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Clinical Reviews

THE RELATIONSHIP OF RADIOCONTRAST, IODINE, AND SEAFOOD ALLERGIES: A MEDICAL MYTH EXPOSED

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Abstract—Background: Radiocontrast agents are some of the most commonly used medications in the emergency department. However, both physicians and patients misunderstand the role that allergies play in reactions to radiocontrast media, especially with regards to shellfish and iodine. **Objectives:** We sought to review the literature describing rates of contrast reactions and risk of contrast administration to patients with iodine allergy, shellfish or seafood allergies, or prior reactions to intravenous iodinated contrast. **Method:** Both authors independently performed literature reviews, including position statements of stakeholder organizations, to gain perspective on important issues. They subsequently performed a systematic search for articles that estimated the risk of administration of iodinated contrast to those with a prior history of contrast reaction, “iodine allergy,” or reaction to seafood or shellfish. **Results:** The risk of reactions to contrast ranges from 0.2–17%, depending on the type of contrast used, the severity of reaction considered, and the prior history of any allergy. The risk of reaction in patients with a seafood allergy is similar to that in patients with other food allergies or asthma. A history of prior reaction to contrast increases the risk of mild reactions to as high as 7–17%, but has not been shown to increase the rate of severe reactions. Severe reactions occur in 0.02–0.5% and deaths in 0.0006–0.006%; neither have been related to “iodine allergy,” seafood allergy, or prior contrast reaction. Low-osmolality contrast media became available in 1988, and many of the higher risk estimates were from the era before it was widely available. **Conclusions:** Iodine is not an allergen. Atopy, in general, confers an increased risk of reaction to contrast administration, but the risk of contrast admin-

istration is low, even in patients with a history of “iodine allergy,” seafood allergy, or prior contrast reaction. Allergies to shellfish, in particular, do not increase the risk of reaction to intravenous contrast any more than that of other allergies. © 2009 Elsevier Inc.

Keywords— iodine; seafood; shellfish; contrast media

INTRODUCTION

Radiocontrast agents are some of the most commonly used medications in the emergency department (ED). However, both physicians and patients misunderstand the role that allergies play in reactions to radiocontrast media, especially with regards to shellfish and iodine. Recent studies have shown that many physicians and patients believe iodine allergies are linked to seafood allergies and that both are related to an increased risk of reaction to radiocontrast media. In a survey of 231 physicians at six academic medical centers in the Midwest, two-thirds of participating radiologists and 89% of cardiologists indicated that they routinely ask their patients if they are allergic to shellfish before administering an iodinated contrast agent (1). Moreover, 35% of radiologists and 50% of cardiologists would withhold radiocontrast or require premedication for patients with shellfish allergies. These actions propagate the myth among patients that they are “allergic to iodine” and should not

receive iodinated contrast or that a shellfish allergy precludes them from receiving intravenous radiocontrast.

We sought to determine the frequency of reactions to intravenous contrast media in general and to estimate the risk of giving intravenous contrast to patients with a history of “iodine allergy,” shellfish allergy, or history of prior contrast reaction.

METHODS

In the initial stage of this study, both authors performed general, unstructured reviews of articles available in MEDLINE to gain perspective on adverse reactions to intravenous contrast. This included review articles on the topic and position statements from stakeholder organizations.

Following the general literature reviews, we performed a systematic review searching for large prospective studies with quantitative information on the risk of reaction in patients with prior reactions to contrast, shellfish, or “iodine allergy.” We searched the MEDLINE 1950-to-current database, intersecting the following: 1) keywords “contrast media,” subheading “adverse effects”; 2) the union of the articles with any of the terms “incidence,” “prevalence,” or “rate” in the title or abstract; 3) the union of articles with “adverse” in the title or abstract. This yielded 312 articles, which both authors reviewed independently based on prospectively defined eligibility criteria: we included review articles whose abstracts indicated prospective data collection with large registries (over 1000 administrations) that quantified risk

and mentioned the subgroups of interest—those with prior contrast, “iodine allergy,” or seafood or shellfish allergy; we excluded any article dealing primarily with nephrotoxicity, magnetic resonance imaging contrast, non-intravenous contrast administration, ultrasound contrast, delayed contrast reactions, or pediatric age groups, as well as systematic reviews combining studies. We reviewed the abstracts of all articles from both searches and the entire articles for articles available in English.

