

SCIENTIFIC CORRESPONDENCE

Penetration of topical, oral, and combined administered ofloxacin into the subretinal fluid

Osman Çekiç, Cosar Batman, Ümit Yasar, Yüksel Totan, Nursabah E Basci, Atilla Bozkurt, Orhan Zilelioglu, S Oguz Kayaalp

Abstract

Aims—To assess the subretinal fluid (SRF) levels of ofloxacin following topical, oral or combined administration.

Methods—31 patients undergoing conventional retinal reattachment surgery were randomly assigned to three groups. Nine patients received topical ofloxacin, 11 patients received oral ofloxacin, and the other 11 patients received combined administration. Collected SRF samples were analysed for drug level by using high performance liquid chromatography.

Results—SRF drug levels after oral and combined administration were significantly higher than that after topical administration ($p=0.0002$ and $p=0.0002$, respectively) while there was no significant difference between oral and combined administration ($p=0.0844$).

Conclusions—Ocular bioavailability of ofloxacin in SRF after oral and combined administration is equivalent. The addition of oral ofloxacin to topical therapy increased drug SRF penetration sixfold.

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Ofloxacin is a fluoroquinolone antibiotic with rapid bactericidal activity interfering with DNA gyrase of bacteria.¹ It has a high oral bioavailability and excellent tissue penetration.^{1,2} Its favourable pharmacokinetic properties also make it useful in ophthalmic infections in the form of a topical 0.3% solution.³⁻⁵

Penetration of topical, systemic, or combined ofloxacin into cornea, aqueous, and vitreous humour has already been studied.⁶⁻¹³ However, no published result was found with regard the subretinal fluid (SRF) level of the drug.

The aim of this study was to determine the SRF concentration of ofloxacin following different type of applications by using a sensitive and reliable method described by Basci *et al.*¹⁴

Materials and methods

Thirty one patients undergoing conventional retinal reattachment surgery were selected for the study. Nine patients (mean age 38.5 years; five male and four female), starting 6 hours

before surgery, received 2 drops of 0.3% ofloxacin solution every 30 minutes for the first 3 hours and hourly instillation for the next 3 hours. Eleven patients (mean age 40.5 years; six male and five female) received a single oral dose of 400 mg ofloxacin 8 hours before surgery. The other 11 patients (mean age 37 years, five male and six female) received a combination of those applications. Drug administration was done by a nurse to ensure compliance.

SRF samples were obtained as described by Lesk *et al.*¹⁵ at the sclerotomy drainage site. Samples were stored immediately in a freezer at -70°C . All the patients had a uninflamed cornea, intact crystalline lens, and posterior capsule. Exclusion criteria included the presence of a fresh vitreous haemorrhage, age less than 18 years, pregnancy, diabetes mellitus, topical or systemic antibiotic or any drug that may interfere with ofloxacin use during 1 week before enrolment, allergy to quinolones, history of central nervous system, renal, or hepatic diseases. Written informed consent was obtained from each patient, and the study was approved by the ethics committee of SSK Ankara Eye Hospital, Ankara, Turkey.

High performance liquid chromatography (HPLC) grade methanol and acetonitrile were obtained from J T Baker (Phillipsburg, NJ, USA) and analytical grade citric acid and pipemidic acid from Sigma (St Louis, MO, USA). The ophthalmic solution of ofloxacin used contained benzalkonium chloride (0.005%), hydrochloric acid, sodium hydroxide (pH approximately 6.4), and sterile water as inactive ingredients.

Stock solutions of ofloxacin (1 mg/ml) and pipemidic acid (1 mg/ml) were prepared in hydrochloric acid (0.01 N) and sodium hydroxide (0.2 M), respectively. Standard solutions of ofloxacin containing pipemidic acid (1 µg/ml) were prepared as internal standard by diluting the stock solutions of ofloxacin.

