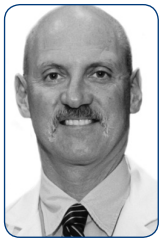
THE LITERATURE

BY ELI MOSES, MD, AND THEODORE PERL, MD

Dose and Administration of Intracameral Moxifloxacin for Prophylaxis of Postoperative Endophthalmitis

Arshinoff SA, Modabber M[1]

ABSTRACT

Arshinoff and Modabber reviewed current and past practices of intracameral antibiotic administration for infection prophylaxis in cataract surgery, including dosage determination and administration protocols, to devise an optimal dose and administration protocol for intracameral moxifloxacin.

This retrospective evaluation of a treatment modality examined 3,430 sequential cases by the same surgeon (S.A.A.) using 100 µg moxifloxacin in 0.1 mL balanced salt solution, followed by 4,601 cases that received 300 to 600 µg moxifloxacin in 0.2 to 0.4 mL balanced salt solution. All intracameral injections were administered at the termination of the surgical procedure, after the main incision was hydrated with balanced salt solution to ensure that it was sealed. The antibiotic was injected via the sideport as the final step of surgery. A single infection in the initial 3,430 cases occurred with a moxifloxacin-resistant strain of *Staphylococcus epidermidis* when the lower dosage was used, prompting a re-evaluation and increase in the dosage as well as a change in the administration technique. No infections occurred in the final 4,601 cases.

The investigators proposed that it is easier and more accurate to dilute an intracameral antibiotic, replace most of the anterior chamber volume with a 0.3- to 0.4-mL injection, and seal the incisions than it is to inject exactly 0.1 mL through the sideport. To determine the best calculated dose to administer, the researchers used the minimum inhibitory concentration of the most likely pathogens (staphylococci) combined with the knowledge that the anterior chamber concentration of moxifloxacin will decrease to 25% of the instilled dose over the first hour, based on the work of Montan et al.[2]

The ideal bactericidal effect for concentration-dependent antibiotics such as moxifloxacin is obtained at concentrations that are at least 10 times the minimum inhibitory concentration of the target organism. The investigators used this information to determine the dose of intracameral moxifloxacin (Vigamox; Alcon) to administer.

AT A GLANCE

- In a retrospective evaluation of a treatment modality that examined 8,031 cases, researchers found that the intracameral administration of 0.3 to 0.4 mL moxifloxacin (prepared by dilution of 3 mL moxifloxacin 0.5% with 7 mL balanced salt solution) as the final step of cataract surgery was safe and more advantageous than traditional medications and dosing regimens.
- The OPUS-3 randomized clinical trial found that lifitegrast 5% ophthalmic solution improved the symptoms of moderate to severe dry eye disease in as little as 2 weeks compared to placebo.

DISCUSSION

Postoperative endophthalmitis after cataract surgery is a rare but devastating complication estimated to occur in 1:1000 cases.[3] Vancomycin, moxifloxacin, and cefuroxime are the three prophylactic antibiotics most commonly used intracamerally, with moxifloxacin the most commonly used outside of Europe.

The European Society of Cataract & Refractive Surgeons performed a large, prospective, randomized, placebo-controlled trial to evaluate the prophylactic effect of intracameral cefuroxime on the incidence of endophthalmitis after cataract surgery.[4] The investigators reported that the risk of endophthalmitis in patients receiving intracameral injections of cefuroxime at the conclusion of cataract surgery was five times lower than in those not receiving intracameral treatment.

Although the European Society of Cataract & Refractive Surgeons' study clearly showed a benefit of intracameral cefuroxime, investigators only tested one antibiotic and concentration, leaving the question of ideal dose and medication unanswered. Cefuroxime, a second-generation cephalosporin, was chosen[2,5] before the availability of fourth-generation fluoroquinolones, which have been shown to be the most effective ophthalmic broad-spectrum antibiotics.[6] Vancomycin, also commonly used intracamerally, is not ideal because of the recent appearance of cases of hemorrhagic occlusive retinal vasculitis.[7] Compared with cephalosporins, moxifloxacin offers broader bactericidal activity against pathogens causing postoperative endophthalmitis.[8]

Arshinoff and Modabber concluded that the intracameral administration of 0.3 to 0.4 mL moxifloxacin (prepared by dilution of 3 mL moxifloxacin 0.5% with 7 mL balanced salt solution) as the final step of cataract surgery showed benefits compared with alternative intracameral antibiotics and carried minimal risk.

Lifitegrast for the Treatment of Dry Eye Disease: Results of a Phase III, Randomized, Double-Masked, Placebo-Controlled Trial (OPUS-3)

Holland EJ, Luchs J, Karpecki PM, et al[9]

ABSTRACT

OPUS-3 was a 12-week phase 3 study assessing the safety and efficacy of lifitegrast 5% ophthalmic solution (Xiidra; Shire) compared with placebo in patients who had dry eye disease (DED). Investigators evaluated adults (18 years and older) with self-reported DED, Schirmer tear tests (without anesthetic) between 1 and 10 mm, elevated fluorescein staining and eye dryness scores, and a history of artificial tear use within 30 days of the study.

The study included 711 patients from 41 centers; 355 patients received lifitegrast (intention-to-treat population), and 356 patients were administered a placebo. The primary endpoint of the study was change in eye dryness score from baseline to day 84. Secondary endpoints included items such as burning, itching, foreign body sensation, and pain. After 14 days of placebo treatment, participants were randomized 1:1 to lifitegrast or placebo for 84 days.

