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COMMENTARY

Doctor I Have an Iodine Allergy

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ABSTRACT

Ophthalmologists frequently face patients who refuse asepsis protocols involving povidone-iodine (PI) due to claims of an allergy to iodine. Such patients usually base this claim on previous reactions to shellfish consumption or to imaging procedures that used iodine-based contrast agents. Allergy to iodine, however, is biologically impossible, and iodine deficiency causes severe developmental problems, including mental retardation. Furthermore, shellfish allergy is due to tropomyosins in muscle tissue, and reactions to intravascular contrast dyes are due to hyperosmolar solutions; neither "allergy" is due to iodine. PI, which contains 9–12% iodine, is the preferred antiseptic for ophthalmic procedures. Experience shows that PI can be administered safely to patients claiming iodine allergy. True allergy to PI is rare and, if indicated, skin patch testing can be performed prior to surgery. Patients who react adversely to highly concentrated (5–10%) PI usually experience toxicity to the corneal and conjunctival epithelium after topical administration. Dilute (0.1–0.25%) PI kills microbes quicker than higher concentrations but for shorter periods of time because the total dose of iodine is smaller. Repeated administration (every 20–30 s) of dilute PI effectively kills microbes for as long as necessary with little risk of epithelial toxicity.

Keywords: Allergies; Asepsis; Contrast dye; Intravitreal injections; Iodine; Povidone-iodine; Shellfish; Surgery

Key Summary Points
Iodine allergy is a myth.
Shellfish allergy is due to tropomycins present in muscle, whereas contrast dye "allergy" is a hyperosmolar reaction; neither is due to iodine.
Povidone-iodine (PI) allergy is rare, but toxicity to the corneal and conjunctival epithelium is sometimes seen.
PI is the preferred antiseptic for ophthalmic procedures.
Frequent administration of dilute (0.1–0.25%) PI may provide better antisepsis than 5–10% PI without toxicity to the epithelium.

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INTRODUCTION

"But doctor I can't receive betadine because I'm allergic to iodine." Ophthalmologists, office staff, and operating suite circulators all too frequently hear these words when patients are being prepped for intravitreal injections or surgical procedures. It usually causes staff to halt their work and query the physician about what to do next. Often the "iodine allergy" is listed in the medical record, which adds credence to the patient's claim. When confronted with this situation some physicians will tell staff to withhold povidone-iodine (PI) and perhaps use chlorhexidine on the skin with sterile saline irrigation of the conjunctiva. Others will question the validity of the allergy claim and insist on the use of PI, which confuses and concerns the patient and staff.

The purpose of this commentary is to address the notion of "iodine allergy" and provide physicians and support personnel with a strategy for managing these challenging patients. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

THE ROLE IN IODINE IN HUMAN PHYSIOLOGY

When considering the possibility of an iodine allergy, one needs to understand the critical role of iodine in human physiology. Iodine is a vital micronutrient that is required by the human body during all stages of life, with fetal development through early childhood being the most critical period. Iodine deficiency disorder (IDD) is the world's most common endocrinopathy and the most easily preventable cause of mental retardation [1]. Unfortunately, one third of the world's population lives in iodine-deficient areas [2] and one fifth of pregnant women in India give birth to children who fail to reach full potential due to maternal IDD. [3]

COMMON REASONS FOR REPORTED IODINE "ALLERGIES"

Patients are usually told they are allergic to iodine because they have had adverse reactions to compounds known to be rich in iodine. The most common causes of these reactions are exposure to iodinated contrast dye used in radiologic procedures and the consumption of shellfish. Suspected links between iodine allergies, radio-opaque contrast dyes, and shellfish are based on several associations that were first suggested in the 1970s. [4]

Radio-opaque contrast dyes rely on iodine to produce images during studies because the innermost electron binding energy of iodine resembles that of the incident X-rays. Photoelectric absorption occurs efficiently, thereby creating a shadow on the photosensitive "film" and producing detailed diagnostic images.

In a 1973 survey, acute reactions to radiocontrast dye occurred in 6% of patients with seafood allergies [5], and a 1975 survey reported that patients with a history of any allergy were 2.2-fold more likely to have a reaction to iodinated contrast media than those who reported to be allergy free [6]. The most frequent allergy reported by patients with adverse events was seafood (15% of patients), although a similar percentage of patients reported allergies to eggs, milk, or chocolate (15%).

