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Aqueous and vitreous penetration of levofloxacin after topical and/or oral administration

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PURPOSE. *To investigate the aqueous and vitreous penetration of levofloxacin, the drug was administered topically and/or orally to patients undergoing vitrectomy.*

METHODS. *Thirty-six patients undergoing initial vitrectomy with phacoemulsification and aspiration (PEA) were enrolled, and were divided randomly into three groups. Group 1 was treated with topical application of levofloxacin (three times on the day before surgery and seven times on the day of surgery), Group 2 received oral administration of levofloxacin (200 mg twice on the day before surgery and 200 mg at 3 hours before surgery), and Group 3 received both topical and oral levofloxacin according to the above schedules. The concentration of levofloxacin was measured in aqueous humor and vitreous fluid samples obtained during surgery.*

RESULTS. *In Groups 1, 2, and 3, the mean levofloxacin concentration in aqueous humor was 0.765±0.624 µg/mL, 1.279±0.440 µg/mL, and 1.823±0.490 µg/mL, respectively, while the mean levofloxacin concentration in vitreous fluid was <0.02 µg/mL, 1.455±0.445 µg/mL, and 1.369±0.530 µg/mL, respectively.*

CONCLUSIONS. *Oral administration of levofloxacin at a dose of 400 mg/day was sufficient for the prophylaxis of ocular infections, because the drug concentrations in both aqueous humor and vitreous fluid were higher than the MIC90 values for major ocular pathogens. Topical application of levofloxacin achieved adequate drug levels in aqueous humor, but not in vitreous fluid, while combined topical and oral administration had an additive effect on the drug concentration in aqueous humor. (Eur J Ophthalmol 2007; 17: 372-6)*

KEY WORDS. *Aqueous and vitreous penetration, Levofloxacin, MIC90, Ocular infections, Oral administration, Topical application*

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INTRODUCTION

Levofloxacin is one of the fluoroquinolone antibiotics and is the S-(-)isomer of ofloxacin. This isomer shows stronger binding to the bacterial DNA-DNA gyrase complex than the other isomer and thus inhibits bacterial DNA synthesis more potently (1, 2) than ofloxacin, which is a racemic mixture of two isomers. Purified levofloxacin has approximately twice the potency of ofloxacin (1, 2). This drug can be administered once daily for mild to moderate infections and twice daily for more serious infections, because its half-life is almost 8 hours. Fluoroquinolones are well tolerated and have a low incidence of adverse effects on the central nervous system (1). Inhibitory levels of antibiotics must be achieved to prevent or treat endophthalmitis caused by many ocular pathogens (3). Ofloxacin has been reported to show excellent penetration into the aqueous humor and vitreous fluid after topical or systemic administration (4-6). Oral levofloxacin is more potent and has lower MIC_{90} values for all ocular pathogens than oral

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ofloxacin (7), and it has been shown that inhibitory aqueous and vitreous levels (above MIC_{90}) are achieved for many pathogens by oral administration of levofloxacin (7). To further investigate the potency of topical administration, as well as the interaction between oral and topical levofloxacin, we studied the levofloxacin levels in aqueous humor and vitreous fluid after oral and/or topical administration to patients undergoing initial vitrectomy with phacoemulsification and aspiration (PEA).

PATIENTS AND METHODS

Thirty-six patients undergoing initial vitrectomy with PEA at Kyushu University Hospital were enrolled between May and July 2002. We obtained informed consent from each patient enrolled, and Institutional Reviewed Board approval for this study was also obtained. Before surgery, levofloxacin was administered orally and/or topically to the patients, who were randomized to three groups. In Group 1, topical application of levofloxacin was performed (two drops of a 0.5% ophthalmic solution were instilled into the eye three times on the day before surgery, and every 20 minutes for 2 hours before the operation on the day of surgery), while Group 2 received oral levofloxacin (200 mg twice orally on the day before surgery, and 200 mg 3 hours before the operation). In Group 3, both topical application and oral administration of levofloxacin were done according to the above schedules. Each patient was admitted to the hospital at least 1 day prior to surgery and the drugs were administered by a nurse to ensure compliance. Before performing PEA, approximately 0.2 mL of aqueous fluid was aspirated from the anterior chamber with a 26-gauge needle and a tuberculin syringe. Standard pars plana vitrectomy was performed after PEA, with approximately 0.5 mL of vitreous fluid being obtained by vitrectomy before infusion of the irrigating solution. Each patient had an intact posterior lens capsule. Collection of the aqueous and vitreous samples was done from 3 to 6 hours after oral administration of levofloxacin; the samples were kept on ice and then immediately frozen at -70 °C. Exclusion criteria included hypersensitivity to fluoroquinolones, renal disease, pregnancy, severe keratitis, and previous ophthalmic surgery. The concentrations of levofloxacin in aqueous humor and vitreous fluid were measured using high-performance liquid chromatography (8). Student *t*-test was performed to assess the significance of differences among Groups 1 to 3.

