Penetration Pharmacokinetics of Topically Administered 0.5% Moxifloxacin Ophthalmic Solution in Human Aqueous and Vitreous

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Objective: To investigate the penetration of 0.5% moxifloxacin hydrochloride into the aqueous and vitreous after topical administration in humans.

Methods: A prospective, nonrandomized study of 20 patients scheduled for vitrectomy surgery between September 1 and December 31, 2003. Aqueous and vitreous samples were obtained and analyzed after topical administration of 0.5% moxifloxacin hydrochloride, every 2 hours (q2h) or every 6 hours (q6h), for 3 days before surgery. Assays were performed using high-performance liquid chromatography.

Results: Mean±SD moxifloxacin concentrations in the q2h group for the aqueous (n=9) and vitreous (n=10) were 2.28±1.23 and 0.11±0.05 µg/mL, respectively. Mean±SD moxifloxacin concentrations in the q6h group for the aqueous (n=10) and vitreous (n=9) were 0.88±0.88 and 0.06±0.06 µg/mL, respectively. The minimum inhibitory concentration for 90% of isolates (MIC90) was far exceeded in the aqueous for a wide spectrum of key pathogens, whereas it was not exceeded in the vitreous for several organisms. However, the minimum inhibitory concentration for 50% of the isolates was exceeded in the q2h vitreous group for Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Bacillus cereus, and other gram-negative pathogens.

Conclusions: The Endophthalmitis Vitrectomy Study revealed that 94.2% of isolates from postoperative endophthalmitis are gram-positive pathogens. Moxifloxacin has a spectrum of coverage that appropriately encompasses the most common organisms in endophthalmitis. The pharmacokinetic findings of this investigation show that relatively high aqueous levels can be achieved after topical administration. Further studies will help define the precise role of 0.5% moxifloxacin ophthalmic solution in the treatment of or prophylaxis against intraocular infections.


Bacterial endophthalmitis is one of the most serious complications after intraocular surgery. The microbiologic spectrum of infecting organisms in postoperative endophthalmitis was investigated in the Endophthalmitis Vitrectomy Study. The Endophthalmitis Vitrectomy Study represents the largest number of postoperative endophthalmitis cases from which bacteriologic data were prospectively obtained. Most (94.2%) of the 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. The spectrum of infecting organisms in posttraumatic endophthalmitis differs from that of postoperative endophthalmitis, with Bacillus species playing a more prominent role.

Numerous strategies have been described to try to decrease the incidence of postoperative endophthalmitis. Unfortunately, it is difficult to demonstrate superiority of one prophylactic strategy over another due to the low occurrence rate of postoperative infection. A commonly used prophylactic technique is the administration of topical antimicrobials, typically a fluoroquinolone, during the perioperative period. The choice of antibiotic can be difficult, as there are many different aspects by which the efficacy of an antibiotic is determined. One of these aspects is bioavailability. The bioavailability of an antibiotic determines its ability to penetrate the tissues of concern and reach bac-
teria. To be bioavailable, a topical ophthalmic antibiotic must have a high rate of penetration and good solubility. The purpose of this investigation was to determine the penetration pharmacokinetics of topically applied 0.5% moxifloxacin hydrochloride ophthalmic solution into the human aqueous and vitreous.

Two newly released fourth-generation fluoroquinolones are 0.5% moxifloxacin (Vigamox; Alcon Laboratories, Inc, Ft Worth, Tex) and 0.3% gatifloxacin (Zymar; Allergan, Inc, Irvine, Calif). They have a spectrum of activity encompassing gram-positive and gram-negative bacteria, including Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae, Escherichia coli, Bacillus cereus, Neisseria gonorrhoeae, and Proteus mirabilis. In addition, 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. New-generation fluoroquinolones such as moxifloxacin, gatifloxacin, grepafloxacin hydrochloride, and trovafloxacin mesylate 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, moxifloxacin and gatifloxacin possess an 8-methoxy side chain (Figure 1), 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 comparable to those of older-generation fluoroquinolones. Each of the fourth-generation fluoroquinolones has its own subtle strengths in results of in vitro testing, however, further studies will show whether these in vitro differences are clinically relevant.

