Iodine allergy: Common misperceptions

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Purpose. The current evidence regarding iodine-containing compounds and iodine allergy cross-reactivity is reviewed.

Summary. Iodine is an essential human nutrient found in the thyroid gland. It is used in the synthesis of the thyroid hormones thyroxine and triiodothyroxine. Patients who report having adverse reactions to iodine-containing substances are often labelled as having an "iodine allergy," which can result in delays in care or patients being denied essential ICM or other iodine-containing drugs. A literature review was conducted to evaluate the evidence regarding iodine allergy and iodine-containing drugs. Of 435 articles considered potentially appropriate for full review (plus 12 additional articles included on the basis of references from the eligible articles), 113 could not be obtained**.** After exclusion of 353 articles that did not meet all inclusion criteria, the remaining 81 articles were included in the review. The results of the literature review indicated that iodine has not been shown to be the allergen responsible for allergic reactions to iodinated contrast media, amiodarone, povidone-iodine, and other iodine-containing compounds.

Conclusion. There is a lack of evidence to support cross-reactivity between iodine-containing compounds in so called iodine-allergic individuals.

Keywords: amiodarone, contrast media, iodine, 3-iodobenzylguanidine, povidone-iodine

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Sixty-six percent to 89% of physicians routinely ask patients prior to a radiographic procedure if they have a shellfish or other seafood allergy or iodine allergy.[1,2] Many healthcare providers and patients believe that because shellfish and some other types of seafood ("shellfish/seafood" hereafter) contain iodine, there will be cross reactions with iodinated contrast media (ICM) and/or other iodine-containing substances.[3] Patients who report having adverse reactions to iodine-containing substances are often labelled as having an "iodine allergy," which can result in delays in care or patients being denied essential ICM or other iodine-containing drugs. For patients with seafood/shellfish or iodine allergy, surveys indicate physicians withhold the radiographic study or recommend premedication in 20% to 75% of cases.[2-6] Research indicates premedication increases costs, increases hospital stay duration, may itself result in adverse effects, and delays imaging studies.[7,8] Further, studies have shown that the usefulness of premedication is doubtful.[7] With over 75 million imaging studies conducted annually worldwide, approximately 5.9% of people having seafood allergies, and physicians routinely basing treatment decisions on these food allergies, this perception of an iodine cross-sensitivity likely influences millions of treatment decisions each year.[9,10]

Iodine is an essential human nutrient that is obtained naturally from foods.[11,12] Iodine is converted to iodide in the digestive process and then concentrates in the thyroid gland (75% of total body stores) for ongoing synthesis of thyroxine and triiodothyroxine. In the United States, dietary iodine intake is approximately 240 to 300 µg per day for men and 190 to 210 µg per day for women, with recommended intake being 150 µg per day for most adults.[11]

"Iodine allergy" confusion is compounded by inaccuracies and inconsistencies in the labeling of iodine-containing drugs (Table 1).[13-34] Some labeling omits mention of iodine as a potential allergen[31]; other labelling states that "iodine allergy" is not an absolute contraindication[13-27] or that the iodine-containing drugs are contraindicated in patients with a known hypersensitivity to iodine.[28-34]

An allergy or hypersensitivity reaction is an immunologically mediated response of the body to a foreign substance (eg, an antigen). Drug allergies are commonly classified by the Gell-Coombs classification of hypersensitivity, which includes immunoglobulin E (IgE)–mediated (type I), cytotoxic (type II), immune complex (type III), and cellular mediated (type IV) hypersensitivity. A more recent classification divides type IV reactions into 4 categories according to the cells recruited.[35] Hypersensitivity reactions include anaphylactoid reactions that manifest like anaphylactic reactions, with similar signs and symptoms, but have a different mechanism and may occur without prior exposure to the antigen.[3]

Our objective in the study described here was to evaluate the evidence regarding "iodine allergy" and iodine-containing drugs. Our hypothesis was that the literature would not support iodine as the agent responsible for hypersensitivity reactions reported in association with use of iodine-containing drugs and, moreover, that cross-sensitivity between drug agents does not occur (that is, an adverse reaction to one iodine-containing drug is not a contraindication to administration of another iodine-containing drug).

Literature review

A comprehensive search of MEDLINE (via PubMed for articles published from database inception to November 2019) and Embase (articles published from 1947 to November 2019) was conducted using variations of the search terms *allergy, hypersensitivity, immediate hypersensitivity, drug hypersensitivity, crossreaction,*

iodopyridones, contrast media, iodine, povidone-iodine, potassium iodide (KI)*, amiodarone, iobenguane, indocyanine green* (ICG)*, shellfish,* and *seafood*. All journal articles or article abstracts referring to hypersensitivity to iodine-containing drugs that mentioned patient allergy history, testing to determine allergenic component, or administration of multiple iodine-containing drugs were included if they mentioned different classes of iodine-containing drugs. The references within articles that met inclusion criteria were hand searched for additional articles.