RESULTS

Group 1 included 4 men and 7 women (11 eyes) with an average age of 66.6 years, Group 2 included 6 men and 5 women (11 eyes) with an average age of 62.2 years, and Group 3 included 6 men and 8 women (14 eyes) with an average age of 61.7 years. The indications for vitrectomy included proliferative diabetic retinopathy (11 eyes), diabetic macular edema (9 eyes), macular hole (5 eyes), epiretinal membranes (4 eyes), high myopia with macular hole and retinal detachment (3 eyes), rhegmatogenous retinal detachment (2 eyes), and cystoid macular edema due to central or branch retinal vein occlusion (2 eyes). In Groups 1, 2, and 3, the mean levofloxacin concentration in aqueous humor was 0.765±0.624 µg/mL, 1.279±0.440 µg/mL, and 1.823±0.490 µg/mL, respectively. The range of levofloxacin concentrations in aqueous humor was 0.19–2.46 µg/mL, 0.68–2.58 µg/mL, and 0.93–2.65 µg/mL in Groups 1, 2, and 3, respectively. The mean levofloxacin concentration in vitreous fluid was less than 0.02 µg/mL, 1.455±0.445 µg/mL, and 1.369±0.530 µg/mL in Groups 1, 2, and 3, respectively, while the range of levofloxacin concentrations in vitreous fluid was <0.02 µg/mL, 0.64–2.41 µg/mL, and 0.71–2.53 µg/mL, respectively (Tab. I).

The mean aqueous level of levofloxacin was significantly higher in Group 3 than in Group 1 ($p<0.001$) or Group 2 ($p=0.014$), while the level in Group 2 was also significantly higher than that in Group 1 ($p=0.027$) (Fig. 1).

The mean vitreous level of levofloxacin was significantly higher in Group 2 than in Group 1 ($p<0.001$), and the level in Group 3 was also significantly higher than that in Group 1 ($p<0.001$). However, there was no significant difference between Group 2 and Group 3 (Fig. 2).

DISCUSSION

Fluoroquinolone antibiotics, including levofloxacin, are sufficiently lipophilic to penetrate the eyeball, and therefore are preferred for the treatment of intraocular infections among the limited number of antibiotics with this property (9). Levofloxacin is the most soluble fluoroquinolone in current use. Previous studies have shown that penetration of fluoroquinolones into the aqueous humor and vitreous fluid occurs after oral or topical administration (4, 7). For example, the mean aqueous concentration of ofloxacin was reported to be 1.54±0.27 µg/mL (mean ± standard error) after oral administration, while the

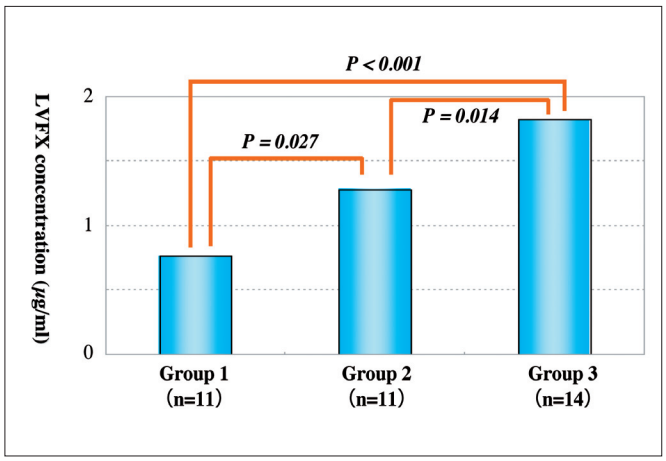

Fig. 1 - *Comparison of the aqueous levels of levofloxacin (LVFX) after topical application and/or oral administration.*

