limitation is the small patient number, but recruitment was challenging, given the infrequent occurrence of life-threatening immediate hypersensitivity reactions. Seven of eight (87.5%) had positive skin testing or basophil activation testing, which might support an IgE-mediated mechanism for life-threatening radiocontrast media anaphylaxis. This is clinically significant, as an IgE-mediated mechanism means reactions will recur on subsequent exposure, and there may not be cross-reactivity with other radiocontrast media. One patient with negative skin testing and basophil activation testing was evaluated remotely (1706 days from reaction), which may have significantly

reduced the sensitivity of testing. Lack of standardisation of the timing of skin testing and basophil activation testing after reaction is a limitation in this study, as this impacts analysis of performance characteristics, but patients are often not referred for review until there is a clinical need many years after the reaction. From our data, basophil activation testing appears to provide additional information to skin testing, demonstrating sensitisation in two further patients. The clinical significance is not definite without comparison with drug provocation testing, but we were unable because of risk of life-threatening reaction. Basophil activation testing was not useful for amidotrizoate with a significant false-positive rate (29%). Ongoing study with skin testing and basophil activation testing of larger cohorts of patients will help uncover the mechanism of life-threatening radiocontrast media anaphylaxis and optimise performance characteristics of basophil activation testing.

Declarations of interest

The authors declare that they have no conflicts of interest.

References

1. Sanchez-Borges M, Aberer W, Brockow K, et al. Controversies in drug allergy: radiographic contrast media. *J Allergy Clin Immunol Pract* 2018; 7: 61–5
2. Rose M, Green S, Crilly H, Kolawole H. Perioperative anaphylaxis grading system: 'making the grade. *Br J Anaesth* 2016; 117: 551–3
3. Harper N, Cook T, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; 121: 159–71
4. Torres M, Trautmann A, Bohm I, et al. Practice parameters for diagnosing and managing iodinated contrast media hypersensitivity. *Allergy* 2021; 76: 1325–39
5. Clement O, Dewachter P, Mouton-Faivre C, et al. Immediate hypersensitivity to contrast agents: the French 5-year CIRTACI study. *EClinicalMedicine* 2018; 1: 51–61
6. Lerondeau B, Trechot P, Waton J, et al. Analysis of cross-reactivity among radiocontrast media in 97 hypersensitivity reactions. *J Allergy Clin Immunol Pract* 2016; 137: 633–5
7. Li J, Best O, Rose M, Green S, Fulton R, Fernando S. Integrating basophil activation tests into evaluation of perioperative anaphylaxis to neuromuscular blocking agents. *Br J Anaesth* 2019; 123: e135–43
8. Pinnobphun P, Buranapraditkun S, Kampitak T, Hirankarn N, Klaewsongkram J. The diagnostic value of basophil activation test in patients with an immediate hypersensitivity reaction to radiocontrast media. *Ann Allergy Asthma Immunol* 2011; 106: 387–93