

VITREOUS PENETRATION OF TOPICAL MOXIFLOXACIN AND GATIFLOXACIN IN HUMANS

PATRICK COSTELLO, MD,* SOPHIE J. BAKRI, MD,† PAUL M. BEER, MD,*
RAVINDER J. SINGH, PhD,‡ NAOMI S. FALK, MD,*
GEORGE B. PETERS, MD,* J. ANDRE MELENDEZ, PhD§

Purpose: To determine the vitreous penetration of the new fourth-generation topical fluoroquinolones moxifloxacin 0.5% and gatifloxacin 0.3%.

Methods: A prospective randomized clinical trial comprising 12 eyes of 12 patients scheduled for pars plana vitrectomy between August 2003 and September 2003 was performed in a clinical practice. The patients were randomly assigned to receive topical moxifloxacin 0.5% (n = 6) or gatifloxacin 0.3% (n = 6). One half the patients in each antibiotic group received 1 drop every 15 minutes for a total of 3 doses starting 1 hour before surgery, and the other one half self-administered the antibiotic drop 4 times daily for 3 days before surgery and at 7 AM on the day of surgery. Undiluted vitreous samples were obtained and analyzed using high-performance liquid chromatography.

Results: Either moxifloxacin 0.5% or gatifloxacin 0.3% was detected in the vitreous in all 12 patients in the study. There was no significant difference between the mean vitreous concentration of moxifloxacin 0.5% given over 1 hour preoperatively ($0.012 \pm 0.011 \mu\text{g/mL}$) and that given in the 3-day regimen ($0.011 \pm 0.008 \mu\text{g/mL}$) ($P = 0.93$). There was also no significant difference between the mean vitreous concentration of gatifloxacin 0.3% given over 1 hour preoperatively ($0.001 \pm 0.0003 \mu\text{g/mL}$) and that given over 3 days ($0.008 \pm 0.006 \mu\text{g/mL}$) ($P = 0.11$). Vitreous concentrations of moxifloxacin 0.5% and gatifloxacin 0.3% in each eye were all lower than the 90% minimum inhibitory concentration for the commonest bacterial isolates causing endophthalmitis. With both dosing regimens, the mean vitreous concentration of moxifloxacin 0.5% was higher than that of gatifloxacin 0.3% administered at the same regimen, but this was not statistically significant.

Conclusion: Both topical moxifloxacin 0.5% and gatifloxacin 0.3% penetrated the vitreous in the uninflamed eye, but the vitreous concentrations attained were all lower than the 90% minimum inhibitory concentration for the commonest bacterial pathogens causing acute postoperative endophthalmitis.

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Postsurgical infectious endophthalmitis is a devastating complication of intraocular surgery. Even with early intervention, the median visual acuity as-

sociated with endophthalmitis occurring after cataract extraction is 20/100.¹ The causative agents introduced to the eye during surgery usually originate on the ocular surface, with *Staphylococcus epidermidis* and *Staphylococcus aureus* being the most common pathogens implicated in bacterial endophthalmitis.² Several prophylactic techniques have been studied for the prevention of postoperative endophthalmitis, but only preoperative sterilization with povidone-iodine solution has been shown to be moderately important to clinical outcome.³ All other reported prophylactic interventions, including postoperative subconjunctival antibiotic injection, preoperative lash trimming, pre-

From *Lions Eye Institute, Albany Medical College, Albany, New York; †Department of Ophthalmology, Mayo Clinic, Rochester, Minnesota; ‡Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota; and §Department of Immunology and Microbiology, Albany Medical College, Albany, New York.

Reprint requests: Paul M. Beer, MD, Lions Eye Institute, 35 Hackett Boulevard, Albany Medical College, Albany, NY 12208.

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operative saline irrigation, preoperative topical antibiotics, antibiotic-containing irrigating solutions, and the use of intraoperative heparin, have received the lowest clinical recommendation.³

There is no clear consensus on preoperative prophylaxis with antibiotic therapy. Many ophthalmologists choose to use topical antibacterial prophylaxis in the preoperative period.^{4,5} The US Food and Drug Administration approval of the fourth-generation topical fluoroquinolones Zymar (gatifloxacin ophthalmic solution 0.3%) and Vigamox (moxifloxacin HCl ophthalmic solution 0.5%) has made additional choices available in the treatment of ocular bacterial infections. These drugs have been shown to be more effective than their second- and third-generation predecessors in combating gram-positive bacteria, particularly isolate strains of *S. aureus* and coagulase-negative staphylococci that were resistant to ciprofloxacin and ofloxacin in vitro.⁶

