Are Topical Antibiotics Helpful as Prophylaxis for Intravitreal Injections?

The community standard is evolving toward focusing on antisepsis.

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Intravitreal injection has rapidly become one of the most common medical procedures performed in the United States, with more than 1 million injections performed for Medicare recipients alone in 2010 (Ross Brechner, personal communication, 2011). Endophthalmitis is a rare complication of intravitreal injection, with a reported incidence of 1 in 1000 to 1 in 5000 injections.[1,2] Although such an incidence may seem comfortingly low at first glance, given the frequency of the procedure, associated cases of endophthalmitis could number in the thousands per year in this country, resulting in a huge burden to patients and the health care system.

NO CONSENSUS

There is no established gold standard for endophthalmitis prophylaxis in the peri-intravitreal–injection period, and practices continue to evolve. The American Academy of Ophthalmology's Preferred Practice Pattern: Age-Related Macular Degeneration (AMD)[3] cites the incidences of endophthalmitis as reported in numerous clinical trials of intravitreal pharmacologic injections, but it offers no guidance on prophylaxis.

There have been attempts to gauge common practice and establish consensus for endophthalmitis prophylaxis. Of particular interest is the comparative safety and efficacy of antisepsis compared with topical ophthalmic antibiotics. Before the approval of anti-VEGF agents for the treatment of AMD, Aiello and colleagues[4] reported that, among a panel of investigators, surgeons, and industry representatives, there was relative agreement on the use of povidone-iodine on the ocular surface, eyelids, and eyelashes for prophylaxis in intravitreal injection, but no clear consensus on the value of pre- or post-intravitreal–injection topical antibiotics.

More recently, Green-Simms and colleagues assessed injection techniques among retinal specialists in the United States through an anonymous survey.[5] Among 765 respondents (44% response rate), 99.6% reported using povidone-iodine, 34% reported using preinjection antibiotics, and 81% reported using postinjection antibiotics.

ANTISEPSIS

Povidone-iodine is a disinfectant and antiseptic agent commonly used for preoperative preparation of skin and mucous membranes. Most commercial preparations have 3 components: diatomic iodine, which is bactericidal; povidone (polyvinylpyrrolidone), a water-soluble polymer used to deliver the iodine; and excipients such as glycerin and citric acid. Povidone is used as a suspending or coating agent and is present in many pharmaceuticals and contact lens solutions.

Povidone-iodine prep is widely used for prophylaxis before cataract surgery, in which setting it has been shown to reduce the rate of postoperative endopthalmitis in a prospective trial.[6] There have been no reports of resistance to its bactericidal effects.

Povidone-iodine, used perioperatively as an antisep-

tic agent in ophthalmic procedures, provides broad-spectrum microbicidal activity. As part of the preparation for intravitreal injection at the Retina Consultants of Houston and the Bascom Palmer Eye Institute, 10% povidone-iodine is routinely applied to the lids and lashes and a 5% povidone-iodine solution is applied to the conjunctival surface at the site of eventual ocular penetration before any viscous anesthetic agents are applied. The 5% povidone-iodine solution is applied to the ocular surface for at least 30 seconds, and typically some minutes, before intravitreal injection.

Povidone-iodine is inexpensive, with the average cost of a 30 mL bottle of 5% ophthalmic preparation solution being $12.00 (www.redbook.com). It provides bactericidal activity over a wide range of concentrations, from 0.1% to 10%, with rapid kill times of 15 to 120 seconds.[7]

Adverse reactions to povidone-iodine are usually related to its irritant effect or to an allergic contact dermatitis, which occurs in less than 0.5% of cases.[8] The irritant effect is proportional to duration of exposure to povidone-iodine. Therefore, it is important to thoroughly irrigate povidone-iodine from the ocular surface, including from the conjunctival fornices, after use in order to minimize any irritant effect and maximize patient comfort.

Anaphylactic reaction to iodine does not exist. Anaphylaxis to povidone-iodine has been reported but is very rare. Most well-documented and investigated cases have been related to the povidone carrier component of povidone-iodine. No cases of anaphylaxis related to ophthalmic use of povidone-iodine have been reported.

Many retina specialists apply additional povidone-iodine to the conjunctiva immediately before insertion of the needle for intravitreal injection via the pars plana. Animal studies suggest that introduction of a small amount of povidone-iodine into the vitreous cavity is unlikely to result in ocular toxicity.[9]

ANTIBIOTICS

Topical antibiotics are frequently used prophylactically in patients undergoing intravitreal injections in an attempt to prevent endophthalmitis. However, there is no evidence to show that topical antibiotics reduce rates of post-intravitreal–injection endophthalmitis.