Ofloxacin was measured by using an HPLC method that involves direct injection of the samples. The chromatography system consisted of a Varian 9002 solvent delivery system (Varian Associates Inc, Lexington, MA, USA), Varian 9100 autosampler, Waters 470 scanning fluorescence detector (Waters Chromatography, Milford, MA, USA), and Waters 746 data

SSK Ankara Eye Hospital, Department of Vitreoretinal Surgery, Ankara, Turkey
O Çekiç
C Batman
Y Totan
O Zilelioglu

Hacettepe University, Faculty of Medicine Department of Pharmacology, Ankara, Turkey
Ü Yasar
N E Basci
A Bozkurt
S O Kayaalp

Correspondence to:
Osman Çekiç, MD, 54 Basak Sokak, No 7, 06660 Kucukesat Ankara, Turkey

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Table 1 Subretinal fluid ofloxacin concentrations ($\mu\text{g/ml}$) in treatment groups

Patient No	Topical ofloxacin*	Patient No	Oral ofloxacin†	Patient No	Topical+oral ofloxacin‡
1	0.16	1	0.94	1	1.87
2	0.34	2	1.13	2	4.78
3	0.73	3	1.29	3	2.29
4	0.61	4	3.65	4	1.11
5	0.29	5	2.16	5	1.56
6	0.32	6	0.98	6	3.41
7	0.29	7	1.02	7	1.18
8	0.41	8	2.12	8	3.01
9	0.33	9	0.99	9	4.02
		10	1.11	10	2.88
		11	2.19	11	1.05
Mean (SEM)	0.39 (0.06)	Mean (SEM)	1.60 (0.26)	Mean (SEM)	2.47 (0.38)

*Two drops of 0.3% solution every 30 minutes for 3 hours and every 60 minutes for the next 3 hours before surgery.

†A single dose 400 mg 8 hours before surgery.

‡A single dose 400 mg 8 hours before surgery and two drops of 0.3% solution every 30 minutes for 3 hours and every 60 minutes for the next 3 hours before surgery.

module. The separation was performed on a Novapak C18 cartridge column (100×8 mm internal diameter, particle size $4 \mu\text{m}$, Waters Chromatography) compressed in a Radial-Pak cartridge holder (RCM 8×10 , Waters Chromatography) in conjunction with a pre-column module (Guard-Pak, Waters Chromatography). The method utilised a mobile phase composed of a mixture of methanol-acetonitrile-0.4 M citric acid (3:1:10, vol/vol/vol) with a flow rate of 1 ml/min at ambient temperature. The column effluent was monitored with fluorescence detection at 290 nm (excitation) and 500 nm (emission). Drug concentrations were determined against a calibration curve constructed from standard ofloxacin concentrations, and calculated from peak area values.

Kruskal-Wallis analysis of variance (ANOVA) and Mann-Whitney U test were performed to compare data.

Results

Table 1 shows SRF levels of ofloxacin in the groups. There was a statistically significant difference among groups ($p = 0.0001$) (Fig 1). The concentration of ofloxacin in SRF produced by topical administration was significantly lower than the oral and combined group ($p = 0.0002$ and $p = 0.0002$, respectively). The difference between concentrations of ofloxacin in SRF obtained with oral and combined

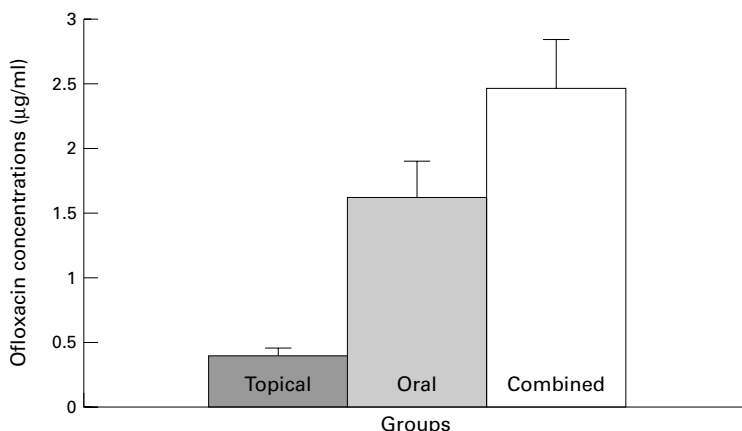


Figure 1 Comparison of subretinal fluid levels of ofloxacin obtained after different modes of administration.

administration was not statistically significant ($p = 0.0844$).