Ocular penetration of fluoroquinolones has been studied in the aqueous and vitreous humor of humans and animals in normal and inflamed eyes when administered both topically and orally.⁷⁻¹⁰ In humans, topical ciprofloxacin 0.3% and topical ofloxacin 0.3% reached the 90% minimum inhibitory concentration (MIC₉₀) for the commonest ocular pathogens in the aqueous but not in the vitreous.⁷ Oral levofloxacin levels in the vitreous did not reach the MIC₉₀.⁸ Vitreous and aqueous concentrations of oral gatifloxacin attained the MIC₉₀ in both aqueous and vitreous.¹¹ Vitreous levels of oral moxifloxacin in inflamed and normal rabbit eyes reached the MIC₉₀,¹² and aqueous levels of oral moxifloxacin, ciprofloxacin, and levofloxacin¹³ have also been shown to attain the MIC₉₀. The aqueous penetration of topical moxifloxacin 0.5% and gatifloxacin 0.3% is higher than that of topical ciprofloxacin 0.3%.¹⁴ One study¹⁵ showed that the levels of topical moxifloxacin 0.5% exceeded the MIC₉₀ in the aqueous but not the vitreous for the commonest bacterial pathogens causing endophthalmitis.

The goals of this study were to determine whether topical moxifloxacin 0.5% and gatifloxacin 0.3% penetrate the vitreous, whether the concentration of drug in the vitreous reaches the MIC₉₀ for the most common pathogens causing endophthalmitis, and whether the duration of preoperative treatment affects the concentration in the vitreous at the time of surgery.

Methods

Approval was obtained from the Institutional Review Board of the Albany Memorial Hospital (Albany, NY). After informed consent was obtained, 12 eyes of 12 patients undergoing elective pars plana

vitrectomy between August 2003 and September 2003 were enrolled in the study. Excluded were female patients of childbearing age and patients with known sensitivity to fluoroquinolones, use of antibiotics, or intraocular or laser surgery in the preceding month. Patients who had received surgery for glaucoma (trabeculectomy or a tube), aphakic patients, and pseudophakic patients with an open capsule were also excluded from the study.

Twelve eyes of 12 patients were randomly assigned to 1 of 4 study groups (3 eyes per group). Patients in groups 1 and 2 were administered 1 drop of topical gatifloxacin or moxifloxacin, respectively, every 15 minutes for a total of 3 doses starting 1 hour before surgery. Other preoperative drops were administered 5 minutes before and after the antibiotic drop to avoid any dilution. Patients in groups 3 and 4 self-administered gatifloxacin and moxifloxacin, respectively, 4 times daily for 3 days before surgery and at 7 AM on the day of surgery. The patients taking drops at home for 3 days were contacted by telephone each day to be reminded to take the drops. All 6 of these patients reported 100% compliance with the preoperative antibiotic regimen when presenting for surgery.

At the time of surgery, a 1-mL syringe was attached to the aspiration port of an unprimed disposable vitrectomy cutter. Before the infusion cannula was turned on, 0.2 mL of vitreous was manually aspirated from the syringe as the vitreous cutter engaged the vitreous gel. The vitreous sample was immediately transferred into a plain red top vacutainer tube and frozen. The tubes were delivered on dry ice overnight to the Endocrine Laboratory at the Mayo Clinic (Rochester, MN) for analysis.

Concentrations of gatifloxacin and moxifloxacin were measured using high-performance liquid chromatography–tandem mass spectrometry method on the API 3000 Sciex triple-quadrupole mass spectrometer (ABI-PE Sciex, Toronto, Ontario, Canada). The specific mass-to-charge ratio transitions for gatifloxacin and moxifloxacin were 376 and 402 to 384, respectively. The mobile phase was 40/60 (v/v) acetonitrile/water 1.5 mmol/L ammonium acetate containing 0.05% formic acid. Acetonitrile was added to each sample (1:1 parts) to precipitate proteins. The supernatants were dried under nitrogen and reconstituted in 100 μL of the mobile phase. Thirty microliters of the reconstituted extract was injected onto a reversed-phase 15 × 0.46-cm MAX-RP column and analyzed using a tandem mass spectrometer operating in the positive mode. The interassay coefficients of variation of the analysis were <20%.

Statistical analysis was performed using an unpaired two-tailed Student's *t*-test.

