Vitreous and Aqueous Penetration of Orally Administered Gatifloxacin in Humans

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Objective: To investigate the penetration of gatifloxacin, a novel extended-spectrum fourth-generation fluoroquinolone antibiotic, into the vitreous and aqueous humor after oral administration.

Methods: A prospective, nonrandomized study of 24 consecutive patients scheduled for pars plana vitrectomy between September 2001 and May 2002 at the Cullen Eye Institute. Aqueous, vitreous, and serum samples were obtained and analyzed from 24 patients after administration of two 400-mg gatifloxacin tablets taken 12 hours apart before the operation. Assays were performed using high-performance liquid chromatography.

Results: Mean±SD gatifloxacin concentrations in serum (n=23), vitreous (n=23), and aqueous (n=11) were 5.14±1.36 µg/mL, 1.34±0.34 µg/mL, and 1.08±0.54 µg/mL respectively. Mean±SD sampling times after oral administration of the second gatifloxacin tablet for serum, vitreous, and aqueous were 3.2±1.0 hours, 4.0±1.0 hours, and 3.9±1.1 hours, respectively. The percentages of serum gatifloxacin concentration achieved in the vitreous and aqueous were 26.17% and 21.02%, respectively. Mean inhibitory vitreous and aqueous MIC₉₀ levels were achieved against many pathogens, including *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Propionibacterium acnes*, *Haemophilus influenzae*, *Escherichia coli*, *Bacillus cereus*, *Proteus mirabilis*, and other organisms.

Conclusions: Orally administered gatifloxacin achieves therapeutic levels in the noninflamed human eye, and the activity spectrum appropriately encompass the bacterial species most frequently involved in the various causes of endophthalmitis. Because of its broad-spectrum coverage, low MIC₉₀ levels for the organisms of concern, and good tolerability, gatifloxacin represents a major advance in the prophylaxis or treatment of postoperative, posttraumatic, and bleb-associated bacterial endophthalmitis.

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Bacterial endophthalmitis is one of the most serious complications of intraocular procedures and open-globe injuries. The microbiological spectrum of infecting organisms in postoperative endophthalmitis was investigated in the Endophthalmitis Vitrectomy Study (EVS). The EVS represents the largest number of postoperative endophthalmitis cases from which bacteriologic data were prospectively obtained. The vast majority of confirmed growth isolates (94.2%) were gram-positive pathogens, most commonly *Staphylococcus epidermidis* and *Staphylococcus aureus*. Gram-negative pathogens, the most common being *Proteus mirabilis*, accounted for only 5.9% of confirmed growth isolates.¹ The spectrum of infecting organisms in posttraumatic endophthalmitis differs from that of postoperative endophthalmitis, with *Bacillus* species playing a more prominent role.²

The EVS investigated the use of intravenous amikacin and ceftazidime in conjunction with intravitreal antibiotic injection for postoperative endophthalmitis and found no improved outcomes with the use of systemic antibiotics.³ Later studies found that amikacin and ceftazidime had very poor intravitreal penetration.⁴,⁵ Based on the EVS data, the only conclusion that can be drawn regarding the use of systemic antibiotics is that amikacin and ceftazidime specifically have no role in postoperative endophthalmitis. Since the EVS, there have been major advancements in the development of antibiotics, and the potential uses of these new-generation agents in the treatment of endophthalmitis must be revisited. During the past 10 years, there has been mounting evidence in the literature that agents in the fluoroquinolone class of antibiotics are able...
Gatifloxin is a fourth-generation 8-methoxy fluoroquinolone with a spectrum of activity encompassing gram-positive and gram-negative pathogens, including *Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Bacillus cereus, Neisseria gonorrhoeae, and Proteus mirabilis*. Additionally, gatifloxin has excellent activity against atypical pathogens, such as *Mycoplasma, Legionella, and Chlamydia* species, as well as the anaerobic organism *Propionibacterium acnes*.9,10 Gatifloxin has 96% oral bioavailability, can be administered without regard to food, and reaches peak plasma concentrations 1 to 2 hours after oral dosing. Serum protein binding of gatifloxin is only 20% and is widely distributed throughout the body into many tissues and fluids. The new fluoroquinolones, such as gatifloxin, grepafloxacin, moxifloxacin, and trovafloxacin, represent advances in the evolution of this antibiotic class. The more favorable pharmacokinetic properties of the previously mentioned agents are due to alterations of the original fluoroquinolone moiety. For example, gatifloxin and moxifloxacin possess an 8-methoxy side chain, which may be responsible for their enhanced activity against gram-positive, atypical pathogens and anaerobes while retaining potencies and broad-spectrum coverage against gram-negative organisms comparable to those of older-generation fluoroquinolones.10

