Vitreous and Aqueous Penetration of Orally Administered Moxifloxacin in Humans

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**Objective:** To investigate intraocular penetration of moxifloxacin hydrochloride after oral administration.

**Methods:** Prospective study of 15 patients scheduled for vitrectomy between September and November 2004 at the Barnes Retina Institute, St Louis, Mo. Aqueous, vitreous, and serum samples were analyzed from 15 patients after oral administration of 2 tablets containing 400 mg of moxifloxacin. Assays were performed using high-performance liquid chromatography.

**Results:** The mean ± SD moxifloxacin concentrations in plasma (n=15), vitreous (n=13), and aqueous (n=13) samples were 3.56 ± 1.31 µg/mL, 1.34 ± 0.66 µg/mL, and 1.38 ± 0.80 µg/mL, respectively. Mean ± SD sampling times after oral administration of the second moxifloxacin tablet for plasma, vitreous, and aqueous were 2.9 ± 0.81 hours, 3.77 ± 0.92 hours, and 3.71 ± 0.89 hours, respectively. The percentages of plasma moxifloxacin concentration in the vitreous and aqueous were 37.6% and 44.3%, respectively. Minimal inhibitory concentrations against 90% levels were exceeded against a wide spectrum of gram-positive and gram-negative pathogens in the vitreous and aqueous.

**Conclusions:** Moxifloxacin has a spectrum of coverage that encompasses the most common organisms in endophthalmitis. The pharmacokinetic findings of this investigation reveal that orally administered moxifloxacin achieves therapeutic levels in the noninflamed eye. Because of their broad spectrum of coverage, low minimal inhibitory concentration against 90% levels, good tolerability, and excellent oral bioavailability, fourth-generation fluoroquinolones may represent a major advance for managing posterior segment infections.


**Bacterial Endophthalmitis** is one of the most serious complications of intraocular surgery and open-globe injuries. The microbiologic 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 (94.2%) of confirmed growth isolates 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 those 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 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 use of these new-generation agents in the treatment of endophthalmitis needs to be revisited. During the past decade, there is evidence in the literature that agents in the fluoroquinolone class of antibiotics are able to achieve effective concentrations in the vitreous after oral administration (Table 1).⁹,¹³

Moxifloxacin hydrochloride (Avelox; Bayer Pharmaceuticals Corp, West Haven, Conn) and gatifloxacin (Tequin; Bristol-Myers Squibb Co, Princeton, N J) are 2 newly released fourth-generation fluoroquinolones. They have a spectrum of activity encompassing gram-positive and gram-negative bacteria including *S epidermidis*, *S aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Escherichia coli*, *Bacillus cereus*, *Neis-
seria gonorrhoeae, and Proteus mirabilis. Additionally, the fourth-generation fluoroquinolones have good activity against atypical pathogens such as Mycoplasma, Legionella, and Chlamydia species, as well as the anaerobic organism Propionibacterium acnes.6-8 New-generation fluoroquinolones such as moxifloxacin, gatifloxacin, and trovafloxacin represent advances in the evolution of this antibiotic class. The more favorable pharmacokinetic properties of the previously mentioned agents are a result of the alterations of the original fluoroquinolone moiety. For example, moxifloxacin (Figure 1) and gatifloxacin possess an 8-methoxy side chain, which may be responsible for their enhanced activity against gram-positive pathogens, atypical pathogens, and anaerobes while retaining potencies and broad-spectrum coverage against gram-negative organisms compared with older-generation fluoroquinolones. Each of the fourth-generation fluoroquinolones has its own subtle strengths shown by in vitro testing,6-8 however, further studies will reveal if these in vitro differences are clinically relevant (Table 1).

We chose to study the intraocular penetration of orally administered moxifloxacin in humans for 2 reasons. First, we previously investigated the intraocular penetration of orally administered gatifloxacin in humans and found that this fourth-generation fluoroquinolone penetrated quite well into the vitreous and aqueous; therefore, we thought it would be valuable to learn how the intraocular penetration pharmacokinetics of moxifloxacin compared with that of gatifloxacin.6,13 Second, our group has recently shown that topically administered moxifloxacin can achieve relatively high concentrations in the aqueous.16 Therefore, we thought that it would be of interest to compare the aqueous penetration of moxifloxacin after oral vs after topical administration.

