



# 'Iodine allergy' label is misleading

**Constance H Katelaris**, Professor, Clinical Immunology and Allergy, University of Western Sydney, and Campbelltown Hospital, Sydney; and **William B Smith**, Specialist, Clinical Immunology and Allergy, Royal Adelaide Hospital

## Summary

**'Iodine allergy' is not an accurate label for patients who have had allergic reactions to iodinated radiological contrast media or iodinated antiseptics. Allergy to seafood has nothing to do with iodine content as it is caused by specific immunoglobulin E to proteins. Seafood allergy is not a specific risk factor for reactivity to iodinated radiological contrast media, but a history of any moderate or severe allergic disorder confers a slight increase in risk. Patients with a previous history of allergy to radiological contrast media are at highest risk of a reaction. In some cases the risk of an allergic reaction to contrast media can be reduced by premedication, but, if previous reactions were severe, contrast media will usually remain contraindicated.**

Key words: anaphylaxis, contrast media, seafood allergy.

(*Aust Prescr* 2009;32:125–8)

## Introduction

The term 'iodine allergy' is used frequently and usually refers to a history of an allergic reaction to iodinated radiological contrast media or possibly a contact allergy to povidone-iodine. A misconception has arisen that allergy to seafood is caused by the iodine content of fish and shellfish. In a survey of patients presenting to a paediatric clinic because of suspected seafood allergy, 92% of the parents or patients believed that it was iodine in seafood that was the cause of the allergy.<sup>1</sup>

As a result, a history of seafood allergy is frequently considered to be a contraindication to the use of iodinated radiological contrast media. In a recent survey of radiologists and cardiologists in the USA, over 50% said that a history of seafood or shellfish allergy was sought before the administration of contrast media. One-third of the radiologists and 50% of cardiologists stated that they would withhold contrast media or recommend premedication if there was a history of sensitivity to seafood.<sup>2</sup> Anecdotally, this is also often the case in Australia.

There is significant misunderstanding and confusion regarding seafood allergy, contrast media sensitivity and the role of iodine.

This is clinically important because patients may be denied useful procedures unnecessarily, while true risk factors may not be given due consideration resulting in the correct risk management procedures not being undertaken.

## Dietary sources of iodine

Iodine is an element which is present in many body tissues. It is an essential trace mineral required for thyroid hormone synthesis. Ingested iodine is converted in the gut to iodide, the ionised form of iodine. There are many dietary sources of iodine including iodised salt, fish, vegetables, meat and iodates used as preservatives in bread.

## Potassium iodide

Potassium iodide is used to prevent the uptake of radioactive iodine by the thyroid gland following exposure in a radiation emergency. The effectiveness of potassium iodide as a specific blocker of radioactive iodide uptake is well-established. When used for prophylaxis in Poland after the Chernobyl disaster, it reduced the incidence of thyroid cancers below the expected rate. Potassium iodide is also used in smaller quantities to iodise table salt.

Theoretically it is not possible to be allergic to elemental iodine or simple iodide salts (such as potassium iodide). Indeed no true allergy or anaphylaxis to iodine has been reported. Iodine itself can cause non-allergic adverse reactions such as iododerma (a rare acneiform or ulcerative eruption related to iodide ingestion) or iodide mumps (salivary gland swelling due to iodide overload from contrast media infusion in those with renal insufficiency).

## Iodinated antiseptics

Some topical antiseptics contain povidone-iodine which is a complex of polyvinylpyrrolidone (povidone, PVP) with iodine. Povidone is a polymer similar to dextran and it acts as a carrier that delivers complexed diatomic iodine, which is bactericidal, directly to the bacterial cell surface. Povidone-iodine may cause allergic contact or irritant dermatitis, however this is rare. When patch testing has been conducted, positive reactions may be seen with povidone-iodine, but not iodine or potassium iodide solution. Although povidone itself is considered not to cause contact hypersensitivity, some of its non-iodinated copolymers (PVP-eicosene, PVP hexadecane) have been reported to cause contact dermatitis.

Systemic reactions to povidone-iodine are rare, but there are several case reports of generalised urticaria and even anaphylactic shock. These cases have the characteristics of IgE-mediated reactions and in one case specific IgE against povidone was found. There are also reports of anaphylaxis from povidone alone without iodine. Two of the cases of povidone-iodine anaphylaxis showed positive allergy tests with povidone alone. The conclusion is that in these rare cases, the allergy is against povidone and the iodine probably plays no role.

## Drugs

Iodine is present in some drugs such as amiodarone. Although hypersensitivity to amiodarone is a contraindication to its further use, there is no evidence that iodine is directly involved in allergic reactions to this drug. Hypersensitivity to other iodine-containing compounds should not be considered a contraindication to amiodarone.

