

Intraocular Ciprofloxacin Levels after Oral Administration in Silicone Oil-Filled Eyes

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PURPOSE. To evaluate penetration of oral ciprofloxacin in the retro-silicone oil space fluid (RSOF) in silicone oil (SO)-filled eyes.

METHODS. One dose of 750 mg ciprofloxacin was given to two groups of five patients with vitrectomized eyes with SO endotamponade, 4 hours (group I) and 8 hours (group II) before SO removal. In 10 vitrectomized eyes with SO endotamponade (group III) and another 10 patients scheduled for vitrectomy for the first time (group IV), two 750-mg doses every 12 hours, with the last dose 12 hours before surgery, were given. Blood samples were taken at the time of collection of RSOF samples in groups I, II, and III and of the vitreous in group IV. All samples were assayed for ciprofloxacin by high-performance liquid chromatography.

RESULTS. The mean drug concentration in the RSOF was 0.34 ± 0.09 , 0.37 ± 0.04 , 0.84 ± 0.29 , and 0.44 ± 0.11 $\mu\text{g/mL}$ in groups I, II, III, and IV respectively. The mean serum concentration was 1.29 ± 0.63 , 1.08 ± 0.14 , 1.93 ± 0.84 , and 1.34 ± 0.55 $\mu\text{g/mL}$ in groups I, II, III, and IV respectively with no statistically significant difference between groups III and IV ($P = 0.081$).

CONCLUSIONS. Antibiotic levels in the RSOF in SO-filled eyes after oral administration of ciprofloxacin in two 750-mg doses exceeded the minimal inhibitory concentration for 90% of isolates (MIC_{90}) for most bacterial species and was higher than levels reached in the vitreous in nonvitrectomized eyes ($P = 0.001$). (*Invest Ophthalmol Vis Sci.* 2003;44:505-509) DOI: 10.1167/iovs.02-0499

Ciprofloxacin is a broad-spectrum¹ fluoroquinolone used by different routes of administration in the prevention and treatment of ocular infections. Its high penetration into tissues and biological fluids,² including aqueous and vitreous humor, and its favorable pharmacokinetic profile³ makes it a useful agent for this purpose. Studies have shown that the penetration of oral ciprofloxacin into the human vitreous is clinically significant.⁴⁻⁸ However, the presence of intraocular substitutes that are used as adjuncts in many patients after vitrectomy, could influence the intravitreal pharmacokinetics of systemically administered antibiotics. Mansour et al.⁹ showed in an experimental study in rabbit eyes that the antibiotic levels reached in perfluoropropane-filled eyes after intramuscular ad-

ministration of cefazolin were comparable to the levels reached in vitrectomized eyes without intraocular gas tamponade. We could find no studies, however, that have attempted to demonstrate the possible effect of vitreous substitutes, such as silicone oil (SO) and intraocular gases, on the intravitreal pharmacokinetics of systemically administered antibiotics in human eyes. To develop greater understanding of the role of SO endotamponade on the pharmacokinetics of ciprofloxacin, we studied the penetration of ciprofloxacin in the retro-SO space fluid (RSOF) in SO-filled eyes.

METHODS

Twenty patients who had previously undergone vitrectomy with SO endotamponade and 10 other patients who were undergoing vitrectomy for the first time were enrolled for this prospective randomized study performed from June 2000 to October 2001. In consonance with the tenets of the Declaration of Helsinki for research in human subjects, the study was approved by the Ophthalmic Research Association of Dr. Rajendra Prasad Centre comprising the chief, the faculty, and the residents. Informed consent was obtained from all the patients before the surgical procedure. All patients with silicone oil endotamponade had aphakia except one who had pseudophakia. There was no capsular remnant in any of the aphakic eyes. All patients with significant renal or hepatic disease or allergy to quinolones, pregnant women, and patients who had received any systemic or topical ciprofloxacin in the 2 weeks preceding evaluation were excluded from the study.

One dose of 750 mg ciprofloxacin was given in two groups of five patients with vitrectomized eyes with SO endotamponade, 4 hours (group I) and 8 hours (group II) before removal of the SO. Another 10 patients with vitrectomized eyes with SO endotamponade (group III) received two doses of oral ciprofloxacin every 12 hours, with the last dose administered 12 hours before removal of the SO. A computer-generated program of random numbers was used for randomization of patients into the three groups. Indications for the previous surgery in the SO-filled eyes were retinal detachment with proliferative vitreoretinopathy ($n = 12$), posttraumatic endophthalmitis ($n = 7$), and retained intraocular foreign body ($n = 1$). No patient with any open peripheral or posterior break was included in any of the groups.

