Penetration of Topically Administered 0.5-Percent Caspofungin Eye Drops into Human Aqueous Humor

Chin Fen Neoh,1,2 Lok Leung,3 Anant Misra,4§ Rasik B. Vajpayee,4,5 Geoffrey E. Davies,6 Robert O. Fullinfaw,7 Kay Stewart,1 and David C. M. Kong 1,2*

Department of Pharmacy Practice, Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, 381 Royal Parade, Parkville, Victoria 3052, Australia1; Department of Anti-infective Drug Development and Innovation (FADDI), Monash Institute of Pharmaceutical Sciences, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, 381 Royal Parade, Parkville, Victoria 3052, Australia2; Department of Pharmacy, Royal Victorian Eye and Ear Hospital (RVEEH), 32 Gisborne Street, East Melbourne, Victoria 3002, Australia3; Corneal and Cataract Surgery Unit, Royal Victorian Eye and Ear Hospital (RVEEH), 32 Gisborne Street, East Melbourne, Victoria 3002, Australia4; Department of Ophthalmology, Melbourne Health Pathology, The Royal Melbourne Hospital, Grattan Street, Parkville, Victoria 3050, Australia5; Department of Ophthalmology, Southern Health, 246 Clayton Road, Clayton, Victoria 3168, Australia6.

Received 25 August 2010/Returned for modification 19 November 2010/Accepted 17 January 2011

Ten participants attending elective anterior segment eye surgery received 0.5% caspofungin eye drops either 1 drop hourly for 4 h or 1 drop an hour before surgery. The eye drops were generally well tolerated. In the absence of inflammation or corneal abrasion, topical caspofungin does not achieve clinically relevant concentrations.

Fungal keratitis is a potentially blinding condition, with Candida, Aspergillus, and Fusarium spp. (2, 21) being the common pathogens. Current treatment for fungal keratitis is inadequate (8); thus, alternatives are needed.

Caspofungin has activity against a wide range of fungi, with MIC90 values ranging from 60 to 2,000 ng/ml (15, 23). Caspofungin eye drops are effective for treatment of fungal keratitis in rabbits (11, 18) and have good penetration into animal eyes with inflammation or previous corneal abrasion (10, 23). Clinically, caspofungin is administered mostly intravenously (1, 4, 6, 9, 19, 20) or intravitreally (24) for ocular mycosis. The successful use of topical caspofungin alone (13) or in combination with voriconazole (22) has been reported for two patients. However, the utility of topical caspofungin in fungal keratitis remains unknown, partly due to limited data on its penetration into human aqueous humor after topical administration.

This study aimed to investigate the ocular penetration of 0.5% caspofungin eye drops into human aqueous humor.

The study was approved by the ethics committees of the Royal Victorian Eye and Ear Hospital (RVEEH) and Monash University and was registered under the Australian New Zealand Clinical Trials Registry.

Between October 2009 and January 2010, participants ≥18 years old that were scheduled for elective eye surgery at RVEEH were recruited. Exclusion criteria were as follows: inflammation of the eye to be operated on, kidney or liver failure, breast feeding, pregnancy, trying to conceive, allergy to caspofungin (Cancidas) or any of its components, or using medications known to interact with caspofungin.

Caspofungin eye drops (0.5%) (11, 13, 22) were prepared aseptically; 10.5 ml of water for injection was added to a 50-mg vial of caspofungin. All eye drops were freshly prepared and used within 24 h (7).

Participants received either 1 drop (50 μl) of eye drops to the eye to be operated on, hourly over a period of 4 h prior to surgery (Arm 1), or 1 drop an hour before surgery (Arm 2). The eye drops were administered by RVEEH nursing staff. The date and time of administration, including side effects experienced, were recorded.

During surgery, aqueous humor (50 to 150 μl) was collected through a paracentesis site using a 30-gauge needle before administration of irrigation solutions. The samples were then divided into 30-μl aliquots, stored at −80°C, and analyzed within 1 week using a validated liquid chromatography/mass spectrometry (LC/MS) assay (17).

Ten participants gave consent (Table 1). The aqueous humor caspofungin concentrations for Arm 1 and Arm 2 were 28.9 to 95.1 ng/ml and 29.8 to 34.4 ng/ml, respectively. The sampling times for Arm 1 and Arm 2 were 0.75 to 1.67 h and 0.75 to 1.92 h, respectively. The eye drops were generally well tolerated.

This study is the first to demonstrate that topically administered caspofungin penetrates into uninflamed human eyes, in contrast to results from previous animal studies (10, 23). The difference could be due to the use of a more sensitive analytical approach in humans.
TABLE 1. Patient characteristics, caspofungin concentrations in aqueous humor of study participants, and side effects reported

