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

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INTRODUCTION

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evere 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. 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, iopramide (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 (iopramide, 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 (iopramide, 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...
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 radiocontrast medium reactions are possible (e.g. direct activation of mast cells or basophils) in a so-called “anaphylactoid” fashion. 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:4,6
- 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) 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 gadolinium 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. 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.4,6 Evidence for an IgE-mediated reaction has only rarely been reported and usually only with severe reactions. However,
in many cases a non IgE-mediated mechanism may be more likely in view of the fact that:\textsuperscript{3,4}
\begin{itemize}
  \item RCM are small molecules requiring haptenisation to become immunogenic;
  \item Patients can react on first exposure;
  \item RCM specific IgE have rarely been detected, and positive SPT occur in the minority of patients.
\end{itemize}

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.\textsuperscript{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.\textsuperscript{10}

\textbf{REFERENCES}


\textbf{PRODUCT NEWS}

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\textbf{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.