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Pharmacokinetics of Intravitreal Vancomycin and Ceftazidime in Silicone Oil-Filled Macaque Eyes

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Purpose: This study evaluated the pharmacokinetics of intravitreal vancomycin and ceftazidime in the aqueous humor of macaque eyes filled with silicone oil in the vitreous cavity.

Methods: Intravitreal vancomycin (1 mg/0.1 mL) and ceftazidime (2 mg/0.1 mL) were injected into four normal macaque eyes, four vitrectomized aphakic macaque eyes, and four previously vitrectomized aphakic macaque eyes filled with silicone oil (silicone oil-filled eyes). Aqueous humor samples (0.1 mL) were obtained just before injection and at 2 and 5 hours and 1, 2, 3, 5, 7, and 10 days after injection. In each group, corneal endothelial cell density (ECD) measurements and electroretinogram (ERG) recordings were obtained before injection and after 1 month.

Results: The half-lives of vancomycin in the aqueous humor of normal, vitrectomized, and silicone oil-filled eyes were 29.4, 21.1, and 6.8 hours, respectively, and those of ceftazidime were 20.4, 5.2, and 3.1 hours, respectively. The maximum vancomycin aqueous humor concentrations of normal, vitrectomized, and silicone oil-filled eyes were 151.4, 205.6, and 543.5 µg/mL, respectively, and the maximum ceftazidime aqueous humor concentrations are 64.6, 260.0, and 1176.3 µg/mL, respectively. There was no change in ECD, and ERG was not declined after intravitreal injection in all groups.

Conclusions: The half-lives of vancomycin and ceftazidime in the aqueous humor were shorter in silicone oil-filled eyes than in normal and vitrectomized eyes. High antibiotic concentrations in silicone oil-filled eyes seemed to be well tolerated.

Translational Relevance: This study aids in estimating how often an antibiotic should be intravitreally injected for endophthalmitis of silicone oil-filled eyes.

Introduction

Bacterial endophthalmitis is a potential complication of ocular surgery and ocular trauma that could lead to irreversible loss of vision if not treated promptly.¹⁻³ Since publication of the Endophthalmitis Vitrectomy Study in 1995,¹ intravitreal antibiotics have been recommended for its treatment. Vancomycin is nontoxic in clinical doses and is effective against almost all gram-positive bacteria, includ-

ing methicillin-resistant *Staphylococcus aureus*.^{1,4,5} In the past, aminoglycoside antibiotics, such as amikacin and gentamicin, were widely used for gram-negative bacteria^{1,6,7}; however, macular infarction may occur after intravitreal injection.⁷ Intravitreal ceftazidime, a wide spectrum cephem antibiotic, is as effective as aminoglycosides for gram-negative bacteria but has a low risk of causing macular infarction.⁸ Currently, a combination of vancomycin and ceftazidime is commonly used for endophthalmitis or suspected endophthalmitis.^{6,9,10}

In cases of bacterial endophthalmitis that do not respond to intravitreal vancomycin and ceftazidime, vitrectomy is performed to remove the focus of infection as much as possible. If a retinal tear or detachment is found or caused during vitrectomy, silicone oil may be a possible tamponade.^{11–13} Intravitreal vancomycin and ceftazidime should be continued even after surgery. In addition, endophthalmitis may occur after retinal detachment surgery that requires silicone oil tamponade. In such cases, intravitreal vancomycin and ceftazidime are necessary after surgery. However, the pharmacokinetics of these drugs are likely to differ in silicone oil-filled eyes compared to normal eyes, as they are not oil-soluble and the volume of water distribution is much smaller in silicone oil-filled eyes.^{12,14–16} Therefore, the maximum concentrations and excretion rates are expected to be higher in silicone oil-filled eyes. Not only is it unclear how long effective antibiotic concentrations can be maintained, but there is also concern regarding ocular toxicity due to the temporarily high concentrations of vancomycin and ceftazidime.