Articles included in this review were evaluated for evidence to confirm or refute iodine as an allergen. Iodine-containing compounds evaluated in the review included ICM, povidone-iodine, potassium iodide, radioiodine, indocyanine green, and shellfish/seafood. Pertinent information in the articles was included in a table for review. Key findings from the review of articles were used to categorize articles according to whether or not they supported the misperception of iodine as an allergen. Articles were categorized as possibly supportive of the concept of iodine allergy if evidence presented supported iodine acting as an allergen (eg, case reports demonstrated that patients had positive skin or allergy tests to multiple iodine-containing compounds, evidence of a reaction to multiple iodine-containing compounds, or evidence of IgE antibody recognizing multiple iodine-containing compounds). Evidence presented in reviewed articles was categorized as inconclusive if conflicting evidence was presented (eg, a report documented positive patch tests to one iodine-containing compound but not to others). Articles were categorized as no supportive if no clear, concrete evidence was presented. Food and Drug Administration (FDA)–approved labeling for various drugs was reviewed for supporting data.

One investigator (NW) independently reviewed the titles and abstracts from the search and obtained the required data from studies and case reports that met the inclusion

criteria. Data were reviewed by the other investigators, and any concerns were addressed by the first investigator.

Results

As illustrated in Figure 1, the search provided 3,346 citations. After discarding duplicates and non–English-language articles, 2,387 items remained, of which 1,953 did not meet the inclusion criteria. Of the remaining 435 articles considered potentially appropriate for full review, 113 could not be obtained. Twelve additional articles were included on the basis of references from the eligible articles**.** Three hundred fifty-three reviewed articles were then excluded because they did not meet inclusion criteria, and the remaining 81 articles were included in this review.

The types of reactions documented included a variety of symptoms (eg, rash, anaphylaxis, contact dermatitis, itching, nausea/vomiting) found in multiple categories of the Gell-Coombs classification schema, as well as symptoms not normally recognized as an allergic reaction (eg, nausea/vomiting). The reaction frequency in reviewed studies ranged from 0% to 26.7%, but in most studies the reported reaction frequency was 0%. Most articles did not mention pretreatment.

Iodinated contrast media. ICM are the most widely used contrast agents and are standard for many diagnostic radiographic procedures.[1] All ICM share a common core structure called a tri-iodinated benzene ring. The tri-iodinated structure enables ICM to block x-rays, creating regions of higher density, or contrast, on x-rays and computed tomography scans and thereby allowing visualization of blood vessels, organs, and other body tissues.[9]

ICM can be classified as monomers or dimers according to whether they have 1 or 2 tri-iodinated rings (Figure 2) and whether they are ionic or nonionic. Ionic molecules have a carboxylate substituent, while nonionic molecules do not. Ionic agents usually have higher osmolarity (1,500-2,000 mOsm/L) than nonionic agents (290-860 mOsm/L) (Table 2). The hyperosmolarity and the presence of a charge, which disrupts the electric potential of cell membranes, are thought to contribute to the increased toxicity seen with ionic agents.[9]

Severe acute reactions to ICM are reported, but several observations are inconsistent with true IgE-mediated anaphylaxis: (1) prior exposure to ICM is not necessary; (2) IgE antibodies cannot be consistently demonstrated; and (3) reactions do not consistently recur in a patient.[9] One study found increased levels of total IgE but not anti-IgE, to the specific ICM.[39] Another study found IgE antibodies specific to ioxaglate; however, the ICM was found to have a very low affinity for IgE.[40] Most of the patients who reacted were found to have no detectable IgE in their serum.

Acute hypersensitivity reactions occur within 1 hour of administration and at a higher frequency with use of high-osmolarity agents (5%-15%) vs low-osmolarity agents (0.2%-0.7%).[41,42-44] Reported rates often include allergic-like acute reactions and physiologic reactions. The use of high-osmolarity agents has declined because of the greater likelihood of acute reactions.[9,37]

ICM may have a direct stimulant effect on mast cells and basophils due to the hyperosmolarity of a contrast agent compared to blood, or they may act on mast cells through activation of the complement system.[37,45] Chemotoxic effects may occur because of the presence of basic groups, the large size of ICM, and the complexity of the molecule, which may favor histamine release.[37]

Delayed hypersensitivity reactions occur 1 hour to 1 week after patients receive ICM and may have an incidence as high as 14%.[41,46] The highest risk is seen with use of nonionic, iso-osmolar agents (nonionic dimers). Studies of patients with delayed reactions have shown that reactions are T cell mediated.[47-49] T cells recognize a drug as an antigen and release cytokines.[38] Delayed reactions to ICM can present similarly to acute reactions, but mild symptoms like rash and pruritus are the most common symptoms (Box 1).[9,37,47] It is not likely that unbound iodine can be recognized by T cells or IgE because it is a very small molecule. It has been hypothesized that iodine may act as a hapten, a molecule that is too small to elicit an immune response but becomes immunogenic by associating with a carrier molecule such as a protein.[37,47] Researchers have shown that iodine-protein complexes can form in patients given ICM. While these were hypothesized to play a role in delayed reactions, no evidence to support this hypothesis has been found.[49-51]

