Penetration of Ofloxacin and Ciprofloxacin in Aqueous Humor After Topical Administration

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BACKGROUND AND OBJECTIVE: To compare the aqueous humor levels of 0.3% ofloxacin and 0.3% ciprofloxacin containing eyedrops in patients with healthy cornea.

PATIENTS AND METHODS: Fifty patients with cataract were randomly assigned to have 0.3% ofloxacin containing eyedrop (25 patients) or 0.3% ciprofloxacin containing eyedrop (25 patients). Both drugs were repetitively instilled to each patient for 6 hours before the surgery. Aqueous samples were collected after penetrating the anterior chamber during cataract extraction and assayed by high-performance liquid chromatography method.

RESULTS: The aqueous humor level of ofloxacin (1.43 ± 0.26 µg/ml, mean ± SEM) was significantly higher than that of ciprofloxacin (0.35 ± 0.07 µg/ml) following the topical application (P < .0002).

CONCLUSION: Aqueous humor penetration of topical ofloxacin is about 4 times higher than that of topical ciprofloxacin when the drugs are applied as described above.


INTRODUCTION

Fluoroquinolone antibiotics are active against a broad spectrum of gram-negative and gram-positive bacteria, well tolerated after systemic and topical administrations. They block DNA synthesis in bacteria by inhibiting DNA gyrase. Ciprofloxacin, a synthetic antibacterial agent of the fluoroquinolone family, is widely used for the treatment of conjunctivitis and corneal ulceration. The broad spectrum of activity, good penetration into the tissues and biological fluids and other favorable pharmacokinetic properties increase the usefulness of ciprofloxacin in the treatment of ocular infections. Ofloxacin, as well as other fluoroquinolones, offers several pharmacokinetic characteristics for better intraocular uptake over previous antibacterial agents. These characteristics include low molecular weight and weak binding to proteins and lipophilic properties. The topical formulation of ofloxacin is indicated for various anterior segment diseases including bacterial conjunctivitis, keratitis, and ophthalmia neonatorum.

The present study was designed to get an insight into whether the topical 0.3% ciprofloxacin and 0.3% ofloxacin produce concentrations in aqueous humor corresponding to the effective concentration range for certain common ocular pathogens and to compare
their penetration and local bioavailability. We used a sensitive and reliable method described previously to measure ciprofloxacin\textsuperscript{11} and ofloxacin\textsuperscript{12} concentration in human ocular tissues.

<table>
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<th>Table. Patient Characteristics</th>
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<td>Aqueous humor drug levels (µg/ml)</td>
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**PATIENTS AND METHODS**

Fifty patients undergoing cataract extraction were randomly divided into 2 groups receiving either topical 0.3% ciprofloxacin (n=25) or 0.3% ofloxacin (n= 25). The Table shows patient characteristics. Surgery was performed under retrobulbar anesthesia. At the onset of surgery, an aqueous humor sample was obtained with an irrigating cannula through the anterior chamber from a limbal paracentesis tract. Collected samples were approximately 100 to 150 µl. Immediately after the samples were taken, they were stored in deep freeze at −70°C until the analysis.

No patient had a history of ocular disease other than cataract or was receiving any antibiotic medication other than the solutions tested during the course of the study. A written informed consent was obtained from each patient involved in the study according to the principles outlined in Helsinki Declaration, and the study was approved by the Ethics Committee of the SSK Ankara Eye Hospital in Ankara, Turkey.

The same drug administration schedule was used for all patients. Starting 6 hours before the surgery, 2 drops of solutions were instilled to the operative eye every 30 minutes for the first 3 hours and followed by hourly instillation for the next 3 hours. All of the samples were collected 30 minutes following the last dose. This procedure was done by a nurse to ensure compliance. No adverse reactions were attributed to the antibiotic agents.

Ciprofloxacin and ofloxacin levels in aqueous were determined using high performance chromatography-fluorescence detection method originally described by Basci et al.\textsuperscript{11,12} High performance liquid chromatography-grade methanol and acetonitrile were obtained from Baker (Phillipsburg, NJ,) and analytical-grade citric acid and pipemidic acid from Sigma (St Louis, MO).

