

Fluoroquinolones: Clinical Implications

The effect of gatifloxacin and moxifloxacin on corneal wound healing.

BY RANDALL J. OLSON, MD

With the recent introduction of two new topical fourth-generation fluoroquinolones, clinicians have more options for the prevention of postoperative infection than ever before. Vigamox (moxifloxacin ophthalmic solution 0.5%; Alcon Laboratories, Inc., Fort Worth, TX) and Zymar (gatifloxacin ophthalmic solution 0.3%; Allergan, Inc., Irvine, CA) have both been shown to be highly efficacious anti-infective agents that offer broad-spectrum coverage and a rapid onset of action.¹ However, both my own clinical experience and several recent studies have demonstrated that there is a substantial difference in how these two agents affect the postoperative corneal wound healing process. This article examines why two similar agents have very different effects on corneal wound healing and how these differences relate to clinical practice and patient care.

PRESERVATIVES

Zymar is preserved with 0.005% benzalkonium chloride (BAK), whereas Vigamox is unpreserved. The pres-

ence of BAK in topical ophthalmic medications may concern the clinician because many studies have documented its harmful effect on the ocular surface.^{2,3} Furthermore, BAK may accumulate in the ocular tissues and exert a cytotoxic effect on mammalian cells when used in high concentrations or for an extended period of time.²

Due to the known adverse effects of BAK, it was once widely believed that Zymar would more adversely affect the corneal epithelium than would Vigamox. Given that practical experience is often invaluable in deciding which therapies are most appropriate for our patients, my colleagues and I decided to test this theory. We switched from using third-generation fluoroquinolones to using exclusively the fourth-generation agents. We decided to use Zymar for all surgical patients for 1 month before switching to Vigamox for 1 month, in order to evaluate any differences between the medications. Because we expected to find that surgical wounds would not heal as rapidly or completely when exposed to a drug containing

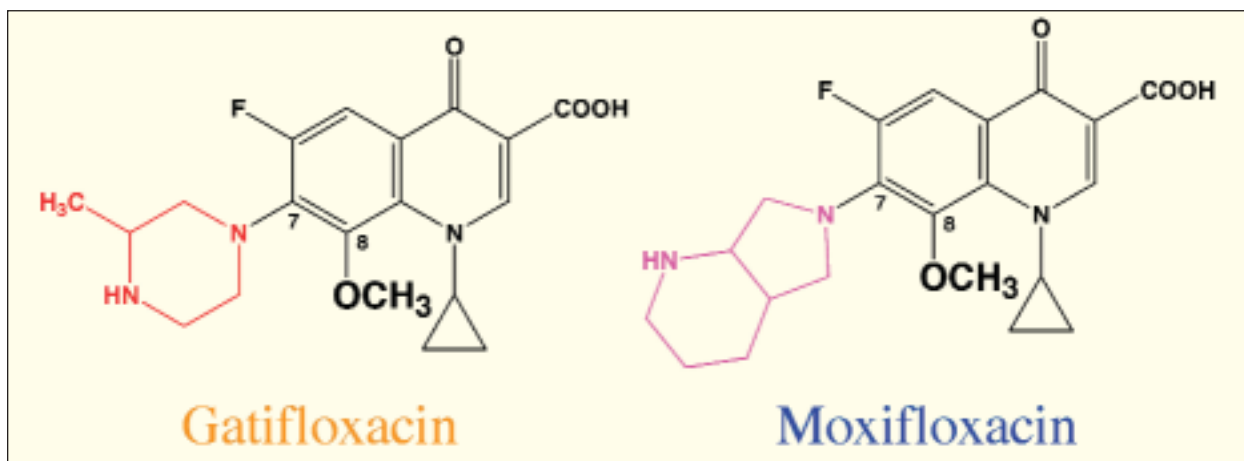


Figure 1. The structures of the two fourth-generation fluoroquinolones are identical except for the substituents at the No. 7 position (highlighted in color) of the quinolone ring system. The different substituents at that position may be responsible for the differences in activity against gram-negative and atypical pathogens. Moreover, it is also likely that these differences influence the effect each of these medications has on wound healing during the postoperative period.

BAK, we were surprised that this was not the case. In fact, corneal transplants treated with Zymar had faster epithelial healing after corneal grafting when compared with eyes treated with Vigamox.

Our finding that the presence of BAK did not seem to inhibit wound healing in eyes treated with Zymar suggests that the potentially harmful effects of BAK are minimal at 0.005% and may be of greater concern when patients require these medications for a chronic condition. The low concentration of BAK preservative is probably not as important when used only for a short period of time, as is the case with postsurgical prophylaxis.

HEALING

Our findings are supported by several recent animal studies. Farley et al⁴ found Vigamox to cause a greater derangement of the corneal epithelial barrier function when compared with Zymar. Vigamox also produced abnormalities of corneal epithelial tight junctions. Moreover, treatment with Zymar resulted in the return of corneal epithelial permeability to near baseline at day 5 despite the potentially harmful presence of BAK.

