Clinical Ophthalmology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Pharmacokinetics and aqueous humor penetration of levofloxacin 1.5% and moxifloxacin 0.5% in patients undergoing cataract surgery

This article was published in the following Dove Press journal:
Clinical Ophthalmology
2 May 2016
Number of times this article has been viewed

Frank A Bucci Jr
Ines Teuma Nguimfack
Angel T Fluet

Bucci Laser Vision Institute, Wilkes-Barre, PA, USA

Purpose: The objective of this study was to compare the pharmacokinetics of levofloxacin 1.5% and moxifloxacin hydrochloride 0.5% ophthalmic solutions in aqueous humor after multiple doses prior to cataract surgery.

Methods: Ninety-eight eyes underwent cataract surgery and met the requirements of PK analysis. Eligible eyes were randomly assigned in a 1:1 ratio to receive levofloxacin or moxifloxacin prior to cataract surgery and were randomized into one of four sampling time points (ie, 1, 2, 4, and 6 hour post-last dose). Randomization was investigator and laboratory-masked. Three days prior to cataract surgery, each patient instilled one drop of the assigned study medication into the operative eye four times daily. One aqueous humor specimen was collected from the eye at the randomized time point. Aqueous humor specimens were assayed for drug concentration using a validated liquid chromatography and tandem mass spectrometer.

Results: Concentrations of the drug in the aqueous humor, as described by mean C_{max} and pooled AUC_{0-6} values, were greater for levofloxacin than moxifloxacin (C_{max}: 1.43, 0.87 µg/ml, respectively, P=0.008; AUC_{0-6} 6.1, 3.8 µg·min/ml, $P<0.001$ respectively). No treatment-emergent adverse events were reported.

Conclusion: Significantly greater drug exposures were attained in aqueous humor following the administration of levofloxacin 1.5% than moxifloxacin 0.5% ophthalmic solution. Achieving considerable higher drug concentration in the aqueous humor with levofloxacin 1.5% may demonstrate a greater potential for bacterial eradication.

Keywords: concentration, endophthalmitis, antibiotics, phacoemulsification, prophylaxis, fluoroquinolone

Introduction

The primary concern of ophthalmic practitioners and surgeons is the preservation of their patients' sight. Microbial keratitis and endophthalmitis can present a substantial risk to vision and treatment must be tailored accordingly. Risk factors of microbial keratitis and endophthalmitis include contact lens wear, ocular surface disease, ocular trauma, and intraocular surgery. Corneal scarring resulting from the host immune response can also threaten sight.[1] Therefore, clinical presentation of microbial keratitis requires aggressive treatment to eliminate infection and limit sight-threatening sequelae. Prophylaxis of endophthalmitis and effective treatment of microbial keratitis by an ophthalmic antimicrobial agent is contingent upon its ability to penetrate the cornea and aqueous.[2] Knowledge of the pharmacokinetics and pharmacodynamics of topical ophthalmic antibiotics in aqueous humor demonstrates the potential for the drugs to penetrate the corneal epithelium.

Correspondence: Frank A Bucci Jr
Bucci Laser Vision Institute, 158 Wilkes Barre Township Blvd, Wilkes Barre, PA 18702, USA
Email buccivision@aol.com

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/OPTH.S91286

Fluoroquinolone antimicrobial agents, like levofloxacin and moxifloxacin, have in vitro activity against the bacterial pathogens that threaten the health of the eye.[3] Levofloxacin ophthalmic solution 1.5% and moxifloxacin 0.5% are commercial compounds and have been approved in the United States for bacterial keratitis and bacterial conjunctivitis.

