

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/371224359>

Iodine Allergy and the Orthopaedic Patient

Article in *The Journal of Bone and Joint Surgery* · June 2023

DOI: 10.2106/JBJS.22.01389

CITATIONS

0

READS

161

3 authors:



Andrew Fraval

Rothman Orthopaedic Institute

22 PUBLICATIONS 242 CITATIONS

SEE PROFILE



Michael A Mont

Lenox Hill Hospital

1,474 PUBLICATIONS 50,193 CITATIONS

SEE PROFILE



Javad Parvizi

Acibadem Hospitals Group

1,239 PUBLICATIONS 70,714 CITATIONS

SEE PROFILE

THE ORTHOPAEDIC FORUM

Iodine Allergy and the Orthopaedic Patient

Andrew Fraval, MD, FRACS, Michael A. Mont, MD, and Javad Parvizi, MD, FRCS

Investigation performed at Rothman Orthopaedic Institute at Thomas Jefferson University, Philadelphia, Pennsylvania

Iodine-based products, as effective antiseptics, have been in use in medicine for decades¹. In orthopaedic surgery, these products are incorporated into skin preparation solutions, adhesive incise draping, surgical irrigation solutions, and other applications². The antiseptic efficacy of iodine-based products has been shown in numerous studies³⁻⁵.

It is not unusual to encounter patients who believe that they have an allergy to iodine as a topical agent or as a contrast medium. The validity of iodine allergies as a clinical entity has been questioned in several studies⁶⁻¹². Furthermore, research has demonstrated that an alteration in practice in response to a documented allergy may negatively impact patient outcomes^{12,13}. Iodine alone is not, and cannot be, an allergen^{6,14}. Iodine in its elemental form is an essential nutrient that is obtained from foods, with a daily recommended intake of 240 to 300 µg per day for men and 190 to 210 µg per day for women⁹. It is essential for normal physiological processes, as it is involved in thyroid hormone synthesis and for this reason cannot act as an allergen^{9,12}.

Allergic reactions to iodine-containing products, such as povidone-iodine (PVP-I), can occur; however, iodine is not the culprit in these situations^{10,12,15,16}. Multiple reports have shown that allergies to iodine-containing products do not cross over to other unrelated iodine-containing products, which has been demonstrated in the setting of iodine-containing pharmaceuticals, contrast agents, and products such as PVP-I^{6,9,17-19}. Furthermore, a distinction between a true allergic reaction and an "irritation" to the product needs to be made⁹. An allergic or hypersensitivity reaction is an immune-mediated response to a foreign substance or antigen. Drug allergies are commonly classified into 4 types of hypersensitivity reactions: immunoglobulin E (IgE)-mediated (type I), cytotoxic (type II), immune-complex

(type III), and cell-mediated (type IV)²⁰. A skin reaction to iodine-containing products may lead to contact dermatitis, which can be divided into allergic contact dermatitis and irritant contact dermatitis. Allergic contact dermatitis is an immune-mediated type-IV hypersensitivity reaction resulting in a T-cell-mediated inflammatory response due to exposure to an allergen²¹. This form of contact dermatitis requires a sensitization episode followed by re-exposure and subsequent activation of the sensitized T cells. Irritant contact dermatitis is a non-immune-mediated response to exposure to an irritating substance and may be seen particularly where prolonged pooling of a PVP-I solution occurs intraoperatively^{21,22}. PVP-I may act as both an allergen and an irritant, which makes a definitive diagnosis of an allergy challenging.

One study investigated iodine sensitivity in patients with a reported allergic reaction to PVP-I skin preparations by utilizing patch tests under occlusion and open conditions. Patch tests under occlusion were positive, whereas open patch tests were negative, indicating irritant contact dermatitis²³. Furthermore, patients who have a confirmed T-cell-mediated allergic reaction to PVP-I commonly have negative patch tests for other iodine-containing substances^{18,19}, which suggests that the reaction is not related to iodine but rather to other compounds within the PVP-I solution.

The prevalence of allergic contact dermatitis (type-IV hypersensitivity reaction) in response to PVP-I is poorly described in spite of the widespread use of this product. In an early report, 2 cases of allergic contact dermatitis were found in 5,000 patients in whom a PVP-I skin preparation solution was utilized, corresponding to a prevalence of 0.04%²⁴. A more contemporary study published in 2005 of 500 patients who underwent formal patch testing to screen for the presence of allergic dermatitis

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (<http://links.lww.com/JBJS/H567>).

showed a substantially higher prevalence of 0.4%²⁵. This higher prevalence of allergic contact dermatitis may have been influenced by the fact that these patients were recruited from a patch-testing clinic and as such may have had higher rates of allergies than a population not recruited from such a clinic.