The link between seafood and iodine allergy is less clear than that between radiocontrast dye and iodine although the origins of these two beliefs are probably related. Shellfish have high tissue concentrations of iodine, and with the "discovery" of a connection between radiocontrast dye and iodine—subsequently proven to be incorrect—physicians probably projected that same association between shellfish and allergies [7]. However, shellfish allergies are due to the presence of tropomyosins, which are proteins important to muscle contraction. Tropomyosins are cross-reactive allergens among crustaceans and mollusks, but not scaled fish. People who are allergic to fish likely react to the protein parvalbumin [8].

As a result of these findings, physicians and other healthcare workers were taught that

adverse reactions to radiocontrast dyes were due to iodine allergies. A 2008 survey of six academic medical centers found that 67% of radiologists and 89% of cardiologists ask about shellfish allergy before giving radiocontrast dye. Additionally, 35% of radiologists and 50% of cardiologists would withhold radiocontrast dye if the patient reported a shellfish allergy [4].

By the time of a 2019 survey, some beliefs regarding shellfish had changed, but the idea of "iodine" allergy was still embraced by a substantial proportion of physicians. In that survey, emergency medicine and radiology residents and senior physicians were asked if they would honor an order to administer radiocontrast dye if a patient reported various allergies. Among the physicians who responded, 20% reported that they would either withhold or consider withholding radiocontrast dye if patients reported shellfish allergies [9].

This moderation in the belief that iodine allergy leads to adverse events with radiocontrast dye may have come from the findings of a systematic review [7], which reiterated that adverse events during the administration of radiocontrast dye were not due to shellfish allergy, but rather were associated with any allergy [6, 10]. Interestingly, the incidence of subsequent adverse events in patients who had previous reactions with contrast dyes were mixed [11, 12].

If iodine has nothing to do with radiocontrast dye-related adverse events and patients with previous reactions to dye can subsequently be imaged successfully, then what is the mechanism of contrast dye-related reactions? The conversion to non-ionic, hypertonic contrast dyes with di- and tri-iodinated rings began in 1978 [13]. Hypertonicity increases the risk of adverse events, including vasodilation, increased capillary permeability, mast cell granulation, and direct cardiotoxicity and nephrotoxicity [7]. A literature review showed that low-osmotic contrast media was associated with a fourfold decrease in all reactions and a fivefold decrease in serious reactions [7]. Pretreatment with corticosteroids does not reduce the rate of severe adverse events, consistent with the adverse event being a hyperosmolar reaction and not an immune-mediated one [14]. Patients who have an adverse reaction to contrast dye can usually be successfully re-imaged with a lower osmolar dye. [7]

OPHTHALMOLOGY

Asepsis has been an important part of ophthalmologic surgery for decades. Tincture of iodine was used for surgical asepsis through the first half of the twentieth century, but this gave way PI, which first came into commercial use in 1955. PI is a chemical complex of triiodide (I_3^-) and the polymer povidone (polyvinylpyrrolidone), with the latter serving as a carrier for the iodine (Fig. 1). PI contains 9–12% of slowly released available iodine [15] that oxidizes water, damages microbial membrane proteins [16], and kills a broad range of organisms, including multidrug-resistant Gram-positive-negative bacteria, mycobacteria, fungi (but not spores), protozoa, and viruses. Bacteria do not develop resistance to PI [17, 18]. Since PI can safely and effectively sterilize skin or mucous membranes in most patients, it has become widely used to prevent infection from ophthalmologic and other surgical procedures, as well as to treat active infections. PI sterilizes the conjunctiva of *Neisseria gonorrhea* and herpes simplex and significantly reduces the number of *Chlamydia* isolates [19]. A single application of PI was found to be more effective than silver nitrate or erythromycin ointment in preventing ophthalmia neonatorum [20]. Experience from several countries demonstrates that topical 1.25% PI may be used to treat corneal ulcers [21–23].

