Radiocontrast Media Hypersensitivity Position Statement

Radiocontrast media (RCM) are a group of medical drugs used to improve the visibility of internal organs and structures of X-ray based imaging, such as plain film radiography and computed tomography (CT) scans. Adverse events related to administration of RCM include hypersensitivity (allergic-type) reactions and radiocontrast-induced nephropathy.

This statement focuses on hypersensitivity reactions to intravenous administered iodinated RCM.

Types of hypersensitivity reactions to iodinated RCM

Hypersensitivity reactions to iodinated RCM can be immediate (within hours) or delayed (days later), with severity ranging from potentially life-threatening anaphylaxis through to delayed rashes. These reactions are rarely IgE-mediated, and allergy testing is therefore of limited use for diagnosis. Hypersensitivity reactions are classified as mild, moderate or severe:

- **Mild reactions to RCM** include flushing, nausea, pruritus, vomiting, headache and mild urticaria. They are usually self-limited and resolve without specific treatment. These are experienced in up to 1% of patients after non-ionic low-osmolality RCM administration. These are side-effects but are not allergic in origin.
- **Moderate reactions to RCM** include severe vomiting, marked urticaria, bronchospasm or facial/laryngeal oedema.
- **Severe reactions to RCM** include hypovolaemic shock, respiratory arrest, cardiac arrest and convulsions. Anaphylaxis is uncommon, occurring in less than one in 100,000 patients. The current non-ionic, low osmolar iodinated RCM, are much less likely to cause reactions than the older, ionic high osmolar RCM.
- **Delayed hypersensitivity reactions to RCM** are experienced between one hour and one week post administration and occur in less than 4% of patients. Maculopapular rash is the most common skin reaction. Less frequent skin reactions include angioedema, urticaria and erythema.

Less common adverse reactions to RCM include sialadenopathy and neutrophilic pustulosis, delayed non-cardiac pulmonary oedema, thyrotoxicosis in people with Grave's disease, renal toxicity and lactic acidosis in people taking metformin.

Risk factors for hypersensitivity reactions to iodinated RCM

Risk factors include:

- Previous reactions to RCM, which increase the likelihood of a recurrent reaction by up to 60%, although many cases will have occurred following exposure to older ionic high osmolar RCM.
- A history of atopic disease (hay fever, asthma or food/drug allergy), which reflects a predisposition to developing allergy, but this is not cross-reactivity between RCM and allergies to foods or drugs (medications).
- Food allergy, which carries a 3-fold risk of reaction although **shellfish allergy is not associated** with an increased risk of adverse reaction to RCM above that of other food allergies. This is because allergic reactions to food are due to allergic reactions to food protein. By contrast, anaphylaxis to RCM is thought to be secondary to complement activation.

It is a common misconception that 'allergy' to topical iodine antiseptic solutions is associated with an increased risk of adverse reactions to intravenous iodinated RCM, but this is untrue.

General precautions to maximise the safe use of iodinated RCM

General precautions are as follows:

- A medical practitioner must be immediately available to attend to the patient in the event of an emergency or complication of RCM administration.
- A patient should not be left alone or unsupervised in the first ten minutes after RCM administration. Leave the cannula in place and keep the patient under observation for 30 minutes after RCM is first administered.
- It is advisable that the patient remains on the premises for at least 15 minutes after RCM administration as most severe reactions occur within this time period. This should be increased to 30 minutes in patients at increased risk of a reaction.
- It is important that all nurses, radiographers and medical practitioners who administer RCM are trained in the recognition of contrast reactions, the procedures for treating these reactions (including anaphylaxis), and resuscitation procedures (including CPR).
- Although anaphylaxis is uncommon, it is important that any service using RCM is equipped and trained to treat anaphylaxis, which has been highlighted by a report from the Coroners Court of Victoria regarding the death of Peta Hickey on 9 May 2019. www.coronerscourt.vic.gov.au/sites/default/files/2021-12/HickeyPeta_233619.pdf

When to consider premedication

In patients who have had previous allergic-type reactions to RCM, in addition to the use of an alternative RCM, premedication *may be helpful* before administration of the iodinated RCM, using the following protocols.