Talwar et al. studied intraocular ciprofloxacin levels after oral administration in silicone oil-filled eyes and found that antibiotic levels in the retro-silicone oil space fluid in silicone oil-filled eyes after oral administration of ciprofloxacin in two 750-mg doses exceeded the minimal inhibitory concentration for 90% (MIC90) of most bacterial species and was higher than the levels in the vitreous in nonvitrectomized eyes.¹⁷ However, to the best of our knowledge, no studies have been conducted on intraocular pharmacokinetics of intravitreally injected antibiotics or other drugs in silicone oil-filled eyes. This study aimed to investigate the intraocular pharmacokinetics of vancomycin and ceftazidime and their toxicity in silicone oil-filled eyes using cynomolgus monkeys.

Methods

This study was conducted in accordance with the principles of the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research. The animal research protocol was approved by the Animal Experimentation Committee at Shiga University of Medical Science (Approval no.: 2017-8-2).

A total of eight male cynomolgus macaques were used in this study. Each macaque was anesthetized with 5 mg/kg intramuscular ketamine hydrochloride and 1 mg/kg intramuscular xylazine hydrochloride. After povidone-iodine was placed on the conjunctiva of each

eye, four macaques underwent pars plana vitrectomy with lensectomy of the right eye. Intravitreal injections of vancomycin and ceftazidime were administered to four normal eyes and four vitrectomized aphakic eyes. After povidone-iodine was placed on the conjunctiva of each eye, vancomycin (1 mg/0.1 mL) and ceftazidime (2 mg/0.1 mL) were injected into the vitreous cavity of the right eye of each macaque using a 30-gauge needle. Aqueous humor samples (0.1 mL) from the right eye were obtained with a 29-gauge needle just before injection and at 2 and 5 hours and 1, 2, 3, 5, 7, and 10 days after injection.

Three months later, vitreous surgery with silicone oil (1000 centistoke) tamponade was performed on the four vitrectomized eyes. The same experiment was conducted on the four silicone oil-filled eyes. The depth of the anterior chamber remained normal at all times after the samples were obtained. All samples were stored in a freezer at -80°C until analysis.

ECD Measurement

Endothelial cell density (ECD) was measured by a noncontact specular microscope (TOPCON SP-2000P; Topcon, Tokyo, Japan) before injection and at 1 month postoperatively. The macaques were anesthetized for measurement as described above. Three ECD measurements were obtained for each eye and the average value was calculated.

Electroretinogram Recording

For electroretinogram (ERG) recordings, all macaques were dark-adapted for 30 minutes prior to testing and anesthetized as described above. After complete pupillary dilation in both eyes, retinal ERG signals were recorded from the cornea using a contact light-emitting diode stimulator. In the stimulation paradigm, a series of flashes (20 J, 200 ms duration) were delivered from the stimulator. The a-waves were measured from the baseline to the trough of the first negative response, and the b-waves from the first trough to the peak of the following positive wave. Oscillatory potential amplitudes (OP1, OP2, and OP3) were measured, summed, and designated as ΣOPs , as previously reported.^{18,19} ERG was measured by a portable ERG device (PE-300; Toyo Medical, Aichi, Japan) before injection and at 1 month postoperatively. In silicone oil-filled eyes, the ERG was measured after removing the silicone oil. Three measurements were obtained for each eye and the average value of the amplitude of each waveform was calculated.