Moxifloxacin 0.5% is manufactured as Vigamox by Alcon, (Alcon Laboratories, Inc., Fort Worth, TX, USA). Levofloxacin 1.5% was originally manufactured by Santen, (Emeryville, CA, USA) and later Johnson and Johnson (New Brunswick, NJ, USA) but is currently distributed by a number of international pharmaceutical companies such as Centaur Pharmaceuticals (Mumbai, India), Incepta Pharmaceuticals (Dhaka, Bangladesh), and Entod Pharmaceuticals (Mumbai, India). These agents both have a dual mechanism of action that involves the inhibition of bacterial topoisomerase IV and DNA gyrase.[4] Consequently, they are less likely to produce resistant organisms because two simultaneous mutations are required to establish resistance.[4] Both drugs have very similar in vitro susceptibility profiles as documented in a nationwide longitudinal surveillance program that included longitudinal data from archived ocular isolates dating back to 2000.[3]

For an antimicrobial agent to demonstrate efficacy in vivo, it must attain concentrations in the target site of both sufficient magnitude and duration of time in order to eradicate bacteria. Measures of predicted antimicrobial efficacy for fluoroquinolones include pharmacokinetic–pharmacodynamic (PK–PD) measures denoting concentration effects relative to pathogen susceptibility.[5,6] Herein, we describe a study comparing the pharmacokinetics in aqueous humor of levofloxacin 1.5% and moxifloxacin 0.5% ophthalmic solutions after instillation of multiple drops into the operative eye of patients undergoing cataract surgery.

Methods

Study design

This was a two-visit, randomized, single-center, single-masked, active-comparator, parallel-group study to compare drug concentrations in aqueous humor following topical ocular instillation of levofloxacin 1.5% or moxifloxacin hydrochloride 0.5% ophthalmic solutions in subjects undergoing cataract surgery. At visit 1 (day 1–14) subjects' eyes were enrolled and randomized to a 1:1 ratio into each treatment arm. Qualified eyes were further randomized into one of four subgroups, which specified the time between the last drop of study medication and the time of aqueous humor sample collection (ie, 1-, 2-, 4-, and 6-hour subgroups).

Patients and treatment

Male and female subjects aged 18 years or older who were planning to undergo elective phacoemulsification with intraocular lens implantation for the treatment of cataract(s) and who met all the inclusion and none of the exclusion criteria at the screening visit were included in this study. A written informed consent and HIPAA form, were signed and collected from each patient. This study was conducted in accordance with International Conference on Harmonization guidelines on Good Clinical Practice and local regulations and was approved by the Great Lakes institutional review board.

Demographic information, medical and medication history were obtained from each patient. For 3 days prior to the day of cataract surgery, subjects instilled one drop of study medication into their operative eye four times daily (at 8 am, 12 pm, 4 pm, and 8 pm). On the day of surgery (visit 2, day 4), patients who were randomized to the 1- and 2-hour subgroups received their final drop of study medication administered by study personnel at the study site, while patients who were randomized to the 4- and 6-hour subgroups self-administered their last drop of study medication while speaking with the study staff on the telephone on the day of surgery. Both the surgeon who collected the aqueous humor samples and the laboratory personnel who performed the concentration analysis were masked to the medication and the subgroup assignment of the patients.

Immediately prior to beginning the cataract surgery (±5 minutes of planned sampling time), the surgeon collected approximately 150 µL of aqueous humor by paracentesis using a 30-gauge needle on a tuberculin syringe. This was performed by inserting the needle through the clear cornea 1 mm from the limbus. If the patient had missed any dose of the study medication, based on each patient's diary of study medication administration, however, the patient was discontinued from the study and no aqueous humor samples were collected. All aqueous humor samples collected were immediately placed into a pre-labeled storage tube and were placed on ice or into a freezer within 10 minutes of collection. All samples were kept frozen (≤–40°C) until shipped to the laboratory for analysis.