Indications for operation in the 20 patients were as follows (Table 2): macular hole (n=8), epiretinal membrane (n=7), branch retinal vein occlusion (n=2), central retinal vein occlusion (n=1), chronic cystoid macular edema (n=1), and intraocular lens exchange (n=1).

Mean ± SD moxifloxacin concentrations in the q2h group for aqueous (n=9) and vitreous (n=10) were 1.8 mg/dL [159.1 µmol/L] and 0.2 mg/dL [23.8 µmol/L], respectively. These results are comparable with already established in vitro MIC90 data. Aqueous and vitreous moxifloxacin concentrations were determined in each of the samples using a previously described high-performance liquid chromatography technique. Aqueous and vitreous moxifloxacin concentrations were compared with already established in vitro MIC90 data.

We performed this study with the approval of the Washington University School of Medicine Institutional Review Board, St Louis, Mo. Twenty adult patients, aged 35 to 86 years (mean±SD age, 67.9±8.5 years), undergoing elective pars plana vitrectomy between September 1 and December 31, 2003, at the Barnes Retina Institute, St Louis, were included in the study. Exclusion criteria included known sensitivity to fluoroquinolones, renal disease (creatinine level >1.8 mg/dL [>159.1 µmol/L]), use of any other antibiotic(s) in the preceding 3 weeks, pregnancy or current breast-feeding, current use of a class IA or class III antiarrhythmic agent, previously vitrectomized eyes, fresh vitreous hemorrhage as indication for vitrectomy (<1 month), or active endophthalmitis.

After informed consent was obtained, patients were asked to self-administer topical 0.5% moxifloxacin ophthalmic solution for 3 days before surgery in the eye scheduled for operation. The first 10 patients received 1 drop of moxifloxacin hydrochloride every 2 hours (q2h group), and the second 10 patients received 1 drop of moxifloxacin hydrochloride every 6 hours (q6h group). On the day of surgery, the patients continued dosages as during the 3 days before surgery. In addition, topical 0.3% moxifloxacin hydrochloride was administered to all eyes, 5 to 10 minutes preoperatively as a single drop. Prospectively completed data forms were designed to include medical history, frequency of moxifloxacin administration, and concentrations of moxifloxacin in the aqueous and vitreous.

Patients were asked to return their bottle of moxifloxacin on the day of surgery to determine compliance with their assigned dosage regimen. Aqueous and vitreous samples were obtained before infusion of any intraocular irrigating solution to obtain pure samples 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 10 minutes, 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. These samples were shipped with dry ice in appropriately packaged 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 technique. Aqueous and vitreous moxifloxacin concentrations were compared with already established in vitro MIC90 data.

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![Figure 1. Chemical structure of moxifloxacin hydrochloride (C21H24FN3O4 Cl– and H).](https://example.com/moxifloxacin-structure.png)
2.28 ± 1.23 and 0.11 ± 0.05 µg/mL, respectively. Mean ± SD moxifloxacin concentrations in the q6h group for aqueous (n = 10) and vitreous (n = 9) were 0.88 ± 0.88 and 0.06 ± 0.06 µg/mL, respectively. Although the mean aqueous concentration of moxifloxacin was significantly different between the q2h and q6h groups, this was not the
After cataract extraction, bacterial endophthalmitis is most commonly caused by Staphylococcus epidermidis (70% of Endophthalmitis Vitrectomy Study isolates). This typically is seen as a moderately severe infection 5 to 7 days after surgery. Less commonly, 2 other forms of endophthalmitis can take place after cataract extraction. The first is a chronic, indolent endophthalmitis that manifests several months after surgery, usually caused by Propionibacterium acnes. A second, less common form of postoperative endophthalmitis is an early, fulminant type that usually manifests 2 to 4 days after surgery and is caused by streptococcal or staphylococcal species or by gram-negative organisms (most commonly Proteus mirabilis). One reason we chose to study the intraocular penetration of moxifloxacin is that the MIC$_{90}$ of moxifloxacin against the pathogens most commonly responsible for postoperative, posttraumatic, and bleb-associated endophthalmitis were generally lower than those for the other fluoroquinolone antibiotics we surveyed (Table 1).