Determination of Vancomycin and Ceftazidime Concentrations in Aqueous Humor

Aqueous humor samples were stored at -80°C until analysis. Aqueous humor vancomycin and ceftazidime concentrations were determined using high performance liquid chromatography with ultraviolet detection (HPLC-UV). HPLC analysis was performed using the Prominence HPLC system (Shimadzu, Kyoto, Japan). As the deproteinization treatment, 100 μL of acetonitrile containing 6.25 $\mu\text{g}/\text{mL}$ of internal standard tinidazole was added to 20 μL of aqueous humor sample. After centrifugation at 12,000 rpm for 10 minutes at 4°C , the supernatant was separated and evaporated to dryness at 40°C . The obtained residue was reconstituted in 200 μL of sodium phosphate buffer (20 mM, pH 2.5). Ten microliters of the reconstituted solution were injected into the HPLC system after filtration. Chromatographic separation was carried out using the Shim-Pack XR-ODS column (75 mm \times 3.0 mm) at 40°C . The flow rate was 0.6 mL/min with the following gradient elution. Sodium phosphate buffer (20 mM, pH 2.5) and acetonitrile were used as mobile phases A and B, respectively. Then, the percentage of mobile phase B was set as follows: 0–6.5 minutes, 7.2%; 6.51 to 7.50 minutes, 40%; and 7.51 to 16 minutes, 7.2%. The detection wavelength was 257 nm for ceftazidime and 240 nm for vancomycin and tinidazole. The calibration curves of vancomycin and ceftazidime were linear at 0.625–40 and 0.625–100 $\mu\text{g}/\text{mL}$, respectively. The lower limit of quantification was 0.625 $\mu\text{g}/\text{mL}$.

Pharmacokinetic Analysis

Intraocular pharmacokinetics were analyzed according to a one-compartment model. If the volume of distribution in the eyeball is defined as V_d , the clearance from the eyeball as CL, and the dose as D, the initial concentration (C_0) is calculated as D/V_d and the elimination rate constant (K_e) as CL/V . The half-life ($t_{1/2}$) is calculated as $\ln(2/K_e)$ and the area under the ocular concentration-time curve (AUC) is calculated as D/CL .

Statistical Analysis

Statistical analyses were performed using PASW Statistics version 18 software (SPSS Japan, Tokyo, Japan). The Kruskal–Wallis test was used to evaluate the pharmacokinetics of vancomycin and ceftazidime. The paired t -test was used to compare differences

between paired data. $P < 0.05$ was considered significant.

Simulation of Pharmacokinetics

Intraocular pharmacokinetics were simulated. For simulation, the dose of the drug was set to 1 mg, and the clearance value used was calculated from the aqueous humor drainage rate (2.8 mL/min).²⁰ Volume of distribution was calculated from the average eyeball volume of cynomolgus monkeys.²¹

Results

In the normal eyes ($n = 4$), mean vancomycin concentration in the aqueous humor peaked at 151.4 $\mu\text{g}/\text{mL}$ at 24 hours (range = 122.5–203.8; Fig. 1) and the half-life of vancomycin in the aqueous humor was 29.4 hours (range = 24.7–36.8; Table 1). Mean vancomycin concentration in the aqueous humor in the vitrectomized eyes ($n = 4$) peaked at 205.6 $\mu\text{g}/\text{mL}$ at 3.5 hours (range = 181.3–228.9; see Fig. 1) and the half-life was 21.1 hours (range = 15.3–28.1; see Table 1). Mean vancomycin concentration in the aqueous humor in the silicone oil-filled eyes ($n = 4$) peaked at 543.5 $\mu\text{g}/\text{mL}$ at 4.25 hours (range = 292.7–720.0; see Fig. 1) and decrease to less than the lower limit of detection on day 5 and thereafter. The half-life was 6.8 hours (range = 4.5–7.9; see Table 1). Mean vancomycin concentration in the aqueous humor significantly differed among the three groups at all time points ($P < 0.05$).