Ten patients with phakic eyes who were undergoing vitrectomy for the first time (group IV) received the same preoperative dose of antibiotic as group III. Indications for vitrectomy in group IV were diabetic vitreous hemorrhage ($n = 3$), Eales' disease ($n = 3$), traumatic vitreous hemorrhage ($n = 2$), branch retinal vein occlusion ($n = 1$), and asteroid hyalosis ($n = 1$). Patients who were undergoing vitrectomy for fresh vitreous hemorrhage were excluded.

Surgical Procedure

The technique for removal of the fluid from the retro-SO space is reported elsewhere (Talwar D et al., manuscript submitted, 2002). A standard three-port pars plana approach was adopted in these patients (groups I, II, and III). The infusion cannula was placed inferotemporally 3 mm from the limbus and secured with a mattress Vicryl 6-0 suture. The infusion cannula was connected to a syringe filled with SO, preferably of the same brand as had been instilled previously in the eye under consideration. In eyes with preexisting hypotony, 1 to 2 mL of SO was injected to build up the intraocular pressure. The nozzle of a

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tuberculin syringe, from which the plunger has been removed, was connected to a 27-gauge cannula (Healon; Alcon Labs, Fort Worth, TX). The distal end of an intravenous fluid tubing, which had been cut short to 10 cm in length, was tightly connected to the distal end of the tuberculin syringe. The proximal end of the intravenous tubing was tightly fitted over the nozzle of a 10-mL disposable syringe. Under visualization with the help of a fundus contact lens and an endoilluminator, the cannula attached to the tuberculin syringe was maneuvered into the retro-SO space just above and nasal to the disc. The fluid in the retro-SO space was aspirated with a controlled suction applied by the assistant. Once enough fluid for sampling had been aspirated, the inferotemporal infusion cannula tubing was disconnected from the syringe filled with SO and immediately connected to the intraocular irrigation fluid. The sampled fluid was then transferred to sterilized vials for analysis while the surgeon proceeded with the procedure for removal of SO.

In patients undergoing vitrectomy (group IV), the ports were made similarly 4 mm from the limbus in phakic eyes. Before turning on the infusion, 0.3 to 0.5 mL of a vitreous humor sample was collected from the midvitreous cavity by using a vitreous cutter attached to a syringe which was used for manually aspirating the vitreous being cut by the cutter.¹⁰ This was then transferred to sterile vials. Simultaneously, venous blood samples were obtained in all the cases. Twenty-four hours later, serum was separated from the whole blood by centrifugation. All the samples were frozen at -70°C until assays were performed.

To ensure absence of bias, the investigators estimating the ciprofloxacin levels were not informed regarding the status of the eyes from which the samples had been obtained. Furthermore, as a check on the accuracy of the estimation of ciprofloxacin, the investigators were also sent two samples with different concentrations of the drug. These had been prepared from a commercially available intravenous antibiotic bottle and had been suitably diluted to obtain concentrations of 2 $\mu\text{g}/\text{mL}$ and 0.2 $\mu\text{g}/\text{mL}$ ciprofloxacin.

Estimation of the Concentration of Ciprofloxacin

A solvent delivery pump (model 510; Waters, Milford, MA) connected to an injector (No. 72251; Rheodyne, Cotati, CA) fitted with a 20- μL

loop and a photodiode array detector (model 996; Waters) were used. The data acquisition and integration were performed on computer (Millennium-32 software; Waters, operated by a Pentium II, Intel, Inc., Mountain Valley, CA, 350-MHz microprocessor). The mobile phase consisted of an aqueous solution of potassium phosphate buffer (0.05 M, pH 3) and acetonitrile in a ratio of 7:3. After mixing the solution, the mobile phase was filtered, degassed, and pumped at the flow rate of 1 mL/min. A C18 column (130 \times 4.3 mm; 4 μm particle size; Nova-Pak, Waters) was used for analytical separation. The UV detection for ciprofloxacin was achieved at 275 nm, and its UV spectrum was confirmed with the photodiode array (PDA) option. The vitreous or serum (100 μL) was mixed with 200 μL of acetonitrile, vortexed for 2 minutes, and centrifuged at 1800g for 5 minutes. Twenty microliters of the supernatant was injected into the high-performance liquid chromatography (HPLC) column for quantification. A separate calibration curve (concentration versus peak area) was plotted by spiking a known amount of ciprofloxacin in drug-free aqueous, vitreous, and serum at various concentration levels. This calibration curve was used for the calculation of levels of ciprofloxacin from the RSOF in SO-filled eyes, vitreous, and the serum.