Pharmacokinetic analysis and sample assay method

Aqueous humor samples were assayed for levofloxacin or moxifloxacin concentration using a validated liquid chromatography and tandem mass spectrometry (LC–MS/MS) method. The LC–MS/MS analysis was performed according to Good Laboratory Practice. Briefly, 50 µL of human aqueous humor samples were deproteinated with 150 µL of high-performance liquid chromatography (HPLC)-grade acetonitrile. These samples were centrifuged and 50 µL of

the supernatant was transferred into an appropriately labeled autosampler vial containing 1 mL of HPLC-grade water. The LC–MS/MS system was composed of a Shimadzu Prominence HPLC system and (Thermo Fisher Scientific, Waltham, MA, USA)/MDS Sciex AP5000 LC–MS/MS. The chromatographic separation was performed using a Phenomenex Luna Phenyl-Hexyl column. The mobile phase used was 85:15:0.1 ratios of water, acetonitrile and formic acid, respectively, at a flow rate of 0.75 mL/min. The levofloxacin and moxifloxacin concentrations were obtained by monitoring the MS/MS transition at 261–362 and 384–402 m/z, respectively, in a 5-minute LC–MS/MS run time. Solutions of levofloxacin and moxifloxacin were each used to create a standard curve and quality control samples. The standard curve for each study medication was linear over the range of 0.0100–10.0 μg/mL (r^2>0.998), while the quality control samples at 0.0500, 0.500, and 5.00 μg/mL were analyzed in repulates of six in each run. The lower limit of quantification for both moxifloxacin and levofloxacin was 0.3 μg/mL. The inter-day accuracy (% bias) and precision (% coefficient of variation) ranged from 3.60–13.0 and 3.10–9.01, respectively. Ion suppression is minimized utilizing atmospheric pressure chemical ionization inlets along with optimized chromatography to avoid interfering peaks of endogenous compounds.

For pharmacokinetic analysis, a pooled concentration vs time profile was created for each treatment arm and non-compartmental analysis was performed to determine the maximum concentration (C_{max}), and the linear trapezoidal method was used to calculate the area under the concentration-time curve at 6 hours ($AUC_{0–6}$).[7,8]

Safety

Treatment-emerged adverse events (non-ocular and ocular) were to be captured when reported, elicited or observed.

Statistical analysis

Sample size (N) calculations were performed for two different powers. The assumptions for the mean concentrations and standard deviations (SD) were derived from previously published data for moxifloxacin 0.5% and levofloxacin 1.5% in aqueous humor absorption studies. Although our dosing regimen and study design (time-stratified) varied considerably from the published literature, we assumed a mean concentration of 1.0 mg/mL with an SD of 0.5 mg/mL for levofloxacin 1.5%, and a mean concentration of 0.6 mg/mL with an SD of 0.3 mg/mL for moxifloxacin 0.5%. The accepted alpha error was 0.05.

The analysis for the aqueous humor concentrations within each of the four treatment subgroups would contain approximately ¼ the number of total samples. The power calculation for 50% yielded an N=7, which satisfied our estimate for an adequate number of samples in each of the four subgroups.

Baseline numeric demographic information was summarized by descriptive statistics. The sample size (N), mean, SD, median, and range values were calculated for continuous demographic variables. The number of patients and the percentage of the total were calculated for categorical variables. For the pooled aqueous humor concentrations in each of the treatment groups, N, mean, SD, median, and coefficient of variation, and range values for each time point were calculated. Since each patient contributed to this pooled non-compartmental analysis at a specified time point, a representative $AUC_{0–6}$, C_{max}, and time to C_{max} (T_{max}) were determined by direct observation. The median $AUC_{0–6}$ calculation was performed using the linear trapezoid method. A Kruskal–Wallis nonparametric one-way analysis of variance (ANOVA) was used to detect differences between the concentrations in each treatment arm at various time points.

For $AUC_{0–6}$ repeated measures of ANOVA were used to detect differences between the treatment groups, whereby the dependent variable was the concentration of each treatment group, the independent variables were time, treatment group, and interaction between time and treatment group. Statistical significance was set at P<0.05. Data management and statistical analysis were performed using Microsoft Excel and Systat 12.

