Fourth-Generation Fluoroquinolones: Potency and Penetration

These properties are critical to the assessment of an agent's effectiveness.

BY EDWARD J. HOLLAND, MD

The rate of infection after cataract and refractive surgery is low, but its occurrence can be devastating. It is thus critical for surgeons to take every possible preventive measure to protect patients against potential infection. One of the best prophylactic measures is to use a topical antibiotic pre-, peri-, and postoperatively and a preoperative preparation with povidone-iodine.

When comparing antibiotic drops, surgeons should consider three important attributes: penetration; potency; and biocompatibility. Numerous studies have shown that Vigamox (moxifloxacin 0.5%; Alcon Laboratories, Fort Worth, TX) excels in all three areas.

THE PENETRATION AND POTENCY OF A DRUG

Effective antibiotics must provide therapeutic levels on the ocular surface as well as in the target areas such as the cornea and aqueous humor. Exceeding the minimum inhibitory concentrations of the pathogens that could cause infection after a drug has penetrated into the target tissue is the true measure of a drug's effectiveness in terms of protecting against infection.

The fourth-generation fluoroquinolones offer the best potency and penetration profile of the available antibiotics, and numerous clinical studies have confirmed that Vigamox provides superior potency and therapeutic penetration.

In 2006, my colleagues and I conducted the first human study that examined the corneal penetration of Vigamox and Zymar (gatifloxacin 0.3%; Allergan, Inc., Irvine, CA).[1] This controlled, randomized, open-label, multiple-dose study included corneas from 48 patients undergoing penetrating keratoplasty. Preoperatively, two drops of Zymar or Vigamox were instilled 5 minutes apart in the study eyes.

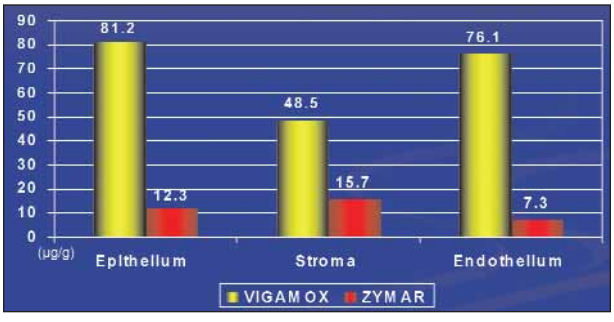

Figure 1. Corneal concentrations of moxifloxacin and gatifloxacin in a human study of penetrating keratoplasty are shown. (Data adapted from Holland et al.[1])

After the drugs' instillation, we evaluated the three major layers of the cornea: the epithelium; the stroma; and the endothelium. In the epithelium, the mean peak level of moxifloxacin was approximately seven times higher than that for gatifloxacin (81.2 vs 12.3 µg/g). Additionally, the mean peak stromal level of moxifloxacin (48.5 µg/g) was three times higher than that for gatifloxacin (15.7 µg/g), and the mean peak endothelial level of moxifloxacin (76.1 µg/g) was approximately 10 times higher than that for gatifloxacin (7.3 µg) (Figure 1).

We also found that the mean peak aqueous humor level of moxifloxacin was three times higher than that for gatifloxacin, and the levels of moxifloxacin were considerably higher relative to minimum inhibitory concentration values for the most common endophthalmitis and keratitis

pathogens, including atypical mycobacteria and fluoroquinolone-resistant *Staphylococcus aureus*.

A study conducted at the Wilmer Eye Institute at Johns Hopkins University in Baltimore found similar results.[2] The investigation included 50 cataract patients, with half receiving preoperative topical Vigamox and half receiving preoperative topical Zymar. Moxifloxacin achieved a 3.8 times higher aqueous concentration than gatifloxacin (1.8 vs 0.48 µg/mL). Comparing these levels to the minimum bacteriocidal concentration (MBC) values of moxifloxacin and gatifloxacin for common causative pathogens gives a surrogate for infection prevention (Figure 2). The tissue level for moxifloxacin exceeded the MBC for the five test organisms, whereas that for gatifloxacin did not.

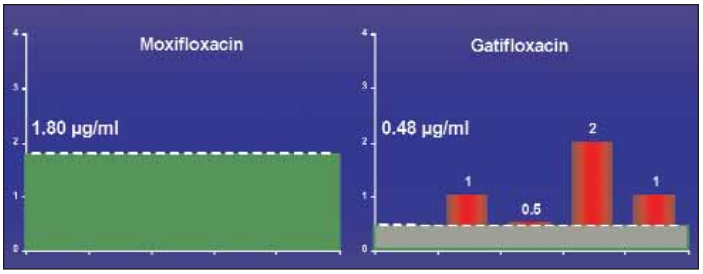

Figure 2. In this model for protection, the MBC values for moxifloxacin and gatifloxacin are overlaid with the drugs' concentrations in human aqueous humor. (Data adapted from Kim et al[2] and from Stroman DW, Cupp G, Dahlin DC, et al. Human ocular concentrations following topical fluoroquinolone administration relative to susceptibility of ocular pathogens. *Invest Ophthalmol Vis Sci*. 2006;47:E-abstract 1881.)

O'Brien and Stroman used disc diffusion analysis to test the aqueous penetration results from the cataract study against *S. aureus*. They found that Vigamox demonstrated activity against this pathogen to create a 24-mm zone of inhibition, whereas the aqueous humor levels achieved by Zymar did not show any activity against *S. aureus*.[3] Additionally, Mather and colleagues published research showing that moxifloxacin is more potent than gatifloxacin against gram-positive pathogens and that moxifloxacin is more efficacious against fluoroquinolone-resistant organisms such as fluoroquinolone-resistant *S. aureus*.[4]

BIOCOMPATIBILITY

In addition to adequate penetration and potency, an ideal drug would offer no negative effects in terms of toxicity or impediment of wound healing. Both Vigamox and Zymar have been found safe and nontoxic.

In a study at Walter Reed Army Hospital in Washington, DC, both fourth-generation fluoroquinolones were safe post-PRK.[5] The eyes treated with Vigamox, however, healed faster and exhibited smaller epithelial defects. Thirty-five patients received Zymar in one eye and Vigamox in their fellow eye after bilateral PRK with a 9-mm epithelial defect. In 18 patients, both eyes healed on the same day. In 13 patients, the moxifloxacin-treated eye healed first, whereas the gatifloxacin-treated eye healed first in four patients. Overall, the moxifloxacin-treated eyes healed in 3 to 7 days versus 3 to 9 days for the gatifloxacin-treated eyes.

Another difference between the two available fourth-generation fluoroquinolones is that Vigamox is self-preserved, whereas Zymar is preserved with benzalkonium chloride (BAK). Some investigators have suggested that BAK enhances an antibiotic's efficacy. A recent study found that BAK is quickly diluted, however, and likely does not have a clinically significant effect.[6] This study included 10 patients who received five separate instillations of a single 35-µL drop of Zymar in each eye. Tear samples were collected at 30 seconds and 1, 3, 5, and 20 minutes after instillation, and investigators measured the concentration of BAK in the tear film at these time points. The results show that BAK rapidly diluted after instillation (16-fold at 1 minute after instillation). By 5 minutes after its instillation, the mean concentrations of BAK had dropped to undetectable levels. Because BAK dilutes so rapidly, it is not maintained at a high concentration for long enough (1 hour) to effectively kill bacteria.

CONCLUSION

Antibiotics should be evaluated by their ability to provide potency after penetrating to the target site. Peer-reviewed studies show that Vigamox is safe and offers superior penetration and potency, which can help surgeons achieve the best possible outcomes for patients by avoiding and/or treating infectious complications. ■

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