

Case Study

PERI-ANAESTHETIC ANAPHYLAXIS DUE TO RADIOGRAPHIC CONTRAST MEDIUM: THE ROLE OF INTRADERMAL TESTING IN DIAGNOSIS AND MANAGEMENT

CL Gray¹
ME Levin²
N Wieselthaler³
R Wood⁴
G Wilson⁵

1. Vincent Pallotti Hospital and Department of Paediatric Allergy, Red Cross War Memorial Children's Hospital

2. Department of Paediatric Allergy, Red Cross War Memorial Children's Hospital

3. Department of Paediatric Radiology, Red Cross War Memorial Children's Hospital

4. Vincent Pallotti Hospital and Department of Paediatric Surgery, Red Cross War Memorial Children's Hospital

5. Department of Anaesthesia, Red Cross War Memorial Children's Hospital and University of Cape Town

Email | Claudiagray.paediatrics@gmail.com

INTRODUCTION

Severe allergic reactions during a general anaesthetic can be caused by a wide variety of agents, ranging from muscle relaxants to anaesthetic agents, cleaning agents, pain killers, latex and antibiotics. The process of deciphering which agents are responsible can be time consuming and difficult.¹ Radiographic contrast media (RCM) are increasingly used in modern diagnostic medicine and may be used whilst the patient is under general anaesthetic, adding an additional agent which can cause a reaction.

This case report illustrates a severe reaction to a non-ionic low molecular weight radiographic contrast medium, iopamide (Ultravist) and illustrates the value of diagnostic testing to identify the offending agent, as well as to identify potential alternative agents. It is one of only a few cases in the literature to demonstrate a clearly positive reaction by intradermal test.

CASE

This describes the case of MH, a 9-year old girl with a background of umbilical and portal vein thrombosis as a neonate, which had led to gastric varices requiring surgical intervention. MH underwent a general anaesthetic in order to undergo contrast-enhanced imaging of her hepatic venous system to assist in surgical planning. She had had several general anaesthetics in the past (with no reactions), but this was the first occasion in which a radiographic contrast medium (RCM) was used intravascularly. She was given cisatracurium as a neuromuscular blocking agent, propofol as an anaesthetic agent and fentanyl as an opioid, all of which she had tolerated in the past. The skin was cleaned in the groin with chlorhexidine, and the theatre was latex-containing. About

half an hour after induction, she was given 3 small doses (10 ml, 5 ml, and 5 ml) of Ultravist 300 (iopamide, a low molecular weight, non-ionic radiocontrast medium), over the period of about 10 to 15 minutes. The concentration and volume of the Ultravist were procedure- and weight-appropriate. After the third injection she developed severe bronchospasm, hypotension and an urticarial rash. She was given adrenaline intravenously down the endotracheal tube, and a further dose intramuscularly. She was also given intravenous steroids and antihistamines. The procedure was abandoned, symptoms settled and she was observed in intensive care overnight, with no further reactions noted. Serial tryptase levels were performed.

Post-procedure she underwent an allergy assessment. Possible causes of the reaction were the radiographic contrast medium, neuromuscular blocking agents and chlorhexidine, with a lower likelihood of a reaction to latex, propofol and fentanyl. Appropriate blood tests were sent off with results shown in Table I.

Although test results were all within normal range, the previous history suggested tolerance to propofol, morphine, and cisatracurium. Therefore, the agent deemed to require further investigation was the radiographic contrast medium.

Six weeks after the reaction, MH underwent a series of skin prick tests and intradermal tests to a variety of non-ionic, low molecular weight radiocontrast media. In the interest of cost savings, only 3 readily available contrast media were tested: Ultravist (iopamide, which she had at the time of the reaction), Omnipaque 350 (iohexol) and Visipaque (iodixanol). Skin prick tests for all 3 drugs were negative at a dilution

TABLE I: RESULTS OF BLOOD TESTS

DRUG/LEVEL	TEST USED	RESULT	NORMAL RANGE
Morphine	Specific IgE by ImmunoCAP	0.02 kU/L	<0.35 kU/L
Chlorhexidine	Specific IgE by ImmunoCAP	0.06 kU/L	<0.35 kU/L
Tryptase	Level 1 hour post reaction	9.36 microg/L	<13.5 microg/L
Tryptase	Level 1.5 hours post reaction	11.6 microg/L	<13.5 microg/L
Cisatracurium	CAST (Cellular Activation Stimulation Test)	9 pg/mL	<40 pg/mL
Propofol	CAST (Cellular Activation Stimulation Test)	45 pg/mL	<100 pg/mL
Iopramide (Ultravist)	CAST (Cellular Activation Stimulation Test)	25 pg/mL	<200 pg/mL
Iohexol (Omnipaque)	CAST (Cellular Activation Stimulation Test)	13 pg/mL	<50 pg/mL

of 1:10 as well as neat. Intradermal testing at 1:10 showed a positive weal and flare response to Ultravist, but not the other reagents. Results are depicted in Table II and Figure 1.