Results

A total of 120 eyes were enrolled and randomized to study treatment. The study flow is depicted in Figure 1. Ninety-nine eyes (51 receiving levofloxacin; 48 receiving moxifloxacin) completed the study and 98 eyes (50 receiving levofloxacin; 48 receiving moxifloxacin) were included in the pharmacokinetic analysis. Five patients of each group were lost due to noncompliance, inability to obtain a sample of aqueous humor within the specified time or other deviations. There were 49 (one patient contributed two samples randomized independently) and 48 patients in the levofloxacin and moxifloxacin groups respectively (mean age 71.5 years; 55% female; 97% Caucasian). The baseline demographic characteristics of the patients are presented in Table 1.

Pharmacokinetic results

Since this was a pooled non-compartmental analysis, each eye contributed one time point to the respective treatment group. One subject contributed two samples (each eye was randomized independently of the other) while all other subjects only contributed one sample. A total of 98 aqueous humor samples were analyzed with 50 samples in the levofloxacin group (14, 14, 10, and 12 concentrations in the 1-, 2-, 4-, and 6-hour

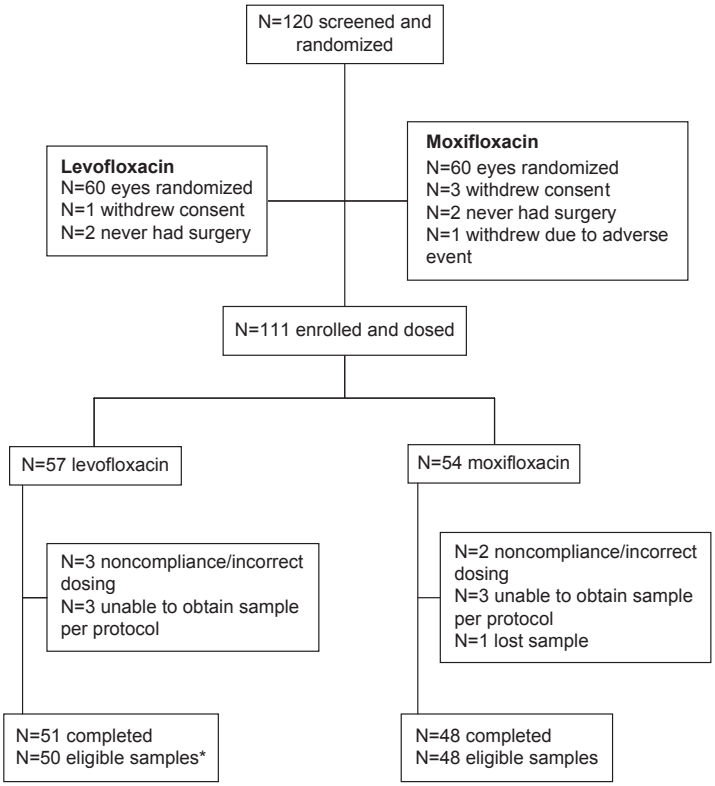

Figure 1 Study disposition by eye.
Notes: *Sample from one subject was excluded from final analysis because the concentration of drug detected (0.0253 μg/mL) was substantially less than that of any other sample measured (0.241 μg/mL).

subgroups, respectively) and a total of 48 samples analyzed in the moxifloxacin group (11, 13, 12, and 12 concentrations in each subgroup, respectively). The mean (25–75th interquartile range) concentration vs time of each treatment group is shown in Figure 2. The mean concentrations of levofloxacin were greater than 50% higher than moxifloxacin concentrations across all

Table 1 Summary statistics of baseline demographic data (analysis population)

Characteristics	Results		
	Levofloxacin group	Moxifloxacin group	Total
Age			
N	50	48	98
Mean (SD)	72.2 (8.46)	70.7 (8.35)	71.47 (8.4)
Median	73.1	71.6	72.1
(Min–max)	(44.3–86.4)	(52.1–85.6)	(44.3–86.4)
Sex, N (%)			
Female	24 (48.0)	30 (62.5)	53 (54.6)
Male	26 (52.0)	18 (37.5)	44 (45.4)
Race, N (%)			
African American	1 (2.0)	1 (2.1)	2 (2.1)
Hispanic	–	1 (2.1)	1 (1.0)
Caucasian	49 (98.0)	46 (95.8)	95 (96.9)

Abbreviation: SD, standard deviation.