The study was carried out with the approval of the institutional review board of Washington University School of Medicine, St Louis, Mo. Fifteen adult patients, ranging in age from 49 to 81 years (mean ± SD = 65.9 ± 8.7 years), undergoing primary elective pars plana vitrectomy surgery between September 2004 and November 2004 at the Barnes Retina Institute were included in the study. Exclusion criteria included the following: (1) known sensitivity to fluoroquinolones, (2) renal disease (creatinine level greater than 1.8 mg/dL), (3) use of any other antibiotic(s) in the preceding 3 weeks, (4) pregnancy or currently breastfeeding, (5) current use of a class IA or III antiarrhythmic agent, (6) fresh vitreous hemorrhage as indication for vitrectomy (≤ 1 month old), or (7) active endophthalmitis.

After informed consent was obtained, patients were asked to take two 400-mg moxifloxacin tablets orally—1 tablet the evening prior to surgery and 1 tablet approximately 3 hours prior to surgery. Prospectively completed data forms were designed to in-
include medical history, collection times of various samples, and concentrations of moxifloxacin in plasma, aqueous, and vitreous. Aqueous, vitreous, and blood samples were obtained before 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 prior to surgery in the preoperative holding area. In the operative suite, approximately 0.1 mL of aqueous fluid was aspirated through a paracentesis site using a 30-gauge needle attached to a syringe. Within 3 minutes of collecting the aqueous sample, 0.2 to 0.3 mL of vitreous fluid was obtained using a vitreous cutting device attached to a syringe via a short length of tubing. Aqueous and vitreous samples were immediately frozen at −83°C. The blood sample was centrifuged and the plasma collected from this was frozen as well. These samples were shipped with dry ice in appropriate packaging material to the University of Houston College of Pharmacy, Houston, Tex. Moxifloxacin concentrations were determined in each of the samples using a previously described high-performance liquid chromatography (HPLC) technique.

Aqueous, vitreous, and serum moxifloxacin concentrations were compared with already established in vitro minimal inhibitory concentration against 90% (MIC90) data. 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.

Indications for operation in the 15 patients were as follows (Table 2): epiretinal membrane (9 patients), macular hole (2), tractional retinal detachment (2), branch retinal vein occlusion (1), and nonclearing vitreous hemorrhage (1).

Mean ± SD moxifloxacin concentrations in plasma (n = 15), vitreous (n = 13), and aqueous (n = 13) were 3.56 ± 1.31 µg/mL, 1.34 ± 0.66 µg/mL, and 1.58 ± 0.80 µg/mL, respectively. Mean ± SD sampling times after oral administration of the second moxifloxacin tablet for plasma, vitreous, and aqueous were 2.94 ± 0.81 hours, 3.77 ± 0.92 hours, and 3.71 ± 0.89 hours, respectively. The percentages of plasma moxifloxacin concentration achieved in the vitreous and aqueous were 37.5% and 44.3%, respectively (Table 2). Positive correlations were observed between plasma and vitreous concentrations of moxifloxacin (r = 0.70) (Figure 2). A similar correlation was also observed between plasma and aqueous concentrations of moxifloxacin (r = 0.76) (Figure 3).

Table 2. Patient Characteristics and Intraocular Moxifloxacin Concentrations After Oral Administration

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y</th>
<th>Indication for Surgery</th>
<th>Phakic Status</th>
<th>Hours From Second Dose to Vitreous Sample</th>
<th>Serum, µg/mL</th>
<th>Aqueous, µg/mL</th>
<th>Vitreous, µg/mL</th>
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<tr>
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<td>TRD</td>
<td>Phakic</td>
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<td>1.4</td>
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<td>4</td>
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<tr>
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<td>1.2</td>
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<td>6</td>
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<tr>
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<td>*</td>
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</tbody>
</table>

Abbreviations: BRVO, branch retinal vein occlusion; ERM, epiretinal membrane; MH, macular hole; NCVH, nonclearing vitreous hemorrhage; TRD, tractional retinal detachment.

*Not detected by high-performance liquid chromatography presumably owing to insufficient sample volume or low concentration.

Figure 2. Moxifloxacin levels obtained in the plasma and vitreous (r = 0.70).
Five of the 15 patients were pseudophakic. The mean±SD moxifloxacin concentration in the plasma, vitreous, and aqueous for these 5 patients were 4.18±1.61 µg/mL, 1.33±0.99 µg/mL, and 1.88±1.11 µg/mL, respectively. These levels were not significantly different from those of the 10 phakic patients whose serum, vitreous, and aqueous concentrations±SD were 3.25±1.09 µg/mL, 1.34±0.53 µg/mL, and 1.45±0.67 µg/mL, respectively (P=.20, P=.97, and P=.40, respectively).

