'Iodine allergy' label is misleading

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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.

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.¹

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 60% 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.² 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
Radiocontrast materials are tri-iodinated benzoic acid derivatives that in solution contain a small amount of free iodide. Non-idiosyncratic reactions to radiocontrast 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 iodium.

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) 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-immediately (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. Liodinated contrast media were formerly hypertonic andionic 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. 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.

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. 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,
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).

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

* 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

There are a number of case reports of premedication failing to prevent subsequent anaphylaxis§, 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


Conflict of interest: none declared

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.

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