The Effect of Fourth-Generation Fluoroquinolones Gatifloxacin and Moxifloxacin on Epithelial Healing Following Photorefractive Keratectomy

JENNA M. BURKA, MD, KRAIG S. BOWER, MD, R. CAMERON VANROEKEL, OD, RICHARD D. STUTZMAN, MD, CHRYSTYNA P. KUZMOWYCH, OD, AND ROBIN S. HOWARD, MA

• PURPOSE: To compare the rate of epithelial healing following photorefractive keratectomy (PRK) with two commercially available fourth-generation fluoroquinolones, gatifloxacin (Zymar, Allergan, Irvine, California) and moxifloxacin (Vigamox, Alcon Laboratories, Fort Worth, Texas).

• DESIGN: Double-masked, randomized, prospective trial.

• METHODS: Thirty-five subjects received gatifloxacin in one eye and moxifloxacin in the fellow eye following PRK with a 9.0-mm epithelial defect. Patients were examined daily after surgery until the epithelium had healed completely in both eyes. Beginning on post-operative day 3, photos were taken and used to confirm epithelial healing or measure the area of residual epithelial defects. Healing times and defect sizes were compared using the Wilcoxon signed-ranks test.

• RESULTS: Both eyes healed on the same day in 18 of the 35 subjects (51.4%). In 13 of 35 (37.1%) subjects, the moxifloxacin-treated eye healed first, compared with only four of 35 (11.4%) subjects whose gatifloxacin-treated eye healed first. All six of the eyes that took 2 days longer than their fellow eye to heal were gatifloxacin-treated. Median healing time for both groups was 4 days (moxifloxacin range: 3 to 7 days; gatifloxacin range: 3 to 9 days; $P = .01$), but only 69% of gatifloxacin-treated eyes had healed by day 4 compared with 80% of the moxifloxacin-treated eyes. Overall, on each post-operative day, defect sizes were greater for the gatifloxacin-treated eyes. This difference was statistically significant on day 4 ($P = .027$).

• CONCLUSIONS: Eyes treated with moxifloxacin healed faster and had smaller defects compared with those treated with gatifloxacin. This provides another factor to consider in selecting antibiotic prophylaxis for corneal refractive surgery. (Am J Ophthalmol 2005;140: 83–87. © 2005 by Elsevier Inc. All rights reserved.)

PROPHYLACTIC ANTIBIOTIC DROPS ARE ROUTINELY used after ocular surgery to prevent post-operative infections. Fluoroquinolones in particular have been useful in covering many of the bacterial pathogens that are responsible for infections after intraocular procedures such as cataract, glaucoma, and corneal surgery.

Two fourth-generation fluoroquinolones approved for ophthalmic use in the United States, gatifloxacin 0.3% ophthalmic solution (Zymar, Allergan, Irvine, California) and moxifloxacin 0.5% topical ophthalmic solution (Vigamox, Alcon Laboratories, Fort Worth, Texas), are frequently used for prophylaxis following laser keratorefractive surgery. Selection of the most appropriate antibiotic is often based on considerations such as spectrum of microbial coverage, bioavailability, ocular tolerance, and cost. When there is no clear evidence to support the superiority of one drug over another in these respects, additional factors may be considered. In the case of the fourth-generation fluoroquinolones, subtle differences in the mechanism of action, concentration, vehicle, pH, solubility, and preservative of each compound may lead to a potential difference in their effect on epithelial healing. Such a difference would have important implications on the selection of antibiotic prophylaxis for photorefractive keratectomy (PRK). Faster epithelial healing speeds visual recovery, allows patients to return to work and other daily activities sooner, and decreases the risk of adverse events.

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From the Center for Refractive Surgery (J.M.B., K.S.B., R.C.V., R.D.S., C.P.K.), Department of Clinical Investigation (R.S.H.), Walter Reed Army Medical Center, Washington, DC.

Inquiries to Kraig S. Bower, MD, Ophthalmology Service, Department of Surgery, Water Reed Army Medical Center, 6900 Georgia Ave, Washington, DC 20307; fax: (202) 782-4653.

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In this study, we performed a prospective within-subject comparison of the rate of epithelial healing between gatifloxacin and moxifloxacin following PRK.