We chose to study the intravitreal penetration of orally administered gatifloxin in humans for 2 reasons. First, older-generation fluoroquinolones, such as ofloxacin, ciprofloxacin, and levofloxacin, have been shown to achieve effective levels in the vitreous after oral administration.6-8 Second, the mean inhibitory concentrations required to inhibit growth of 90% of bacterial isolates tested (MIC90) for gatifloxacin against the pathogens most commonly responsible for postoperative, posttraumatic, and bleb-associated endophthalmitis were generally lower than those of the other fluoroquinolone antibiotics we surveyed (Table 1).9,10

<table>
<thead>
<tr>
<th>Organism</th>
<th>Gatifloxin</th>
<th>Levofloxin</th>
<th>Ofloxacin</th>
<th>Ciprofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitreous penetration, mean ± SD, µg/mL</td>
<td>1.34 ± 0.34</td>
<td>2.39 ± 0.70</td>
<td>0.43 ± 0.47</td>
<td>0.56 ± 0.16</td>
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</tbody>
</table>

Table 1. In Vitro Susceptibilities of Gatifloxin, Levofloxin, Ofloxacin, and Ciprofloxacin6-10

Abbreviations: MIC90, minimum inhibitory concentration at which 90% of isolates are inhibited; MSSA, methicillin-sensitive *Staphylococcus aureus.

†Responsible for more than 2% of postoperative endophthalmitis.1
‡Associated with endophthalmitis resulting from ocular trauma.2
§Most common causative organisms in bleb-associated endophthalmitis.11
¶Most common causative organisms in chronic postoperative endophthalmitis.12

The study was conducted with the approval of the Baylor College of Medicine (Houston, Tex) Institutional Review Board. Twenty-four adult patients aged 25 to 82 years (mean ± SD age, 63.7 ± 14.3 years) undergoing elective pars plana vitrectomy between September 2001 and May 2002 at the Cullen Eye Institute, Houston, were included in the study. Exclusion criteria included known sensitivity to fluoroquinolones, renal disease (serum creatinine level greater than 1.8 mg/dL [159.1 µmol/L]), use of any other antibiotics in the preceding 3 weeks, pregnancy or currently breastfeeding, current use of a class IA or III antiarrhythmic agent, fresh vitreous hemorrhage (less than 1 month old) as an indication for vitrectomy, or active endophthalmitis.

After informed consent was obtained, patients were asked to take a total of two 400-mg tablets of gatifloxin orally, 12 hours apart (loading dosage). Prospectively completed data forms were designed to include medical history, collection times of various samples, and concentrations of gatifloxin in serum, aqueous, and vitreous. Patients were asked to record on each of the 2 gatifloxin blister packs the exact time of oral administration. These packs were returned on the day of the operation. Aqueous, vitreous, and serum samples were obtained be-
fore infusion of any intravenous or intraocular irrigating solution to obtain pure samples. Approximately 8 to 10 mL of venous blood was collected less than 1 hour before surgery in the preoperative holding area. In the operative suite, approximately 0.1 mL of aqueous fluid was aspirated with a 30-gauge needle attached to a syringe through a paracentesis site in those patients with whom it was felt safe to do so (ie, pseudophakic patients or phakic patients with deep anterior chambers). Within 10 minutes, 0.2 to 0.3 mL of vitreous fluid was obtained by using a vitreous cutting device attached to a syringe via a short length of tubing. Aqueous and vitreous samples were immediately frozen at –20°C. The blood sample was centrifuged, and the serum collected from this was frozen as well. These samples were shipped with dry ice in appropriate packaging material to the Hartford Hospital Laboratory, Hartford, Conn. Gatifloxacin concentrations were determined in each of the samples using a previously described high-performance liquid chromatography technique.13 Serum, aqueous, and vitreous gatifloxacin concentrations were compared with already established in vitro MIC90 data.9,10 A t test was performed to determine if any significant differences existed between various subsets of patients, including diabetic vs nondiabetic patients and phakic status.

### RESULTS

Indications for operation in the 24 patients were as follows (Table 2): epiretinal membrane (14 patients), macular hole (5 patients), retinal detachment (3 patients), nonclearing vitreous hemorrhage (1 patient), and tractional retinal detachment secondary to proliferative diabetic retinopathy (1 patient).