In our study, MIC$_{90}$ values were far exceeded in the aqueous for a wide spectrum of pathogens in both the q2h and q6h groups, including Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus pneumoniae, Strep-tococcus pyogenes, Propionibacterium acnes, Haemophilus influenzae, Escherichia coli, Bacillus cereus, Neisseria gonorrhoeae, Proteus mirabilis, and other organisms. Concentration of moxifloxacin in the vitreous did not exceed the MIC$_{90}$ for several organisms; however, in the q2h group, the MIC$_{50}$ was exceeded for Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Bacillus cereus, and other gram-negative pathogens. Moxifloxacin was unable to achieve intraocular levels effective against Pseudomonas species; furthermore, the MIC$_{90}$ for Enterococcus species was exceeded only in the q2h aqueous group. Although Pseudomonas and Enterococcus species are very rarely encountered in postoperative endophthalmitis, 0.5% moxifloxacin may not be a suitable treatment choice for intraocular infections known to be caused by these organisms.

Another reason we chose to study the intraocular penetration of 0.5% moxifloxacin is that older-generation fluoroquinolones such as 0.5% levofloxacin, 0.3% ofloxacin, and 0.3% ciprofloxacin have been shown to achieve effective levels in the aqueous, but not the vitreous, after topical administration in the noninflamed human eye. Table 1 compares the mean intraocular concentrations achieved by several other fluoroquinolones and their corresponding MIC$_{90}$ against the pathogens most commonly responsible for bacterial endophthalmitis. The intent of Table 1 is not to directly compare the intraocular penetration of the different agents, as the dosage frequency of each investigated fluoroquinolone was different. In addition, given the study design of these types of investigations, it is difficult to determine precisely whether samples are being obtained during drug peak or trough levels. Given these limitations of Table 1, several important findings are apparent. First, no topically administered fluoroquinolone investigated achieves intravitreal...

**Figure 2.** Mean intraocular moxifloxacin concentrations achieved after topical administration. q2h indicates drug administered every 2 hours; q6h, drug administered every 6 hours.

**COMMENT**

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levels sufficient to exceed the MIC$_{90}$ for the organisms that most commonly cause bacterial endophthalmitis. Intravitreal concentration of 0.5% moxifloxacin q2h comes very close to the MIC$_{90}$ for *Staphylococcus epidermidis* (the most common causative organism in bacterial endophthalmitis). This concentration may be sufficient for prophylaxis, but not for treatment of active infection. Previous studies suggest that intraocular penetration of systemic antibiotics may be higher in an eye that has sustained trauma, is infected, or is inflamed (ie, the postoperative eye). This may be due to disruption of the blood-ocular barrier, and it is conceivable that the intravitreal penetration of topically administered moxifloxacin may be high enough to exceed the MIC$_{90}$ level for *Staphylococcus epidermidis* and several other organisms of concern in the postoperative setting. Another finding that becomes apparent on reviewing Table 1 is that compared with older-generation fluoroquinolones, moxifloxacin concentration achieved in the aqueous has fewer gaps in coverage for the organisms most commonly implicated in bacterial endophthalmitis.

Previous studies have demonstrated that orally administered fourth-generation fluoroquinolones can achieve therapeutic levels in the noninflamed human eye. Garcia-Saenz and associates investigated the penetration of orally administered moxifloxacin into the human aqueous humor for potential use as a prophylactic agent in cataract surgery. They found 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. Gati-floxacin, another fourth-generation fluoroquinolone, has been shown to achieve mean±SD levels as high as 1.34±0.34 and 1.08±0.54 µg/mL in the human vitreous and aqueous, respectively, after oral administration. Although oral administration of a fourth-generation fluoroquinolone results in intravitreal concentrations several-fold higher than those after topical administration, an interesting finding is that 0.5% moxifloxacin topically administered q2h can achieve aqueous levels comparable to those after oral administration. Therefore, topically administered 0.5% moxifloxacin may be useful in the management of infections limited to the anterior segment. One example of such an infection is localized conjunctival filtering bleb infection, or “blebitis.” The most common causative organisms in delayed-onset bleb-associated endophthalmitis are streptococcal and staphylococcal species. *Haemophilus influenzae* is also commonly encountered in this condition. The concentration of moxifloxacin achieved after topical administration in the aqueous is several-fold higher than the MIC$_{90}$ for these organisms. If blebitis progresses to bleb-associated endophthalmitis, one may consider the addition of an orally administered fourth-generation fluoroquinolone to the current management of bleb-associated endophthalmitis.