Statistical Analysis

Statistical evaluation of the results was performed using an unpaired Student's *t*-test. Results were considered statistically significant at $P < 0.05$.

RESULTS

The mean age of the 20 patients who underwent SO removal in the three groups (groups I, II, and III) was 25, 29, and 32 years respectively (range, 14–72). There was no significant difference in the age of the patients in the three groups ($P = 0.809$). The mean age of the 10 patients undergoing vitrectomy for the first time (group IV) was 43 years, with a range from 20 to 70 years. There were four males and one female in group I, three males and two females in group II, eight males and two females in group III, and six males and four females in group IV.

TABLE 1. Ciprofloxacin Levels in Retrosilicone Oil Space in Groups I, II, and III

Patient	Age/Sex	Diagnosis	TIME (h)	RSOF Levels ($\mu\text{g}/\text{mL}$)	Serum Levels ($\mu\text{g}/\text{mL}$)	RSOF/Serum Ratio
Group I						
1	14/M	(L)opVR for PTE	4	0.35	1.05	0.33
2	30/M	(L)opVR for RD	4	0.22	1.28	0.17
3	14/F	(L)opVR for RD	4	0.42	0.62	0.68
4	25/M	(R)opVR for RD	4	0.46	1.2	0.38
5	45/M	(L)opVR for RD	4	0.28	2.34	0.12
Group II						
6	14/F	(L)opVR for RD	8	0.35	0.93	0.38
7	18/M	(R)opVR for PTE	8	0.44	1.03	0.43
8	20/M	(L)opVR for RD	8	0.32	1.05	0.30
9	35/M	(R)opVR for GRT	8	0.41	1.32	0.31
10	60/F	(L)opVR for RD	8	0.34	1.07	0.32
Group III						
11	25/M	(R)opVR for RIFB	24 + 12	0.46	1.07	0.43
12	16/M	(R)opVR for GRT	24 + 12	0.93	2.4	0.39
13	72/M	(L)opVR for PTE	24 + 12	1.07	2.28	0.47
14	20/M	(R)opVR for PTE	24 + 12	0.62	1.28	0.48
15	40/M	(L)opVR for RD	24 + 12	0.89	1.49	0.60
16	44/F	(L)opVR for RD	24 + 12	1.49	3.69	0.40
17	52/M	(L)opVR for RD	24 + 12	0.88	2.34	0.38
18	20/M	(R)opVR for PTE	24 + 12	0.69	2.44	0.28
19	14/F	(R)opVR for PTE	24 + 12	0.88	1.5	0.59
20	17/M	(R)opVR for PTE	24 + 12	0.57	0.89	0.64

opVR, vitreoretinal surgery; PTE, posttraumatic endophthalmitis; RD, complex retinal detachment; GRT, giant retinal tear; RIFB, retained intraocular foreign body.

TABLE 2. Intraocular and Serum Ciprofloxacin Levels in Different Groups

Group	Mean Age (y)	Mean RSOF OR Vitreous Levels ($\mu\text{g/mL}$)	Mean Serum Level ($\mu\text{g/mL}$)	Mean Intraocular/Serum Ratio
I	25	0.34 ± 0.09	1.29 ± 0.63	0.33
II	29	0.37 ± 0.04	1.08 ± 0.14	0.34
III	32	0.84 ± 0.29	1.93 ± 0.84	0.46
IV	43	0.44 ± 0.11	1.34 ± 0.55	0.35

The mean concentrations of ciprofloxacin in the RSOF in groups I, II, and III and the range are given in Tables 1 and 2. The Ciprofloxacin levels in RSOF in group III were significantly higher than those in groups I ($P = 0.003$) and II ($P = 0.004$).

In group IV, the mean vitreous concentration of ciprofloxacin was $0.44 \pm 0.11 \mu\text{g/mL}$ (range, 0.28–0.62; Table 3). Ciprofloxacin levels in the RSOF in group III were significantly higher than the vitreous drug concentration in group IV ($P = 0.001$).

The mean serum concentration was 1.29 ± 0.63 , 1.08 ± 0.14 , 1.93 ± 0.84 , and $1.34 \pm 0.55 \mu\text{g/mL}$ in groups I, II, III, and IV, respectively, with no statistically significant difference between groups III and IV ($P = 0.081$). The concentrations estimated by the investigator performing the HPLC in the two samples sent to test for accuracy of ciprofloxacin estimation were 2.2 and $0.23 \mu\text{g/mL}$ in the samples with a concentration of 2 and $0.2 \mu\text{g/mL}$, respectively.

