Penetration of Topically Administered 0.5-Percent Caspofungin Eye Drops into Human Aqueous Humor\textsuperscript{v}

Chin Fen Neoh,\textsuperscript{1,2} Lok Leung,\textsuperscript{3} Anant Misra,\textsuperscript{4,§} Rasik B. Vajpayee,\textsuperscript{4,5} Geoffrey E. Davies,\textsuperscript{6} Robert O. Fullinfaw,\textsuperscript{7} Kay Stewart,\textsuperscript{1} and David C. M. Kong\textsuperscript{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, Australia; Faculty for 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, Australia; Department of Pharmacy, Royal Victorian Eye and Ear Hospital (RVEEH), 32 Gisborne Street, East Melbourne, Victoria 3002, Australia; Corneal and Cataract Surgery Unit, Royal Victorian Eye and Ear Hospital (RVEEH), 32 Gisborne Street, East Melbourne, Victoria 3002, Australia; Centre for Eye Research Australia, University of Melbourne, c/- Royal Victorian Eye & Ear Hospital, Locked Bag 8, East Melbourne, Victoria 3002, Australia; Health Systems Program Office, Land Systems Division, Defence Materiel Organisation, Victoria Barracks Melbourne HWI, 256-310 St. Kilda Road, Southbank, Victoria 3006, Australia; and Special Chemistry, Melbourne Health Pathology, The Royal Melbourne Hospital, Grattan Street, Parkville, Victoria 3050, Australia.

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 MIC\textsubscript{90} 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 \textgammadagi\textperthousand\ x\textperthousand\textsubscript{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 (Candidas) 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 \textmu l) 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 \textmu l) was collected through a paracentesis site using a 30-gauge needle before administration of irrigation solutions. The samples were then divided into 30-\textmu l aliquots, stored at $-\text{80}^\circ\text{C}$, 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 28.9 to 95.1 ng/ml and 29.8 to 34.4 ng/ml, respectively. The eye drops were generally well tolerated.

This study is the first to demonstrate that topical administration of 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
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</td>
<td>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>
</tr>
<tr>
<td></td>
<td>2</td>
<td>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>
</tr>
<tr>
<td></td>
<td>3</td>
<td>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>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Female</td>
<td>74</td>
<td>No</td>
<td>Phakic</td>
<td>57.1</td>
<td>0.75</td>
<td>None reported</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Female</td>
<td>59</td>
<td>No</td>
<td>Phakic</td>
<td>28.9</td>
<td>0.83</td>
<td>None reported</td>
</tr>
<tr>
<td>Arm 2 (1 drop 1 h prior to surgery)</td>
<td>1</td>
<td>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>
</tr>
<tr>
<td></td>
<td>2</td>
<td>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>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Male</td>
<td>58</td>
<td>No</td>
<td>Phakic</td>
<td>34.4</td>
<td>1.58</td>
<td>None reported</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Female</td>
<td>59</td>
<td>No</td>
<td>Phakic</td>
<td>32.2</td>
<td>1.33</td>
<td>None reported</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>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>
</tr>
</tbody>
</table>

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. Ltd. 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