Preinjection topical antibiotics, when added to povidone-iodine preparation, do not reduce conjunctival bacteria more than the antiseptic preparation alone.[10,11] Rather, topical antibiotics may actually increase the risk of microbial resistance.[12] The kill times for topical antibiotics are longer than for povidone-iodine, and their application immediately before an injection provides insufficient time for an adequate biologic effect.[13]

For these reasons, topical antibiotics given either before the day of intravitreal injection or immediately before injection are generally not recommended.

Many retina practitioners prescribe postinjection topical fluoroquinolones because of their broad-spectrum antimicrobial activity and their benign side-effect profile. The value of this practice is debatable, however, and recent data suggest that it should be reconsidered.

In an analysis of antibiotic susceptibility in conjunctival flora of patients undergoing intravitreal injection, Moss and colleagues[14] found that most organisms (>80%) were sensitive to gentamicin, but fewer were sensitive to fluoroquinolones. Resistance to ciprofloxacin was seen in 42% of isolates, to levofloxacin in 39%, and to gatifloxacin in 22%.

Resistance to fluoroquinolones is frequent in bacterial isolates from patients with endophthalmitis, and recent use of topical fluoroquinolones has been shown to be a significant predictor of fluoroquinolone resistance in *Staphylococcus aureus* ocular isolates.[15]

At Bascom Palmer Eye Institute, increasing rates of resistance to all the topical fluoroquinolones have been seen among bacterial isolates over the past 20 years. Miller and coworkers[16] evaluated the in vitro susceptibility and cross-resistance of gatifloxacin and moxifloxacin vs older fluoroquinolones among coagulase-negative staphylococci (CNS) recovered from patients with clinical endophthalmitis. In the first 5 years of their study (1990-1994), 96.6% of the CNS were sensitive to gatifloxacin and moxifloxacin fluoroquinolones. By 10 years later (2000-2004), the percentage of CNS sensitive to gatifloxacin and moxifloxacin had declined to 65.4%.[17] An update of these previous studies will be published in the *Archives of Ophthalmology* in 2012.

Frequent use of fluoroquinolones in association with intravitreal injection appears to promote the emergence of microbial resistance by selecting for resistant strains. In a 1-year longitudinal study of patients undergoing repeated exposure to ophthalmic antibiotics in association with intravitreal injections, Kim and Toma[18] found significant increases in multiple drug-resistance of CNS isolated from treated eyes. At the end of 1 year, resistance to at least 3 antibiotics was seen in 81.8% of isolates and to at least 5 antibiotics in 67.5% of isolates. This phenomenon may be intensified in the setting of monthly intravitreal injections when the same topical antibiotic is used repeatedly in the same eye.

MEDICOLEGAL ISSUES AND COSTS

There may be a perception in the vitreoretinal field that peri-injection antibiotics are the standard of care, but their widespread use may in fact be more a function

of medicolegal concerns than of clinical evidence.

The Ophthalmic Mutual Insurance Company (OMIC) covers approximately 25% of practicing ophthalmologists in the United States against malpractice claims. From 2006 through the first quarter of 2011, OMIC received no claims or lawsuits related to endophthalmitis prophylaxis for intravitreal injection or lack thereof.

Therefore, OMIC has stated, "Decisions regarding use of antimicrobial and antiseptic prophylaxis should be based on best available science and not risk mitigation" (personal communication, David W. Parke II, MD, OMIC claims committee chair).

Further motivating against the use of topical antibiotics for peri-intravitreal–injection endophthalmitis prophylaxis are the costs of the commonly used agents, which can range from approximately $13 (polymyxin/trimethoprim 10 mL) to more than $90 (gatifloxacin 5 mL, moxifloxacin 3 mL) (www.redbook.com).

CONCLUSIONS

Antisepsis has a long-standing role in ocular preparation before intraocular procedures. Povidone-iodine is inexpensive, is widely available, and displays broad-spectrum, fast-acting bactericidal activity with no evidence of resistance. Topical antibiotics add costs and increase the risk of bacterial resistance without clinical evidence of reduced rates of endophthalmitis.

