Pharmacokinetics of Intracameral Voriconazole Injection

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Elimination of voriconazole after intracameral injection exhibited an exponential decay with a half-life of 23 min. Voriconazole levels in the vitreous humor were below the detectable limit. The aqueous concentrations achieved with a 25-μg dose during the first 2 h were greater than the previously reported MICs of organisms most involved in fungal endophthalmitis. A rapid decline in intracameral concentration suggests that frequent supplementation of intracameral voriconazole may be required in clinical settings.

Exogenous fungal endophthalmitis, a potentially devastating infection, results from intraocular surgery, ocular trauma, and contiguous spread from fungal keratitis. Intraocular infection is considered to be the mainstay of treatment for fungal endophthalmitis, and amphotericin B was the only antifungal agent approved for intraocular injection in the past. Voriconazole is a broad-spectrum antifungal agent, which inhibits the fungal enzyme cytochrome P450 demethylase. Clinically, voriconazole has been shown to be an effective form of primary therapy in the treatment of invasive aspergillosis and is an effective form of salvage therapy for refractory infections caused by *Fusarium* species (9). In experimental studies, voriconazole has been shown to be less toxic to the retina than amphotericin B and to exhibit an exponential decay with a half-life of 2.5 h in rabbit vitreous humors and a very low aqueous concentration, below the therapeutic levels for fungal species (2, 11). Therefore, intracameral voriconazole injection is considered to be the most direct and effective method for achieving a higher aqueous concentration.

Voriconazole (VFEND; Pfizer, Inc., New York, NY) was obtained in pure powder form and reconstituted in sterile water to obtain a concentration of 25 μg/25 μL. Twenty-three New Zealand White rabbits were used in the study. All care and handling of rabbits were performed in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research, with the approval of the Institutional Authority for Laboratory Animal Care at Taichung Veterans General Hospital. Treatment was administered using a 30-gauge needle attached to a 100-μL microsyringe. An anterior chamber injection of 25 μg voriconazole in 25 μL sterilized distilled water was performed at 11 o’clock, and then the needle penetrated out of the cornea at 1 o’clock. Aqueous humor samples were obtained using a 27-gauge needle attached to a regular insulin syringe. Sampling was performed at set time intervals (15, 30, 45, 60, 90, 120, 150, 180, and 240 min) after injection and before enucleation of the eyes. Four to six eyes per time interval up to 240 min were enucleated on the same day. The entire vitreous humor was isolated according to the technique described by Abel and Boyle (1). Analysis of the samples was performed with high-performance liquid chromatography in a masked fashion. The procedures of voriconazole extraction from aqueous and vitreous humors were as described in a previous study (11).

The mean voriconazole levels measured for vitreous and aqueous humors at all sampling times are listed in Table 1. An exponential decay model was used to fit the data, and a least-square regression analysis was performed. The equations used for the calibration curve were as follows: $y = 45.349e^{-0.0581x}$ and $R^2 = 0.9813$. The elimination rate constant ($K$) was derived from the slope of the line of the log concentration versus time, and the elimination half-life was calculated by $0.693/K$. The aqueous humor voriconazole concentration showed an exponential decay with a half-life of 22 min. The vitreous concentration was below the detection limit at each time point.

The concentration of a drug in the anterior chamber depends on its dosage, the volume of distribution, and the elimination rate. The volume of the anterior chamber is approximately 0.3 ml in the phakic eye and probably increases to around 0.5 ml in the pseudophakic eye. The elimination of a drug in the anterior chamber may be affected by a variety of factors, including its molecular weight, protein binding, and tissue absorption. Drugs in the anterior chamber are predominantly eliminated across the trabecular meshwork and may be affected by their molecular weights and binding to reversible proteins, such as soluble aqueous proteins and iris melanin (6). Therefore, elimination of a drug with a high molecular weight and a high degree of protein binding in the anterior chamber will be delayed. The absorption of a drug by tissues in the anterior chamber, such as the cornea, iris, and ciliary body, might also be affected by the intracameral concentration of the drug, especially if it is later rereleased into the anterior chamber, as has been demonstrated for intracameral cyclosporine in a rabbit model (8). Voriconazole is available as a lyophilized powder for solution and has a molecular weight of 349.3. Vancomycin and gentamicin have molecular weights of 1485.73 and 477.6, respectively. The half-lives of vancomycin and gen-
taminicin in the anterior chamber following intracameral delivery are 3.27 h and 0.85 h, respectively, in humans (4, 7). In rabbits, iris and ciliary tissues are unpigmented. Since highly lipophilic agents cannot bind to melanin in these tissues, apparently increased aqueous humor clearance may occur. The half-life of amikacin (which has a molecular weight of 585.6) following intracameral injection is 0.58 h in rabbits (5). These results may explain the rapid elimination of intracameral voriconazole in rabbits.

With the normal volume of the aqueous humor in rabbits assumed to be 0.3 ml, the injected dose of 25 μg/25 μl in rabbit eyes resulted in an initial aqueous concentration of 76.92 μg/ml. In contrast, the voriconazole levels achieved were low in the vitreous humor. The peak aqueous levels achieved were thus over 100 times the MICs of voriconazole in Candida and Aspergillus species. Even with Fusarium species, intracameral voriconazole reached an effective inhibitory concentration. Our study showed a rapid decline in aqueous concentration and an exponential decay with a half-life of 22 min. In such a case, aqueous levels will be below the MICs of most fungi within 2 h and below those of Fusarium species within 1.5 h, and therefore, rapid supplementation of intracameral voriconazole may be required in clinical settings. Fortunately, drug elimination has been noted to be slower in humans than in rabbits. Elimination of voriconazole from serum has been reported to involve a half-life of 2.5 to 3 h in rabbits, versus 6.5 h in humans (3, 10). Furthermore, voriconazole penetrates well into the anterior chamber through the cornea (12, 13). A combination of topical administration and intracameral injection would prolong the therapeutic levels of voriconazole in the anterior chamber. Further studies are needed to detect the half-lives of voriconazole in the human aqueous humor and the aqueous concentration achieved by combined administration, in which case the frequency at which to supplement intracameral injection would need to be determined.

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REFERENCES


### TABLE 1. Measured aqueous and vitreous levels of voriconazole at different time intervals after intracameral injection of 25 μg/25 μl in rabbits

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Aqueous voriconazole concn (μg/ml)</th>
<th>No. of eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>25.36 ± 4.17</td>
<td>4</td>
</tr>
<tr>
<td>30</td>
<td>13.48 ± 2.42</td>
<td>4</td>
</tr>
<tr>
<td>45</td>
<td>7.73 ± 0.95</td>
<td>6</td>
</tr>
<tr>
<td>60</td>
<td>5.10 ± 0.52</td>
<td>6</td>
</tr>
<tr>
<td>90</td>
<td>2.67 ± 0.57</td>
<td>6</td>
</tr>
<tr>
<td>120</td>
<td>1.40 ± 0.52</td>
<td>6</td>
</tr>
<tr>
<td>150</td>
<td>0.39 ± 0.12</td>
<td>4</td>
</tr>
<tr>
<td>180</td>
<td>0.15 ± 0.07</td>
<td>4</td>
</tr>
<tr>
<td>240</td>
<td>0.00 ± 0.00</td>
<td>4</td>
</tr>
</tbody>
</table>

* Values shown are means ± standard deviations. Values for all vitreous samples were below the detection limit (0.1 μg/ml).