Type-I allergic reactions leading to anaphylaxis that are a result of PVP-I exposure may occur but are exceedingly rare, with approximately 9 cases having been reported in the literature since 1998²⁶. Anaphylactic reactions have been documented to occur with topical application of PVP-I for skin preparation as well as with use of PVP-I for wound lavage²⁶. Although the occurrence of such a reaction is rare, it can lead to dire consequences, and thus the use of a PVP-I wound lavage should be avoided in patients with a documented anaphylactic reaction to PVP-I²⁶.

Patients who have an intolerance or allergy to shellfish are often assumed to also have an iodine allergy. The source of this speculation, along with the science behind such a link, is not clear, but it may have originated from early investigations seeking to identify risk factors for an adverse reaction to iodine-containing contrast media⁶. Shellfish allergies have an estimated prevalence of 0.5% in the United States population²⁷. A positive association between shellfish allergies and iodine-containing contrast media was also reported in a recent cohort study published in 2013, in which the prevalence of and risk factors for an allergic reaction to contrast media were investigated in 55,286 patients²⁸. However, this study had methodological flaws in that the only food allergies investigated were those related to shellfish. Furthermore, the researchers found that patients who had documented but unspecified drug allergies also had significantly higher rates of allergic reactions to iodinated contrast media. These findings support the notion that individuals who have an allergy to 1 product may also have allergies to other products, a manifestation of atopy⁶. According to 1 study from 1975, patients who had a known history of any allergy were 2.2 times more likely to have an allergy to iodine-containing contrast media. Interestingly, in this study, the frequency of an allergic reaction to such contrast media was similar among individuals who had allergies to shellfish, chocolate, eggs, and/or milk²⁹.

Avoiding the use of iodine-containing products in patients who have shellfish allergies is currently a common medical practice^{11,12}. There is no scientific basis for this practice. Shellfish allergies are, in fact, caused by proteins called tropomyosins, which have no relationship to iodine⁶. Although it is true that shellfish may contain relatively high levels of iodine compared with other foods, the allergenic proteins are not iodinated, and a shellfish allergy does not depend on the iodine content of the shellfish. Recent guidance by the American College of Radiology states that there is no cross-reaction between iodine-containing contrast media and iodine or shellfish allergies³⁰. Thus, the existence of a shellfish allergy in a patient should not prevent the use of iodine-containing products in that patient. The link between shellfish allergy and iodine allergy is an example of a persistent myth in medicine that has no scientific basis.

On the basis of a review of the available literature on alleged "iodine allergies," we would advise the following recommendations for patients undergoing orthopaedic procedures. When a

shellfish allergy is present in isolation, iodine-containing products can safely be used because there is no scientific basis for the association of an allergic reaction to shellfish with an allergic reaction to iodine-containing products. Also, when an iodine allergy is present in isolation, a clarification of the allergy needs to be sought. It is important to determine if the patient is at risk from the use of iodine-containing products such as PVP-I or if the diagnosis was made on the basis of an exposure to shellfish, iodinated contrast agents, or iodine-containing medications. A review of the exposure that led to the reaction should be conducted and clarification of the clinical manifestations obtained. Particular attention should be paid to the presence of symptoms suggestive of an anaphylactic response, such as urticaria, angioedema, nausea, vomiting, and/or wheezing²⁰. In our experience, most patient iodine allergies are unrelated to the use of PVP-I and, following clarification of the allergy, the utilization of these products can be considered safe. In the setting of a patient with a documented allergy to products containing PVP-I, patch testing of the skin may be utilized to confirm if an allergic reaction exists that is distinct from irritant contact dermatitis. Of the 9 reported cases in the literature of anaphylaxis due to PVP-I, all were associated with positive patch testing postoperatively²⁶. A separate study of patients with contact dermatitis associated with PVP-I demonstrated that, following patch testing, the majority of these reactions were deemed to be irritant rather than allergic contact dermatitis²⁵. When irritant contact dermatitis is present, PVP-I lavage can safely be utilized since an immunogenic response will not be present. When uncertainty exists regarding a patient with a documented allergy to a product containing PVP-I, we would recommend utilizing a chlorhexidine-based skin preparation solution and avoiding the use of PVP-I lavage intraoperatively because of the possibility of an anaphylactic response.