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Table 1. Study Patient Characteristics and Vitreous Concentrations of Moxifloxacin 0.5% and Gatifloxacin 0.3% Using Two Different Dosing Regimens

Patient	Age (y)	Lens	Drug	Regimen	Surgical Indication	Vitreous Concentration of Drug ($\mu\text{g/mL}$)
1	71	Phakic	GAT	QID \times 3 d	ERM	0.0064
2	77	Phakic	GAT	QID \times 3 d	ERM	0.00348
3	59	Pseudophakic	MOX	QID \times 3 d	ERM	0.0114
4	69	Phakic	MOX	QID \times 3 d	ERM	0.0196
5	75	Pseudophakic	MOX	QID \times 3 d	VH	0.0028
6	53	Pseudophakic	GAT	QID \times 3 d	RRD	0.0152
7	56	Phakic	GAT	Q 15 min \times 3	ERM	0.00153
8	54	Phakic	GAT	Q 15 min \times 3	ERM	0.00083
9	73	Pseudophakic	MOX	Q 15 min \times 3	ERM	0.0069
10	74	Phakic	MOX	Q 15 min \times 3	ERM	0.00408
11	81	Phakic	MOX	Q 15 min \times 3	ERM	0.025
12	63	Phakic	GAT	Q 15 min \times 3	CRVO	0.00121

GAT, gatifloxacin 0.3%; ERM, epiretinal membrane; MOX, moxifloxacin 0.5%; VH, vitreous hemorrhage; RRD, rhegmatogenous retinal detachment; CRVO, central retinal vein occlusion undergoing retinal endovascular surgery.

Results

The indications for pars plana vitrectomy surgery in the 12 patients were epiretinal membrane (n = 9), vitreous hemorrhage (n = 1), retinal detachment (n = 1), and central retinal vein occlusion undergoing retinal endovascular surgery. Eight patients were phakic, and four were pseudophakic (Table 1).

Either moxifloxacin 0.5% or gatifloxacin 0.3% was detected in the vitreous in all 12 patients in the study (Table 1). There was no significant difference between the mean vitreous concentration of moxifloxacin 0.5% given over 1 hour preoperatively ($0.012 \pm 0.011 \mu\text{g/mL}$) and that given with the 3-day regimen ($0.011 \pm 0.008 \mu\text{g/mL}$) ($P = 0.93$). There was also no significant difference between the mean vitreous concentration of gatifloxacin 0.3% given over 1 hour preoperatively ($0.001 \pm 0.0003 \mu\text{g/mL}$) and that given over 3 days ($0.008 \pm 0.006 \mu\text{g/mL}$) ($P = 0.11$).

The mean vitreous concentration of 1 drop of moxifloxacin 0.5% given every 15 minutes 3 times starting 1 hour before surgery ($0.012 \mu\text{g/mL}$) was higher than that of the same dosing regimen of gatifloxacin 0.3%

($0.001 \mu\text{g/mL}$), but this was not statistically significant ($P = 0.17$). The mean vitreous concentration after 1 drop of moxifloxacin 0.5% administered 4 times per day for 3 days before surgery ($0.011 \mu\text{g/mL}$) was higher than that of gatifloxacin 0.3% administered at the same regimen ($0.008 \mu\text{g/mL}$), but this was not statistically significant ($P = 0.65$). The sample size was not large enough to determine whether pseudophakic or phakic eyes had a higher vitreous penetration of drug at each time point. Vitreous concentrations of moxifloxacin 0.5% and gatifloxacin 0.3% in each eye were all lower than the MIC_{90} for the commonest bacterial pathogens causing endophthalmitis⁶ (Table 2).

Discussion

Endophthalmitis is one of the most serious complications of intraocular surgery, and it is therefore important to investigate the role of potential new therapies that may be used as an adjunct for its prophylaxis and treatment. There is currently no strong evidence to suggest that the administration of preoperative topical

Table 2. Mean Vitreous Concentrations of Topical Moxifloxacin 0.5% and Gatifloxacin 0.3% Compared With Their MIC_{90} for the Commonest Bacterial Pathogens Causing Endophthalmitis

Finding	Moxifloxacin 0.5%	Gatifloxacin 0.3%
MIC_{90} ($\mu\text{g/mL}$) <i>Staphylococcus aureus</i>	0.064	0.11
<i>Staphylococcus epidermidis</i>	0.047	0.09
<i>Streptococcus pneumoniae</i>	0.125	0.22
Mean vitreous concentration \pm SD ($\mu\text{g/mL}$)		
QID \times 3 d before surgery	0.011 ± 0.008	0.008 ± 0.006
Q 15 min \times 1 h before surgery	0.012 ± 0.011	0.001 ± 0.0003

MIC_{90} , 90% minimum inhibitory concentration.