<table>
<thead>
<tr>
<th>Study arm (type of application)</th>
<th>Patient no.</th>
<th>Gender</th>
<th>Age (yr)</th>
<th>Presence of diabetes mellitus</th>
<th>Type of lens</th>
<th>Caspofungin concn in aqueous humor (ng/ml)</th>
<th>Postsampling time (h)</th>
<th>Description of side effects (duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1 (1 drop every hour for 4 h prior to surgery)</td>
<td>1 Female</td>
<td>66</td>
<td>Yes</td>
<td>Phakic</td>
<td>95.1</td>
<td>1.67</td>
<td>Tingling sensation after the first drop (a few seconds)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 Male</td>
<td>88</td>
<td>No</td>
<td>Phakic</td>
<td>63.8</td>
<td>1.17</td>
<td>Tingling sensation after the first drop (a few seconds)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 Male</td>
<td>62</td>
<td>Yes</td>
<td>Phakic</td>
<td>36.7</td>
<td>1.33</td>
<td>Tingling sensation after the first drop (a few seconds)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 Female</td>
<td>74</td>
<td>No</td>
<td>Phakic</td>
<td>57.1</td>
<td>0.75</td>
<td>None reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 Female</td>
<td>59</td>
<td>No</td>
<td>Phakic</td>
<td>28.9</td>
<td>0.83</td>
<td>None reported</td>
<td></td>
</tr>
<tr>
<td>Arm 2 (1 drop 1 h prior to surgery)</td>
<td>1 Female</td>
<td>84</td>
<td>No</td>
<td>Phakic</td>
<td>32.6</td>
<td>0.75</td>
<td>Tingling sensation after the first drop (a few seconds)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 Male</td>
<td>74</td>
<td>Yes</td>
<td>Phakic</td>
<td>31.5</td>
<td>1.08</td>
<td>Tingling sensation after the first drop (a few seconds)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 Male</td>
<td>58</td>
<td>No</td>
<td>Phakic</td>
<td>34.4</td>
<td>1.58</td>
<td>None reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 Female</td>
<td>59</td>
<td>No</td>
<td>Phakic</td>
<td>32.2</td>
<td>1.33</td>
<td>None reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 Female</td>
<td>76</td>
<td>Yes</td>
<td>Phakic</td>
<td>29.8</td>
<td>1.92</td>
<td>Burning sensation (~10 min; nurse administered 2 drops of normal saline, and 5 min later the burning sensation ceased)</td>
<td></td>
</tr>
</tbody>
</table>

The low concentrations, however, indicate that topical caspofungin does not have good penetration into uninfamed eyes, consistent with caspofungin being a large molecule (1,213 Da) and highly protein bound (96.5%) (5). Compounds of >500 Da experience difficulty penetrating the intact corneal epithelium after topical administration due to frictional force that reduces diffusion (16). While the concentrations observed were below the MIC<sub>90</sub> for most fungal species (15, 23), topical caspofungin may still be useful for fungal keratitis. Disruption of the corneal surface or inflammation in rabbit models has resulted in higher caspofungin concentrations in aqueous humor after systemic or topical administration (10, 23). As the cornea is the primary site of infection in keratitis, high corneal concentrations of antifungal agents are desirable. An earlier study (10) reported higher mean caspofungin concentrations in the cornea than in the aqueous humor of rabbits after a single 1 mg/kg intravenous dose. The higher corneal concentrations could be due to differences in protein binding and the retention of caspofungin in the stroma (10). The results obtained from the rabbit models could be extrapolated to a human setting, given that there is no difference between the protein distribution and components in the aqueous humor of humans and rabbits (3). As fungal keratitis will generally compromise the corneal epithelium’s integrity, topical caspofungin could achieve concentrations above the MIC<sub>90</sub> in patients with keratitis, but this remains to be demonstrated. Clinical resolution with topical caspofungin has been demonstrated for keratitis caused by Fusarium species in rabbit models (18) and keratitis caused by Alternaria (22) or Candida (13) species in patients.

Arm 1 participants had higher caspofungin concentrations with greater variability than Arm 2 participants. The nature of scheduled elective surgery and access to the operating theater have no doubt contributed to the variable sampling times. For this reason, it is not appropriate to report the concentrations as means ± standard deviations. The possibility of drug accumulation upon repeated dosing and the reason for the variability in Arm 1 cannot be confirmed due to small sample sizes. Findings from animal studies have been inconsistent. Continuous topical administration (1 drop every 30 min for 6 h) with 0.7% caspofungin produced higher levels (4.94 ± 1.80 µg/ml) than a single application (1.76 ± 0.88 µg/ml) at 2 h after the last dose (23). Conversely, daily intravenous administration of 0.5% caspofungin for 7 consecutive days (10) did not lead to higher concentrations in the aqueous humor or cornea.

Minimal side effects were noted, with transient tingling sensations being the most common. A saturated caspofungin solution has a pH of 6.6 (Candidas package insert; Merck & Co. Inc., Whitehouse Station, NJ) and should be well tolerated in the eyes (12). Side effects associated with systemic administration are unlikely, given that each topically administered dose (50 µl) of 0.5% caspofungin contains only 0.25 mg caspofungin. Following the 2-hourly regimen (22), the total daily topical caspofungin dose is 3 mg, which is 6% of a standard 50 mg intravenous dose. There was no toxicity on human ocular cells after 1 month of treatment with 75 µg/ml caspofungin (14).

In conclusion, caspofungin eye drops are well tolerated but have a low level of penetration into the uninfamed human eye.

The support from study participants, the RVEEH Day Surgery Unit nursing staff, pharmacy staff, and Dermot Cassidy is gratefully acknowledged. We thank Merck Sharp & Dohme (Australia) Pty. Limited for the provision of pure substance caspofungin. We thank Jian Li and Hui He for their input in developing the analytical assay for caspofungin.

This study was supported by the Contributing to Australian Scholarship and Science (CASS) Foundation. Scholarship support to C.F.N. by the University of Technology MARA is acknowledged.

REFERENCES