Discussion

Topical ofloxacin penetrates ocular structures better than the other fluoroquinolones.⁶⁻⁹ Its useful clinical concentration in tear film layer lasts longer after topical application.^{5 16} As topical ofloxacin is formulated at a pH of 6.4, it is very soluble and its increased solubility may explain its prolonged effective tear levels after topical application.¹¹

In this study, topical ofloxacin yielded a mean of $0.39 \mu\text{g/ml}$ concentration in SRF which was comparable with vitreal ofloxacin level following topical administration.^{12 13} Donnenfeld *et al*¹² found a mean vitreal level of $0.37 \mu\text{g/ml}$ following topical administration in patients with bullous keratopathy. We recently reported $0.37 \mu\text{g/ml}$ of vitreal ofloxacin level in patients with healthy cornea following the same topical administration with the current study.¹³

In a previous study, in patients receiving two oral doses of 400 mg ofloxacin, mean intravitreal level was found to be $1.75 \mu\text{g/ml}$.¹¹ In the current study, a SRF ofloxacin level of $1.60 \mu\text{g/ml}$ was attained following a single 400 mg oral dose. It seems that SRF drug concentration is similar to that in vitreal. Oral administration of ofloxacin yielded an approximately four times higher SRF concentration than topical administration.

The ocular absorption of ofloxacin was shown to be increased in the inflamed eye.^{17 18} In this study we used patients having an operation for non-infective reasons. Diabetes is another factor that affects drug levels in ocular compartments.¹⁹ None of our patients was diabetic. On the other hand, combined use of same topical and systemic antibiotics increases vitreal drug level.²⁰ In this study, the addition of oral ofloxacin to topical therapy increased SRF penetration about sixfold. Donnenfeld *et al*¹² measured sevenfold more vitreal drug concentration following addition of oral ofloxacin to the topical therapy.

The most common organisms responsible for endophthalmitis are *Staphylococcus epidermidis* 50%, *Staphylococcus aureus* 30%, and streptococcal species 10%.¹² *Bacillus cereus*, *Proteus mirabilis*, and *Pseudomonas aeruginosa* together with *Staphylococcus epidermidis* are common causes of endophthalmitis after penetrating trauma.^{15 21 22} We found a concentration of ofloxacin in SRF was above MIC_{90} for *Staphylococcus epidermidis*, *Staphylococcus aureus*,^{1 23} *Proteus mirabilis*,¹ and *Bacillus cereus*⁶ in all patients following oral and combined application whereas in only two of nine patients after topical administration of the drug. Four patients in the oral and six patients in the combined ofloxacin group reached MIC_{90} for *Streptococcus pneumoniae*. Concentrations in three groups were below the therapeutic concentration required to inhibit *Pseudomonas aeruginosa*. A mean concentration of a drug in a particular compartment which is above MIC_{90} for a bacterium can not be interpreted as a guarantee of successful therapy

there by members of that species, nor indeed does a concentration below it necessarily predict treatment failure.⁶

In conclusion, topical ofloxacin can penetrate SRF but it does not seem to be prophylactically effective against most ocular pathogens. In the posterior ocular inflammations with or without retinal detachment, either oral ofloxacin alone or combined therapy may result in higher drug levels in SRF.