In summary, it seems the reaction was related to the Ultravist radiographic contrast medium, but probably not in a typical IgE-mediated fashion (skin test negative; and lack of convincing rise in tryptase). However, several other mechanisms of radio-contrast medium reactions are possible (e.g. direct activation of mast cells or basophils) in a so-called "anaphylactoid" fashion.^{2,3} The intradermal test to Ultravist was convincingly positive with large weal and flare. It was totally negative to Omnipaque and Visipaque.

Based on these results, a recommendation was made to re-attempt the procedure using Omnipaque (Iohexol) as the contrast medium, at the lowest possible total dose (maximum 30 mL was advised), after a premedication regime as follows:^{4,5}

- Oral prednisolone syrup 10 mL 12 hours pre-procedure, and again 2 hours pre-procedure;
- Oral cetirizine 20 mg about 2 hours pre-procedure;
- IV Phenergan 25 mg (diluted 1:10 with normal saline) slow bolus just pre-procedure;
- IV Ranitidine 50 mg diluted to total 20 mL slow bolus just pre-procedure.

The same anaesthetic, analgesic and cleaning reagents were used as per previous anaesthetic. MH tolerated the repeat procedure well without any signs of reactions.

DISCUSSION

Iodinated radiographic contrast media (RCM) are increasingly used in modern diagnostic medicine. RCM are tri-iodinated benzene derivatives, which are either ionic (the benzene ring includes a COO⁻ cation⁺ group) or non-ionic (which contain a non-ionic R (OH)₂ group). The ionic RCM carry a higher risk of adverse reactions and are generally no longer used for intravenous application. The non-ionic RCM are of low molecular weight and differ from each other by their ring structure or non-ionic molecule. MRI procedures are contrasted with gad-

TABLE II: RESULTS OF SKIN PRICK TESTS AND INTRADERMAL TESTS TO VARIOUS RADIOGRAPHIC CONTRAST MEDIA

	SKIN PRICK TEST 1:10 DILUTION	SKIN PRICK TEST NEAT	INTRADERMAL TEST 1:10 DILUTION
ULTRAVIST (IOPROMIDE) 300	Negative	Negative	Positive wheal (11 mm) and flare
OMNIPAQUE (IOHEXOL) 300	Negative	Negative	Negative
VISIPAQUE (IODIXANOL)	Negative	Negative	Negative

olinium preparations, which are paramagnetic metal ions with a different molecular structure to the RCM, and are generally associated with fewer reactions.⁴⁻⁶

Hypersensitivity reactions to RCM may be divided into immediate (within 1 hour of administration) and non-immediate responses (over 1 hour post administration), the latter representing mostly late exanthemous reactions. Most immediate reactions are apparent within 5 minutes of administration, usually urticaria or nausea, less often severe reactions with respiratory or cardiovascular involvement.

Several large observational studies indicated that mild adverse reactions of the immediate type occur in 3.8-12.7% of patients receiving intravenous injections of high-osmolar, ionic RCM and in 0.7-3.1% of patients receiving low-osmolar non-ionic RCM.⁷⁻⁹ Severe immediate reactions have been reported to occur with a frequency of 0.1-0.4% for ionic RCM and 0.02-0.04% for non-ionic RCM. The fatality rate is 1:100 000 radiocontrast medium administrations. However, because of the frequency of use of RCM, they are amongst drugs most often causing fatal anaphylaxis.

The mechanisms of immediate hypersensitivity reactions to RCM are not entirely clear. It seems they are at least in part associated with histamine release from basophils and mast cells.^{2,4,5,6} Evidence for an IgE-mediated reaction has only rarely been reported and usually only with severe reactions. However,



Figure 1: Reaction 20 minutes after intradermal injection of radiographic contrast media

in many cases a non IgE-mediated mechanism may be more likely in view of the fact that:^{3,4}

- RCM are small molecules requiring haptens to become immunogenic;
- Patients can react on first exposure;
- RCM specific IgE have rarely been detected, and positive SPT occur in the minority of patients.

Other mechanisms of histamine release may be due to a direct membrane effect related to the osmolarity of the RCM solution or the chemical structure of the RCM molecule, or activation of the complement system. Patients with a previous severe reaction to RCM, those with mastocytosis and those with a general allergic predisposition (e.g. asthma) are at greater risk of a severe reaction.^{4,5}

In the diagnosis of RCM hypersensitivity reactions, skin prick tests and intradermal tests with 1:10 diluted RCM are specific but not sensitive. The prevalence of positive skin prick tests is exceptionally low; the yield for intradermal tests seems higher.¹⁰

No commercial assay is available for the routine measurement of RCM-specific IgE. The role of basophil activation tests has not yet been fully established. Because only a fraction of patients show a positive result for the above tests, research is needed into more sensitive new diagnostic methods.