Much of the basic science and clinical evidence supporting the use of PI as asepsis for ophthalmologic surgery originated in the early 1990s. An early prospective study showed that 3 days of pre-operative PI use reduced conjunctival bacteria similarly to 3 days of a combination antibiotic (Neosporin) ointment [24]. The first large-scale study on the routine use of PI as prophylaxis against endophthalmitis showed that post-cataract surgery rates of endophthalmitis were reduced fourfold versus routine use of a silver nitrate solution [25]. In another study, a single application of PI just before

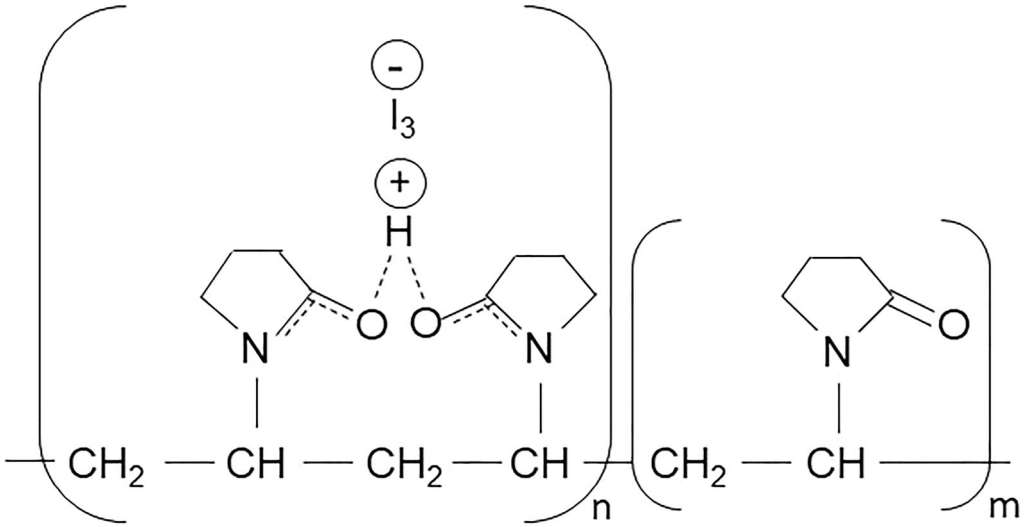

Fig. 1 Povidone-iodine consists of repeating polyvinylpyrrolidone units bound to triidodide anions. Release of an iodine atom creates the antiseptic effect

incisional ophthalmologic surgery reduced the incidence of positive limbus bacterial cultures from 78 to 28% [26]. A survey of 469 surgical centers in Germany reported that pre-operative PI on the conjunctiva together with intracameral antibiotics significantly reduced rates of endophthalmitis [27]. The authors of an evidence-based update of MEDLINE literature from 1966 to 2000 concluded that the "current literature most strongly supports the use of preoperative povidone-iodine antisepsis." [28] As a result of these and numerous other studies, the pre-operative use of PI to sterilize the conjunctiva and reduce the incidence of endophthalmitis has become standard of care.

Topical antibiotics had long been used to prevent endophthalmitis after intravitreal injections despite a lack of supporting evidence [29], but because of a lack of efficacy and concerns over inducing bacterial resistance, many surgeons have discontinued the use of peri-ocular antibiotic injections [30]. Patients who receive intravitreal anti-vascular endothelial growth factor (VEGF) injections without having received PI because of a self-reported iodine allergy, however, may have a very high endophthalmitis rate (9.4%; 5 of 53 patients) [31]. And surprisingly, the rate of intravitreal injection-related endophthalmitis may be higher in patients who receive topical antibiotics [32]. The Diabetic Retinopathy Clinical Research network (DRCT.net) has stopped the use of peri-injection antibiotics, but it has mandated that all patients receive PI, even those who report iodine "allergy." Major ophthalmic organizations uniformly recommend the use of pre-injection PI, but draping of the patient varies according to location (common in Europe and the Middle East but rare in the USA).

The use of topical PI for injections and surgery is widely accepted, but uncertainty regarding optimal concentration and dosing frequency still exists. Furthermore, because of conflicting and incomplete data, there is no uniform recommendation regarding the optimal exposure time to 5% PI before beginning a procedure, although major societies are in alignment. The European Society of Cataract and Refractive Surgery, American Society of Cataract and Refractive Surgery, and American Academy of Ophthalmology recommend that a 5–10% solution of PI be applied to the periorbital skin, conjunctiva, and cornea for at least 3 min prior to starting surgery [33]. An expert panel recommended a minimum exposure time of 30 s before performing an intravitreal injection [34], but a 2-min exposure to 5% PI is the

recommended protocol prior to intravitreal injection in France [35]. Another study found that a 15-s exposure to 5% PI did not decrease the number of conjunctival colony-forming units and that there was no difference in the number of colony-forming units after a 2-min exposures to 1% or 5% PI, although greater corneal epithelial toxicity was seen in the 5% group [36]. Lower concentrations of PI (1.25%) are commonly used in China and Japan. [37].