According to Gao et al,⁵ Zymar significantly facilitated epithelial wound closure in the initial phase of corneal wound healing, and there was no significant increase or delay in epithelial healing in rabbits treated with Zymar. Conversely, Vigamox significantly delayed epithelial wound healing at the early stage of healing.

MOLECULAR STRUCTURES

I believe that the differences described thus far may be at least partially explained by the different molecular structures of these agents. The structures of the two fourth-generation fluoroquinolones are identical except for the substituents at the No. 7 position (Figure 1) of the fluoroquinolone ring system. These substituents may be responsible for the differences in activity against gram-negative and atypical pathogens. Moreover, it is also likely that these differences influence the effect that each of these medications has on wound healing during the postoperative period.

TOXICITY

Numerous studies have reported that Vigamox is more cytotoxic than Zymar. For example, a recent study by Matsumoto et al⁶ found that all of the fluoroquinolones that they evaluated caused a concentration-dependent decrease in the rate of corneal epithelial cell migration and healing. At the lower evaluated concentrations, Vigamox and Zymar were approximately equivalent. However, at higher concentrations, Vigamox more effectively inhibited corneal epithelial cell migration

than Zymar at the same concentration. In the more sensitive human cell cultures, Zymar prevented cell proliferation to a lesser extent than did either moxifloxacin or ciprofloxacin.

In a study where Zymar was administered in either non-surgical or cataract surgery patients, researchers concluded that Zymar 0.3% has no statistically significant effect on corneal toxicity as determined by endothelial cell counts.⁷ Nonsurgical subjects received one drop of Zymar q.i.d. in their left eye for 2 days, and then one drop every 10 minutes for 1 hour on the third day. Surgical patients received one drop of Zymar in the eye undergoing surgery q.i.d. for 2 days, and then one drop every 10 minutes for 1 hour on the day of surgery. The surgical group also received one drop of ketorolac 0.5% between 10 and 15 minutes after each dose of Zymar during the 2 days before surgery and 10 minutes after the last dose of Zymar on the day of surgery. Baseline endothelial cell counts were $2,400 \pm 442$ in the surgical group and $2,520 \pm 212$ in the nonsurgical group. The mean differences from baseline 1 hour after the last dose of Zymar were -51 ± 213 ($P=.47$) in the surgical group and -7 ± 150 ($P=.84$) in the control group. In the nonsurgical group, the mean difference from baseline 3 weeks after the last dose was 18 ± 147 ($P=.58$).

The difference in the molecular structure of fluoroquinolone agents may also be responsible for the greater incidence of hyperemia and pupil miosis that has been noted with Vigamox, meaning that the moxifloxacin molecule may be inciting inflammatory cytokines. It is this inflammatory process that may account for the greater irritation reported with Vigamox compared with Zymar, and the resulting inflammation may inhibit wound healing.

Zymar has also demonstrated statistically significantly greater ocular tolerability when compared to Vigamox.⁸ In fact, this same study established that Vigamox was associated with a statistically significant increase in conjunctival hyperemia and conjunctival vascularity when compared with Zymar. Additionally, there was significantly less pain and irritation associated with the administration of Zymar than with Vigamox.

STERILE AQUEOUS

An in vivo study comparing the impact of preoperative Zymar and Vigamox on immediate postoperative aqueous cultures in patients undergoing phacoemulsification revealed no significant differences in the agents' ability to sterilize the aqueous humor prior to or after surgery.⁹ The positive aqueous culture rate was significantly lower than what has been previously been reported in the literature. The investigators concluded that the reduced positive aqueous culture rate could be the result of two factors: (1) dramatically less aqueous contamination during the col-

lection of the specimen secondary to an improved collection technique using a fine needle through the clear cornea, and (2) a real reduction in bacterial exposure to the aqueous during phacoemulsification secondary to the increased efficacy of Zymar and Vigamox.

USE IN CLINICAL PRACTICE

The presence or absence of BAK has little impact on the toxicity of these medications with routine use. Evidence suggests that the use of Vigamox in the postoperative period may inhibit the healing of corneal wounds, especially corneal re-epithelialization, a core component of corneal wound healing. Moreover, toxicity likely allows for the greater penetration of Vigamox into healing ocular tissues, a difference that may lead to further and deeper irritation.

When choosing an anti-infective medication for postsurgical prophylaxis, the clinician should consider the agent's efficacy, the speed of onset of action, and the effect the medication may have on wound healing in the postoperative period. Both Zymar and Vigamox are highly helpful anti-infective agents with broad-spectrum coverage and a rapid onset of action. There appears, however, to be a difference in toxicity between the two fourth-generation fluoroquinolones, and evidence exists that Vigamox may inhibit corneal wound healing. These findings suggest that Zymar is the preferred fourth-generation fluoroquinolone for the prophylaxis of postsurgical infection. ■

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