SUBJECTS AND METHODS

THIS PROSPECTIVE, RANDOMIZED, DOUBLE-MASKED STUDY was conducted at the Center for Refractive Surgery, Walter Reed Army Medical Center, Washington, DC, between June and September 2004. All subjects were aged 21 years or older with a manifest spherical equivalent (MSE) of less than −6.00 diopters and astigmatism of less than 3 diopters. All participants demonstrated refractive stability over at least 12 months (no more than 0.5 diopters change in either spherical or cylindrical portion of the manifest refraction) and had a best spectacle-corrected visual acuity of 20/20 or better. Subjects were excluded for current or prior eye disease or eye surgery, pregnancy, flight status, or any medical problems precluding refractive surgery. Subjects were specifically excluded who had dry eyes, ocular surface disease, epithelial basement membrane dystrophy, or a history of recurrent corneal erosions. The study protocol was approved by the Internal Review Board/Human Use Committee, Department of Clinical Investigation, Walter Reed Army Medical Center. All subjects enrolled into the study voluntarily agreed to participate and gave written informed consent.

Subjects were randomized into one of two groups. After surgery, group A used moxifloxacin in the right eye and gatifloxacin in the left. Group B used gatifloxacin in the right eye and moxifloxacin in the left. The bottles were masked and marked only as "right eye" and "left eye." This allowed an analysis of both intersubject and intrasubject differences.

All subjects had PRK performed bilaterally on the same day using the LADARVision excimer laser system (Alcon Surgical, Fort Worth, Texas) with Jupiter 2 5.11 software. A 9.0-mm LASEK trephine was used to mark the cornea and incise the epithelium. Chemical cleavage of the epithelium was performed using an alcohol 20% solution for 25 seconds in a 9.5-mm well. The alcohol was irrigated from the surface of the cornea, and the epithelium was removed using a micro-hoe or Merocel sponge. The dimensions of the defect were measured digitally on the LADARVision treatment screen and recorded in the brief operative note. Immediately after laser ablation was completed, topical antibiotic drops were given and a therapeutic bandage contact lens (Proclear compatibles, Cooper Vision, Norfolk, Virginia; BC 8.6, DIA 14.2, PWR +0.50) was applied to the ablated surface for all patients. Patients used the topical antibiotic four times daily for 1 week or until the epithelial defect had healed. In addition, all patients were instructed to use fluorometholone 0.1% ophthalmic suspension (FML, Allergan) four times daily; non-preserved carboxymethylcellulose sodium 0.5% (Refresh Plus, Allergan) every 2 hours while awake for the first 72 hours, then four times daily until complete epithelialization, then four times daily as needed; and diclofenac 0.1% ophthalmic solution (Voltaren, Novartis Ophthalmics, Duluth, Georgia) up to four times daily as needed for pain for the first 48 hours post-operatively.

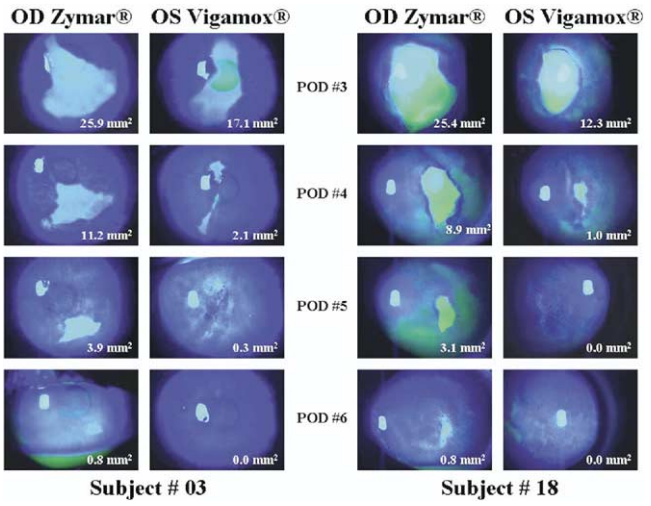

FIGURE 1. Epithelial defect size on post-operative days 3 to 6 in two study participants. Slit-lamp photographs were taken with Cobalt blue filter after instillation of topical fluorescein drops (original magnification ×16). The photographs on the left represent a patient whose moxifloxacin-treated eye healed on day 6 and whose gatifloxacin-treated eye healed on day 7. This subject also had a peripheral corneal infiltrate on post-operative day 4. The photographs on the right represent a patient whose moxifloxacin-treated eye healed on post-operative day 5 and whose gatifloxacin-treated eye healed on day 7. Calculated surface area of epithelial defects is shown at bottom right of each photograph.