## Seafood allergy

Allergy to seafood (fish, crustaceans and molluscs) has nothing to do with iodine content. It is caused by specific IgE against allergenic proteins including, but not limited to, parvalbumins in fish and tropomyosins in crustaceans and molluscs. Cross-reactive allergy within each of these three groups of animals is common, but is less common between the groups. (Those allergic to prawns are often allergic to crab, but those allergic to crustaceans are not usually allergic to fish.) While it is true that seafood may contain relatively high levels of iodine compared with other foods, the allergenic proteins are not iodinated and seafood allergy does not depend on the iodine content of the seafood.

## Contrast media

Radioccontrast materials are tri-iodinated benzoic acid derivatives that in solution contain a small amount of free iodide. Non-idiosyncratic reactions to radioccontrast media are due to direct toxic or osmolar effects. The only adverse effect of contrast material that can convincingly be ascribed to free iodide is iodide mumps and other manifestations of iodism.

### ***Idiosyncratic (including allergic) reactions***

Immediate and non-immediate hypersensitivity-type reactions after contrast media are not common. However, contrast media are frequently used (estimated at 70 million administrations worldwide per year<sup>3</sup>) and often in large volumes so reactions are an important problem. Immediate reactions consist of allergic-type manifestations such as pruritus, erythema, urticaria, angioedema and anaphylaxis. Non-immediate (more than one hour after administration) reactions are predominantly cutaneous and consist of urticaria, angioedema, maculopapular rash or rarely, more severe reactions such as Stevens-Johnson syndrome.<sup>3</sup>

Iodinated contrast media were formerly hypertonic and ionic

solutions, whereas newer products are closer to isosmolarity and are non-ionic. The incidence of hypersensitivity-like reactions is much lower with non-ionic, low-osmolar contrast media. Anaphylaxis has been estimated to occur at a frequency of 0.1–0.4% with ionic and 0.02–0.04% with non-ionic contrast media.<sup>2</sup> In the case of hyperosmolar and ionic contrast media, the predominant mechanism of the reaction is thought to be a direct non-immunological effect on mast cells and basophils or activation of the complement system. Severe reactions are associated with elevation of histamine and mast cell tryptase in the same way as allergic anaphylaxis. These reactions to contrast media were previously termed 'anaphylactoid', but the term 'nonallergic anaphylaxis' is now preferred.

There is growing evidence that a proportion of the rare cases of anaphylaxis to non-ionic contrast media is IgE-mediated, in other words, a true allergic anaphylaxis. Some research suggests that intradermal testing or *in vitro* IgE detection might be useful in these cases, but this is an evolving area. The role of the iodine atom (as a part of the iodinated molecular complex) in these cases is unknown. It is known, however, that none of 23 patients with documented contrast sensitivity reacted to subcutaneous sodium iodide.

### ***Risk factors for hypersensitivity***

A number of studies have shown that while patients with an allergy to seafood are at a slightly greater risk of reacting to contrast media, seafood allergy is not a specific risk factor. It is food allergy in general which increases the risk, as does severe hay fever or asthma, indicating that the atopic state is the risk factor, not seafood allergy itself. A large case-control study established that the presence of cardiovascular disease, asthma and the use of beta-blockers were risk factors for severe reactions. Although the odds ratio for anaphylaxis is between 7 and 20, the absolute risk in these patients remains relatively low.<sup>4</sup> The presence of these risk factors alone should not be sufficient to contraindicate administration of contrast media, but should signal caution. The only substantial risk factor for severe immediate reactions to contrast media is a history of a previous severe reaction, but this may be a relative or absolute contraindication (see Table 1). Systemic mastocytosis is theoretically another significant risk factor. Whether these risk factors apply equally to ionic and non-ionic contrast media is not established, but non-ionic contrast media have a lower incidence of reactions in all of these cases.

Risk factors for non-immediate reactions are an elevated serum creatinine, a history of drug allergy or contact hypersensitivity, and previous non-immediate reactions. There is no evidence that previous non-immediate reactions to contrast media increase the risk of anaphylaxis to contrast media.

A history of contact allergy to iodinated antiseptics is not a specific contraindication to the administration of contrast media,

Table 1

**Management of patients having contrast media**

Risk factors	Management
None	Routine procedure*
Severe food allergy Moderate–severe asthma Significant cardiovascular disease Beta blocker use	Close observation High-level preparedness Use non-ionic low-osmolarity contrast media if not routine
Previous mild–moderate immediate reaction to contrast media	Premedication (see box) Close observation High-level preparedness Use non-ionic low-osmolarity contrast media if not routine
Previous mild–moderate non-immediate cutaneous reaction to contrast media	Premedication (see box) Use non-ionic low-osmolarity contrast media if not routine <sup>†</sup>
Previous anaphylaxis to contrast media	Contrast media probably contraindicated <sup>‡</sup>
Previous severe non-immediate cutaneous reaction to contrast media (e.g. vasculitis, Stevens-Johnson syndrome, toxic epidermal necrolysis)	Contrast media contraindicated <sup>‡</sup>