In analyzing data from studies, we used a categorization scheme for contrast reactions that were similar to one we found in many of the studies:

- Mild, requiring no treatment
- Moderate, requiring some treatment
- Severe, requiring hospitalization or life-threatening
- Fatal

Where appropriate, we combined data of similar type into a table. We compared selected proportions using Fisher’s exact test.

RESULTS

In the systematic review, both authors selected seven articles from the 312, with an overlap of six of them. Four of the common articles and the two discrepant articles were available in English. The data from four of these are summarized in Table 1 (2–5). Two studies are not shown in the table. One, by Bettmann et al., provided data only in percentages and model coefficients (6). This

Table 1. Studies Assessing Risk of Contrast Administration in Patients with History of Allergy or Prior Contrast Reactions*

Author, Year	Injections	Type of Contrast	All Reactions	Severe Reactions	Deaths
Shehadi, 1975 (2)					
All cases	112,003	HOCM	5546 (5%)	38 (0.03%)	8 (0.007%)
Seafood allergy	207		31 (15%)	1 (0.5%)	0
Other food allergy†	307		41 (13%)	0	0
Asthma	340		38 (11%)	0	0
Prior contrast reaction	1918		321 (17%)	NS	NS
Shehadi and Toniolo, 1980 (3)					
All cases	302,083	HOCM	14,301 (4.7%)	NS	18 (0.006%)
General allergy	16,483		1907 (11.6%)		
Valls et al., 2003 (4)					
All cases	19,554	Selective	338 (1.7%)	13 (0.06%)	0
Low risk	13,670	HOCM	304 (2.2%)	10 (0.07%)	
High risk (including allergy, prior contrast reaction)	5884	LOCM	34 (0.6%)	3 (0.05%)	
Kopp et al., 2008 (5)					
All cases	74,717	LOCM	1.5%‡	14 (0.02%)	0
Prior contrast reaction	2.1%		7.4%	0	
General allergy	10.3%		4.1%	0	

* Table includes patients with high-osmolality (HOCM) and low-osmolality (LOCM) contrast media.

† Eggs, milk, chocolate, fruit.

‡ This study excluded “tolerance indicators,” such as feeling of heat on injection, as adverse reactions.

study evaluated 75,616 injections, 36% of which were with high-osmolality contrast media (HOCM). They found, after adjusting for multiple variables including type of injection, co-morbidities including other allergies, and pretreatment, that a prior contrast reaction had an adjusted odds ratio of 2.04 for any contrast-mediated reaction and 1.46 for a serious reaction, with the latter not achieving statistical significance (6). The other study, by Katayama and Tanaka, looked at prior exposure to contrast, not prior reactions (7). They found that the rate of all reactions in 9827 patients with prior contrast exposure (7.0%) was similar to that in their overall study population of 33,400 (7.5%) (7). The abstracts of the two non-English studies described findings that were similar to the English studies.

Only one study estimated the risk of contrast administration in patients with seafood allergy. This study, from 1975, used only HOCM and found similar rates of all reactions for patients with various types of atopy, such as asthma, seafood allergy, other food allergies, and prior contrast reaction. In fact, compared with 31/207 reactions in patients with a seafood allergy, the reaction rates were statistically similar in patients with asthma ($p = 0.2$), other food allergies ($p = 0.6$), and prior contrast reactions ($p = 0.6$). One patient out of 207 (0.5%) with a seafood allergy had a severe reaction (2). We were unable to find any articles that estimated the risk of injection in patients with an “iodine allergy.”

As shown in Table 1, there were more data on the risk of injection in patients with prior contrast reactions. The studies generally show that those with prior contrast reactions have a relatively higher rate of mild reactions (two- to sixfold), but that the absolute risk declined from 17% in 1975 to 7.4% in 2008. Few studies estimated the risk of a severe reaction in patients with prior contrast reactions, but the highest estimate was 0.05% (5 in 10,000).

In our unstructured review, we found several articles comparing rates of reaction between low-osmolality contrast media (LOCM) and HOCM. Cochran et al. compared rates of reaction during an era of HOCM-only injections, 1985–1987, to an era of LOCM-only injections, 1991–1999 (8). The reaction rate declined from 101/1453 (7.0%) in the HOCM era to 155/68,701 (0.2%) (8). Another study, by Katayama et al., compared reaction rates in 169,284 cases of LOCM injection and 168,363 cases of HOCM injection (9). They found that rates of reactions were higher with HOCM than with LOCM both for all reactions (13% vs. 3%, respectively) and for severe reactions (0.2% vs. 0.04%, respectively). One death occurred in each group (0.0006%) (9). In the Valls study, shown in Table 1, reaction rates were lower in high-risk patients given LOCM than in low-risk patients given HOCM (4).