Post-operatively, patients were examined daily until the epithelium was healed completely in both eyes. The primary outcome measure was epithelial healing time. Specifically, we compared the time in days to complete epithelial healing between the eyes of a same subject. We considered significant a difference of 1 day or more between eyes. Secondary outcome measures included size of defects, subjective complaints, adverse events, and visual outcomes. The size of the defect was measured through the contact lens at the slit lamp on post-operative days 1 and 2. On post-operative day 3, the bandage contact lens was removed and the epithelial defect measured at the slit lamp. Topical fluorescein sodium 2.5% was instilled and the eye examined; photographs were taken and used to document the area of any remaining defects. Images were viewed in Adobe Photoshop 7.0 and the surface area of the remaining defect calculated (Figure 1). If a significant epithelial defect was present, a new bandage contact lens was placed. Subjective complaints of pain, foreign body sensation, photophobia, tearing, stinging with the antibiotics, and quality of vision were assessed using a 10-point

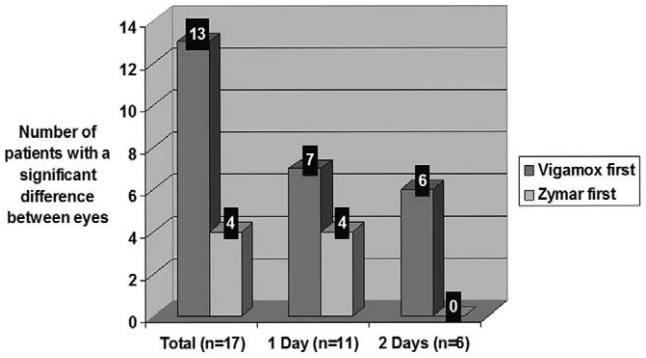

FIGURE 2. Within-subject difference in epithelial healing following photorefractive keratectomy. Graph illustrates which eye healed first in those subjects whose eyes did not heal on the same day. This graph shows the total number of subjects with a difference in healing time and breaks those results down into those with 1- and 2-day differences.

scale and were recorded. Neither the patients nor the examiners were aware of which antibiotics the patients received in which eye.

Results were recorded in an Excel spreadsheet for analysis. Data were analyzed using the Wilcoxon signed-rank test. A P value of less than .05 was considered statistically significant.

RESULTS

FORTY SUBJECTS WERE ENROLLED IN THE STUDY. FIVE SUBjects withdrew from the study: three subjects were excluded before treatment because of abnormal pre-operative corneal topography, one subject withdrew before treatment when it was determined he would be unable to participate in the follow-up schedule, and one subject underwent treatment but withdrew from the study after having general anesthesia for unrelated surgery several days after her PRK. Data from the 35 remaining subjects were analyzed. Twenty-two men and 18 women, aged 21 to 47 years, completed the study. Pre-operative refractive error ranged from −1.00 to −5.75 diopters. The mean MSE was -2.82 ± 1.24 for moxifloxacin eyes and -2.76 ± 1.35 for gatifloxacin eyes ($P = .551$, ns).

Both eyes healed on the same day in 18 of the 35 subjects (51.4%). In the majority of the remaining 17 subjects, however, the moxifloxacin-treated eye healed first. Moreover, all six of the eyes that took 2 days longer than their fellow eye to heal were gatifloxacin-treated (Figure 2). Although median healing time for both groups was 4 days (moxifloxacin range: 3 to 7 days, gatifloxacin range: 3 to 9 days, $P = .01$; Table 1), only 69% of gatifloxacin-treated eyes had healed by day 4 compared with 80% of the moxifloxacin-treated eyes (Table 2). Successful removal of the bandage contact lens was accomplished earlier ($P = .042$) in the moxifloxacin group (median: 3, range: 3 to 7) than the gatifloxacin group (median: 4, range 3 to 9).

Overall, on each post-operative day, defect sizes were greater for the gatifloxacin-treated eyes. This difference was statistically significant on day 4 ($P = .027$), and a similar trend was seen on day 5 ($P = .055$). Figure 1 shows photographs taken of two subjects that illustrate the difference in defect sizes.

There was no significant difference in subjective symptoms between the moxifloxacin- and gatifloxacin-treated eyes. One gatifloxacin-treated eye developed peripheral corneal infiltrates on post-operative day 4 that resolved after removal of the bandage contact lens (Figure 3). There were no significant adverse effects reported in the moxifloxacin-treated eyes. All subjects were seen for 1-month follow-up at which time no eye had lost more than 1 line of best-corrected visual acuity. Best-corrected visual acuity was comparable for both the moxifloxacin and gatifloxacin-treated eyes, −0.06 and −0.07 logarithm of the minimum angle of resolution (logMAR), respectively ($P = .695$, ns).

