Allergy to Povidone–Iodine and Cephalosporins: The Clinical Dilemma in Ophthalmic Use

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THE HUMAN IMMUNE SYSTEM PROTECTS US AGAINST many diseases, but when activated inappropriately and excessively, a detrimental hypersensitivity reaction can occur. Gell and Coombs described 4 types of immunologically mediated hypersensitivity reactions.[1] In common clinical practice, the term *allergy* is used to refer to a wide variety of reactions. In actuality, *allergy* refers to a type I reaction in which an allergen first sensitizes and then on subsequent exposure initiates an immunoglobulin E (IgE)-mediated activation of mast cells and basophils with release of inflammatory mediators, creating an immediate hypersensitivity reaction. Localized IgE-mediated reactions include urticaria, allergic rhinitis, and allergic asthma. Anaphylaxis, or a systemic IgE-mediated reaction involving multiple organ systems, can progress to cardiovascular collapse and death.

There is wide misunderstanding and improper reporting about what constitutes true allergy. It is imperative to define a specific allergy and distinguish IgE-mediated, potentially life-threatening anaphylaxis from other adverse reactions that themselves may be annoying and uncomfortable but are self-limited. It is also important to understand the allergic cross-reactivity expected with commonly used medications. Two commonly reported allergies are to iodine and penicillin. Clinicians frequently withhold povidone–iodine (PI) preparations when patients report allergy to iodine or seafood and β-lactam antibiotics such as cephalosporins when patients report allergy to penicillin. In most circumstances, such changes to clinical practice may be unnecessary.

POVIDONE–IODINE

IODINE IS AN ESSENTIAL MINERAL REQUIRED FOR THE SYNthesis of thyroid hormones. Simple molecules such as oxygen or iodine are widely believed to lack the complexity required for antigenicity. True allergy to molecular iodine does not exist.

PI is a disinfectant and antiseptic agent used for preoperative preparation of the skin and mucous membranes and the treatment of contaminated wounds. Because of its broad spectrum of microbicidal activity, PI is used widely in ophthalmology to prepare the eyelids, eyelashes, and conjunctiva before intraocular surgery to decrease the risk of endophthalmitis.[2] PI is composed of 2 main components: polyvinylpyrrolidone (povidone) and diatomic iodine. Povidone is a synthetic polymer similar to dextran that serves as a carrier to deliver iodine. Povidone is used widely as a suspending or coating agent and is present in many hairsprays, cosmetics, and pharmaceuticals.

There are 3 types of reactions that patients may experience to PI. In up to 4% of patients, PI can have an irritant effect that is proportional to the duration of exposure.[3] This irritant effect can cause a severe chemical burn if skin or mucus membranes are exposed to PI for long periods. Less commonly, patients can develop a contact dermatitis to PI that typically develops after repeated exposure and can resolve without intervention.[4] Finally, anaphylaxis to PI is rare. There have been at least 10 reported cases of anaphylaxis to topical PI, including after application to open wounds or sores in 3 cases and application to mucus membranes in 4 cases.[5] Many such cases involve a reaction to povidone; in each case reporting thorough allergic evaluation, none reported a positive reaction to iodine.[5] No cases of anaphylaxis related to ophthalmic use of PI have been reported.

Is a seafood allergy a contraindication to the use of PI? Although seafood does contain relatively high levels of iodine, a seafood allergy is not related to iodine content. A seafood allergy typically is mediated by IgE against specific protein allergens, commonly tropomyosin in crustaceans and molluscs and parvalbumins in fish. Based on a review of current literature, a seafood allergy does not equate to an iodine allergy and is not a contraindication to the use of topical PI.[6]

Is allergy to iodinated contrast media (CM) a contraindication to the use of PI? There are approximately 15 million CM injections each year in the United States, with an estimated 0.04% risk of developing a severe reaction after receiving low osmolality, nonionic CM. While these reactions can be IgE mediated more commonly they are anaphylactoid reactions, IgE-independent, dose-dependent mast cell and basophil degranulation responses occurring by poorly understood mechanisms.[7] The structure of povidone, with or without iodine, is not similar to that of CM, and direct cross-reactivity has not been demonstrated. Reported allergy to CM is not a contraindication to the use of topical PI.

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What are alternatives to PI for preoperative surgical field preparation? Chlorhexidine may be more effective than PI at reducing surgical site infections in some instances.[8] It is important to recognize, however, that chlorhexidine is potentially ototoxic and can be toxic to corneal endothelium.[9] Under most circumstances, chlorhexidine is not used to prepare the eyelids, eyelashes, and conjunctiva before intraocular surgery. Chloroxylenol (Techni-care; Care-Tech Laboratories, Inc, St. Louis, Missouri, USA) is a bactericidal preparation for ocular use, but was removed from the market in 2009 by the Food and Drug Administration. Therefore, PI currently is the best option for surgical site antisepsis before intraocular surgery.

PENICILLIN AND CEPHALOSPORIN CROSS-SENSITIVITY

PENICILLINS AND CEPHALOSPORINS POSSESS A 4-MEMBER β-lactam ring and interfere with the formation of peptidoglycan cross-links within bacterial cell walls, thereby killing susceptible strains. Both contain a bicyclic core, but differ in that the penicillin 5-member thiazolidine ring is replaced in cephalosporins with a 6-member dihydrothiazine ring. Cephalosporins are classified according to their antibacterial spectrum, a property dependent on their side chain configurations.