The effect of premedication is difficult to estimate from the studies we found, because we used observational studies. In these studies, many patients were selected for premedication because they were considered high risk. In the first study by Shehadi et al., the authors state that they did not observe an effect of steroids, but the authors note that the higher-risk patients received steroids (2). The Bettmann study, after adjusting for multiple variables, did not find a significant effect of pretreatment on adverse events requiring treatment (6). Premedication was not done, even in high risk patients, in the Valls study (4). The Kopp study found no significant effect of premedication on adverse event rates in patients with prior contrast reactions (5). We were able to find only one randomized controlled trial examining the effects of steroid premedication on adverse events. This study, published by Lasser et al. in 1987, compared two steroid regimens to placebo in patients receiving HOCM (10). Only one regimen, in which a single dose was given 2 h before injection, was close to being practical for use in an ED setting; the other regimen involved two doses, one given 12 h before injection. In 2491 patients given placebo, the overall reaction rate was 9.4%, and 0.5% had severe reactions. In 1759 patients given the one-drug regimen, the overall and severe reaction rates were almost exactly the same, 9.4% and 0.5%, respectively. The 12-h, two-dose regimen did decrease overall reactions to 6.4% and severe reactions to 0.2%, but the decrease in severe reactions was not statistically significant ($p = 0.07$, Fisher’s exact test) (10).

DISCUSSION

The Historical Link Between Shellfish Allergy and Iodinated Contrast Media

One possible early link between shellfish allergies and radiocontrast is a 1973 study by Witten et al., which showed that acute reactions were associated with a history of seafood allergy in 6% of patients (11). However, other reactions to contrast were also seen frequently in patients with other reported allergies: 6% of those with a history of asthma, 7% of those with a history of hives of unknown cause, and 6% of those with a history of “miscellaneous food allergies” (11). The fact that seafood allergies were placed in a category distinct from “miscellaneous food allergies” suggests that the idea of an association between allergies to seafood and to contrast media existed even before 1973.

Another article that is widely cited to link seafood allergies with radiocontrast dye reaction was a 1975 study by Shehadi (2). This study showed that patients with a history of any allergy were 2.2 times more likely

to have a reaction to contrast media than patients with no allergy history. The number one allergy listed in this article was an allergy to seafood. Thirty-one (15%) of 207 patients with seafood allergy had an adverse reaction; one was serious and none were fatal (Table 1). This frequency of reaction to the contrast agent was similar among patients with allergies to other substances: 15% of those with allergy to eggs, milk, or chocolate; 11% of those with asthma; 10% of those with hay fever; and 7% of those allergic to penicillin.

The Link between Seafood and “Iodine” Allergies

How seafood allergies and “iodine” allergies became linked is unclear. It is possible that we, as physicians, created that link through radiocontrast material. Older ionic agents dissociate into ions that contain an iodinated benzene ring and were thus considered “iodine-based.” Once the myth was created that seafood allergy increased the risk of contrast allergy, it is possible that individuals allergic to shellfish came to believe they were allergic to iodine as well.

The Iodine Allergy Myth

Iodine is not and cannot be an allergen. Iodine is found throughout our bodies in thyroid hormones and amino acids. Iodine is added to most salt used in the United States as a public health measure to prevent iodine deficiency. Without iodine in the body, a person cannot survive. Due to its antiseptic properties, iodine is used in many medicinal compounds, for example, povidone-iodine skin prep. Patients who experience reactions to these products are reacting to allergens in the solution, not to the iodine.

Both fish and shellfish contain iodine, but it is not the source of people’s allergies. The major allergens in shellfish are tropomyosins, which are proteins important in muscle contraction and which have no relation to iodine. Tropomyosins are cross-reactive allergens among crustaceans and mollusks but not scaled fish (12). People who are allergic to fish are most likely reacting to the muscle protein parvalbumin, and thus people who are allergic to shellfish can generally eat scaled fish.

