

# Subretinal fluid levels of topical, oral, and combined administered ciprofloxacin in humans

Osman Çekiç, Coşar Batman, Ümit Yaşar, Nursabah E Başçi, Orhan Zilelioğlu, Atilla Bozkurt

## Abstract

**Aims**—To investigate the subretinal fluid (SRF) penetration of ciprofloxacin following topical, oral, and combined administration.

**Methods**—34 patients undergoing conventional retinal reattachment surgery were randomly assigned to three groups. Twelve patients received topical ciprofloxacin, 11 patients received oral ciprofloxacin, and the other 11 patients received combined drug administration. SRF drug level was measured by using high performance liquid chromatography method.

**Results**—The highest drug concentrations of all tested modes were attained following combined administration and lowest following topical administration ( $p < 0.001$ ). The SRF drug concentration following oral administration was also significantly higher than that of topical administration ( $p < 0.001$ ). Concentrations after oral and combined administration did not differ significantly ( $p = 0.217$ ).

**Conclusions**—Topical ciprofloxacin can penetrate SRF. Ocular bioavailability of ciprofloxacin in SRF after oral and combined administration is equivalent.

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Ciprofloxacin is a fluoroquinolone with a broad antimicrobial spectrum. In ophthalmology, it is widely used for the treatment of conjunctivitis and corneal ulceration.<sup>1,2</sup> Ciprofloxacin has been also suggested as a possible agent in the prevention and treatment of intraocular infections.<sup>3,4</sup>

Studies have shown the penetration of topical, oral, or intravenous ciprofloxacin into the human aqueous humour or vitreous.<sup>5–19</sup> Although the subretinal fluid (SRF) level of the drug following oral administration has been reported in a previous study,<sup>18</sup> the SRF ciprofloxacin level following topical application has not been studied before. The SRF levels of antibiotics may have particular importance in penetrating trauma cases with or without retinal detachment.

This study was designed to assess the penetration of ciprofloxacin into the SRF after different mode of administrations.

## Patients and methods

Thirty four patients undergoing conventional retinal reattachment surgery were included into the study. Twelve (median age 42 years; six male and six female) received two drops of 0.3% ciprofloxacin solution every 30 minutes

for the first 3 hours and hourly instillation for the next 3 hours. Eleven (median age 39 years; six male and five female) received orally a single dose of 1000 mg ciprofloxacin 6 hours before surgery. The remaining 11 patients (median age 41 years; six male and five female) received combination of those applications.

SRF samples were obtained at the sclerotomy drainage site as described previously.<sup>18</sup> Samples were stored at  $-70^{\circ}\text{C}$  until analysed. 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, ongoing treatment with local and systemic antibiotic or any drug that may interfere with ciprofloxacin, known allergies to quinolone derivatives, history of central nervous system, renal, or hepatic diseases. Written informed consent was obtained from each patient.

SRF ciprofloxacin levels were measured by using a high performance liquid chromatography (HPLC) method as described by Basci *et al.*<sup>7</sup> The chromatographic system consisted of a Model PU-980 HPLC pump (Jasco, Tokyo, Japan), a Model 7125 Injector (Rheodyne, Cotati, CA, USA), a Model 470 fluorescence detector, and Model 746 data module (Waters, Milford, MA, USA). The separation was performed on a Novapak C<sub>18</sub> cartridge (100 × 8 mm internal diameter, particle size 4 μm) (Waters) compressed in a Radial-Pak cartridge holder (RCM 8 × 10, Waters) in conjunction with a precolumn module (Guard-Pak, Waters) containing a Novapak C<sub>18</sub> insert. The mobile phase consisted of methanol-acetonitrile-citric acid (0.4 M) (3:1:10, vol/vol/vol) at a flow rate of 1 ml/min at ambient temperature. The column effluent was monitored with fluorescence detection at 278 nm (excitation) and 450 nm (emission). Drug concentrations were determined against a calibration curve constructed from standard ciprofloxacin concentrations.

Kruskal–Wallis analysis of variance and Mann–Whitney U test were performed to compare data.

## Results

The concentration range in SRF produced by topical administration was 0.07 μg/ml to 0.54 μg/ml (median 0.205 μg/ml; mean (SEM)) 0.23 (0.04) μg/ml, by oral administration it was 0.36 μg/ml to 1.21 μg/ml (0.68 μg/ml; 0.74 (0.09) μg/ml), and by addition of oral ciprofloxacin to topical therapy it was 0.50 μg/ml to 2.12 μg/ml (0.86 μg/ml; 1.05 (0.17) μg/ml) (Table 1).

SSK Ankara Eye Hospital, Department of Vitreoretinal Surgery, Ankara, Turkey  
O Çekiç  
C Batman  
O Zilelioğlu

Hacettepe University Medical Faculty, Department of Pharmacology, Ankara, Turkey  
Ü Yaşar  
N E Başçi  
A Bozkurt

Correspondence to: Osman Çekiç, Başak Sokak, No 54-7, 06660, Küçüksesat, Ankara, Turkey

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Table 1 Subretinal fluid ciprofloxacin levels following different application modes (µg/ml)

Patient no	Topical ciprofloxacin*	Patient no	Oral ciprofloxacin†	Patient no	Topical+oral ciprofloxacin‡
1	0.20	1	0.52	1	1.92
2	0.31	2	0.94	2	0.93
3	0.21	3	0.48	3	0.54
4	0.07	4	0.41	4	0.58
5	0.54	5	1.21	5	1.41
6	0.22	6	0.74	6	0.81
7	0.12	7	0.66	7	2.12
8	0.44	8	0.36	8	1.28
9	0.10	9	1.01	9	0.50
10	0.15	10	1.10	10	0.63
11	0.24	11	0.68	11	0.86
12	0.11				
Mean (SEM)	0.23 (0.04)	Mean (SEM)	0.74 (0.09)	Mean (SEM)	1.05 (0.17)

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

†A single dose 1000 mg 6 hours before the operation.