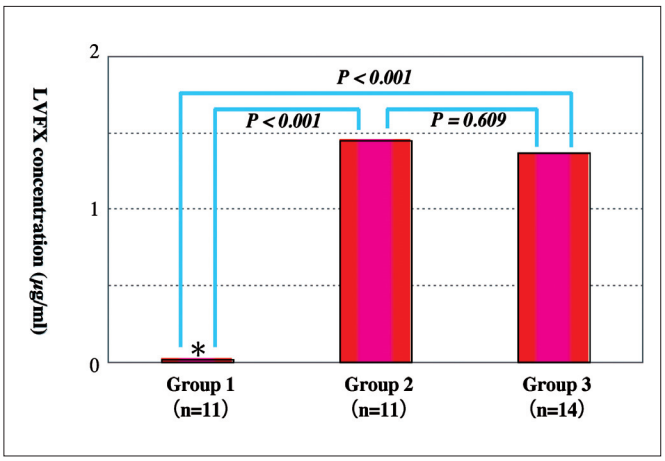

Fig. 2 - *Comparison of the vitreous levels of levofloxacin (LVFX) after topical application and/or oral administration. *All samples had a drug level of less than 0.02 mg/mL.*

TABLE I - INTRAOCULAR LEVOFLOXACIN CONCENTRATIONS (μg/mL) IN THE THREE GROUPS

Patient no.	Group 1			Group 2			Group 3		
	Diagnosis	Aqueous	Vitreous	Diagnosis	Aqueous	Vitreous	Diagnosis	Aqueous	Vitreous
1	PDR	0.51	<0.02	ERM	0.72	1.34	PDR	0.93	1.07
2	PDR	0.28	<0.02	DME	1.35	1.62	DME	2.20	1.90
3	DME	0.94	<0.02	DME	0.98	1.54	MH	2.13	1.06
4	ERM	0.55	<0.02	MHRD	1.77	1.15	MH	1.55	0.84
5	PDR	0.58	<0.02	PDR	1.64	1.90	MHRD	1.61	1.00
6	PDR	0.19	<0.02	MH	0.68	0.64	PDR	2.65	1.54
7	MHRD	1.12	<0.02	RD	0.76	0.91	PDR	2.60	0.71
8	CRVO	2.46	<0.02	MH	1.27	1.63	BRVO	1.61	2.53
9	ERM	0.39	<0.02	ERM	1.37	2.10	PDR	1.22	1.08
10	DME	0.71	<0.02	RD	1.92	1.90	DME	1.39	1.47
11	DME	0.68	<0.02	MH	1.61	1.27	PDR	2.08	1.89
12							PDR	1.76	1.01
13							DME	1.85	1.08
14							DME	1.94	1.98
Mean±SEM		0.765±0.624	<0.02		1.279±0.440	1.445±0.445		1.823±0.490	1.369±0.530

Group 1: topical.* Group 2: oral.† Group 3: topical† and oral.*
*Two drops of 0.5% ophthalmic solution three times on the day before surgery and every 20 minutes for 2 hours on the day of surgery
†200 mg × 2 on the day before surgery and 200 mg at 3 hours before surgery

mean vitreous level was 1.77±0.24 μg/mL. In addition, the mean aqueous concentration of ofloxacin was reported to be 1.44±0.24 μg/mL after topical administration, while the vitreous level was 0.37±0.05 μg/mL. Although aqueous levels of ofloxacin were not significantly different following oral or topical administration (p>0.8), the vitreous level of this drug was significantly higher after oral administration than after topical administration (p<0.001) (4). Thus, topical administration of ofloxacin achieved good penetration into the aqueous humor, but not into the vitreous fluid. Another study has shown good ocular penetration of levofloxacin after oral administration, with the mean aqueous level of the drug after an oral dose of 1000 mg daily being 1.98±1.02 μg/mL (mean ± standard error), while the mean

TABLE II - *IN VITRO* SENSITIVITY TO LEVOFLOXACIN (LVFX): MINIMUM CONCENTRATION INHIBITING 90% OF ISOLATES (μg/mL) (1, 2)

Pathogen	MIC^{90} of LVFX (μg/mL)
Bacillus cereus	2.0
Enterococcus faecalis	1.0–3.13
Staphylococcus aureus	0.25–0.5
Staphylococcus epidermidis	0.25–0.41
Streptococcus pneumoniae	0.06–2.0
Haemophilus influenzae	0.015–0.05
Pseudomonas aeruginosa	1.0–8.0
Propionibacterium acnes	0.75

vitreous level was 2.48±0.68 μg/mL (7).