The decision to avoid the use of products containing PVP-I may place the patient at risk in a similar manner to utilizing a prophylactic antibiotic other than cefazolin in the setting of a penicillin allergy³¹. The use of PVP-I lavage intraoperatively has been associated with a reduction in periprosthetic joint infection following revision and primary surgery^{4,32,33}. Given the advantage of PVP-I lavage, further research would be of benefit to establish validated protocols for how to safely treat patients who have documented allergic reactions to iodine-containing products, with the goal of minimizing unnecessary changes in practice that may be associated with inferior outcomes. ■

Andrew Fraval, MD, FRACS¹

Michael A. Mont, MD²

Javad Parvizi, MD, FRCS¹

¹Rothman Orthopaedic Institute at Thomas Jefferson University, Philadelphia, Pennsylvania

²Rubin Institute for Advanced Orthopedics, Sinai Hospital of Baltimore, Baltimore, Maryland

Email for corresponding author: andrew.fraval@rothmanortho.com

References

1. Eggers M. Infectious Disease Management and Control with Povidone Iodine. *Infect Dis Ther*. 2019 Dec;8(4):581-93.
2. Durani P, Leaper D. Povidone-iodine: use in hand disinfection, skin preparation and antiseptic irrigation. *Int Wound J*. 2008 Jun;5(3):376-87.
3. Rezapoor M, Tan TL, Maltenfort MG, Parvizi J. Incise Draping Reduces the Rate of Contamination of the Surgical Site During Hip Surgery: A Prospective, Randomized Trial. *J Arthroplasty*. 2018 Jun;33(6):1891-5.
4. Hart A, Hernandez NM, Abdel MP, Mabry TM, Hanssen AD, Perry KI. Povidone-Iodine Wound Lavage to Prevent Infection After Revision Total Hip and Knee Arthroplasty: An Analysis of 2,884 Cases. *J Bone Joint Surg Am*. 2019 Jul 3;101(13):1151-9.
5. Atkins GJ, Alberdi MT, Beswick A, Blaha JD, Bingham J, Cashman J, Chen AF, Cooper AM, Cotacio GL, Fraguas T, Gambhir A, Gromov K, Guerra E, Hooper G, Khlopas A, Kieser D, Klaber I, Kyte R, Levine B, Mont MA, Nikolaou V, Nuñez J, Overgaard S, Parvizi J, Saxena A, Sayago G, Shahcheraghi H, Sodhi N, Solomon LB, Starczak Y, Tan TL, Tarabichi M, Olivan RT, Virolainen P, Wyatt M. General Assembly, Prevention, Surgical Site Preparation: Proceedings of International Consensus on Orthopedic Infections. *J Arthroplasty*. 2019 Feb;34(2S):S85-92.
6. Schabelman E, Witting M. The relationship of radiocontrast, iodine, and seafood allergies: a medical myth exposed. *J Emerg Med*. 2010 Nov;39(5):701-7.
7. Long B, Chassee T, Jones JS. BET 2: Is there an association between iodine, shellfish and contrast agent allergies? *Emerg Med J*. 2019 Nov;36(11):698-9.
8. Stewart MW, Doctor I. Have an Iodine Allergy. *Ophthalmol Ther*. 2022 Jun;11(3):931-8.
9. Wulf NR, Schmitz J, Choi A, Kapusnik-Uner J. Iodine allergy: Common misperceptions. *Am J Health Syst Pharm*. 2021 Apr 22;78(9):781-93.
10. Huang SW. Seafood and iodine: an analysis of a medical myth. *Allergy Asthma Proc*. 2005 Nov-Dec;26(6):468-9.
11. Baig M, Farag A, Sajid J, Potluri R, Irwin RB, Khalid HM. Shellfish allergy and relation to iodinated contrast media: United Kingdom survey. *World J Cardiol*. 2014 Mar 26;6(3):107-11.
12. Bruen R, Stirling A, Ryan M, Sheehan M, MacMahon P. Shelling the myth: allergies to iodine containing substances and risk of reaction to iodinated contrast media. *Emerg Radiol*. 2022 Feb;29(1):67-73.
13. Bohm I, Nairz K, Morelli JN, Keller PS, Heverhagen JT. Iodinated Contrast Media and the Alleged "Iodine Allergy": An Inexact Diagnosis Leading to Inferior Radiologic Management and Adverse Drug Reactions. *Röfo Fortschr Geb Röntgenstr Nuklearmed*. 2017 Apr;189(4):326-32.
14. Katelaris CHSW. 'Iodine allergy' label is misleading. *Aust Prescr*. 2009;32:125-8.