Allergy to β-lactam antibiotics are the most commonly reported medication allergy. Penicillin allergy alone is reported by 10% of patients.[10] Traditionally, it was accepted that there was a 10% allergic cross-sensitivity between penicillin and cephalosporins because of their shared β-lactam ring.

Despite this high prevalence of reported allergy, penicillin and its derivatives such as cephalosporins are first-line treatments for many infections and are used widely in ophthalmology. Ceftazidime is often administered intravitreally for coverage of gram-negative organisms in the management of endophthalmitis. The addition of prophylactic intracameral cefuroxime in a prospective trial by the European Society of Cataract & Refractive Surgeons significantly decreased the rate of postcataract endophthalmitis from 2.96 to 0.62 per 1000 surgeries.[11] Because of the fear of cross-reactivity, however, cephalosporins often are avoided for patients with reported penicillin allergies. For example, in this European Society of Cataract & Refractive Surgeons study, patients with reported penicillin or cephalosporin allergy were excluded.

Despite historical concerns, however, many cephalosporins can be administered safely to patients reporting penicillin allergy for multiple reasons. First, more than 90% of patients who report a history of penicillin allergy lack penicillin-specific IgE and can tolerate the antibiotic safely.[10]

Second, it is imperative to distinguish IgE-mediated potentially life-threatening allergies from self-limited adverse reactions. For example, although up to 10% of patients experience an adverse reaction when exposed to β-lactam antibiotics, such as cutaneous eruptions, penicillin-induced anaphylaxis has an incidence of 1.5 to 4 per 10 000.[10,12] The incidence of anaphylaxis to cephalosporins is not as thoroughly studied, but is likely less common than with penicillin.[10] A thorough clinical history and diagnostic testing can help to identify patients at high risk of true allergy.[10,12,13]

TABLE. Cephalosporins with Possible Cross-Reactivity to Penicillin That Should Be Used with Caution in Patients Reporting a Penicillin Allergy

Cephalothin	First generation
Cefalotin	First generation
Cephalexin	First generation
Cefaloridine	First generation
Cefazolin	First generation
Cefaloram	First generation
Cefprozil	Second generation
Cefamandole	Second generation
Cefaclor	Second generation

Third, the often quoted approximately 10% cross-reactivity to cephalosporins among penicillin allergic patients is an overestimate for many reasons.[13] Such reports focused on cephalosporins with side chains similar to that of penicillin, and allergy was based on patient history without confirmatory skin testing. In addition, some of the cephalosporins produced before 1980 may have been contaminated by trace amount of penicillin.[14]

Fourth, recent reviews and a large meta-analysis have concluded that in the setting of a confirmed penicillin allergy, cross-reactivity is most likely to occur with cephalosporins containing side chains similar to penicillin, most commonly first and older second-generation cephalosporins (Table).[13–15] Therefore, such cephalosporins should be used with caution in known penicillin-allergic patients in that anaphylaxis has been reported after subconjunctival cefazolin injection.[16] In contrast, cephalosporins with modified and typically more complex side chains, such as most of the second-generation (cefuroxime, cefprozil) and third-generation (ceftazidime, cefpodoxime) cephalosporins, did not confer a significant risk of allergic cross-reactivity.[17]

Such differences in the risk of allergic cross-reactivity between penicillin and cephalosporins may be appreciated by considering their molecular structures. Allergy to penicillin is mediated by major or minor antigenic determinants after physiologic degradation of the bicyclic core and binding to host proteins. The immunogenic determinants of nonpenicillin β-lactam antibiotics are less well understood, but most allergic reactions to cephalosporins are determined by the specific side chains rather than their β-lactam core. In support of this, although little is known

about the extent of cross-reactivity among different cephalosporins, case reports have described patients allergic to one cephalosporin who tolerated a different cephalosporin.[10]

The diagnosis of penicillin allergy has implications beyond direct cross-reactivity with similarly structured antibiotics. Drug-allergic patients may have an increased risk of developing allergic reactions to unrelated, non–cross-reacting compounds.[13] For example, patients with a history of allergy to penicillin have an approximately 3-fold greater risk of a subsequent reaction to any medication.[10,15] Such findings may account for reports of anaphylaxis in penicillin-allergic patients to otherwise non–cross-reacting cephalosporins such as cefuroxime.[18]

In summary, PI and cephalosporins play important roles in ophthalmic care, and their use should not be limited by unsupported patient-reported allergy. Reports of seafood or CM allergies should not prohibit the use of PI. PI can be irritating with longer exposure time and should be irrigated completely after use. Penicillin allergies are reported far more commonly than they actually exist, and such a report should not prevent the use of second- and third-generation cephalosporins with distinct side chains.

When patients report allergy to iodine or penicillin, a detailed history of the allergy should be obtained. Significant events in the medical history (i.e., anaphylaxis) may direct the physician to consider further diagnostic testing and consultation with an allergy specialist to assist in the treatment decision process. Such testing, however, need not be incurred based on unfounded and undocumented patient-reported allergy, so as to allow for timely management using the proper agent.

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