POVIDONE-IODINE DOSING

The microbial killing activity of PI does not appear to be related to the concentration of the drop, but rather to the amount of free iodine [38]. Free iodine concentrations in PI solutions are as follows: 5 ppm in a 10% solution; 13 ppm in a 1% solution; 24 ppm in a 0.1% solution; and 13 ppm in a 0.01% solution. Because of this, lower concentrations of PI (down to 0.1%) have higher peak bactericidal activity (i.e., the time to kill bacteria is shorter for 0.1–1% PI than for 2.5–10% PI). Once free iodine reacts with bacteria it becomes inactive, and since solutions with lower concentrations of PI do not have the large iodine reservoirs of high concentrations, the killing effect cannot be sustained. Solutions with higher concentrations of PI take longer to kill bacteria, but their effect is longer.

Dilute PI is prepared by mixing the commercially available product (5 or 10%) with physiologic saline [39]. The shorter duration of action of dilute PI can be compensated for by repeatedly applying drops every 20–30 s for the duration of the surgery [40]. Repeated administration (every 30 s) of dilute PI (0.25%) throughout a cataract surgery combines a high peak killing activity with a prolonged duration of action [41]. It is recommended that dilute PI be discarded at the end of the day during which it is prepared [42]. Conjunctival irrigation of 5% PI results in fewer cultures than 2 drops of 5% PI. [41].

Repeated use of PI is limited by corneal endothelial and epithelial toxicity. Exposure of rabbit endothelial cells to 0.25% PI was found to be toxic [42], as was a 2 ml injection of 1% PI into an anterior chamber [43], but injections of only 0.05 ml of 0.5–1% PI had no effect on endothelial cell counts [44] nor did replacing the aqueous solution with 0.1% PI. After repeated intraoperative surface irrigation with 0.25% PI during cataract surgery, the anterior chamber contamination rate was found to be 0% [39] and the concentration of PI was 0.008% [45]. Corneal epithelial toxicity resulting from conjunctival lavage with PI is dose dependent but unusual with concentrations less than 1%. [44].

PI can be used safely in most patients, but it should not be used in pregnant women before 32 weeks of gestation, patients receiving lithium, or patients suffering from hyperthyroidism or dermatitis herpetiformis (Duhring's disease) [46]. The overall incidence of skin irritation due to PI is 2.8%, and true allergy may occur in up to 0.4% of patients [47]. Patch testing has confirmed that allergic reactions to PI are not caused by iodine but rather by the non-iodinated copolymers in povidone. Some patients may develop a skin rash that may be a simple irritation, but in others the rash may be part of an allergic reaction. The latter can be sufficiently severe to resemble a chemical burn or can even cause an anaphylactic reaction [48]. Most cases of post-procedure pain are from sensitivity to concentrated PI (5–10%) rather than an allergy. [49].

For those rare patients with true allergy to PI, 0.02% aqueous chlorhexidine can be used on the eye [33]. This can be prepared by diluting a 20% chlorhexidine digluconate solution with acetate buffer (pH 5.9, osmolality 270 mOsmol/kg) under a laminar flow hood, filtering the solution through a 0.22-μm filter, and aseptically dispensing it into HDPE droppers. This solution can be stored for 1 month (after opening) or 6 months (sealed) [50].

CONCLUSIONS

Povidone-iodine is a potent and well-tolerated topical antiseptic that is used in a variety of invasive procedures. Appreciation of its effectiveness and safety has resulted in increased use as both a prophylactic agent for procedures and a treatment of active infections in

ophthalmology. The following take-away points are important to PI use in clinical practice:

1. Iodine allergy is a myth that was wrongly advanced from a perception of adverse reactions to iodine-containing radiocontrast dyes and shellfish allergies. The author recommends that patients reporting iodine allergy should be counseled regarding why this is not possible. Claimed iodine allergy should never be a reason for withholding PI prophylaxis.
2. Povidone-iodine allergy is rare. If after a complete history is obtained, concern over allergy to PI persists, patients can be referred for skin patch testing. Patients with demonstrated allergy to PI can be treated with dilute chlorhexidine (0.02%) to the cornea and conjunctiva.
3. Compared to a single application of 5–10% PI, dilute PI (0.1–0.25%) kills microbes much faster but its effect is briefer. Repeated application of dilute PI every 20 s produces a long kill time with minimal surface toxicity and can be administered instead of a single 5–10% drop.

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