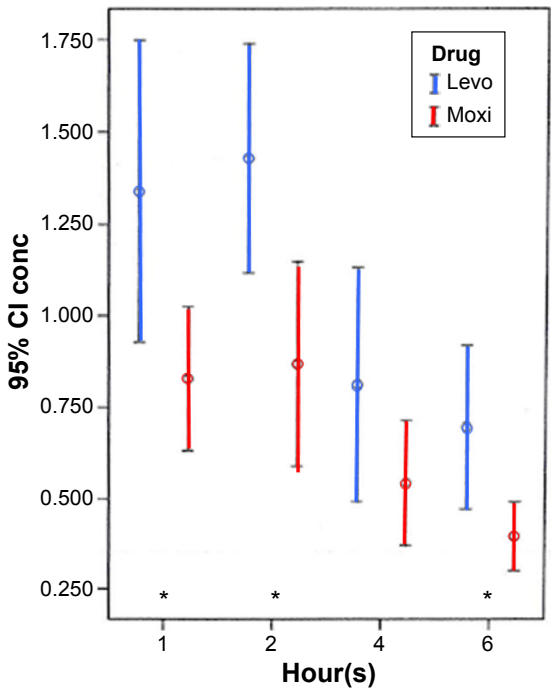

Figure 2 Mean levofloxacin and moxifloxacin concentrations in aqueous humor over 6 hours after last dose of study ophthalmic solution.
Notes: Error bars represent the 25–75th interquartile range. *P-value <0.05 between levofloxacin and moxifloxacin group (Kruskal–Wallis non-parametric one-way ANOVA).
Abbreviations: ANOVA, analysis of variance; CI, confidence interval; conc, concentration; Levo, levofloxacin; Moxi, moxifloxacin.

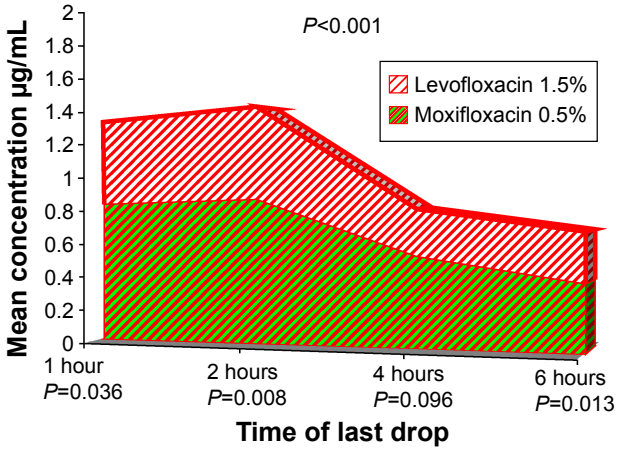

Figure 3 Aqueous humor concentrations over time, AUC_{0-6}.
Notes: Levofloxacin = AUC_{0-6}(levo) =6.2 µg/mL; moxifloxacin = AUC_{0-6}(moxi) = 3.8 µg/mL.
Abbreviations: levo, levofloxacin; moxi, moxifloxacin; AUC_{0-6}, area under the concentration-time curve.

time points, and the mean levofloxacin concentrations were statistically significantly greater than the mean moxifloxacin concentrations at 1 hour (1.34 vs 0.83 µg/mL, *P*=0.025), 2 hours (1.60 vs 0.796 µg/mL, *P*=0.008) and 6 hours (0.70 µg/mL vs 0.40 µg/mL, *P*=0.016) post last dose. Non-compartmental estimates of AUC_{0-6} and C_{max} for each treatment arm are depicted in Figures 3 and 4. The pooled AUC_{0-6} of levofloxacin aqueous humor concentration was significantly greater than that of moxifloxacin (6.2 µg·hr/mL and 3.8 µg·hr/mL respectively, *P*<0.001), and a significant between-treatment difference was observed in mean C_{max} values (1.43 µg/mL and 0.87 µg/mL respectively, *P*=0.008).