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- 1 Drew RH, Gallis HA. Ofloxacin: its pharmacology, pharmacokinetics, and potential for clinical application. *Pharmacotherapy* 1988;**8**:35-46.
- 2 Just PM. Overview of the fluoroquinolone antibiotics. *Pharmacotherapy* 1993;**13**(suppl 2):4-17.
- 3 The Ofloxacin Study Group. Ofloxacin monotherapy for the primary treatment of microbial keratitis. A double-masked, randomized, controlled trial with conventional dual therapy. *Ophthalmology* 1997;**104**:1902-9.
- 4 Gwon A, the Ofloxacin Study Group. Topical ofloxacin compared with gentamicin in the treatment of external ocular infection. *Br J Ophthalmol* 1992;**76**:714-8.
- 5 Akkan AG, Mutlu I, Özyazgan S, et al. Comparative tear concentrations of topically applied ciprofloxacin, ofloxacin, and norfloxacin in human eyes. *Int J Clin Pharmacol Ther* 1997;**35**:214-7.
- 6 Diamond JP, White L, Leeming JP, et al. Topical 0.3% ciprofloxacin, norfloxacin, and ofloxacin in treatment of bacterial keratitis: a new method for comparative evaluation of ocular drug penetration. *Br J Ophthalmol* 1995;**79**:606-9.
- 7 Durmaz B, Marol S, Durmaz R, et al. Aqueous humor penetration of topically applied ciprofloxacin, ofloxacin and tobramycin. *Arzneimittelforschung* 1997;**47**:413-5.
- 8 Akkan AG, Mutlu I, Özyazgan S, et al. Penetration of topically applied ciprofloxacin, norfloxacin and ofloxacin into the aqueous humor of the uninflamed human eye. *J Chemother* 1997;**9**:257-62.
- 9 Çekiç O, Batman C, Totan Y, et al. Penetration of ofloxacin and ciprofloxacin in aqueous humor after topical administration. *Ophthalmic Surg Lasers* 1999;**30**:465-8.
- 10 Hanioglu-Kargi S, Basci N, Soysal H, et al. The penetration of ofloxacin into human aqueous humor given by various routes. *Eur J Ophthalmol* 1998;**8**:33-6.
- 11 Verbraeken H, Verstraete A, Van de Velde E, et al. Penetration of gentamicin and ofloxacin in human vitreous after systemic administration. *Graefes Arch Clin Exp Ophthalmol* (suppl) 1996;**234**:59-65.
- 12 Donnenfeld ED, Perry HD, Synder RW, et al. Intracorneal, aqueous humor, and vitreous humor penetration of topical and oral ofloxacin. *Arch Ophthalmol* 1997;**115**:173-6.
- 13 Çekiç O, Batman C, Yasar U, et al. Penetration of ofloxacin in human aqueous and vitreous humors following oral and topical administration. *Retina* 1998;**18**:521-5.
- 14 Basci NE, Hanioglu-Kargi S, Soysal H, et al. Determination of ofloxacin in human aqueous humor by high-performance liquid chromatography with fluorescence detection. *J Pharm Biomed Anal* 1997;**15**:663-6.
- 15 Lesk MR, Ammann H, Marcil G, et al. The penetration of oral ciprofloxacin into the aqueous humor, vitreous, and subretinal fluid of humans. *Am J Ophthalmol* 1993;**115**:623-8.
- 16 Richman J, Zolezio H, Tang-Liu D. Comparison of ofloxacin, gentamicin, and tobramycin concentrations in tears and in vitro MICs for 90% of test organisms. *Antimicrob Agents Chemother* 1990;**34**:1602-4.
- 17 Behrens-Baumann W. Absorption of topically administered ciprofloxacin, ofloxacin and gentamicin in the inflamed rabbit eye. *Ophthalmologica* 1996;**210**:119-22.
- 18 Gatti G, Panozzo G. Effect of inflammation on intraocular penetration of intravenous ofloxacin in albino rats. *Antimicrob Agents Chemother* 1995;**39**:549-52.
- 19 Cunha-Vaz J, Debreu JRF, Campos AJ, et al. Early breakdown of the blood-retinal barrier in diabetes. *Br J Ophthalmol* 1975;**59**:649-56.
- 20 Seal DV, Bron AJ. Infections of the eye. In: O'Grady F, Lambert HP, Finch RG, Greenwood D, eds. *Antibiotic and chemotherapy*. 7th ed. Edinburgh: Churchill Livingstone, 1997:788.
- 21 David DB, Kirkby GR, Noble BA. Bacillus cereus endophthalmitis. *Br J Ophthalmol* 1994;**78**:577-80.
- 22 Alfaro DV, Davis J, Kim S, et al. Experimental Bacillus cereus post-traumatic endophthalmitis and treatment with ciprofloxacin. *Br J Ophthalmol* 1996;**80**:755-8.
- 23 Todd PA, Faulds D. Ofloxacin: a reappraisal of its antimicrobial activity, pharmacology and therapeutic use. *Drugs* 1991;**42**:825-76.