In the present study, oral administration of levofloxacin achieved good penetration into both aqueous and vitreous, whereas topical application resulted in poor penetration of the vitreous (Tab. I). Such lower vitreous concentrations may have been related to the strong barriers required to penetrate into vitreous space, and also to dilution by the larger volume of vitreous fluid compared with aqueous humor (4). After oral administration, however, there was no statistical difference of the levofloxacin concentration between aqueous humor and vitreous fluid.

Aqueous humor levels of levofloxacin showed a significant difference following oral versus topical administration (p=0.027) (Fig. 1). Oral administration of at least 200 mg of levofloxacin at 3–6 hours before surgery achieved aqueous levels comparable to those seen after repeated topical application. Interestingly, the levofloxacin level in the aqueous humor after combined oral and topical administration was significantly higher than that achieved by oral administration alone (p=0.014) (Fig. 1). This suggests that there was an additive effect between oral and topical administration of the drug.

The mean vitreous concentration of levofloxacin after oral administration alone was higher than that after combined administration (Fig. 2). Although the type of patients included in each group and the small sample size of our study may account for this result, this finding suggests that there was no additive effect on the vitreous concentration after oral plus topical administration of the drug. Further investigation will be required to determine whether the failure to increase vitreous levels after topical application was secondary to factors such as poor retinal circulation, breakdown of the blood-retinal barrier, or more rapid vitreous clearance.

Based on previous findings, the mean inhibitory concentration of levofloxacin was achieved for many of the gram-positive and gram-negative organisms responsible for endophthalmitis, apart from *Bacillus cereus, Enterococcus faecalis*, and *Pseudomonas aeruginosa* in aqueous humor, or *Enterococcus faecalis* and *P aeruginosa* in vitreous fluid (1, 2). In patients given an oral dose of 500 mg of levofloxacin, inhibitory levels for a variety of gram-negative organisms were reached in the vitreous after approximately 200 minutes, but not after 80 minutes. When the concentration of levofloxacin after two doses of 500 mg was compared with that achieved after a single dose, two doses produced higher drug levels (7). These results indicate that the half-life of levofloxacin (nearly 8 hours [1]) is long enough to allow for once-daily dosing, but twice-daily administration will achieve inhibitory intraocular concentrations for the majority of ocular pathogens although a single dose will fail to do so. These results also indicate that about 3 hours is required before levofloxacin shows an adequate antibacterial effect.

In our study, the schedule for oral administration of levofloxacin (200 mg twice on the day before surgery and 200 mg at 3 hours before the operation) was planned to achieve a high concentration. Inhibitory levels for most ocular pathogens were obtained in both aqueous humor and vitreous fluid after oral administration of levofloxacin at a dose of 400 mg/day (200 mg bid), but the levels were lower than in a previous study (7). In the vitreous fluid, levels above the MIC_{90} were reached for *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Haemophilus influenzae*, but not for *B cereus, E faecalis*, or *P aeruginosa*. Inhibitory concentrations were also achieved for the anaerobic *Propionibacterium acnes* (Tab. II). In addition, combined topical application and oral administration of levofloxacin caused a further increase in the aqueous humor concentration.

CONCLUSIONS

Inhibitory aqueous and vitreous levels (above the MIC_{90}) for many ocular pathogens were achieved when levofloxacin was administered orally at a dose of 400 mg/day (200 mg bid). However, the concentration of levofloxacin in the aqueous humor was lower after topical application than after oral administration. The aqueous humor levels of levofloxacin achieved with administration

via both routes exceeded the MIC_{90} for many of the bacteria that frequently cause intraocular infections. On the other hand, penetration of levofloxacin into the vitreous fluid after topical application was less effective than that achieved after oral administration. The excellent posterior segment penetration of oral levofloxacin should provide broad-spectrum coverage in patients with penetrating eye injuries or for surgical prophylaxis, and this drug could possibly be used as adjunctive therapy for endophthalmitis. Topical plus oral application of levofloxacin had an additive effect on the aqueous concentration, but not on the vitreous concentration.

Proprietary interest: None.

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