Although one study found that broad cross-sensitivity between ICM was a result of the presence of ICM-specific T cells, no data indicating that iodine was the causative moiety in ICM delayed reactions was found.[47] A similar study used lymphocyte activation tests to analyze T-cell reactivity.[48] Skin prick tests (SPTs), intradermal tests (IDTs), and patch tests in 9 patients showed positive skin tests to multiple ICM. Skin biopsy specimens showed T-cell infiltrate (CD4+ and/or CD8+ T cells) in the dermis. Many of the patients had other drug allergies. Lymphocyte transformation tests have been used to study whether ICM reactions have an immunologic etiology.[49] Tests were done on several patient groups: patients with or without a history of ICM allergy and patients with or without exposure to ICM. Administration of Iodo-proteins created for the experiment did not result antigenicity in patients who had amidotrizoate reactions. KI was used for lymphocyte proliferation tests to

see if lymphocytes were induced by ICM because of iodine. No obvious correlation between responses induced by ICM or iodide was found.

A total of 50 articles mention ICM, 7 articles were classified as possibly supportive of the concept of iodine allergy, 3 as inconclusive, and 40 articles as providing no supporting evidence. Articles classified as possibly supportive included 3 case reports, 1 prospective study, and 4 retrospective studies. Kanny et al[48] discussed a patient who had an allergy to Lugol's solution and ICM, but no information about the type of reaction was given and the patient was not tested with other compounds besides ICM. One report did not include information on the vehicle or concentration used for the patch test substances.[52] Another report used a concentration of povidone-iodine known to cause irritant reactions.[53] Ridley et al. presented a case of rash to diatrizoate and topical iodine, which is known to cause irritant reactions.[54] Another study provided limited information on patients who had positive skin tests to iodine, povidone-iodine, povidone, and ICM including if these were separate incidents or if individuals reacted to multiple substances.[55]

Other case reports did not show cross-reactivity between ICM and other iodine-containing compounds.[56-65] In most reports, patients had an SPT, IDT, and/or patch tests to iodine, povidone-iodine, KI, and ICM to evaluate cross-sensitivity, but only ICM tests were positive and irritant reactions to povidone-iodine were common. None of the reports supported the notion that iodine is an allergen.

Four studies evaluated the administration of ICM to patients with previous intolerance to an iodine-containing compound in 231 patients.[66-69] Some patients received premedication. No reactions occurred. One study surveyed patients before receiving ICM about previous reactions to ICM and if they had a drug and/or food allergy. No risk factors for allergic reactions to ICM were found to be more prevalent in the subjects reporting an

allergic reaction, including patients with allergy to iodine, povidone-iodine, or seafood.[70] In one study, only 1 of 13 patients with a history of hypersensitivity to ICM developed a reaction after an oral provocation test with iodine.[71]

Studies have also shown that changing the ICM can reduce subsequent adverse reactions to ICM. One study compared use of premedication vs contrast agent switching on the rate of adverse reactions to ICM. Three mild reactions were observed in the ICM switch group (reaction rate, 5.2%; $P < 0.001$ for comparison with a control group of patients who received a previously offending contrast agent without premedication); among patients in the premedication-only group there were 47 reactions (reaction rate, 17.3%; $P < 0.01$ for comparison with control group).[72] Another study showed similar results in patients with moderate to severe hypersensitivity reactions to low-osmolar ICM. Switching to an alternative contrast agent was associated with a significantly lower rate of a reaction compared to administering the same ICM responsible for the initial reaction (27.6% vs 13.4%, $P = 0.002$).[73]

Amiodarone. Another drug with iodine in its structure is amiodarone, an antiarrhythmic. Amiodarone-induced hypersensitivity reactions are rare, with only a couple published cases of anaphylaxis. The FDA-approved labeling for amiodarone list anaphylactic and anaphylactoid reactions, angioedema, and urticaria as having occurred in postmarketing reports.[31]

Five articles mention amiodarone, including 4 case reports and 1 retrospective study.[74-79] The retrospective study was classified as possibly supportive, while the case reports were classified as providing no supporting evidence. The retrospective review studied patients with an "allergy" to iodine and/or ICM who received amiodarone.[74,75] In the study group, 167 patients (71%) reported a reaction to ICM, 55 patients (24%) to iodine, and

12 patients (5%) to both. After amiodarone administration, only 1 patient (0.4%) from the iodine group had a hypersensitivity reaction, but no additional information was provided about the prior reaction.