The ratio of the concentration of ciprofloxacin in the RSOF to the serum concentration (RSOF-to-serum ratio) was also calculated for all the patients in each of the groups. The mean RSOF-to-serum ratio in patients in group III (0.46 ± 0.11) was greater than the ratio of the concentration of ciprofloxacin in the vitreous to the serum concentration (VIT-to-serum ratio) in group IV (0.35 ± 0.10) and was statistically significant ($P = 0.028$). The mean RSOF-to-serum ratios in groups I and II were similar (0.33 ± 0.22 and 0.34 ± 0.05 , respectively). The mean RSOF-to-serum ratio of combined groups I and II was 0.34 ± 0.04 , which was lower than the mean RSOF-to-serum ratio in group III ($P = 0.055$).

Groups III and IV showed a significant correlation of intraocular concentration to serum concentration with a correlation coefficient of 0.854 ($P = 0.002$) in group III, and 0.681 ($P = 0.030$) in group IV. Such a correlation was absent in groups I and II.

DISCUSSION

There have been major developments in surgical techniques for management of vitreoretinal disorders in the past two

decades.¹¹ Foremost among these has been the use of vitreous substitutes^{12,13} for intermediate or long-term tamponade of the retina, which has significantly influenced the outcome of vitreous surgery in recent times. Vitreous substitutes such as SO and perfluoropropane gas are used increasingly today in the treatment of complex retinal detachments.^{12,13} Rarely, endophthalmitis has been reported in eyes that have undergone vitreoretinal surgery with SO endotamponade.¹⁴ Furthermore, the role of SO endotamponade has been described recently in the management of posttraumatic endophthalmitis.¹⁵

The pharmacokinetics of systemically administered antibiotics in SO-filled eyes would therefore be of interest to the clinician. The present study was an attempt to find out whether systemically administered antibiotics could reach intraocular concentrations higher than the MIC₉₀ levels for common pathogens responsible for intraocular infection in eyes with SO endotamponade.

SO or intraocular gases are immiscible with water. When injected into the eye for intraocular tamponade, SO occupies almost the entire vitreous cavity. Only a small amount of fluid is usually present in the space between the SO bubble and the retinal surface (retro-SO space) in these eyes. Consequently, the entire amount of a drug entering into the intraocular space after systemic administration would remain sequestered in the RSOF, because it is not possible for it to disperse into the vitreous cavity. The presence of SO in the vitreous cavity could also by itself alter the blood-ocular barrier¹⁶ and thus alter the intraocular drug levels reached after systemic administration of antibiotics. However, there are no studies available that have evaluated the penetration of antibiotics into the RSOF in SO-filled eyes. In the only relevant study on the subject, Mansour et al.⁹ studied the intraocular antibiotic levels reached after vitrectomy with perfluoropropane injection in an experimental study in an endophthalmitis model of rabbit eyes. In this study, intraocular antibiotic levels after intramuscular injection of cefazolin were found to be similar in vitrectomized eyes, with or without perfluoropropane gas tamponade. Based on their results, they hypothesized that intraocular gas tamponade

TABLE 3. Intravitreal Ciprofloxacin Levels in Group IV

Patient	Age/Sex	Diagnosis	Time (h)	Vitreous Levels ($\mu\text{g/mL}$)	Serum Levels ($\mu\text{g/mL}$)	Vitreous/Serum Ratio
1	30/M	(R) Vit. hem. in Eales vasc.	24 + 12	0.62	2.4	0.26
2	70/F	(L) Asteroid hyalosis	24 + 12	0.49	1.07	0.46
3	35/M	(R) Vit. hem. in Eales vasc.	24 + 12	0.4	1.28	0.31
4	25/M	(R) Traumatic vit. hem.	24 + 12	0.58	2.34	0.25
5	54/F	(L) Vit. hem. with PDR	24 + 12	0.5	1.03	0.49
6	60/F	(R) Vit. hem. with PDR	24 + 12	0.29	1.05	0.28
7	62/M	(L) Vit. hem. with BRVO	24 + 12	0.28	1.03	0.27
8	20/M	(R) Vit. hem. in Eales' vasc	24 + 12	0.42	0.93	0.45
9	30/M	(R) Traumatic vit. hem.	24 + 12	0.33	1.28	0.26
10	50/F	(L) Vit. hem. with PDR	24 + 12	0.49	1.05	0.49

vit. hem., vitreous hemorrhage; Eales vasc., Eales vasculitis; PDR, proliferative diabetic retinopathy; BRVO, branch retinal vein occlusion.