DISCUSSION

CORNEAL REFRACTIVE SURGERY HAS BECOME ONE OF THE most frequently performed ophthalmic procedures. Although laser-assisted in-situ keratomileusis is by far the most common procedure, surface ablations are indicated in patients with thin corneas, epithelial basement membrane dystrophy, or recreational or occupational activities that significantly increase the risk of trauma. In the U.S. Army refractive surgery program, PRK constitutes more than 70% of laser refractive procedures.[1] Bacterial keratitis is the most serious and potentially devastating complication of PRK,[2,3] and prophylactic antibiotics are initiated immediately following surgery and continued until epithelial healing is complete to reduce the risk. Fluoroquinolones, with excellent broad-spectrum coverage and good ocular tolerance, have been frequently used for this purpose.

Two newer fourth-generation fluoroquinolones, gatifloxacin (Zymar) and moxifloxacin (Vigamox), have distinct advantages over their predecessors.[4–8] The latter have gaps in coverage, particularly against α-hemolytic *Streptococcus* and some *Staphylococcal* species. This is potentially significant, given that gram-positive organisms are the most common cause of bacterial infections following PRK.[2] *Staphylococcus aureus*, *Streptococcus viridans* and *Streptococcus pneumonia* have been shown to be more susceptible to gatifloxacin and moxifloxacin than to ciprofloxacin, levofloxacin, and ofloxacin.[8] Although current literature has documented developing resistance to the ciprofloxacin, levofloxacin, and ofloxacin,[4–6] emerging antibiotic resistance has not yet been a major problem with the fourth-generation fluoroquinolones. Furthermore, these agents are more effective than earlier generations

TABLE 1. Healing Times and Defect Sizes for Vigamox- and Zymar-Treated Eyes

	Mean ± SD Vigamox	Mean ± SD Zymar	Median (range) Vigamox	Median (range) Zymar	Significance *P* Value*
Healing time (d)	3.9 ± 1.0	4.3 ± 1.5	4 (3–7)	4 (3–9)	.010
Contact lens out (d)	3.8 ± 1.0	4.1 ± 1.4	3 (3–7)	4 (3–9)	.042
Defect size (mm)					
POD 3	5.0 ± 8.9	6.9 ± 9.9	0.6 (0–43.5)	0.6 (0–30.5)	.233
POD 4	1.4 ± 5.1	3.1 ± 6.9	0.0 (0–27.8)	0.0 (0–30.2)	.027
POD 5	0.5 ± 2.4	1.1 ± 3.3	0.0 (0–13.6)	0.0 (0–18.2)	.055
POD 6	0.1 ± 0.6	0.4 ± 1.7	0.0 (0–3.4)	0.0 (0–10.2)	.250

POD = Postoperative day.
*Wilcoxon signed-ranks test.

TABLE 2. Eyes Showing Complete Epithelial Healing on Each Post-operative Day (POD) Following Photorefractive Keratectomy

Healed by POD	Vigamox (n = 35)		Zymar (n = 35)	
	n	%	n	%
3	14	40.0	13	37.1
4	28	80.0	24	68.6
5	32	91.4	26	74.3
6	34	97.1	32	91.4
7	35	100.0	34	97.1
8	35	100.0	34	97.1
9	35	100.0	35	100.0

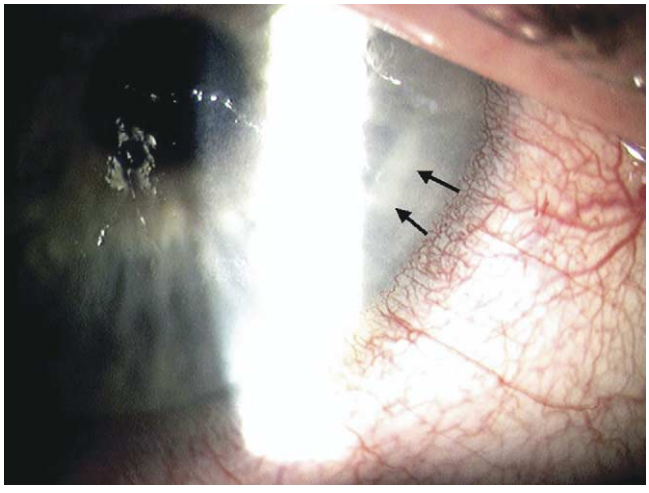

FIGURE 3. Peripheral corneal infiltrate following photorefractive keratectomy. Slit-lamp biomicroscope photograph (original magnification ×16) of peripheral corneal infiltrate (arrows) seen in a gatifloxacin-treated eye on post-operative day 4. This is the right eye of Subject 3 shown in Figure 1. The infiltrate was asymptomatic, peripheral, under intact epithelium, and was out of the treatment zone. It was felt to be sterile and resolved after removal of the bandage contact lens and increasing the topical corticosteroids.

against atypical mycobacteria, an important pathogen following refractive surgery.