Mean ceftazidime concentration in the aqueous humor in the normal eyes ($n = 4$) peaked at 64.6 $\mu\text{g}/\text{mL}$ at 19.3 hours (range = 21.4–146.1; Fig. 2) and the half-life of ceftazidime in the aqueous humor was 20.4 hours (range = 6.5–35.3; see Table 1). Mean ceftazidime concentration in the aqueous humor in the vitrectomized eyes ($n = 4$) peaked at 260.0 $\mu\text{g}/\text{mL}$ at 3.5 hours (range = 250.3–310.5; see Fig. 2) and decreased to less than the lower limit of detection on day 3 and thereafter. The half-life was 5.2 hours (range = 3.8–7.9; see Table 1). Mean ceftazidime concentrations in the aqueous humor in the silicone oil-filled eyes ($n = 4$) peaked at 1176.3 $\mu\text{g}/\text{mL}$ at 4.3 hours (range = 571.1–1420.6; see Fig. 2) and decreased to less than the lower limit of detection on day 3 and thereafter. The half-life was 3.1 hours (range = 1.7–5.3; see Table 1). Mean ceftazidime concentration in the aqueous humor significantly differed among the 3 groups at 2 hours, 5 hours, 1 day, 3 days, and 5 days ($P < 0.05$).

In normal eyes, mean ECD before injection and at 1 month after injection was 2992 ± 840 and $3050 \pm$

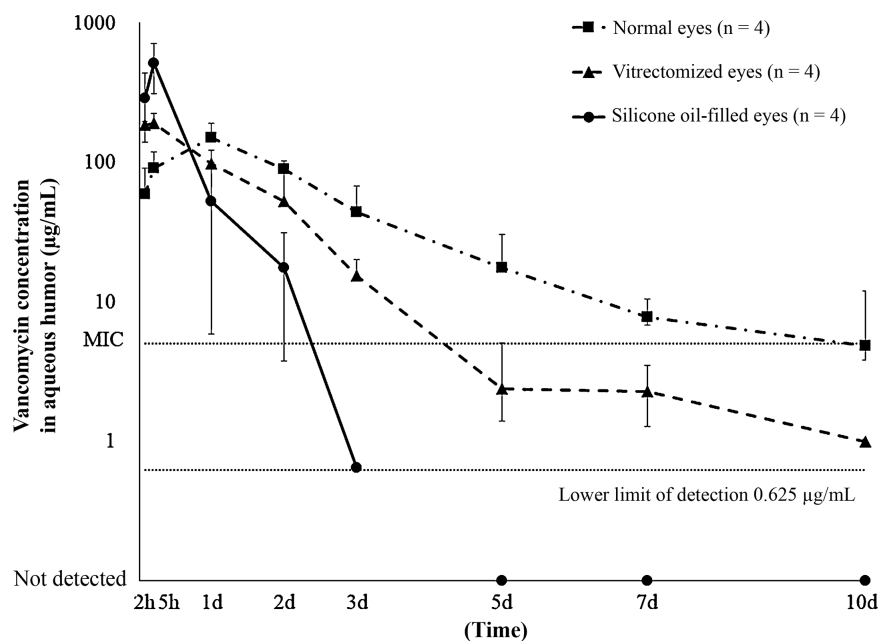


Figure 1. Vancomycin concentrations in the aqueous humor of normal, vitrectomized, and silicone oil-filled eyes after intravitreal injection.

Table 1. Pharmacokinetic Parameters of Vancomycin and Ceftazidime

	Vancomycin			Ceftazidime		
	Normal Eyes (n = 4)	Vitrectomized Eyes (n = 4)	Silicone Oil-Filled Eyes (n = 4)	Normal Eyes (n = 4)	Vitrectomized Eyes (n = 4)	Silicone Oil-Filled Eyes (n = 4)
$C_{max} \pm SD, \mu\text{g/mL}$	151.4 ± 38.5	205.6 ± 19.7	543.5 ± 187.8	64.6 ± 55.7	260.0 ± 35.6	1176.3 ± 405.0
$t_{1/2} \pm SD, \text{h}$	29.4 ± 5.4	21.1 ± 5.4	6.8 ± 2.3	20.4 ± 14.0	5.2 ± 1.9	3.1 ± 1.9
$AUC \pm SD, \text{mg}\cdot\text{h/mL}$	11.2 ± 2.8	6.7 ± 1.9	9.2 ± 6.9	1.4 ± 0.5	2.3 ± 0.5	14.2 ± 10.0

C_{max} , maximum drug concentration; $t_{1/2}$, half-life; h, hour; AUC, area under the curve.