TABLE 4. MIC₉₀ of Common Ocular Pathogens for Ciprofloxacin

Bacterial Species	MIC ₉₀ ($\mu\text{g/ml}$)*	MIC ₉₀ ($\mu\text{g/ml}$)†
<i>Escherichia coli</i>	0.083	0.02
<i>Enterobacter</i>	0.206	
<i>Klebsiella</i>	0.295	
<i>Proteus</i>	0.267	0.06
<i>Pseudomonas</i>	0.626	0.50
<i>Haemophilus influenzae</i>	0.014	
<i>Staphylococcus aureus</i>	0.796	0.57
<i>Staphylococcus epidermidis</i>	0.375	0.25
<i>Streptococcus pyogenes</i>	0.782	
<i>Propionibacterium acnes</i>		0.35
<i>Bacillus cereus</i>		0.25
<i>Serratia</i>		0.12

* Keren et al.⁴† Lebel and Bergeron¹⁷

may have a role in the surgical management of endophthalmitis.⁹

The MIC₉₀ for the different bacterial species studied by various investigators^{4,17} is shown in Table 4. In a recent study of pharmacokinetics of ciprofloxacin in the human eye by Morlet et al.⁸ the MIC₉₀ for common ocular pathogens was considered to be 0.5 $\mu\text{g/ml}$. It was observed that after administration of two doses of 750 mg ciprofloxacin 12 hours apart, the concentrations in both aqueous and vitreous were lower than the MIC₉₀ for common bacterial ocular pathogens in many patients. The present study considered 0.8 $\mu\text{g/ml}$ as the MIC₉₀ for common ocular pathogens, including *Staphylococcus aureus*, *Streptococcus*, and *Pseudomonas*, based on the results of previous studies (Table 4). Intraocular ciprofloxacin levels greater than the MIC₉₀ for these pathogens were reached in 6 of the 10 eyes in group III. In contrast, none of the eyes in group IV reached an intraocular concentration more than 0.8 $\mu\text{g/ml}$ ($P = 0.0147$). It is important to remember that all the eyes in group III were aphakic except one, which was pseudophakic, compared with group IV where all eyes were phakic. The clearance of intravitreal drugs is faster in aphakic eyes due to the aqueous pathway's being available for removal of the antibiotic, along with the posterior route.¹⁸ However, despite this, the antibiotic concentrations were higher in the RSOF.

The RSOF levels reached after multiple doses of ciprofloxacin were higher than those after a single dose (Table 1). However, any comparison of intraocular drug levels in different groups must be accompanied with assessment of the serum levels of the antibiotics. The mean serum level in group III was 44% higher than that in group IV, but the difference was not statistically significant ($P = 0.081$). This could have been a consequence of the large variability in the serum levels of ciprofloxacin in our patients (as evident from the high standard deviation; Table 2). A similarly high interpatient variation in serum levels was also observed by Morlet et al.⁸ It is therefore more prudent to evaluate the intraocular to serum antibiotic ratio in different groups. The ratio of intraocular to serum antibiotic levels in patients with SO-filled eyes was significantly higher (31% greater than that in nonvitrectomized eyes; $P = 0.028$). This suggests that in the presence of similar serum antibiotic levels, eyes with SO endotamponade are likely to have significantly higher intraocular levels of antibiotic than are nonvitrectomized eyes. This may be a consequence of accumulation of the drug in the retro-SO space in SO-filled eyes.

It should also be noted that in groups I, II, and III, patients with open breaks were excluded to obviate the effects of a

bare choroid or an open break in communication with the vitreous cavity, on the intraocular levels of the antibiotics. We were careful to exclude all patients with any such condition during the enrollment process for this study, to rule out the possibility that the higher antibiotic levels in SO-filled eyes were a consequence of the increased antibiotic permeability into the vitreous cavity through the exposed choroid. It could be argued that the lower intravitreal levels in group IV may have been due to the samples' being taken from the midvitreal cavity compared with group III, where the RSOF was harvested in proximity to the retina. However, the midvitreal was considered to be the safest site for sampling in group IV during the initial phase of vitrectomy before starting the infusion fluid. Moreover this was considered to be adequate based on previous studies that have shown that dispersal of molecules, especially water-soluble molecules, within the vitreous cavity is usually complete within a period of a few hours after systemic administration.¹⁹⁻²¹

In the present study, we therefore concluded that the compartmentalization of the vitreous cavity by SO would help to maintain therapeutic antibiotic levels of ciprofloxacin in the RSOF after systemic administration and may have a role in management of intraocular infection in patients with SO-filled eyes.

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