Two case series including 6 patients reported uneventful amiodarone administration to amiodarone-naïve patients with documented reactions to ICM.[76,77] In another report, a patient developed itching and urticaria during iohexol injection.[78] After the surgery, the patient developed atrial fibrillation and was given intravenous amiodarone. Three days later the patient was started on oral amiodarone and developed lip swelling and tingling. It is unlikely that this reaction was the result of iodine cross-sensitivity because the patient tolerated the intravenous amiodarone. The patient either reacted to an excipient in the tablet or was sensitized to amiodarone the first time he received it. In another report, a patient with a shellfish allergy tolerated amiodarone.[79]

Some amiodarone reactions could be the result of iodine toxicity resulting from more than 1 mg/day of iodine being absorbed (Table 3). A 300-mg maintenance dose of amiodarone has been reported to yield 9 mg/day of iodine at steady state,[80] well in excess of the highest normal dietary intake of iodine (190-300 µg/day).[11] Iodine toxicity case reports include sensitivity reactions, iodide mumps, thyroiditis, hypothyroidism, and hyperthyroidism.[81,82]

Povidone-iodine. Povidone-iodine is a broad-spectrum topical antiseptic used to treat and prevent infection.[28,83] It is a complex of povidone (synthetic polymer of 1-vinyl-2-pyrrolidone) and iodine. Allergic contact dermatitis and irritant contact dermatitis (ICD) are adverse reactions seen with topical antibacterial preparations containing iodide. One study found the incidence of contact dermatitis with povidone-iodine use to be 0.4%.[83]

Thirty-five articles mention povidone-iodine, including 20 case reports, 11 prospective studies, and 4 retrospective studies. Seven articles were classified as possibly supportive, 3 as inconclusive, and 25 as providing no supporting evidence. Articles classified as possibly supportive included 4 case reports and 3 retrospective studies. Three of these were mentioned in the ICM section. Case reports must be examined carefully when iodine solutions are used for skin testing to show possible cross-sensitivity among iodine-containing compounds, because many factors can affect skin patch test results. Iodine and iodine hydro-alcohol solutions are well-known local irritants.[83-85] Irritant reactions often mimic allergic reactions, and iodine concentrations above 1% are considered an irritant. Petrolatum may increase the irritant potential of iodine by increasing contact with the skin surface, while solutions with alcohol can remove sebum from the skin and increase iodine penetration, increasing the chance of irritation. False-positive responses have been seen after testing povidone-iodine.

Importantly, there are cases of individuals reacting to povidone-iodine but having negative skin tests for other iodine-containing substances.[54,71,86-101] Patients often had reactions described as erythematous, vesicular, or maculopapular. Some of these case reports were able to show that povidone was the allergen recognized by the immune system.[86-80,99,100] Other reports analyzed cases that involved positive tests for more than 1 iodine-containing substance.[102-106] However, often there was a lack of information in the reports to sufficiently analyze the case, the reports were not reliable (ie, a low Naranjo probability score[107] was calculated), allergy testing was not conducted properly, or test results were interpreted as irritant reactions. The Naranjo adverse drug reaction probability scale estimates the probability of a drug being the cause of an adverse event (eg, allergy),

and a low Naranjo probability score indicates that it is doubtful that a suspected offending drug was the cause of an adverse event.

In the other study categorized as possibly supportive of the concept of iodine allergy, patients with delayed reactions to ICM had SPTs, IDTs, and patch tests with ICM, povidone-iodine (1% and 10% aqueous), iodized alcohol, iodoform 5%, and KI.[105] Only 3 patients had positive patch tests to povidone-iodine and iodized alcohol and 1 to povidone-iodine and KI. The high concentration used likely caused an irritant reaction.

Six articles discussed the irritant potential of povidone-iodine. A study with 24 volunteers tested iodine in petrolatum or 70% isopropyl alcohol and povidone-iodine to determine the irritant potential and threshold of iodine.[84] Iodine was found to have an irritant threshold of 1%, and vehicles used were found to increase the irritant potential of iodine. Another study in patients with povidone-iodine contact dermatitis found a high frequency of irritant reactions to patch tests with various povidone-iodine preparations in controls.[96] Only 2 of the cases were interpreted as positive for povidone-iodine rather than irritant. Another study had similar results, as all seven patients had irritant reactions to povidone-iodine and patch tests with iodine 0.5% (petrolatum) were negative.[97] De la Cuadra et al[98] discussed 4 cases of povidone-iodine dermatitis. Although patch tests were positive for povidone-iodine, repeat open application tests (ROATs) in control patients were negative. Three patients had negative patch tests to iodine 0.5% (petrolatum). Iijima et al[108] conducted patch tests in 19 patients with povidone-iodine contact dermatitis. Patch tests were done under occlusion and open, with multiple concentrations, and multiple iodine-containing compounds (eg, 5% KI, 10% povidone-iodine solution). Patch tests with povidone-iodine under occlusion were positive. Open patch tests with 1% povidone-iodine and other iodine derivatives were negative, indicating an irritant reaction. Geraldes et al[94]

studied 8 patients with ICM hypersensitivity. Patch tests with ICM, povidone-iodine (2%), and KI showed irritant reactions to povidone-iodine and no reaction to KI.