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antibiotics reduces the incidence of postoperative endophthalmitis.³ Recently, topical fourth-generation fluoroquinolones have become available. The MICs of topical gatifloxacin 0.3% and moxifloxacin 0.5% have been shown to be statistically lower than those of the second-generation fluoroquinolones for all gram-positive bacteria tested.¹⁶ Both drugs have been shown to reach their respective MIC₉₀ for most pathogenic organisms in the aqueous humor of rabbits.¹⁷ Topical ofloxacin used 3 days before surgery has been shown to be more effective in eliminating bacteria from the conjunctiva than an application of ofloxacin 1 hour before surgery.¹⁸

An inoculum of bacteria entering the vitreous poses a greater risk than the same inoculum of bacteria in the aqueous.¹⁹ The incidence of endophthalmitis with cataract surgery is higher when there is rupture of the posterior capsule requiring anterior vitrectomy.^{19,20} The best prophylaxis for postoperative endophthalmitis would be an antibiotic that reaches therapeutic levels in the vitreous humor. Penetration of an antibiotic into the vitreous cavity is an important aspect of its pharmacokinetic profile, and the goal of our study was to quantify the vitreous levels of these new topical fourth-generation fluoroquinolones after administration 4 times per day over 3 days versus once every 15 minutes 1 hour before surgery.

Although present in the vitreous in all eyes in the study, neither antibiotic reached the MIC₉₀ for most bacteria implicated in endophthalmitis. Prophylactic topical ofloxacin has been shown to reduce the number of conjunctival bacterial colonies in eyes where the drug is administered over 3 days versus the number of colonies in eyes which receive the drug 3 times over 1 hour before surgery. A reduction in bacterial colonies may decrease the incidence of endophthalmitis by limiting the size of bacterial inoculum entering the eye. Although administering the drop over 3 days before surgery may not increase the vitreous concentration of the drug, lowering the conjunctival bacterial load may be beneficial for endophthalmitis prophylaxis. It is possible that administering the antibiotic drops more frequently may result in vitreous concentrations that exceed the MIC₉₀.

We found a difference in the mean concentration of gatifloxacin after 1 hour of topical application versus 3 days of application. Patient 6 had a concentration severalfold greater than those of Patients 1 and 2. This may be related to the pseudophakic status of Patient 6: $0.012 \pm 0.011 \mu\text{g/mL}$ versus $0.011 \pm 0.008 \mu\text{g/mL}$ with the 3-day regimen ($P = 0.93$). There was also no significant difference between the mean vitreous concentration of gatifloxacin 0.3% given over 1 hour

preoperatively ($0.001 \pm 0.0003 \mu\text{g/mL}$) and that given over 3 days ($0.008 \pm 0.006 \mu\text{g/mL}$) ($P = 0.11$).

Overall, moxifloxacin 0.5% reached intravitreal concentrations that were 2 to 10 times greater than gatifloxacin. Furthermore, the MIC₉₀ for the three most common causative organisms is two times lower for moxifloxacin than for gatifloxacin. Even with these advantages, moxifloxacin levels were still six times below their respective MIC₉₀ levels. Gatifloxacin vitreous concentrations were 11 to 220 times below their respective MIC₉₀ levels (Table 2). As with previous studies examining vitreous levels after topical application of a fluoroquinolone, vitreous levels in our patients were shown to be consistently below the MIC₉₀ levels of both gatifloxacin and moxifloxacin.

There are several limitations to this study. The total number of patients was small. Sources for human error were identified before the study and included the aspiration, handling, and transfer of samples. Despite running the samples in triplicate, errors in the high-performance liquid chromatography assay are also possible. Although 100% compliance with drop administration was reported and patients were called each day, this is another potential source for error. The nursing staff in the preoperative holding area of the hospital was meticulous about spacing the drops 15 minutes apart in the patients taking drops 1 hour before surgery, but in this busy atmosphere, patients could have missed a drop or had drops spaced at different frequencies. However, the most likely significant factor in the varying drug concentrations found in these patients relates to expected variations in pharmacokinetic data from one case to another. No patients had any obvious corneal disease at the time of surgery, another factor which may affect absorption of medication.

In summary, our study did not show a significant difference for either gatifloxacin 0.3% or moxifloxacin 0.5% in reaching the human vitreous. Both drugs reached the vitreous at levels 6 to 220 times below the MIC₉₀ for the most common bacterial pathogens causing endophthalmitis. There was no significant difference in vitreous concentration of either drug when administered over 3 days before surgery versus 1 hour before surgery. It would be desirable for topical administration of antibiotics to reach therapeutic levels in the vitreous, but this goal has not been achieved with this new generation of fluoroquinolones, using the regimen described in this article.

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AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES

1

AQ1: AUTHOR— Correct to insert “annual meeting of the AAO”? Was there a numerical designation for the meeting (e.g., 33rd, etc)?

AQ2: AUTHOR— Please provide manufacturers with their locations for Zymar and Vigamox.

AQ3: AUTHOR— If vacutainer is a trade name, please provide manufacturer with its location.

AQ4: AUTHOR— Please confirm changes to sentence starting “This may be related to the pseudophakic status…”