807 cells/mm², respectively. Mean ECD before injection and at 1 month after injection in vitrectomized eyes was 2221 ± 314 and 2143 ± 290 cells/mm², respectively. In silicone oil-filled eyes, mean ECD before injection and at 1 month after injection was 2387 ± 215 and 1992 ± 161 cells/mm², respectively. The differences were not significant.

Amplitudes of the a-wave and b-wave and ΣOPs before and after intravitreal injection of antibiotics are shown in Table 2. There was no significant difference in amplitude or implicit time of each ERG pattern before and after intravitreal injection of antibiotics in all groups.

No complications, such as uveitis or endophthalmitis occurred.

A simulation study shows that maximum drug concentration in the aqueous humor peaked at 322 $\mu\text{g/mL}$ and the half-life in the aqueous humor was 12.8 hours in normal eyes. Maximum drug concentration in

the aqueous humor peaked at 1250 $\mu\text{g/mL}$ and the half-life in the aqueous humor was 3.3 hours in silicone oil-filled eyes (Fig. 3).

Discussion

Compared to normal and vitrectomized eyes, we found that maximum aqueous humor vancomycin and ceftazidime concentrations were higher in silicone oil-filled eyes and their half-lives were shorter. Furthermore, these findings were in agreement with our intraocular pharmacokinetics simulation results. Especially with vancomycin, the results were in good agreement with the simulation. Maximum drug concentration in the normal eye simulation peaked at 322 $\mu\text{g/mL}$ and the half-life was 12.8 hours. Maximum drug concentration in the silicone oil-filled eyes peaked at 1250 $\mu\text{g/mL}$ and the half-life was 3.3 hours. The

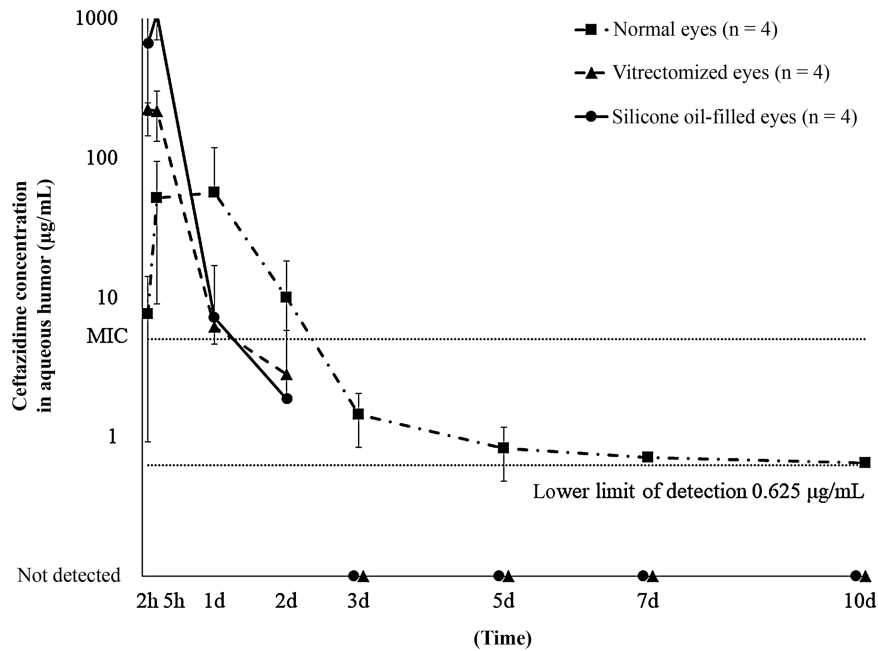


Figure 2. Ceftazidime concentrations in the aqueous humor of normal, vitrectomized, and silicone oil-filled eyes after intravitreal injection.