Potassium iodide. Potassium iodide is sometimes used as an expectorant, to decrease viscosity of mucus in chronic pulmonary conditions and to block radioactive iodine from entering the thyroid.[29-30] Skin rashes are the most common reaction seen with KI, but reactions may include angioedema and symptoms of serum sickness (fever, arthralgia, lymph node enlargement, and eosinophilia). Some of the adverse reactions seen with KI may be the result of iodine toxicity rather than an immunologically mediated reaction.

Eighteen articles mention KI, including 10 case reports, 5 prospective studies, 1 retrospective study, and 2 in vitro studies. Three articles were classified as possibly supportive, 2 as inconclusive, and 13 articles as providing no supporting evidence. Articles classified as possibly supportive included 1 case report, 1 retrospective study, and 1 prospective study. All of these were discussed in previous sections.

One reported case involving KI described dermatitis associated with use of a topical formulation of bismuth-iodoform impregnated gauze; the patient had positive patch tests to the gauze, to iodoform, and to high-concentration KI 25% (petrolatum).[109]

Radioiodine treatment. Iobenguane I 131 and iobenguane I 123 (MIBG; 3-iodobenzylguanidine) are substituted benzylguanidines with ^{131}I or ^{123}I in the meta position of the benzene ring. They are used for the treatment of hyperthyroidism and cancer. The labeling for iobenguane I 123 lists hypersensitivity as a possible rare adverse reaction.[25,26]

Four case reports included in this review mention radioiodine, and all were classified as not providing supporting evidence.[110-113] In 2 reports, patients with ICM hypersensitivity (eg, anaphylaxis) tolerated radioiodine.[110-111] In another report, a patient who previously tolerated KI developed a maculopapular eruption after an injection of I 131 MIBG.[112] Patch,

scratch, and drug-induced lymphocyte stimulation tests with KI were negative. Another report of urticaria after I 131 and I 123 administration was attributed to an inactive ingredient in the capsule.[113] The patient later tolerated a test dose of I 131.

Indocyanine green. Indocyanine green (ICG) is a tricarbocyanine dye used for determining cardiac output, hepatic function, liver blood flow, and ophthalmic angiography.[32] It contains approximately 5% sodium iodide. Anaphylactoid and urticarial reactions have been reported with ICG use. Michie et al[114] demonstrated that reactions to ICG likely involve nonimmunologic histamine release rather than an antigen-antibody reaction. Interestingly there is also a report of an adverse reaction with an iodine-free formula of ICG.[115]

Three articles mention ICG; all are case reports and were classified as not providing supporting evidence.[114,116,117] Bjerregaard et al[116] reported a case of hypotension after ICG injection in a patient with ICM allergy who tolerated ICG later. In another case, a woman developed urticaria after intravenous ICG, and SPTs with sodium iodide were negative.[117]

Seafood. IgE-mediated seafood allergy has never been attributed to iodine. In shellfish, the major allergens are proteins called tropomyosin, and in fish the allergen is parvalbumin.[45] Unlike reactions reported in association with ICM administration, allergic reactions to seafood are usually immediate reactions and include urticaria, angioedema, asthma, rhinitis, vomiting, and diarrhea.[118]

Eleven articles mention seafood, including 1 case report, 5 prospective studies, 4 retrospective studies, and 1 systematic review. One article (a retrospective study) was classified as possibly supportive and 9 articles as providing no supporting evidence. In this case-control study of 55,286 subjects, seafood allergy was found to occur in 41 or 579 patients (7.1%) with ICM allergy compared to 21 patients (1.8%) in a control group.[119]

Approximately 13.1% of patients had a history of other drug allergies. However, no comparison to other food allergies was made.

Witten et al[120] asked patients about their allergy history before diatrizoate administration. Twenty-five percent of the patients had a history of allergy, many with multiple allergies. 166 patients with a positive allergy history developed minor adverse effects (eg, nausea, vomiting, arm pain), and 74 patients developed acute reactions (eg, urticaria, edema, bronchospasm, hypotension, shock). Of these patients, 6% had allergy to seafood, 6% to other foods, and 13% to iodides. Later studies did not show the same increased risk. In a large review of ICM administration, 5% of patients had a hypersensitivity reaction.[121] The incidence of a reaction in patients with seafood allergy was 14.98% compared to an incidence of 14.63% for patients with egg, milk, or chocolate allergy. In an observational retrospective study of 70 patients with reactions to ICM, researchers conducted SPT, IDT, and patch tests to shrimp.[122] Only 1 patient had a positive reaction to shrimp. This patient had developed a shrimp allergy several years after the reaction to ICM.