In a patient with a hypersensitivity reaction to a RCM, that particular RCM should be avoided and an alternative found, ideally via allergy testing, as in this case. Moreover, premedication is advised for those with a history of a previous reaction, even when using a different RCM.^{4,5}

CONCLUSION

Peri-anaesthetic anaphylaxis is a complex topic, and requires careful history taking, reconstruction of the order of events, and step-by-step allergy testing. This case demonstrates the diagnostic pathway in proving an allergic reaction to a specific radiographic contrast medium, and the successful repeat of a procedure requiring RCM with no further reactions after careful selection of suitable alternative.

REFERENCES

1. Ewan PW, Dugue P, Mirakian R, et al. BSACI guidelines for the investigation of suspected anaphylaxis during general anaesthesia. *Clin Exp Allergy* 2009;40:15-31.
2. Brockow K. Immediate and delayed reactions to radiocontrast media: is there an allergic mechanism? *Immunol Allergy Clin North Am* 2009;29:453-468.
3. Trcka J, Schmidt C, Seitz CS, et al. Anaphylaxis to iodinated contrast material: nonallergic hypersensitivity or IgE-mediated allergy? *Am J Roentgenol* 2008;190:666-670.
4. Brockow K, Ring J. Anaphylaxis to radiographic contrast media. *Curr Opin Allergy Clin Immunol* 2011;11:326-331.
5. Brockow K, Christiansen C, Kanny G, et al, for ENDA* and the EAACI interest group. Management of hypersensitivity reactions to iodinated contrast media. *Allergy* 2005;60:150-158.
6. Christiansen C. Hypersensitivity reactions to iodinated contrast media: an update. In: Pichler W, editor. *Drug hypersensitivity*, 1st ed. Basel: Karger; 2007:140-148.
7. Palmer FJ. The RACR survey of intravenous contrast media reactions. Final Report. *Australia Radiol* 1988;32:426-8.
8. Kopp AF, Mortelet KJ, Cho YD, et al. Prevalence of acute reactions to iopromide: post-marketing surveillance study of 74 717 patients. *Acta Radiol* 2008;49:902-911.
9. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000;30:1144-1150.
10. Brockow K, Romano A, Aberer W, et al. Skin testing in patients with hypersensitivity reactions to iodinated contrast media: a European multicentre study. *Allergy* 2009;64:234-241.

PRODUCT NEWS

INOVA PHARMACEUTICALS TAKES GREAT PLEASURE IN ANNOUNCING THE ARRIVAL OF A NEW, NON-SEDATING HISTAMINE H₁-RECEPTOR AND PLATELET-ACTIVATING FACTOR (PAF) ANTAGONIST. ¹

Rupanase 10mg is available from 30 April 2015 at an SEP Excl VAT of R128.18 for 20 tablets.

The dual action of Ruphanase 10mg targets the allergic cascade at multiple points to block mediators, Histamine and PAF, in both the allergic and inflammatory responses associated with allergic rhinitis and urticaria.²

The 10mg, once daily dose can be taken with or without meals, making it convenient as well as providing your patients with symptom control.^{2,3}

Rupatadine has a complete anti-allergic and anti-inflammatory profile.¹

Hit allergic rhinitis and urticaria hard with Ruphanase 10mg. For any further information please contact Deline Kritzingier at iNova Pharmaceuticals on (011) 087 0000.



RUPHANASE¹⁰

inova
pharmaceuticals
A Veeva Company

REF: 1. Picado C. Rupatadine: pharmacological profile and its use in the treatment of allergic disorders. *Expert Opinion in Pharmacotherapy* 2006;7(14): 1989-2001. 2. Muller J, et al. Update on rupatadine in the management of allergic disorders. *Allergy* 2015; 70(100): 1-24. 3. South African Package Insert, 02 October 2014.

Scheduling status: [S2] **Proprietary name (and dosage form):** RUPHANASE 10 Tablets. **Composition:** Each tablet contains 12.80 mg rupatadine fumarate equivalent to Rupatadine 10 mg base. Contains sugar: lactose monohydrate 61.1 mg per tablet. **Pharmacological classification:** A.5.7.1 Antihistaminics. **Indications:** RUPHANASE 10 is indicated for the symptomatic treatment of allergic rhinitis and urticaria in adults and adolescents (over 12 years of age). **Registration number:** 46/5.7.1/0119. **Name and business address of applicant:** iNova Pharmaceuticals (Pty) Ltd, Co. Reg. No. 1952/001640/07, 15e Riley Road, Bedfordview, Tel. No. 011 087 0000 www.inovapharma.co.za. For full prescribing information, refer to the package insert approved by the MCC (Medicines Control Council). Further information is available on request from iNova Pharmaceuticals, IN1194/15