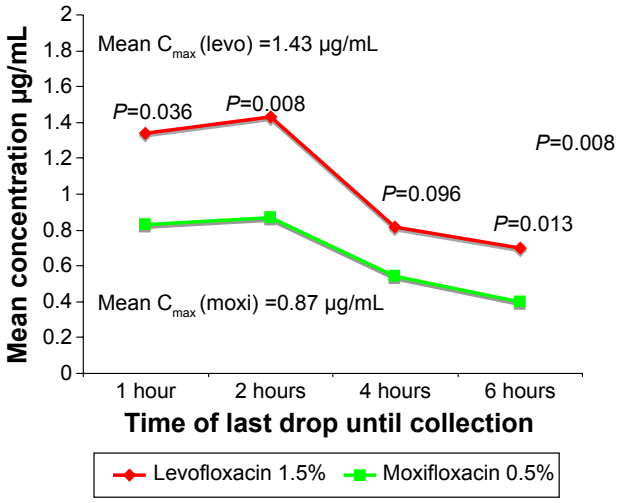

Figure 4 Aqueous humor concentrations over time·C_{max}.
Abbreviations: C_{max}, maximum concentration; levo, levofloxacin; moxi, moxifloxacin.

Safety

No treatment-emergent adverse events were reported during the course of the study.

Discussion

Knowledge of the PK–PD activity of topical fluoroquinolones at target tissues helps to inform clinicians of the abilities of the drugs to obtain clinically meaningful concentrations at the potential sights of infection in the eye. Research on the perioperative use of topical fluoroquinolones has revealed the abilities of several fluoroquinolones to obtain considerable concentrations at the ocular sites studied (ie, aqueous, vitreous, corneal tissue), and suggests that the abilities of these agents to acquire concentrations exceeding the minimum inhibitory concentrations (MICs) for common pathogens are a factor in the success of therapy.[2,9–12]

This is the first report of a study comparing the human ocular penetration of levofloxacin 1.5% and moxifloxacin hydrochloride 0.5%. Levofloxacin and moxifloxacin, the two antimicrobial agents studied, have in vitro spectrums of activity covering the bacterial pathogens most commonly associated with ocular infections.[3] This study compared their pharmacokinetics in aqueous humor, in an effort to observe their ability to penetrate the cornea.

As shown in Figure 2 the mean levofloxacin concentrations were statistically significantly higher than mean moxifloxacin concentrations at the 1-, 2-, and 6-hour time points (*P*-value <0.05). Moreover the mean AUC_{0-6} was greater (*P*-value <0.001) for levofloxacin 1.5%. Notably, the preparation of levofloxacin utilized in this study has a drug concentration three-fold that of the moxifloxacin preparation used. This higher concentration is likely a factor in the higher concentrations achieved in the aqueous humor. Considerable inter-subject variability in drug concentration was evident across time points (Figure 2) as is typical of pharmacokinetics of ophthalmic solutions.[13–15] Such inter-subject variability may be due to variations in drug administration, tear turnover, absorption by vascularized tissues, protein binding, aqueous humor turnover, etc.

Comparison of the concentrations of drug reached at target sites to bacterial susceptibility (ie, MIC) can impact clinical decision-making. The PK–PD measures most closely associated with efficacy for concentration-dependent killing antimicrobial agents, like levofloxacin and moxifloxacin, are the C_{max}:MIC and AUC:MIC of the drug to the microorganism.[4,16] To date, many preclinical and clinical studies of fluoroquinolones for the treatment of a host of infectious diseases have identified the relevance of C_{max}:MIC and/or the AUC:MIC to treatment efficacy.[10–15,17]