Anaphylactoid vs. Anaphylactic Reactions

Anaphylaxis is a severe allergic reaction. After exposure to an allergen, the immune system becomes sensitized by creating immunoglobulin E (IgE) specific to that allergen. When re-exposed, the allergen-IgE complex causes mast

cells and basophils to degranulate, releasing histamines and other inflammatory factors. When transported through the circulatory system, these inflammatory factors cause the typical anaphylactic symptoms of urticaria, bronchospasm, hypotension, and vasodilatation. With each exposure, the severity of the anaphylactic reaction escalates. It is this trend toward increased severity that causes both physicians and patients to fear the word “allergy.”

Reactions to intravenous contrast are not allergic and therefore not anaphylactic (13). These reactions are not caused by IgE and thus require no pre-exposure. These types of reactions are termed “anaphylactoid.” In anaphylactoid reactions, mast cells and basophils degranulate as a result of direct stimulation rather than immune system triggering by IgE. Thus, anaphylactoid reactions share clinical features with IgE-mediated anaphylactic reactions: urticaria, bronchospasm, hypotension, and even cardiac arrest. Nearly all life-threatening reactions to intravenous contrast occur immediately or within the first 20 min after contrast media injection.

Although prior allergic reaction to seafood, shellfish, or iodine-containing solutions would create IgE sensitized to those allergens, this sensitized IgE would play no role in a reaction to intravenous contrast media, as the reaction to contrast is not IgE mediated (13). For the same reason, a patient who had an adverse event after contrast injection is unlikely to experience a similar or more severe reaction if given contrast again (6). Non-immune-mediated means no immune system memory. Though we found few studies that quantify the risk of re-reaction in patients with prior contrast, we found estimates of only 7% (LOCM) and 17% (HOCM) for all reactions and much lower for severe reactions. If the previous reaction were caused by an immune-mediated mechanism (a true allergy), the risk of re-exposure would approach 100%. The cause of anaphylactoid reaction to contrast media is not the iodine in the i.v. contrast, but is thought to be its hyperosmolality compared to blood, related to its relatively high ionic content (14).

Ionic (High Osmolar) vs. Non-Ionic (Low Osmolar) Dyes

A major innovation in intravenous radiocontrast media in the United States came with the approval of the first non-ionic contrast agent, metrizamide (Amipaque), in 1978 (15). Contrast agents that are non-ionic but high osmolar have been developed over the years, but most non-ionic agents used today are low osmolar and have low molecular weight. For simplicity, the terms “low osmolar” and “low molecular weight” are used interchangeably.

When the first ionic contrast material was developed in the early 1920s, iodine was the substance used to make

the dye radiopaque (16). Early dyes used mono-iodinated rings but were quickly replaced with di-iodinated and tri-iodinated rings, which are still used today and can more easily create a sufficient radiopaque concentration of iodine in the bloodstream. The cations that were used to carry iodide anions in the early formulations were sodium, the sugar meglumine, or both. They were inexpensive and easy to produce but created a solution that was hypertonic relative to blood. In fact, these iodinated ionic contrast agents have about five times the osmolality of plasma because both the anions (iodide) and the cations (sodium or meglumine) are osmotically active (17).

Hyperosmolar fluid, regardless of its composition, is a severe irritant throughout the body; it causes vasodilatation, increased capillary permeability, and direct cardiotoxicity and nephrotoxicity, and it may possibly be the direct cause of mast cell degranulation, leading to urticaria and an allergic-type response (though the exact mechanism remains unclear).

Most hospitals now use non-ionic contrast agents, at least in higher-risk patients. Approximately 90% of the iodinated contrast media in use in 2004 was nonionic (13,18). Non-ionic contrast still uses iodine as a radiopacification agent, but the newer iodinated molecules are created with different side chains that reduce dissociation in solution. Fewer molecules in solution decrease the osmolality and therefore cause fewer side effects and reactions. These compounds are usually about one-half to one-third as osmotically active as the ionic forms. They are about 10 times more expensive to produce but are still relatively inexpensive, at 10–20 dollars per test (19).

Based on our literature review, the use of LOCM had the largest and most clearly documented effect on adverse reaction rates. Based on studies involving over 300,000 patients, LOCM was associated with a fourfold or greater decrease in all reactions and a fivefold decrease in severe reactions. By contrast, steroid premedication given as early as 2 h before the procedure has not improved adverse reaction rates. Even with longer protocols, steroid premedication has not shown a statistically significant improvement in severe adverse reaction rates.