Holland and colleagues reported a significant improvement in eye dryness score for the lifitegrast group compared with the placebo group at day 84 (P = .0007). Additionally, there was a significant improvement in the key secondary endpoints of change in eye dryness score at day 14 and day 42 for the lifitegrast group compared with the placebo group (P = .0001). No statistically significant differences were observed in ocular discomfort score. Ocular adverse events included instillation site irritation (18.2%) and instillation site reaction (12.6%). The most common nonocular adverse event was dysgeusia, which occurred in 12.9% of the participants in the lifitegrast group.

DISCUSSION

The cause of DED is multifactorial and has not been fully elucidated. Evidence, however, suggests that inflammation of the ocular surface and lacrimal gland may play a key role in the pathogenesis of the disease.[10] The FDA approved lifitegrast ophthalmic solution 5.0% for the treatment of the signs and symptoms of DED in adult patients. Lifitegrast is a lymphocyte function-associated antigen-1 antagonist that blocks the binding of intercellular adhesion molecule-1 to lymphocyte function-associated antigen-1 on the T-cell surface, thereby inhibiting the T-cell recruitment, T-cell activation, and proinflammatory cytokine release associated with DED.[11]

Previous randomized clinical trials have studied lifitegrast. They included a phase 2 study, the phase 3 safety and efficacy trials OPUS-1 and OPUS-2, and a safety trial SONATA. The objective of the OPUS-3 trial was to evaluate the safety and efficacy of lifitegrast compared with placebo in moderate to severe DED. OPUS-3 represents the first statistically significant symptom improvement in two phase 3 clinical studies for an investigational drug therapy for DED. The therapeutic benefit of lifitegrast was observed at 2 weeks at the earliest.

It is worth noting that the investigators were unable to assess the drug's long-term efficacy, because the trials were carried out over 12 weeks. The trials also did not assess the concomitant use of artificial tears or other DED therapy such as punctal plugs and topical cyclosporine. Conclusions about the efficacy of using lifitegrast along with other therapies therefore cannot be made. Other limitations are the exclusion of patients with a history of LASIK within 12 months before the study and the exclusion of contact lens wearers. Investigators also did not assess patients with mild DED; the study population consisted of moderate to severe DED baseline symptomatology.

As in previous DED research,[12] outcomes for DED signs and symptoms were poorly correlated in the lifitegrast clinical trials. Overall, however, this study demonstrated that the drug improved patient-reported symptoms of DED from as early as 2 weeks with no serious ocular side effects. ■

1. Arshinoff SA, Modabber M. Dose kinetics and administration of intracameral moxifloxacin for prophylaxis of postoperative endophthalmitis. *J Cataract Refract Surg*. 2016;42(12):1730-1741.
2. Montan PG, Wejde G, Setterquist H, et al. Prophylactic intracameral cefuroxime. Evaluation of safety and kinetics in cataract surgery. *J Cataract Refract Surg*. 2002;28:982-987.
3. Gower EW, Lindsley K, Nanji AA, et al. Perioperative antibiotics for prevention of acute endophthalmitis after cataract surgery. *Cochrane Database Syst Rev*. 2013;7:CD006364
4. Barry P, Seal DV, Gettinby G, et al; the ESCRS Endophthalmitis Study Group. ESCRS study of prophylaxis of postoperative endophthalmitis after cataract surgery; preliminary report of principal results from a European multicenter study. *J Cataract Refract Surg*. 2006;32: 407-410
5. Montan PG, Wejde G, Koranyi G, Rylander M. Prophylactic intracameral cefuroxime. Efficacy in preventing endophthalmitis after cataract surgery. *J Cataract Refract Surg*. 2002;28:977-981.
6. Mah FS. Fourth-generation fluoroquinolones: new topical agents in the war on ocular bacterial infections. *Curr Opin Ophthalmol*. 2004;15:316-320.
7. Witkin AJ, Shah AR, Engstrom RE, et al. Postoperative hemorrhagic occlusive retinal vasculitis; expanding the clinical spectrum and possible association with vancomycin. *Ophthalmology*. 2015;122:1438-1451.
8. Mather R, Karenchak LM, Romanowski EG, Kowalski RP. Fourth generation fluoroquinolones: new weapons in the arsenal of ophthalmic antibiotics. *Am J Ophthalmol*. 2002;133:463-466.
9. Holland EJ, Luchs J, Karpecki PM, et al. Lifitegrast for the treatment of dry eye disease: results of a phase III, randomized, double-masked, placebo-controlled trial (OPUS-3). *Ophthalmology*. 2017;124(1):53-60.
10. Stern ME, Schaumburg CS, Pflugfelder SC. Dry eye as a mucosal autoimmune disease. *Int Rev Immunol*. 2013;32:19-41.
11. Perez VL, Pflugfelder SC, Zhang S, et al. Lifitegrast, a novel integrin antagonist for treatment of dry eye disease. *Ocul Surf*. 2016;14:207-215.
12. Bartlett JD, Keith MS, Sudharshan L, Snedecor SJ. Associations between signs and symptoms of dry eye disease: a systematic review. *Clin Ophthalmol*. 2015;9:1719-1730.

Section Editor Edward Manche, MD
- director of cornea and refractive surgery, Stanford Laser Eye Center, Stanford, California
- professor of ophthalmology, Stanford University School of Medicine, Stanford, California
- edward.manche@stanford.edu

Eli Moses, MD
- cataract, cornea, and refractive surgeon at Corneal Associates of New Jersey, Fairfield
- elibmoses@gmail.com
- financial interest: none acknowledged

Theodore Perl, MD
- director, Corneal Associates of New Jersey, Fairfield
- financial disclosure: consultant to Shire