One limitation of this study is that it only examined a single dosing regimen, ie, four times daily for 3 days for a single type of surgery, ie, cataract surgery. Other studies have assessed fluoroquinolone concentrations in various ocular tissues after different dosing regimens. While it is not possible to use these results as a direct comparison to the present study, it may be useful to consider the available data when deciding appropriate treatment regimens. In a study of fluoroquinolone concentration in aqueous humor with sampling performed during penetrating keratoplasty, topical preoperative administration of two preoperative doses of one drop given 5 minutes apart resulted in an aqueous humor C_{max} of 0.9 μg/mL and T_{max} of 2 hours for moxifloxacin 0.5% vs C_{max} of 0.3 μg/mL at 1 hour for gatifloxacin 0.3%.[14] Instillation of one drop of antibiotic every 10 minutes for four doses beginning 1 hour prior to cataract surgery documented mean aqueous humor concentrations of 1.80 (SD ±1.21) μg/mL for moxifloxacin 0.5% and 0.48 (±0.34) μg/mL for gatifloxacin 0.3%.[9] Solomon et al documented that administration of gatifloxacin 0.3%, moxifloxacin 0.5% or ciprofloxacin 0.3% four times daily for 3 days prior to cataract surgery resulted in mean aqueous concentrations of 0.63 μg/mL (SD, 0.3), 1.31 μg/mL (SD, 0.46), and 0.15 μg/mL (SD, 0.11) for gatifloxacin, moxifloxacin, and ciprofloxacin, respectively.[11] The instillation of topical ofloxacin 0.3% or moxifloxacin 0.5% every 10 minutes for 1 hour prior to vitrectomy resulted in aqueous concentrations of 0.816+0.504 μg/mL and 1.576+0.745 μg/mL for ofloxacin and moxifloxacin, respectively.[10] Similarly, when one drop of levofloxacin 1.5% or gatifloxacin 0.3% was administered 15 minutes and 10 minutes prior to penetrating keratoplasty, mean aqueous humor concentrations of levofloxacin and gatifloxacin were 0.976 (±2.215) μg/mL and 0.0523 (±0.143) μg/mL, respectively (P=0.002).[2]

Another limitation of the current study is that all of the subjects had an intact epithelium which indicated underestimation of the aqueous concentrations that could be achieved in patients with disrupted epithelium. Bacterial infections can disrupt the epithelium and that disruption can enhance the penetration of topically applied fluoroquinolones.[17,18]

Topical antibiotics are able to achieve adequate antimicrobial concentrations in the aqueous humor. In such cases, the clinical efficacy of fluoroquinolones is dependent on the penetration of the cornea in sufficient concentrations to achieve their bactericidal effects.[19] The higher concentrations achieved by levofloxacin 1.5% relative to those reached by moxifloxacin may demonstrate the ability of the drug concentration gradient to effectively drive the drug into the corneal tissue and ultimately, to bacteria threatening corneal health.

In conclusion, the pharmacokinetics in aqueous humor of two ophthalmic fluoroquinolone formulations was compared using data from a randomized study. The mean C_{max} and AUC_{0-6} in aqueous humor for levofloxacin 1.5% were uniformly greater than those of moxifloxacin 0.5%. These findings demonstrate considerable corneal penetration of the agents when topically applied to the ocular surface. Comparisons of concentration effects to MICs of common pathogens may indicate substantial ability of the agents studied to interact with bacterial pathogens in the anterior chamber.