\* Always be prepared to treat unexpected allergic reactions (see Emergency management of anaphylaxis in the community: wall chart. Aust Prescr 2007;30:115)

† Risk of anaphylaxis probably not increased

‡ Suggest consult immunologist

**Premedication**

Cetirizine 10 mg  
Prednisolone 25 mg  
Ranitidine 150 mg

} repeat after 12 hours

This regimen is given on the day before and on the day of the procedure. It is also given on the day after the procedure if there is a history of delayed reaction.

but may slightly increase the risk of a non-immediate reaction to the same degree as any other contact hypersensitivity. A history of anaphylaxis to povidone-iodine does not contraindicate the use of contrast media because the structure of povidone, with or without iodine, is not similar to that of contrast media and cross-reactivity has not been demonstrated.

**Using contrast media in patients with risk factors**

When preparing a patient for a procedure using contrast media, risk factor assessment should include asking about severe food allergy, drug allergy, asthma, cardiovascular disease or beta blocker use and previous reactions to contrast media. Management strategies in the presence of these risk factors might include:

- close observation and preparedness to treat a reaction
- giving low-osmolarity non-ionic contrast media (if this is not yet routine)
- premedication (see box).

There are a number of case reports of premedication failing to prevent subsequent anaphylaxis<sup>5</sup>, so in some cases contrast media should be avoided. Other diagnostic tests may be more suitable.

**Conclusion**

There is little evidence to support iodine as a cause of allergic reactions. Any reactions to substances containing iodine are probably caused by other parts of the molecule. The term 'iodine allergy' is therefore misleading.

Seafood allergy is not caused by the iodine contained in fish, crustaceans and molluscs. A history of seafood allergy does not therefore specifically contraindicate the use of iodinated contrast media. Each patient should be assessed for factors which increase the risk of a reaction to contrast media and managed according to the severity of the risk.

**References**

1. Huang SW. Seafood and iodine: an analysis of a medical myth. *Allergy Asthma Proc* 2005;26:468-9.
2. Beaty AD, Lieberman PL, Slavin RG. Seafood allergy and radiocontrast media: are physicians propagating a myth? *Am J Med* 2008;121:158.e1-4.
3. Brockow K, Christiansen C, Kanny G, Clement O, Barbaud A, Bircher A, et al. Management of hypersensitivity reactions to iodinated contrast media. *Allergy* 2005;60:150-8.
4. Lang DM, Alpern MB, Visintainer PF, Smith ST. Elevated risk of anaphylactoid reaction from radiographic contrast media is associated with both beta-blocker exposure and cardiovascular disorders. *Arch Intern Med* 1993;153:2033-40.

5. Worthley DL, Gillis D, Kette F, Smith W. Radiocontrast anaphylaxis with failure of premedication. *Intern Med J* 2005;35:58-60.

Conflict of interest: none declared

### Self-test questions

The following statements are either true or false (answers on page 143)

1. Seafood allergy is caused by the iodine content of fish.
2. Beta blockers reduce the risk of a hypersensitivity reaction to iodinated contrast media.

## Patient support organisation

### Anaphylaxis Australia

Anaphylaxis Australia supports and helps people affected by anaphylaxis and food allergies to manage their everyday lives while minimising the risk to their health and wellbeing. As a charitable non-profit organisation, it aims to raise public awareness and provides advocacy and education, for example through parents, schools and workplaces.

Anaphylaxis Australia has information on its website and offers support in all states. It has many educational resources for sale including DVDs, books, action plans, and medication and

training accessories. There are also information packs for health professionals. Doctors can order free brochures for their patients.

Mailing address PO Box 3182  
ASQUITH NSW 2077

Web [www.allergyfacts.org.au](http://www.allergyfacts.org.au)

Phone 1300 728 000  
(02) 9482 5988 for administration and orders only

Fax (02) 9482 4113

Email [coordinator@allergyfacts.org.au](mailto:coordinator@allergyfacts.org.au)

## Help us to improve *Australian Prescriber*

During October and November we will be surveying our readership. We want to know who is reading *Australian Prescriber* and what your perceptions are of its content and format.

This survey is part of our regular evaluation to ensure that *Australian Prescriber* is meeting the needs of its readers. The more responses we receive, the easier it will be for the Editorial Executive Committee to determine the future direction of *Australian Prescriber*.

A paper copy survey will be sent out to a sample of doctors, pharmacists and dentists within Australia. If you do not receive one of these, you can fill in the online survey, which will pop up when you log on to [www.australianprescriber.com](http://www.australianprescriber.com)

Both surveys will take about five minutes to fill in and all responses will be confidential. Respondents to the survey of the paper copy have the chance to win a prize.