Fluoroquinolones work by inhibiting topoisomerase II (DNA gyrase) and topoisomerase IV, thereby inhibiting the ability of the bacteria to replicate.[9] The mechanism of action that provides the fluoroquinolones their antibacterial efficacy may delay the healing process, increasing the risk of infection and other complications, particularly haze and scarring, that may have a negative effect on visual outcome.[10]

Previous studies evaluated epithelial healing with second- and third-generation fluoroquinolones. Patel and associates[10] compared epithelial healing rates of ciprofloxacin versus ofloxacin and found that eyes treated with ofloxacin healed significantly faster than those treated with ciprofloxacin. Moreira and associates[11] compared the healing of rabbit corneas treated with ciprofloxacin and ofloxacin to a control group who only received artificial tears. They reported a significantly delayed healing time with both fluoroquinolones relative to the control group, but no difference between the two antibiotics.

Laboratory studies on epithelial healing with fourth-generation fluoroquinolones have so far produced mixed results. An in vivo rabbit epithelial cell culture model, (Matsumoto and associates abstract, presented at American College of Toxicology Meeting, October, 2003) demonstrated less inhibition of epithelial cell migration with gatifloxacin than with moxifloxacin. However, the fluoroquinolones used in that study were not the commercially available preparations, but rather 0.2 to 1.0 mmol/l solutions. Another study compared moxifloxacin and gatifloxacin, (J. Gao and associates unpublished data, 2004) and the rate of epithelial healing in rabbit corneas after anterior keratectomy. In that study gatifloxacin did not affect the rate of epithelial healing, whereas moxifloxacin-treated corneas demonstrated a delay in healing as well as decreased collagen IV expression. Conversely, (R.W. Yee and associates "Wound healing and the importance of proper selection of an antibacterial prophylaxis agent," Refractive Eyecare for Ophthalmologists, 2003) another

found that moxifloxacin was less toxic to corneal epithelium than gatifloxacin, levofloxacin, and ofloxacin in vitro using human corneal epithelial cells. The same investigators also studied wound healing following PRK on chicken eyes and found that both gatifloxacin and moxifloxacin demonstrated faster rates of healing than levofloxacin.

In light of the conflicting laboratory evidence, we conducted a prospective randomized clinical trial to evaluate the effect of commercially available fourth-generation fluoroquinolones on epithelial healing after PRK. The results of our study demonstrate faster epithelial healing with moxifloxacin than with gatifloxacin. Overall, moxifloxacin-treated eyes healed first and had smaller defects than gatifloxacin-treated eyes. For those subjects in whom there was a day or more difference in time to complete re-epithelialization, the faster healing eye was three times more likely to be moxifloxacin treated, and all six patients who had a 2-day difference healed faster in the moxifloxacin-treated eye. Moreover, the therapeutic bandage contact lens was removed earlier in the moxifloxacin-treated eyes.

This study was designed to provide a within-subject comparison where the only difference was the antibiotic used perioperatively. Gatifloxacin and moxifloxacin differ in several key points that may contribute to the effect on epithelial healing. Gatifloxacin comes as a 0.3% solution whereas moxifloxacin is formulated as a 0.5% solution. The pH of moxifloxacin is 6.8, whereas gatifloxacin is prepared at a pH of 6.0. Because of this, moxifloxacin is more soluble than gatifloxacin at tear pH, which is normally approximately 7.5 but can increase during an infection as a result of phagocytosis. As the pH rises, the antibiotics become less soluble and can form precipitates on the corneal surface.[12] Previous studies of ciprofloxacin, the least soluble of the commercially available fluoroquinolones, demonstrated that precipitation of the antibiotic in an epithelial defect might delay corneal re-epithelialization by blocking epithelial migration or inhibiting re-generation.[10,12] We did not observe precipitates on the contact lens or cornea of any eye in this study, so this does not explain the difference in epithelial healing.

Another key difference between the two formulations is the use of preservative. Gatifloxacin is preserved with benzalkonium chloride (BAK) 0.005%, whereas moxifloxacin is preservative-free. Preservatives can have an adverse effect on epithelial stability, and several studies report a delay in epithelial healing with drops containing BAK.[13,14] However, Collin and Grabsch[15] found that BAK 0.01% had no effect on the rate of corneal re-epithelialization following keratectomy.

Although it is not clear which of these or other possible factors play the critical role in epithelial healing, our study suggests that moxifloxacin has a more favorable epithelial healing profile in a clinical post-PRK setting. It remains to be determined whether this difference in epithelial healing time is associated with important differences in visual outcomes. In the meantime, this epithelial healing study provides another factor to consider in selecting antibiotic prophylaxis for corneal refractive surgery.

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