Recent guidance by the American College of Radiology (ACR) and the American Academy of Allergy, Asthma, and Immunology (AAAAI) advises that there is no cross reaction of ICM and iodine or seafood allergies.[35,41]

In addition to the more detailed information provided above, summary data on the literature reviewed are provided in the appendix.

Discussion

There is a misconception that ICM hypersensitivity reactions are related to their iodine content. Iodine, however, as an atom that is an essential nutrient, cannot be an allergen. People who react to medications or foods containing iodine are reacting to other allergens.

Studies have found that ICM reactions are more frequent in patients with prior reactions to ICM, other drug allergy, food allergy, or atopic conditions.[45,120] The type of food or drug allergy was not found to be significant. Patients with hypersensitivity to multiple iodine-containing compounds may have a "multiple drug allergy syndrome," in which a person who is allergic to one drug is more likely to be allergic to other drugs.[123-125]

FDA-approved prescribing information is sometimes updated, but there is a lack of incentive to update the labeling and change warnings regarding iodine. It is unlikely that manufacturers would conduct allergy studies with iodine derivatives to determine if warnings regarding iodine could be removed from labeling. A reluctance to update the labeling has serious consequences for healthcare, as some providers exclusively follow the recommendations in the labeling instead of the actual evidence.

Overall, only 3 articles were classified as inconclusive and 11 articles were classified as possibly supporting "iodine allergy." However, looking closer at the evidence in the studies and case reports, it is clear that the evidence is weak. Different methods, types of tests, concentrations, vehicles, and iodine-containing compounds are discussed in the articles. Some studies only included a small number of patients and did not include a control group. Most articles evaluated clearly show that iodine is not the allergen responsible for the adverse reactions seen with iodine-containing compounds.

The likely mechanisms of adverse reactions to iodine-containing compounds do not appear to involve IgE-mediated responses to iodine. ICM adverse reactions are likely the result of activation of nonspecific immune mediators by the ICM. Hypersensitivity reactions to seafood are IgE-mediated reactions to tropomyosin or parvalbumin. Adverse reactions to iodine-containing antiseptics are likely ICD or povidone allergy. Little or no evidence exists that iodine or iodide can behave as an antigen that is recognized by the immune system.

Review limitations. We identified a number of limitations of this review. First, most of the included articles are case reports that were produced retrospectively on the basis of patient and provider recall. Data from medical records may be limited and not contain all relevant data. Case reports are also subjective, and the quality and interpretation of the observation can be affected by the observer's subjectivity. Non–English-language papers were excluded, which could have constituted selection bias. Lastly, the authors were not able to obtain all the articles that were chosen to be analyzed.

Conclusion

Iodine is an essential trace element, and iodine deficiency results in serious health consequences. The idea that iodine cross-sensitivity can exist between various iodinated substances is not supported by evidence. The use of the term "iodine allergy" can result in individuals not receiving radiologic procedures that could be lifesaving and essential to improving their health. Guidelines published by ACR and AAAAI state that there is no reason to avoid ICM use in patients with "allergies" to seafood or iodine; instead, the specific agents that are causing the adverse reactions (eg, iohexol, seafood, povidone-iodine) should be documented in the allergy record. Clinical decision support systems should be updated to stop broad alert triggering upon ordering of iodine derivatives.

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Figure 1. Flow chart of methodology for selection of studies for review.

Figure 2. Structure of amiodarone, iobenguane, iodinated contrast media, and povidone-iodine. The asterisk on povidone-iodine represents that the structure is repeated. Iodinated contrast media have 1 or 2 tri-iodinated benzene rings. Ionic tendency is governed by the presence or absence of a carboxylate functional group present on an organic side chain. Ionic contrast media have a salt cation, such as sodium, calcium, or methylglucamine. Sources: references 36 and 37.

Key Points

- There is little or no published evidence that iodine or iodide can behave as an antigen that is recognized by the immune system.
- The term “iodine allergy” should no longer be used because its use substantiates a cross-sensitivity that is not supported by evidence.
- There is a lack of evidence to support cross-reactivity between iodine-containing compounds in so called iodine-allergic individuals.

Table 1. Manufacturers' Recommendations Concerning Allergies[13-34]

Drug(s)	Brand Name(s)	Level of Warning	Recommendations
Amiodarone	Cordarone, Nexterone, Pacerone	Contraindications	Known hypersensitivity to the drug or to any of its components, including iodine, contraindicate use.
Diatrizoate meglumine, diatrizoate sodium	Cystografin, Cystografin Dilute, Gastrografin, MD-76, MD-Gastroview	Warnings	A history of sensitivity to iodine per se or to other contrast agents is not an absolute contraindication to the use of diatrizoate meglumine but calls for extreme caution in administration.
Indocyanine green	IC-Green	Contraindications	IC-Green contains sodium iodide and should be used with caution in patients who have a history of allergy to iodides because of the risk of anaphylaxis.
Iobenguane I 123 MIBG)	Adreview	Warnings and Precautions	Prior to administration, question the patient for a history of prior reactions to iodine, an iodine-containing contrast agent or other products containing iodine. If the patient is known or strongly suspected to have hypersensitivity to iodine, an iodine-containing contrast agent or other products containing iodine, the decision to administer AdreView should be based upon an assessment of the expected benefits compared to the potential hypersensitivity