Table 2. ERG Parameters in Normal Eyes, Vitrectomized Eyes, and Silicone Oil-Filled Eyes

		Normal Eyes		Vitrectomized Eyes		Silicon Oil-Filled Eyes	
		Pre	1M	Pre	1M	Pre	1M
a wave	Amplitude, μV	293.7 ± 31.4	304.0 ± 20.9	345.3 ± 12.3	339.4 ± 15.9	332.0 ± 34.6	327.7 ± 36.0
	Implicit time, ms	9.6 ± 0.3	9.7 ± 0.2	9.2 ± 0.2	9.3 ± 0.4	10.4 ± 0.5	10.5 ± 0.4
b wave	Amplitude, μV	304.0 ± 20.9	338.0 ± 30.8	391.6 ± 1.5	389.3 ± 2.7	374.7 ± 14.7	373.3 ± 11.2
	Implicit time, ms	31.5 ± 2.5	31.2 ± 1.2	33.8 ± 1.7	33.6 ± 1.7	39.8 ± 5.6	34.2 ± 6.2
ΣOPs	μV	124.3 ± 15.9	122.7 ± 15.0	146.2 ± 2.8	144.0 ± 10.7	141.3 ± 21.4	136.0 ± 19.3

ERG, electroretinography; Pre, before injection; 1M, 1 month after injection; ΣOPs , sum of amplitudes of oscillatory potentials.

peak concentration is about four times higher and the half-life is about a quarter shorter in silicone oil-filled eyes in the simulation. In the current study in normal eyes, mean vancomycin concentration peaked at 151.4 $\mu\text{g/mL}$ and the half-life was 29.4 hours. In the silicone oil-filled eyes, mean vancomycin concentration peaked at 543.5 $\mu\text{g/mL}$ and the half-life was 6.8 hours. The peak concentration is also about four times and the half-life is also about a quarter in silicone oil-filled eyes. The results obtained in macaque eyes are supported by the simulation. Vancomycin and ceftazidime are hydrophilic antimicrobials¹⁶; therefore, they do not dissolve in silicone oil. The volume of water distribution is smaller in silicone oil-filled eyes. Therefore, in the current study, the concentration immediately

after administration was high, and the half-life was shortened because the drug was rapidly excreted.

Common gram-positive bacteria that cause endophthalmitis, such as *Staphylococcus*, *Streptococcus*, and *Enterococcus* are almost always susceptible to vancomycin and concentrations of 5 $\mu\text{g/mL}$ are inhibitory.^{16,22–28} In this study, the MIC of vancomycin was set to 5 $\mu\text{g/mL}$. Because we found aqueous humor vancomycin concentrations below the MIC on day 10 for normal eyes, day 5 for vitrectomized eyes, and day 3 for silicone oil-filled eyes, we recommend intravitreal injection of vancomycin every 3 days in silicone oil-filled eyes. Common gram-negative bacteria that cause endophthalmitis, such as *Pseudomonas* species, *Proteus mirabilis* are almost