The analytical column was 100 mm x 8 mm in internal diameter cartridge packed with 4 µm Novapak C\textsubscript{18} (Waters Chromatography Division, Milford, MA,) compressed in a Radial-Pak cartridge holder (RCM 8 x 10, Waters, Milford, MA) in conjunction with a pre-column module (Guard-Pale, Waters, Milford, MA) containing a Novapak C\textsubscript{18} insert. All experiments were performed at a flow rate of 1 ml/min at ambient temperature. The mobile phase consisted of methanol-acetonitrile 0.4 M citric acid (3:1:10, v/v/v).

The excitation and emission wavelengths were set to 278 nm and 450 nm respectively for ciprofloxacin, and 290 nm and 500 nm for ofloxacin. Drug concentrations were determined against a calibration curve constructed from their standard concentrations, and calculated from peak values and expressed as micrograms of drug per ml of aqueous humor. The Mann-Whitney U-test was used to compare the data related to independent groups.

**RESULTS**

Levels of ciprofloxacin in aqueous humor in the ciprofloxacin group was 0.35 ± 0.07 µg/ml (mean ± SEM) and that of the ofloxacin group was 1.43 ± 0.26 µg/ml. Maximum and minimum concentrations produced by ciprofloxacin instillation in aqueous humor were 1.09 µg/ml and 0.11 µg/ml and those by ofloxacin instillation were 2.08 µg/ml and 0.13 µg/ml (Table). There was a
statistically significant difference between the aqueous humor levels of the drugs (P < .0002).

**DISCUSSION**

Ciprofloxacin and ofloxacin have similar spectrums of activity, with ciprofloxacin being moderately more active against gram-negative bacteria such as Pseudomonas aeruginosa. Ofloxacin is moderately more active against gram-positive bacteria such as Staphylococcus aureus and Streptococcus pneumoniae. Ciprofloxacin is lipophilic enough to enter into the eyeball, and is preferred for the treatment of intraocular infections much like a limited number of antibiotics with the same property. When applied locally at a constant concentration into the conjunctival sac, ciprofloxacin penetrates into the aqueous humor and its concentration there is dependent on the number of doses instilled at intervals of 15 to 60 minutes in human subjects without eye infection. Topical ofloxacin also penetrates the cornea well and achieves therapeutic aqueous humor levels against a wide variety of bacteria. The major difference between ciprofloxacin and ofloxacin is their solubility. Ofloxacin is the most soluble of all the fluoroquinolones in medical use currently.

In the present study, 6 doses of 2 drops instilled at 30 minute intervals followed by 3 doses at 60 minute intervals yielded a mean concentration in aqueous humor of 0.35 ± 0.07 μg/ml with 0.3% ciprofloxacin and of 1.43 ± 0.26 μg/ml with 0.3% ofloxacin. The difference between levels was statistically significant. The local bioavailability of ofloxacin at aqueous humor was 4 times better than those of ciprofloxacin. This data are similar to those found by Donnenfeld et al. indicating ofloxacin levels in the aqueous humor were 4.5 times greater than those of ciprofloxacin.

In the study, we observed that a concentration above minimal inhibitory concentrations for 90% of strains tested (MIC90) for Staphylococcus epidermidis, Bacillus species, Pseudomonas aeruginosa and Enterobacteria in aqueous humor was achieved in 14 of 25 patients, and for Staphylococcus aureus in aqueous humor was in 3 of 25 patients instilled with ciprofloxacin solution. The concentrations were below the therapeutic concentration required to inhibit Streptococcus pneumoniae.

The mean aqueous humor concentration of ofloxacin was 1.43 ± 0.26 μg/ml when the drug was applied as described above. This value is greater than the MIC90 of ofloxacin against most of the common ocular pathogens, including Staphylococcus aureus and Streptococcus epidermidis, the two most common causes of endophthalmitis. However, 2 patients in the ofloxacin group reached MIC90 for Streptococcus pneumoniae which is the third most common cause of endophthalmitis. The concentrations were below the therapeutic concentration required to inhibit Pseudomonas aeruginosa.

In conclusion, the aqueous humor penetration of topical ofloxacin is about 4 times higher than that of topical ciprofloxacin when the drugs are applied as described above.

**REFERENCES**