15. Beaty AD, Lieberman PL, Slavin RG. Seafood allergy and radiocontrast media: are physicians propagating a myth? *Am J Med*. 2008 Feb;121(2):158.e1-4.
16. Dewachter P, Mouton-Faivre C. [Allergy to iodinated drugs and to foods rich in iodine: iodine is not the allergenic determinant]. *Presse Med*. 2015 Nov;44(11):1136-45.
17. Krohne TU, Allam JP, Novak N, Holz FG. ["Iodine allergy": A medical myth with risks for the ophthalmological patient]. *Ophthalmologe*. 2016 Dec;113(12):1023-8.
18. Nishioka K, Seguchi T, Yasuno H, Yamamoto T, Tominaga K. The results of ingredient patch testing in contact dermatitis elicited by povidone-iodine preparations. *Contact Dermat*. 2000 Feb;42(2):90-4.
19. de la Cuadra-Oyanguren J, Zaragoza-Ninet V, Sierra-Talamantes C, Alegre de Miquel V. Postsurgical contact dermatitis due to povidone iodine: a diagnostic dilemma [English Edition]. *Actas Dermosifiliogr*. 2014 Apr;105(3):300-4.
20. Baldo BA, Pham NH. Classification and descriptions of allergic reactions to drugs. In: *Drug Allergy*. Springer Cham;2021.
21. Nassau S, Fonacier L. Allergic Contact Dermatitis. *Med Clin North Am*. 2020 Jan;104(1):61-76.
22. Borrego L, Hernández N, Hernández Z, Peñate Y. Povidone-iodine induced post-surgical irritant contact dermatitis localized outside of the surgical incision area. Report of 27 cases and a literature review. *Int J Dermatol*. 2016 May;55(5):540-5.
23. Iijima S, Kuramochi M. Investigation of irritant skin reaction by 10% povidone-iodine solution after surgery. *Dermatology*. 2002;204(Suppl 1):103-8.
24. Zamora JL. Chemical and microbiologic characteristics and toxicity of povidone-iodine solutions. *Am J Surg*. 1986 Mar;151(3):400-6.
25. Lachapelle JM. Allergic contact dermatitis from povidone-iodine: a re-evaluation study. *Contact Dermat*. 2005 Jan;52(1):9-10.
26. Xiang BB, Yao YT, Jiao SL. Successful prolonged cardiopulmonary resuscitation after intraoperative cardiac arrest due to povidone-iodine allergy: A case report. *World J Clin Cases*. 2021 Nov 26;9(33):10362-8.
27. Mikita CP, Padlan EA. Why is there a greater incidence of allergy to the tropomyosin of certain animals than to that of others? *Med Hypotheses*. 2007;69(5):1070-3.
28. Pradubongsa P, Dhana N, Jongjarearnprasert K, Janpanich S, Thongngarm T. Adverse reactions to iodinated contrast media: prevalence, risk factors and outcome-the results of a 3-year period. *Asian Pac J Allergy Immunol*. 2013 Dec;31(4):299-306.
29. Shehadi WH. Adverse reactions to intravascularly administered contrast media. A comprehensive study based on a prospective survey. *Am J Roentgenol Radium Ther Nucl Med*. 1975 May;124(1):145-52.
30. American College of Radiology. ACR Manual of Contrast Media. Version 10.3. 2018. Accessed 2019 Jan 28. <https://www.acr.org/Clinical-Resources/Contrast-Manual>
31. Wyles CC, Hevesi M, Osmon DR, Park MA, Habermann EB, Lewallen DG, Berry DJ, Sierra RJ. 2019 John Charnley Award: Increased risk of prosthetic joint infection following primary total knee and hip arthroplasty with the use of alternative antibiotics to cefazolin: the value of allergy testing for antibiotic prophylaxis. *Bone Joint J*. 2019 Jun;101-B(6_Supple_B):9-15.
32. Calkins TE, Culvern C, Nam D, Gerlinger TL, Levine BR, Sporer SM, Della Valle CJ. Dilute Betadine Lavage Reduces the Risk of Acute Postoperative Periprosthetic Joint Infection in Aseptic Revision Total Knee and Hip Arthroplasty: A Randomized Controlled Trial. *J Arthroplasty*. 2020 Feb;35(2):538-543.e1.
33. Shohat N, Goh GS, Harrer SL, Brown S. Dilute Povidone-Iodine Irrigation Reduces the Rate of Periprosthetic Joint Infection Following Hip and Knee Arthroplasty: An Analysis of 31,331 Cases. *J Arthroplasty*. 2022 Feb;37(2):226-231.e1.