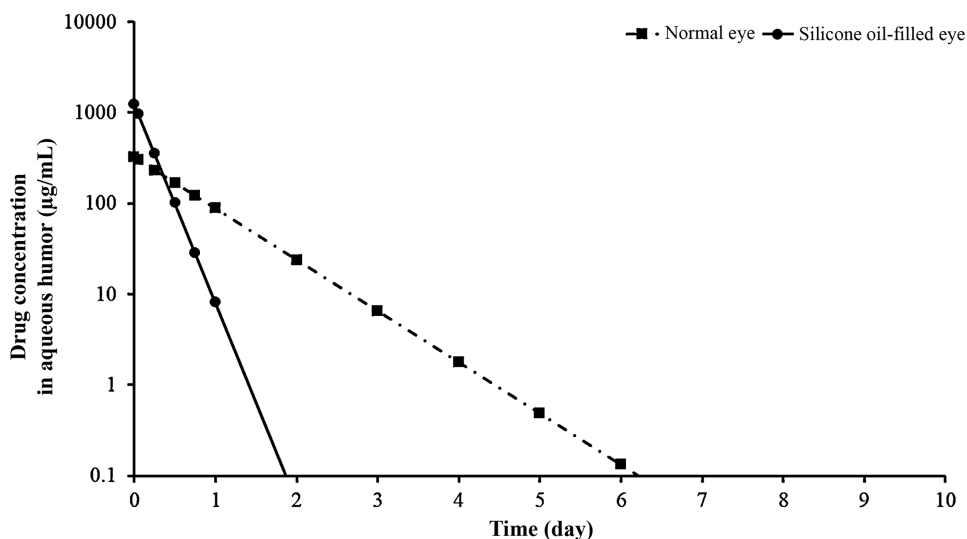


Figure 3. Simulation of intraocular pharmacokinetics in the normal eye and silicone oil-filled eye.

always susceptible to ceftazidime, and concentrations of 5 µg/mL are inhibitory.^{16,26,27,29–32} In this study, the MIC of ceftazidime was set at 5 µg/mL. In our study, aqueous humor ceftazidime concentrations were below MIC at 3 days for normal eyes, on day 2 for vitrectomized eyes, and on day 2 for silicone oil-filled eyes. Therefore, intravitreal injection of ceftazidime is recommended every 2 days for silicone oil-filled eyes.

We also found shorter half-lives of vancomycin and ceftazidime in the aqueous humor in vitrectomized eyes compared with normal eyes. In the current study, after vitrectomy and lensectomy in macaque eyes, the vitreous vancomycin half-life shortened from 29.4 hours to 21.1 hours and the vitreous ceftazidime half-life decreased from 20.4 hours to 5.2 hours. Results from previous studies indicate that vitrectomy with lensectomy shortened the half-life of intravitreal molecules.^{33–38} After vitrectomy and lensectomy in rabbit eyes, the vitreous vancomycin half-life shortened from 25.1 to 9.0 hours,³⁶ and the vitreous ceftazidime half-life shortened from 10.1 to 5.1 hours.³⁴ In our past studies, after vitrectomy and lensectomy in macaque eyes, the half-life shortened from 2.8 to 1.5 days for bevacizumab,^{37,38} from 2.3 to 1.4 days for ranibizumab,³⁵ and from 2.2 to 1.5 days for aflibercept.³⁵ Thus, vitrectomy with lensectomy may increase intravitreal drug clearance.

No change was found in ECD after intravitreal antibiotic injection, although silicone oil-filled eyes exhibited higher peak concentrations of vancomycin and ceftazidime. Previous studies have showed that intravitreal injection of vancomycin does not affect ECD³⁹ and ceftazidime in the aqueous humor does not affect ECD at concentrations up to 3000 µg/mL.⁴⁰

We found no changes in ERG patterns after intravitreal antibiotic injection even in silicone oil-filled eyes showing higher peak concentration of the drugs. Several previous studies have reported that intravitreal injection of vancomycin and ceftazidime does not cause retinal damage.^{5,6,8,9}

Limitations of this study should be mentioned. The number of experimental cynomolgus monkeys used was small. Although antibiotic intraocular pharmacokinetics reportedly change in the setting of endophthalmitis,^{22,36,41,42} we did not examine eyes with endophthalmitis. We clearly showed that intravitreal injections of vancomycin and ceftazidime did not damage the cornea and retina for at least 1 month. However, this time period may not be long enough to show decreases in endothelial cell density or ERG changes because silicone oil tamponade may stay inside the eye for longer than 1 month.

In conclusion, intravitreal injection of vancomycin and ceftazidime shows higher peak concentration of the drugs and shorter half-lives in silicone oil-filled eyes than in vitrectomized and normal eyes. Intravitreal antibiotic injections for endophthalmitis should be administered at shorter intervals in silicone oil-filled eyes.

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