Mean ± SD gatifloxacin concentrations in serum (n = 23), vitreous (n = 23), and aqueous (n = 11) were 5.14 ± 1.36 µg/mL, 1.34 ± 0.34 µg/mL, and 1.08 ± 0.54 µg/mL, respectively. Mean ± SD sampling times after oral administration of the second gatifloxacin tablet for serum, vitreous, and aqueous were 3.2 ± 1.0 hours, 4.0 ± 1.0 hours, and 3.9 ± 1.1 hours, respectively. The percentages of serum gatifloxacin concentration achieved in the vitreous and aqueous were 26.17% and 21.02%, respectively (Table 2).

Patient 16 was removed from the study because no aqueous specimen was collected and there was an insufficient vitreous sample volume to perform high-performance liquid chromatography. Although a serum gatifloxacin concentration was determined for this patient, it was not felt that it added any value to the study, and, therefore, this patient’s data were removed from any data analysis (Table 2).

Three of 23 patients were diabetic. The mean ± SD gatifloxacin concentrations in the serum and vitreous for these 3 patients were 6.18 ± 1.10 µg/mL and 1.23 ± 0.13 µg/mL, respectively. These levels were not significantly different from those of the 20 nondiabetic patients whose mean serum and vitreous concentrations were 5.49 ± 1.51 µg/mL and 1.36 ± 0.36 µg/mL, respectively (P = .16 and P = .54, respectively).

Eleven of 23 patients were phakic. The mean ± SD gatifloxacin concentrations in the serum, vitreous, and aqueous for these 11 patients were 5.30 ± 1.44 µg/mL, 1.23 ± 0.28 µg/mL, and 0.62 ± 0.25 µg/mL, respectively. These levels were not significantly different from those of the 1 aphakic and 11 pseudophakic patients whose mean serum, vitreous, and aqueous concentrations...
Endophthalmitis is one of the most serious complications of intraocular procedures or open-globe trauma. Systemic antibiotics have had an uncertain role in the prophylaxis or treatment of endophthalmitis because the EVS was unable to demonstrate any benefit with the use of intravenous antibiotics in postoperative infection. During the past 10 years, the results of several studies have indicated that fluoroquinolone antibiotics achieve significant concentrations in the vitreous after oral administration. Unfortunately, many of the older-generation fluoroquinolones achieved intravitreal levels that barely reached the MIC₉₀ against the pathogens most commonly responsible for postoperative, posttraumatic, and bleb-associated endophthalmitis. If one is to consider the use of a systemic antibiotic for the prophylaxis of, or as an adjunct in the treatment of, endophthalmitis, one must find a systemic antibiotic with the highest possible intravitreal penetration, as well as the lowest MIC₉₀ for the organisms of concern. We believe that gatifloxacin may represent a major advance in this regard.

After cataract extraction, bacterial endophthalmitis is most commonly caused by *Staphylococcus epidermidis* (70% of EVS isolates). This typically presents as a moderately severe infection 5 to 7 days postoperatively. Less commonly, 2 other forms of endophthalmitis can develop after cataract extraction. The first is a chronic, indolent endophthalmitis that presents several months postoperatively, usually caused by *Propionibacterium acnes*. A second, less-common form of postoperative endophthalmitis is an early, fulminant type that usually presents 2 to 4 days postoperatively and is caused by *Streptococcus* or *Staphylococcus* species as well as gram-negative organisms (most commonly *Proteus mirabilis*). In our study, vitreous levels of gatifloxacin were 5.4 times the MIC₉₀ for *Staphylococcus epidermidis*, 10.3 times the MIC₉₀ for *Staphylococcus aureus*, 2.7 times the MIC₉₀ for *Propionibacterium acnes*, 2.7 times the MIC₉₀ for *Streptococcus* species, and 5.4 times the MIC₉₀ for *Proteus mirabilis*. Gatifloxacin was unable to achieve intravitreal levels effective against *Enterococcus* or *Pseudomonas* species. Fortunately, these 2 organisms are only very rarely encountered in postoperative endophthalmitis.