‡A single dose 1000 mg 6 hours before the operation and two drops of 0.3% solution every 30 minutes for 3 hours and every 60 minutes for the next 3 hours before the operation.

There was significant difference in SRF drug levels among three application modes ( $p < 0.001$ ). The level of ciprofloxacin in SRF following topical administration was significantly lower than the oral and combined administration ( $p < 0.001$  and  $p < 0.001$ , respectively). The concentrations attained by oral and combined administration did not differ significantly ( $p = 0.217$ ).

### Discussion

Intraocular infection is one of the most serious complications of intraocular procedures or penetrating ocular trauma. Despite the use of the best available treatment, the visual prognosis of patients with intraocular infections remains poor.<sup>3, 18</sup> As systemically administered antibiotics penetrate relatively poorly into the eye, direct intravitreal antibiotic injections together with pars plana vitrectomy are commonly preferred for the initial treatment of endophthalmitis.<sup>3, 20</sup> However, in a short time most of the injected antibiotic has left the eye and maintenance of therapeutic intraocular antibiotic levels would need to be supplemented by other forms of treatment.<sup>21</sup> Thus, repeated intravitreal injections or the use of systemic antibiotics with the highest possible intraocular penetration is indicated.<sup>3, 18</sup> If adequate intraocular concentrations of appropriate antibiotics could be achieved by systemic administration, the problems of repeated intravitreal injection could be avoided.<sup>3</sup>

Penetration of topical ciprofloxacin into the human aqueous has been well studied.<sup>5-15</sup> Although physiologically the flow of aqueous humour is from posterior to anterior, owing to concentration gradient, posterior diffusion of the drug may occur. Previously, penetration of topical ciprofloxacin into the vitreous was first reported by us.<sup>14</sup> Topical ofloxacin can also penetrate vitreous and subretinal fluid in subjects with an intact crystalline lens.<sup>22, 23</sup>

In the current study, topical ciprofloxacin yielded a mean concentration in the SRF of 0.23 µg/ml. This result is comparable with vitreous ciprofloxacin levels following topical administration.<sup>14, 15</sup> It is not unexpected finding. Subretinal fluid is derived from the choroid. However, once a detachment formed, osmolality equilibrates and a steady state is

reached within minutes between subretinal space and vitreous.<sup>24</sup>

A range from 0.19 µg/ml to 1.21 µg/ml vitreous drug level was reported following systemic administration with different dosing regimens.<sup>15-19</sup> In the only report about SRF penetration of oral ciprofloxacin, Lesk *et al*<sup>18</sup> reported 0.71 µg/ml mean subretinal ciprofloxacin level after two doses of 750 mg oral ciprofloxacin administered 17.5 and 5.5 hours preoperatively. In the present study a similar mean SRF ciprofloxacin level (0.74 µg/ml) was attained following a single 1000 mg oral dose given 6 hours before surgery. With this dosing regimen, oral administration of ciprofloxacin yielded an approximately three times higher SRF level than topical administration.

None of the our patients in this study underwent operation for inflammation or penetrating injury reasons. Inflamed or traumatised eyes would yield higher intraocular ciprofloxacin levels.<sup>25-27</sup> Apart from this, combined use of same topical and systemic antibiotics increases the vitreal drug level.<sup>23, 25</sup> In the current study, the addition of oral ciprofloxacin to the topical regimen increased the SRF ciprofloxacin level by about 4.5-fold. However, although the highest SRF drug level was attained by combined administration, we could not find any statistical difference between drug levels following oral and combined administrations.

The most common Gram positive pathogens involved in post-traumatic endophthalmitis are *Staphylococcus* species and *Bacillus* species; Gram negative organisms are *Pseudomonas* species.<sup>26</sup> In this study, SRF ciprofloxacin levels following topical administration were below the therapeutic concentration required to inhibit those bacteria.<sup>17, 18</sup> In most of the subjects in the oral and combined treatment group, concentrations were above the MIC<sub>90</sub> for *S aureus*, *S epidermidis*, and *P aeruginosa*. Only three subjects in the oral group and four of 11 in combined group could reach the MIC<sub>90</sub> for *B cereus* whereas in only one subject was the SRF drug level above the MIC<sub>90</sub> for *S pneumoniae*.

These results demonstrate that topical ciprofloxacin can penetrate into the SRF but it alone does not seem to be prophylactically effective against most of ocular pathogens. In most cases, combining the oral therapy with topical therapy increases the SRF drug level and its efficacy significantly except against some Gram positive organisms including streptococcal species. Oral or a combination of oral and topical ciprofloxacin can be used for certain microorganisms as an adjunctive therapy once a patient has received intravitreal therapy for intraocular infections including posterior segment of the eye caused by a penetrating trauma.

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