For non-urgent imaging:

- Prednisone 50mg given orally 13, 7 and 1 hour/s before administration, and
- Non-sedating oral antihistamine (cetirizine 10mg, loratadine 10mg or fexofenadine 180mg) taken 1 hour before administration.

For urgent imaging:

- Hydrocortisone Sodium Succinate (e.g. Solu-Cortef®) 200mg given intravenously 5 hours and 1 hour before administration, and
- Non-sedating oral antihistamine (cetirizine 10mg, loratadine 10mg or fexofenadine 180mg) taken 1 hour before administration.

Note: Pre-medications are not normally used for primary prevention.

When to consider alternative imaging modalities

In patients who have a history of moderate to severe hypersensitivity reactions to RCM, alternative imaging modalities may meet the clinical needs without the risks associated with repeat exposure. Further guidance on a case-by-case basis is recommended from medical imaging departments.

Options include:

- CT scans without RCM.
- CT scans with a low osmolar or iso-osmolar RCM agent (iodixanol).
- Ultrasonography.
- Magnetic resonance imaging (MRI).
- Nuclear imaging.

Note: Non-iodinated gadolinium-based contrast (Magnevist Solution for injection) can be used for MRI, or microbubbles can be used for ultrasound. Sometimes carbon dioxide can be used for digital subtraction angiography, but this cannot be used for imaging above the diaphragm, due to risk of cerebral hypoxia.

Rapid IV desensitisation to iodixanol has been described in serious allergic reactions (see Appendix).

If iodinated RCM enhanced imaging is required, the risks and benefits should be discussed with the patient.

Investigation of patients with suspected adverse reactions to RCM

Skin prick testing or intradermal testing can be used, however, as most reactions are not IgE mediated, it is expected to be positive in less than 10% of cases:

- If skin test results are positive, this can be helpful to avoid the culprit agent, but if negative then interpretation can be difficult.
- There are studies using delayed reading intradermal testing with RCM claiming to predict tolerance of alternative reagents when the primary problem has been delayed rash only.
- The most important factor in investigating a reaction is a contemporary written documentation of the RCM agent used, the type of reaction and the time relationship between contrast exposure and the onset of symptoms.

Whilst old types of RCM used to result in a higher frequency of non-IgE mediated reactions, it is possible that more reactions due to the newer RCM may be due to IgE mediated reactions:

- There is increasing use of skin tests to determine IgE mediated allergy to RCM and to determine cross-reactivity between different RCMs.
- Therefore, in moderate and severe reactions, referral to a clinical immunology/allergy specialist to diagnose and find a safe alternative RCM should be considered.
- In delayed-type hypersensitivity due to RCM, skin testing may also have a role with delayed reading. RCM can rarely cause DRESS and AGEP and in these settings, skin tests may be useful.

The alternative to RCM in some clinical settings are sometimes higher risk than undertaking skin tests and challenges, even with their limitations. For example, in someone who had acute coronary syndrome, not treating the underlying coronary artery disease carries significant risk. However, it would be extremely difficult to perform an angiogram without RCM.

Treatment of hypersensitivity reactions to RCM

- Nurses, radiographers and medical practitioners who administer intravenous RCM shall be trained in the recognition of contrast reactions, the procedures for treating these reactions, and resuscitation procedures. Including the availability of oxygen, adrenaline.
- Delayed rashes may be treated with oral corticosteroids for a few days if necessary.

To donate to immunology/allergy research go to www.allergyimmunology.org.au/donate

References and further reading

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Appendix - Visipaque contrast desensitization

Dose no.	Dilution	Concentration (mg/mL)	Dose (mg)	Volume to administer (mL)	Time of administration (min)
1	1:1000	0.32	1.6	5	0
2	1:500	0.625	3.2	5	10
3	1:250	1.25	6.4	5	20
4	1:125	2.5	12.8	5	30
5	1:62.5	5	25.6	5	40
6	1:32	10	51.2	5	50
7	1:16	20	102.4	5	60
8	1:8	40	204.8	5	70
9	1:4	80	409.6	5	80
10	1:2	160	819.2	5	90
11	1:1	320	1638.4	5	100

*Coronary angiography proceeded after dose 11, with a total of 300 mL of Visipaque RCM.