The importance of finding a good bacterial endophthalmitis prophylaxis technique for cataract surgery was emphasized in a recent study by Ciulla et al. Performing a systematic review of the literature from 1966 to 2000 to assess the bacterial endophthalmitis prophylaxis tech-
in the aqueous and vitreous were several-fold higher than the MIC₉₀ for organisms that are most commonly associated with posttraumatic endophthalmitis (Table 1). In addition, previous studies suggest that intraocular penetration of systemic antibiotics may be higher in an eye that has sustained trauma, is infected, or is inflamed. This may be secondary to disruption of the blood-ocular barrier.²⁰,²¹

The guidelines set forth by the EVS regarding the treatment of postoperative endophthalmitis should not be translated to posttraumatic endophthalmitis.² The incidence of endophthalmitis from open-globe trauma is many times greater than after ocular surgical procedures. In addition, as many as 42% of cases from rural areas have more than 1 organism cultured; often, more virulent bacteria are isolated, compared with postoperative endophthalmitis. For example, Bacillus infections are rare in postoperative endophthalmitis but may occur with a frequency of 20% to 46% in posttraumatic cases.²² Bacillus species produce severe, rapidly progressive endophthalmitis. Therefore, in the setting of open-globe trauma, rapid administration of an oral antibiotic known to penetrate into the posterior segment may help prevent ocular damage secondary to infection. Based on our data, it appears that oral administration of gatifloxacin may be a promising choice for prophylaxis against endophthalmitis in open-globe injuries before and after surgical intervention.

Two groups have recently studied the fourth-generation fluoroquinolones for possible use in ophthalmology. Mather et al²² have described the fourth-generation fluoroquinolones as “new weapons in the arsenal of ophthalmic antibiotics.” They performed an in vitro study determining the differences in susceptibility patterns and potencies of second-, third-, and fourth-generation fluoroquinolones to 93 bacterial endophthalmitis isolates. They demonstrated that coagulase-negative staphylococci that were resistant to second-generation fluoroquinolones (eg, ciprofloxacin and ofloxacin) were statistically most susceptible to fourth-generation fluoroquinolones, specifically gatifloxacin and moxifloxacin. Additionally, Streptococcus viridans and Streptococcus pneumoniae were least susceptible to older-generation fluoroquinolones. Overall, fourth-generation fluoroquinolones retained equivalent potencies to gram-negative bacteria as compared with older-generation fluoroquinolones, such as levofloxacin and ciprofloxacin, while also demonstrating enhanced potencies for gram-positive bacteria.

In another recent study, García-Saenz et al²³ investigated the penetration of orally administered moxifloxacin into the human aqueous humor for potential use as a prophylactic agent against bacterial endophthalmitis in cataract surgery. They found that moxifloxacin achieved a mean aqueous concentration of 2.3±0.9 µg/mL; however, their reported MIC₉₀ for Staphylococcus epidermidis was 2.00 µg/mL. The concentration achieved is borderline for the most common causative organism in postoperative endophthalmitis. This is not the case with gatifloxacin because intraocular concentrations after oral administration were found to be several times higher than the MIC₉₀ for S epidermidis. Additionally, penetration of moxifloxacin into the vitreous was not investigated; therefore, no conclusions can be made regarding its use in open-globe trauma involving the posterior segment or its use as an adjuncive therapy for endophthalmitis treatment.

Gatifloxacin is very well tolerated, and most adverse reactions are described as mild in nature. The most common adverse reactions include nausea, vaginitis, diarrhea, headache, and dizziness. In our series, one patient complained of mild gastrointestinal discomfort, and another patient vomited 30 minutes after taking the second gatifloxacin dose. The concentrations of gatifloxacin in serum and vitreous in this patient were above the mean level for the rest of the group. The dosage of gatifloxacin recommended by Bristol-Myers Squibb Co (New York, NY) is one 400-mg tablet every 24 hours. In our study design, we chose to use a loading dose of one 400-mg tablet twice a day before sample collection to achieve peak plasma concentrations more rapidly. In the appropriate clinical setting, one may consider using a loading dose of gatifloxacin followed by one 400-mg tablet a day thereafter. Because gatifloxacin is eliminated primarily by renal excretion, a dosage modification is recommended for patients with a creatinine clearance of less than 40 mL/min (<0.07 mL/s). Gatifloxacin should be avoided in patients receiving a class IA (quinidine or procainamide) or class III (amiodarone or sotalol) arrhythmogenic agent because gatifloxacin may have the potential to prolong the QTc interval of the electrocardiogram in some patients.

In summary, orally administered gatifloxacin achieves therapeutic aqueous and vitreous levels in the noninflamed human eye, and the activity spectrum appears to appropriately encompass the bacterial species most often involved in the various causes of endophthalmitis. Because of its broad spectrum of coverage, low MIC₉₀ levels for the organisms of concern, good tolerability, and excellent bioavailability with oral administration, gatifloxacin may represent a major advance in the prophylaxis or treatment of postoperative, posttraumatic, and bleb-associated bacterial endophthalmitis.

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REFERENCES

3. Endophthalmitis Vitrectomy Study Group. Results of the Endophthalmitis Vi-


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