No ocular or systemic adverse events occurred as a result of participation in this study.

**COMMENT**

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 management of endophthalmitis as the EVS was unable to show any visual benefit with the use of intravenous antibiotics in postoperative infection. During the past 10 years, there have been several studies indicating 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. Most recently, it has also been reported that gatifloxacin, a fourth-generation fluoroquinolone similar to moxifloxacin, could achieve therapeutic intracocular levels after oral administration (Table 1). If we are to consider the use of a systemic antibiotic for prophylaxis or as an adjunct in endophthalmitis management, we must find a systemic antibiotic with the highest possible intravitreal penetration, as well as the lowest MIC90 for the organisms of concern. The fourth-generation fluoroquinolones (ie, moxifloxacin and gatifloxacin) may represent a major advance in this regard.

One goal of performing this investigation was to learn how the intraocular penetration pharmacokinetics of moxifloxacin compared with gatifloxacin after oral administration. Oral administration of gatifloxacin in humans can achieve plasma, vitreous, and aqueous concentrations±SD of 5.14±1.36 µg/mL, 1.34±0.34 µg/
of their broad spectrum of coverage, low MIC₉₀ levels bacterial species involved in endophthalmitis. Because the dosing regimen of each investigated fluoroquinolone was different (except for moxifloxacin and gatifloxacin). The intent, however, is to provide a summary of several fluoroquinolone penetration studies. Given the study design of these types of investigations, it is difficult to precisely determine if samples are being obtained during drug peak or trough levels. Given these limitations of Table 1, several important findings are apparent. Compared with the older-generation fluoroquinolones, moxifloxacin and gatifloxacin have fewer gaps in coverage for the organisms most commonly implicated in bacterial endophthalmitis. Additionally, vitreous concentrations of these 2 agents exceed their respective MIC₉₀ levels by the greatest margin (inhibitory quotient). Levofloxacin, a third-generation fluoroquinolone, is a fair alternative in terms of high vitreous penetration and low MIC₉₀ levels. It should be noted that moxifloxacin MIC₉₀ values are half of gatifloxacin for gram-positive organisms. There may be a theoretical advantage of moxifloxacin over gatifloxacin for gram-positive organisms since vitreous penetration of the 2 agents is very similar. Further studies will reveal if these in vitro differences are clinically relevant.

Previous studies have shown that orally administered moxifloxacin can achieve therapeutic levels in the noninflamed human eye. Garcia-Saenz et al¹⁸ investigated the penetration of orally administered moxifloxacin into the human aqueous humor for potential use as a prophylactic agent in cataract surgery. They reported that moxifloxacin achieved a mean±SD aqueous concentration of 2.33±0.85 µg/mL. Unfortunately, penetration of moxifloxacin into the vitreous was not investigated in their study. In our study, we found aqueous levels±SD of moxifloxacin to be slightly lower at 1.58±0.80 µg/mL.

Moxifloxacin is 50% bound to serum proteins and 90% of the drug is bioavailable after oral administration. Peak plasma concentrations occur approximately 1 hour after oral dosing. Dosage modification is not necessary in patients with renal disease or in patients with mild to moderate hepatic insufficiency. Moxifloxacin is very well tolerated with the majority of adverse reactions being described as mild in nature. These most commonly include nausea, diarrhea, and dizziness. No ocular or systemic adverse events were reported in our study. The Food and Drug Administration approved dosage of moxifloxacin is 400 mg once daily. As with other fourth-generation fluoroquinolones, moxifloxacin should be avoided in patients receiving a class IA (quinidine or procainamide) or class III (amiodarone or sotalol) antiarrhythmic agent because it may have the potential to prolong the QTc interval of the electrocardiogram in some patients.

Orally administered moxifloxacin achieves therapeutic aqueous and vitreous levels in the noninflamed human eye and the activity spectrum appears to encompass appropriately the most frequently encountered bacterial species involved in endophthalmitis. Because of their broad spectrum of coverage, low MIC₉₀ levels for the organisms of concern, good tolerability, and excellent bioavailability with oral administration, fourth-generation fluoroquinolones may represent a major advance in the management of posterior segment infection. It is unknown whether the use of oral fourth-generation fluoroquinolones will reduce the rate of postoperative endophthalmitis but these medications could be considered as prophylaxis in high-risk patients such as those with relative immunocompromise, vitreous loss during cataract surgery, or patients with chronic blepharitis or lacrimal drainage abnormalities.

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REFERENCES