In light of these factors, many practitioners are trending away from routine use of topical antibiotics in association with intravitreal injections. Two large clinical trials by the Diabetic Retinopathy Clinical Research Network suggest that they are not needed.[19]

While the community standard continues to evolve, there appears to be a shift toward antisepsis and away from reliance on peri-injection antibiotics for endophthalmitis prophylaxis.[20] ■

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1. McCannel CA. Meta-analysis of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents: causative organisms and possible prevention strategies. *Retina*. 2011;31(4):654-661.
2. Moshfeghi AA, Rosenfeld PJ, Flynn HW Jr, et al. Endophthalmitis after intravitreal anti-vascular endothelial growth factor antagonists: a six-year experience at a university referral center. *Retina*. 2011;31(4):662-668.
3. American Academy of Ophthalmology. Preferred Practice Pattern: Age-Related Macular Degeneration. http://one.aao.org/CE/PracticeGuidelines/PPP_Content.aspx?cid=f413917a-8623-4746-b441-f817265eafb4#references. Accessed May 9, 2012.
4. Aiello LP, Brucker AJ, Chang S, et al. Evolving guidelines for intravitreous injections. *Retina*. 2004;24(5 Suppl):S3-19.
5. Green-Simms AE, Ekdawi NS, Bakri SJ. Survey of intravitreal injection techniques among retinal specialists in the United States. *Am J Ophthalmol*. 2011;151(2):329-332. Epub 2010 Dec 18.
6. Speaker MG, Menikoff JA. Prophylaxis of endophthalmitis with topical povidone-iodine. *Ophthalmology*. 1991;98(12):1769-1775.
7. Berkelman RL, Holland BW, Anderson RL. Increased bactericidal activity of dilute preparations of povidone-iodine solutions. *J Clin Microbiol*. 1982;15(4):635-639.
8. Wykoff CC, Flynn HW Jr, Han DP. Allergy to povidone-iodine and cephalosporins: the clinical dilemma in ophthalmic use. *Am J Ophthalmol*. 2011;151(1):4-6.
9. Whitacre MM, Crockett RS. Tolerance of intravitreal povidone-iodine in rabbit eyes. *Curr Eye Res*. 1990;9(8):725-732.
10. Halachmi-Eyal O, Lang Y, Keness Y, Miron D. Preoperative topical moxifloxacin 0.5% and povidone-iodine 5.0% versus povidone-iodine 5.0% alone to reduce bacterial colonization in the conjunctival sac. *J Cataract Refract Surg*. 2009;35(12):2109-2114.
11. Moss JM, Sanislo SR, Ta CN. A prospective randomized evaluation of topical gatifloxacin on conjunctival flora in patients undergoing intravitreal injections. *Ophthalmology*. 2009;116(8):1498-1501. Epub 2009 Jun 5.
12. Haas W, Pillar CM, Torres M, Morris TW, Sahm DF. Monitoring antibiotic resistance in ocular microorganisms: results from the Antibiotic Resistance Monitoring in Ocular micRorganisms (ARMOR) 2009 surveillance study. *Am J Ophthalmol*. 2011;152(4):567-574.e3. Epub 2011 Jun 8.
13. Hyon JY, Eser I, O'Brien TP. Kill rates of preserved and preservative-free topical 8-methoxy fluoroquinolones against various strains of Staphylococcus. *J Cataract Refract Surg*. 2009;35(9):1609-1613.
14. Moss JM, Sanislo SR, Ta CN. Antibiotic susceptibility patterns of ocular bacterial flora in patients undergoing intravitreal injections. *Ophthalmology*. 2010;117(11):2141-2145. Epub 2010 Jun 18.
15. Fintelmann RE, Hoskins EN, Lietman TM, at al. Topical fluoroquinolone use as a risk factor for in vitro fluoroquinolone resistance in ocular cultures. *Arch Ophthalmol*. 2011;129(4):399-402.
16. Miller D, Flynn PM, Scott IU, Alfonso EC, Flynn HW Jr. In vitro fluoroquinolone resistance in staphylococcal endophthalmitis isolates. *Arch Ophthalmol*. 2006 Apr;124(4):479-83.
17. Flynn Jr HW, Wykoff CC, Rosenfeld PJ. Antiseptics vs. Antibiotics for Intravitreal Injections. Paper presented at: Retina Subspecialty Day, American Academy of Ophthalmology Annual Meeting; October 21-22, 2011; Orlando, FL.
18. Kim SJ, Toma HS. Antimicrobial resistance and ophthalmic antibiotics: 1-year results of a longitudinal controlled study of patients undergoing intravitreal injections. *Arch Ophthalmol*. 2011;129(9):1180-1188.
19. Bhavsar AR, Googe JM Jr, Stockdale CR, et al; Diabetic Retinopathy Clinical Research Network. Risk of endophthalmitis after intravitreal drug injection when topical antibiotics are not required: the diabetic retinopathy clinical research network laser-ranibizumab-triamcinolone clinical trials. *Arch Ophthalmol*. 2009;127(12):1581-1583.
20. Wykoff CC, Flynn HW Jr, Rosenfeld PJ. Prophylaxis for endophthalmitis following intravitreal injection: antisepsis and antibiotics. *Am J Ophthalmol*. 2011;152(5):717-719.e2.