The importance of finding a good bacterial endophthalmitis prophylaxis technique for cataract surgery was emphasized in a recent study by Ciulla and colleagues. After a systematic review of the literature from 1966 to 2000 to assess commonly used bacterial endophthalmitis prophylaxis techniques with cataract surgery, they found that only a preoperative povidone-iodine preparation could receive a moderate clinical recommendation (moderately important to clinical outcome). All other measures received the lowest clinical recommendation level, including topical antibiotics (possibly relevant but not definitely related to clinical outcome). Furthermore, the study showed that no prophylactic technique in the literature could receive the highest of 3 possible clinical recommendations (crucial to clinical outcome). Unfortunately, at the time of the review by Ciulla et al, the fourth-generation ophthalmic preparations (0.5% moxifloxacin and 0.3% gatifloxacin) were not available for clinical use and therefore were not included. Although the purpose of our investigation was not to precisely define the role of moxifloxacin in treating intraocular infection, given our results, one could postulate that the use of topical 0.5% moxifloxacin before and after surgery as prophylaxis against endophthalmitis is effective. Ciulla et al estimate that there are nearly 2000 cases of endophthalmitis after cataract surgery alone annually in the United States. If all intraocular surgeries and cases of open-globe trauma were included, this number would be far greater. Therefore, the importance of finding good prophylaxis against postoperative endophthalmitis cannot be underestimated.

Topically administered 0.5% moxifloxacin is very well tolerated, with most adverse reactions described as mild. These most commonly include dry eye, ocular hyperemia, ocular discomfort, and ocular itching. In our series, only 1 patient from the q2h group complained of mild ocular discomfort. No patients in our series complained of nonocular adverse events. The dosage of 0.5% moxifloxacin recommended by Alcon Laboratories, Inc, is 1 drop 3 times daily (bacterial conjunctivitis indication). In our study design, we chose to use q2h and q6h regimens. Our rationale for the q2h dosage was to determine whether intensive topical therapy could be used to obtain therapeutic levels in the vitreous. The q6h dosage schedule was included in the study, as this is a commonly used regimen for cataract surgery prophylaxis. After calculating the number of drops that were self-administered, patient compliance in both groups was considered excellent (Table 2). As expected, there was more varied compliance in the q2h group, given the difficulty of self-administering drops throughout the night. Although not precisely known, one may expect higher intraocular moxifloxacin concentrations with more stringent patient compliance.

Given the results of this study, several future investigations may be useful. Studies are currently under way at our institution investigating various methods of moxifloxacin drug delivery. One such study uses a novel dissolving cross-linked corneal collagen shield delivery device impregnated with moxifloxacin. The 0.5% moxifloxacin preparation is unique in that it is free of preservatives, specifically benzalkonium chloride. The lack of this preservative is valuable when using a collagen shield delivery device, as there is a theoretical risk of preservatives causing corneal damage after sustained drug delivery. Another study that may be valuable is an investigation of the intraocular penetration of topically administered 0.3% gatifloxacin to determine whether...
higher intraocular concentrations can be achieved with this other fourth-generation fluoroquinolone.

In summary, moxifloxacin has a spectrum of coverage that appropriately encompasses the most common causative organisms in endophthalmitis. The pharmacokinetic findings of this investigation show that topically administered 0.5% moxifloxacin can achieve relatively high aqueous concentrations. Although vitreous concentrations are lower, the levels achieved may be adequate for prophylaxis, as the MIC50 is exceeded for many key bacterial pathogens in the q2h group. It is also conceivable that intravitreal levels of moxifloxacin may be higher in an eye that has undergone surgery. Future studies will be needed to precisely define the role of topically administered 0.5% moxifloxacin in the treatment of or prophylaxis against intraocular infections.

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REFERENCES