			risks.
Iobenguane I 131 MIBG	Azedra	None	None
Iodixanol	Visipaque	Warnings and Precautions	There is an increased risk in patients with a history of a previous reaction to contrast agent, and known allergies (ie, bronchial asthma, drug or food allergies) or other hypersensitivities.
Iohexol	Omnipaque	Warnings and Precautions	There is an increased risk in patients with a history of a previous reaction to contrast agent, and known allergies (ie, bronchial asthma, drug or food allergies) or other hypersensitivities.
Iohexol	Oraltag	Contraindications	Oraltag is contraindicated in patients with a known hypersensitivity to iodinated contrast agents.
Iopamidol	Isovue, Isovue-M, Scanlux	Precautions	Patients at increased risk include those with a history of a previous reaction to a contrast medium, patients with a known sensitivity to iodine per se, and patients with a known clinical hypersensitivity (bronchial asthma, hay fever, and food allergies).
Iopromide	Ultravist	Warnings and Precautions	Increased risk is associated with a history of previous reaction to a contrast agent (3-fold risk increase), a known sensitivity to iodine and known allergic disorders (that is, bronchial asthma, hay fever and food allergies) or other hypersensitivities (2-fold risk increase).
Iothalamate meglumine	Conray	Precautions	A positive history of bronchial asthma or allergy, including food allergy, a family history of allergy, or a previous

			reaction or hypersensitivity to a contrast agent, may imply a greater than usual risk.
Iothalamate meglumine	Cysto-Conray II	Precautions	The susceptible population includes patients with a history of a previous reaction to a contrast medium, patients with a known sensitivity to iodine per se and patients with a known clinical hypersensitivity: bronchial asthma, hay fever, and food allergies. A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent where a diagnostic procedure is thought essential, but caution should be exercised.
Ioversol	Optiray	Warnings and Precautions	There is an increased risk in patients with a history of a previous reaction to contrast agent, and known allergies (ie, bronchial asthma, drug or food allergies), and other hypersensitivities.
Ioxaglate meglumine, Ioxaglate sodium	Hexabrix	Precautions	A positive history of bronchial asthma or allergy (including food allergy), a family history of allergy, or a previous reaction or hypersensitivity to a contrast agent may imply a greater than usual risk.
Ioxilan	Oxilan	Precautions	Increased risk is associated with a history of previous reaction to a contrast agent, a known sensitivity to iodine and known allergies (ie, bronchial asthma, hay fever, and food allergies) other hypersensitivities, and underlying immune disorders, autoimmunity or immunodeficiencies that

			predispose to specific or nonspecific mediator release.
Potassium iodide	SSKI, Thyroshield, Lugol's Solution	Contraindications	Use is contraindicated in patients with a known sensitivity to iodides.
Povidone-iodine	Betadine	Contraindications	Do not use on individuals known to be sensitive to iodine, or other components of this product.

Abbreviation: MIBG, meta iodobenzylguanidine.

Table 2. Radiocontrast Media Classification[13-24,38]

Generic Name(s)	Brand Name(s)	Ionic or Nonionic	Monomer or Dimer	Osmolality, mOsm/kg	Iodine Concentration, mg/mL	Osmolarity
Diatrizoate meglumine, diatrizoate sodium	Cystografin	Ionic	Monomer	556	141	High
	Cystografin Dilute	Ionic	Monomer	349	85	High
	Gastrografin	Ionic	Monomer	1,940	370	High
	Gastroview	Ionic	Monomer	1,940	370	High
	MD-Gastroview	Ionic	Monomer	2,000	367	High
	MD-76	Ionic	Monomer	1,551	370	High
Iodixanol	Visipaque 270	Nonionic	Dimer	290	270	Iso-osmolar
	Visipaque 320	Nonionic	Dimer	290	320	Iso-osmolar
Iohexol	Omnipaque 140	Nonionic	Monomer	322	140	Low
	Omnipaque 180	Nonionic	Monomer	408	180	Low
	Omnipaque 240	Nonionic	Monomer	520	240	Low
	Omnipaque 300	Nonionic	Monomer	672	300	Low
	Omnipaque 350	Nonionic	Monomer	844	350	Low
	Oraltag 9	Nonionic	Monomer	30	9	Low
	Oraltag 21	Nonionic	Monomer	55	21	Low
Iopamidol	Isovue 200	Nonionic	Monomer	413	200	Low
	Isovue 250	Nonionic	Monomer	524	250	Low
	Isovue 300	Nonionic	Monomer	616	300	Low
	Isovue 370	Nonionic	Monomer	796	370	Low
	Isovue-M 200	Nonionic	Monomer	413	200	Low
	Isovue-M 300	Nonionic	Monomer	616	300	Low