Expert Opinion

In its *Manual on Contrast Media*, the American College of Radiology states the following (13):

The predictive value of specific allergies, such as those to shellfish or dairy products, previously thought to be helpful, is now recognized to be unreliable. Any patient who describes an “allergy” to a food or contrast

media should be questioned further to clarify the type and severity of the “allergy” or reaction, as these patients could be atopic and at increased risk for reactions.

The American Academy of Asthma, Allergy, and Immunology states the following in a 2004 position paper (14):

There is an apparent concern about seafood allergy in relation to an increased risk of reactions based upon the higher content of iodine in fish. However, the risk of reactions to [radiocontrast media] was similarly elevated (about a 3-fold relative risk compared to average) for persons with allergy to egg, milk or chocolate, indicating that a general atopic disposition, rather than an iodine-specific reactivity, accounts for the increased incidence of reactions in this sub-group. Thus, reactions to [radiocontrast media] should not be construed as an indication of an IgE antibody-mediated iodine allergy.

Guidelines have been developed by the American College of Radiology for the use of low-osmolality, nonionic agents (13). According to these guidelines, non-ionic agents should be used in patients who are at increased risk of adverse reactions. This includes patients with previous intravenous contrast reactions, asthma, multiple true allergies, or diseases that increase the risk of adverse reactions (e.g., pheochromocytoma, hyperthyroidism, thyroid cancer, renal failure). Some experts recommend premedication with an antihistamine and a steroid. However, the only effect of steroid premedication has been to decrease the total number of adverse events in patients receiving lengthy premedication protocols; steroids have not been shown to decrease severe events, and they have not been shown to have any significant effect when given <3 h before intravenous administration of a contrast agent (13). In addition, a recent systematic review questions the convention of premedication and suggests that the practice of routine prophylaxis should be abandoned (20).

CONCLUSIONS

- The evidence suggests that asking if patients are allergic to shellfish or iodine has no relevance to radiocontrast allergies. This questioning perpetuates the myth of an association between shellfish, iodine, and contrast agents. Instead, ask if they have *any* allergies, have had a previous reaction to a contrast agent, or have evidence of atopy, such as asthma. Educate nurses and technicians to stop propagating this myth as well.
- If your patient offers an allergy to iodine or shellfish, ask the patient if they mean to say that they have had a reaction to intravenous contrast in the

past. Educate them that they do not have an “allergy” to iodine, and that an allergy to shellfish does not change the risk of reaction to intravenous contrast any more than any other allergy.

- If your hospital does not routinely use a low osmolality, non-ionic agent, request this type of medium for atopic patients, patients who had a reaction to an intravenous contrast agent in the past, and patients with systemic disease that increases their risk for contrast reaction.
- Do not delay emergent studies for steroid premedication. Only lengthy 12-h premedication protocols have shown any effect on reaction rates, and this small benefit was manifested primarily by decreasing minor reactions. No steroid protocol has shown a significant benefit in decreasing severe or fatal reactions.
- Monitor all patients for at least 20 min after administration of radiocontrast.
- Treat any severe reaction to radiocontrast the same way you would treat a severe anaphylactic reaction.

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ARTICLE SUMMARY**1. Why is this topic important?**

Radiologic studies utilizing intravenous contrast are vital to the diagnosis of disease processes in the Emergency Department. Many patients claim to be “allergic” to iodine or seafood, and this often results in a delay of care for premedication or a decision to not order appropriate studies.

2. What does this review attempt to show?

We attempt to analyze the existing literature to enable clinicians to put the concepts of “iodine allergy,” shellfish allergy, and prior contrast reaction in the proper perspective.

3. What are the key findings?

a) Allergies to shellfish are associated with the same small increase in the risk of reaction to contrast injection as are other forms of atopy such as asthma and other food allergies.

b) Reactions to radiocontrast are anaphylactoid, not immunoglobulin E-mediated, and do not carry a risk of escalation with repeated exposure.

c) Low molecular weight, non-iodinated contrast agents significantly decrease the risk of reactions to intravenous contrast.

4. How is patient care impacted?

Improving clinicians’ understanding of the risk of contrast will allow better selection of patients for procedures requiring iodinated contrast media. Understanding the means available to mitigate risk will help protect all high-risk patients who require contrast media.