Acknowledgment

This study was funded by a grant from Johnson and Johnson, New Brunswick, NJ, USA.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Green M, Apel A, Stapleton F. Risk factors and causative organisms in microbial keratitis. *Cornea*. 2008;27(1):22–27.
2. Holland EJ, McCarthy M, Holland S. The ocular penetration of levofloxacin 1.5% and gatifloxacin 0.3% ophthalmic solutions in subjects undergoing corneal transplant surgery. *Curr Med Res Opin*. 2007; 23(12):2955–2960.
3. Asbell PA, Colby KA, Deng S, et al. Ocular TRUST: nationwide antimicrobial susceptibility patterns in ocular isolates. *Am J Ophthalmol*. 2008;145(6):951–958.
4. Abbott RL, Halfpenny CP, Zegan M, Kremer PA. Bacterial Corneal Ulcers. In: Tasman W, Jaeger EA, editors. *Duane's Ophthalmology Solution*. Online Access Code (CD-ROM). Philadelphia, PA: Wolters Kluwer, Lippincott Williams and Wilkins; 2008.
5. Ambrose PG, Grasela DM, Grasela TH, et al. Pharmacodynamics of fluoroquinolones against Streptococcus pneumoniae in patients with community-acquired respiratory tract infections. *Antimicrob Agents Chemother*. 2001;45(10):2793–2797.
6. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis*. 1998; 26(1):1–10.
7. Gibaldi M, Perrier D. *Pharmacokinetics*. 2nd ed. New York: Informa HealthCare; 1982.
8. Yeh KC, Kwan KC. A comparison of numerical integrating algorithms by trapezoidal, Lagrange, and spline approximation. *J Pharmacokinet Biopharm*. 1978;6(1):79–98.
9. Kim DH, Stark WJ, O'Brien TP, Dick JD. Aqueous penetration and biological activity of moxifloxacin 0.5% ophthalmic solution and gatifloxacin 0.3% solution in cataract surgery patients. *Ophthalmology*. 2005;112(11):1992–1996.
10. Lai WW, Chu KO, Chan KP, et al. Differential aqueous and vitreous concentrations of moxifloxacin and ofloxacin after topical administration one hour before vitrectomy. *Am J Ophthalmol*. 2007;144(2): 315–318.
11. Solomon R, Donnenfeld ED, Perry HD, et al. Penetration of topically applied gatifloxacin 0.3%, moxifloxacin 0.5%, and ciprofloxacin 0.3% into the aqueous humor. *Ophthlamology*. 2005;112(3):466–469.

12. Kim DH, Stark WJ, O'Brien TP. Ocular penetration of moxifloxacin 0.5% and gatifloxacin 0.3% ophthalmic solutions into the aqueous humor following topical administration prior to routine cataract surgery. *Curr Med Res Opin*. 2005;21(1):93–94.
13. Akkan AG, Mutlu I, Ozyazgan S, et al. Comparative tear concentrations of topically applied ciprofloxacin, ofloxacin, and norfloxacin in human eyes. *Int J Clin Pharmacol Ther*. 1997;35(5):214–217.
14. Holland EJ, Lane SS, Kim T, Raizman M, Dunn S. Ocular penetration and pharmacokinetics of topical gatifloxacin 0.3% and moxifloxacin 0.5% ophthalmic solutions after keratoplasty. *Cornea*. 2008; 27(3):314–319.
15. Raizman MB, Rubin JM, Graves Al, Rinehart M. Tear concentrations of levofloxacin following topical administration of a single dose of 0.5% levofloxacin ophthalmic solution in healthy volunteers. *Clin Ther*. 2002;24(9):1439–1450.
16. U.S. Food and Drug Administration [homepage on the Internet]. FDA Approved Drug Products. Drugs@FDA. Available from: https://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed October 12, 2015.
17. Behrens-Baumann W. Absorption of topically administered ciprofloxacin, ofloxacin and gentamicin in the inflamed rabbit eye. *Ophthalmologica*. 1996;210(2):119–122.
18. Fukuda M, Inoue A, Sasaki K, Takahashi N. The effect of the corneal epithelium on the intraocular penetration of fluoroquinolone ophthalmic solution. *Jpn J Ophthalmol*. 2004;48(2):93–96.
19. Sutphin JE, Wells JM. Ocular Pharmacology of Antibacterial Agents. In: Tasman W, Jaeger EA, editors. *Duane's Ophthalmology Solution*. Online Access Code (CD-ROM). Philadelphia, PA: Wolters Kluwer, Lippincott Williams and Wilkins; 2008.