Iopromide	Ultravist 300	Nonionic	Monomer	607	300	Low
	Ultravist 370	Nonionic	Monomer	774	370	Low
Iothalamate meglumine	Conray	Ionic	Monomer	1,400	282	High
	Conray 43	Ionic	Monomer	1,000	202	High
	Cysto-Conray II	Ionic	Monomer	400	81	High
Ioversol	Optiray 240	Nonionic	Monomer	502	240	Low
	Optiray 300	Nonionic	Monomer	651	300	Low
	Optiray 320	Nonionic	Monomer	702	320	Low
	Optiray 350	Nonionic	Monomer	792	350	Low
Ioxaglate meglumine, Ioxaglate sodium	Hexabrix	Ionic	Dimer	600	320	Low
Ioxilan	Oxilan 300	Nonionic	Monomer	610	300	Low
	Oxilan 350	Nonionic	Monomer	721	350	Low

Table 3. Iodine Content of Select Iodine-Containing Compounds

Compound	Iodine Content
Amiodarone[31]	75 mg in 200-mg tablet 18.7 mg/mL of iodine in 50-mg/mL solution
Cod, baked, 3 oz[11]	99 µg
Iobenguane I 123 or I 131[110]	20 µg of sodium iodide in 100 mCi
Iodized salt, approximately ¼ tsp[11]	71 µg
5% Lugol's solution[34]	50 mg/mL of iodine; 100 mg/mL of potassium iodide
Potassium iodide[28-30,64]	1 g/mL of solution 65 mg per tablet
Povidone-iodine[64]	10 mg/mL
Seaweed, 1 g[11]	16-2,984 µg
Shrimp, 3 oz[11]	35 µg
Tuna, 3 oz[11]	17 µg

Box 1. Signs and Symptoms of Reactions to Iodinated Contrast Media[9,37,47]

Acute Reactions	**Delayed Reactions**
Pain on injection	Rash
Nausea	Pruritus
Vomiting	Stevens-Johnson syndrome
Rash	Nausea
Flushing	Vomiting
Pruritus	Diarrhea
Urticaria	Hypotension
Bronchospasm	Iodide mumps
Dyspnea	
Hypotension	
Laryngeal edema	
Cardiovascular collapse	

Figure 1

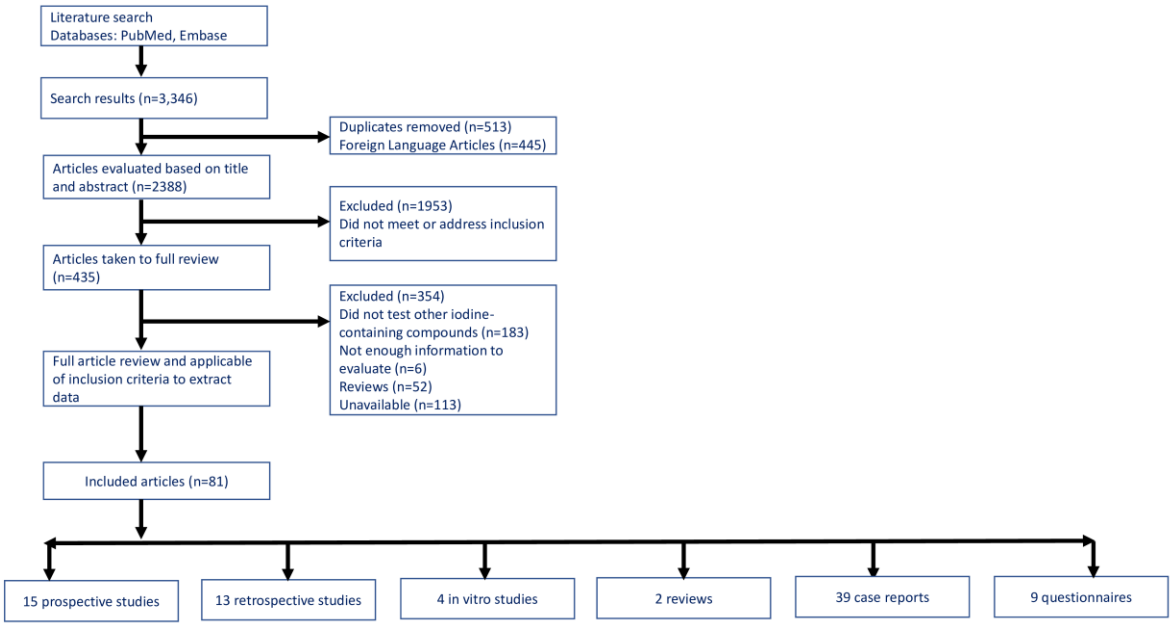

Figure 2