Pharmacokinetics and Safety of Intravitreal Caspofungin

Ying-Cheng Shen, Chiao-Ying Liang, Chun-Yuan Wang, Keng-Hung Lin, Min-Yen Hsu, Hon-Leung Yuen, Li-Chen Wei

Department of Ophthalmology, Taichung Veterans General Hospital, Taiwan, Republic of China, and The Institute of Nanoengineering and Microsystems, National Tsing Hua University, Hsinchu, Taiwan, Republic of China

Caspofungin exhibits potent antifungal activities against Candida and Aspergillus species. The elimination rate and retinal toxicity of caspofungin were determined in this study to assess its pharmacokinetics and safety in the treatment of fungal endophthalmitis. Intravitreal injections of 50 µg/0.1 ml of caspofungin were administered to rabbits. Levels of caspofungin in the vitreous and aqueous humor were determined using high-performance liquid chromatography (HPLC) at selected time intervals (10 min and 1, 2, 4, 8, 16, 24, and 48 h), and the half-lives were calculated. Eyes were intravitreally injected with caspofungin to obtain concentrations of 10 µg/ml, 50 µg/ml, 100 µg/ml, and 200 µg/ml. Electroretinograms were recorded 4 weeks after injections, and the injected eyes were examined histologically. The concentrations of intravitreal caspofungin at various time points exhibited an exponential decay with a half-life of 6.28 h. The mean vitreous concentration was 6.06 ± 1.76 µg/ml 1 h after intravitreal injection, and this declined to 0.47 ± 0.15 µg/ml at 24 h. The mean aqueous concentration showed undetectable levels at all time points. There were no statistical differences in scotopic a-wave and b-wave responses between control eyes and caspofungin-injected eyes. No focal necrosis or other abnormality in retinal histology was observed. Intravitreal caspofungin injection may be considered to be an alternative treatment for fungal endophthalmitis based on its antifungal activity, lower retinal toxicity, and lower elimination rate in the vitreous. More clinical data are needed to determine its potential role as primary therapy for fungal endophthalmitis.

Fungal endophthalmitis, although uncommon, can cause serious ocular devastation and has an ominous prognosis even with prompt treatment. Fungal endophthalmitis can be either exogenous, such as in cases of ocular surgery, trauma, and keratitis, or endogenous, with infection spreading to the eye, such as in patients receiving immunosuppressive therapy and intravenous infusion from indwelling catheters. According to previous studies, fungal endophthalmitis accounts for 8% to 18% of culture-proven endophthalmitis. In the past decade, intravitreal antibiotic injection has become a mainstay of treatment for fungal endophthalmitis. Amphotericin B and voriconazole are the two antifungal agents used for injection into the vitreous. However, amphotericin B may cause retinal necrosis at low concentrations, and a variety of fungal species have shown resistance to it (6–8). Although previous studies have shown voriconazole to have a broad spectrum of activity and to be effective as primary therapy in the treatment of invasive aspergillosis, 50 µg/ml of intravitreal voriconazole has been found to cause small foci of retinal necrosis in animal studies (9–11). Moreover, voriconazole has a relatively rapid elimination rate in the vitreous, and supplementary injection is frequently required in clinical treatment (12, 13). Systemically administered voriconazole which would be given simultaneously with intravitreal injection would penetrate into the vitreous. In addition to voriconazole, fluconazole also penetrates well into the vitreous, and both agents have been effective in treating fungal endophthalmitis through intravenous administration (14, 15). Intravitreal injection of liposomal amphotericin B, which has less toxicity than amphotericin B, was used to treat a patient with bilateral endogenous Candida endophthalmitis (16).

Caspofungin noncompetitively inhibits (1,3)-β-D-glucan synthase, an enzyme that is necessary for the synthesis of the cell wall in many fungal species, and exhibits potent in vitro and in vivo antifungal activity against Candida spp. and Aspergillus spp., including pathogens resistant to azole or amphotericin B (17–20). Furthermore, caspofungin’s synergistic effects have been observed in combination with a polyene or an azole, and attempts have been made to use these combinations as systemic therapy of endophthalmitis. In vitro studies have shown MICs of caspofungin ranging from 0.03 to 1 µg/ml for Candida species and a MIC of 0.06 µg/ml for the vast majority of Aspergillus species. Caspofungin has low oral bioavailability (less than 0.2%). It is distributed well to tissues through intravenous administration but with minimal penetration into the eye due to its high level of protein binding and high molecular mass (1,213 Da). Intravitreal injection of caspofungin could be considered as an alternative in treating fungal endophthalmitis if lower retinal toxicity and slower elimination in the vitreous could be documented. Because the treatment options for fungal endophthalmitis are limited and caspofungin has good fungicidal and fungistatic activity, the safety and pharmacokinetics of caspofungin as an intravitreal agent need to be evaluated.

In this study, we determined the elimination rate and retinal toxicity of intravitreal caspofungin in rabbits and tried to assess the safety and optimum dosage of intravitreal injection required to maintain therapeutic levels in the vitreous.

Received 28 May 2014 Returned for modification 16 June 2014 Accepted 15 September 2014 Published ahead of print 22 September 2014 Address correspondence to Li-Chen Wei, lichen5883@yahoo.com.tw.
Y.-C.S. and C.-Y.L. contributed equally to this work.
H.-L.Y. and L.-C.W. contributed equally to this work.
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MATERIALS AND METHODS

Animals. Caspofungin (Cancidas; Merck & Co., Albuquerque, NM, USA) was obtained in pure powder form and reconstituted in sterile water to yield a concentration of 50 μg/0.1 ml. Seventeen New Zealand White rabbits weighing 2 to 2.5 kg were acclimated for at least 1 week under standardized temperature (25 to 28°C), humidity (50 to 60%), and light (12 h light-dark) conditions before the experiment. All care and handling of rabbits was 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.

The rabbits were anesthetized with a mixture of ketamine hydrochlo- ride (35 mg/kg; Parke-Davis, Morris Plains, NJ) and xylazine (5 mg/kg; Astra, Astra Södertälje, Sweden) intramuscularly in the hindquarter. Both eyes of each rabbit were included in the experiment. An anterior chamber paracentesis was performed followed by an injection of 30 μg caspofungin in 0.1 ml sterilized distilled water at a site 2 mm posterior to the limbus. Treatment was administered using a 30-gauge needle attached to a regular insulin syringe with the bevel positioned upward in the midvitreous of the eyes, slowly and under direct visualization. A cotton tipped applicator was applied to the injection site immediately after removal of the needle to prevent fluid reflux from the injection site. Mydriasis was achieved with two to three drops of 1% tropicamide, and the fundus was examined by indirect ophthalmoscopy before and after injections. Aqueous humor samples were obtained using a 30-gauge needle, and the sampling was performed on two rabbits at each time interval (10 min and 1, 2, 4, 8, 16, 24, and 48 h) after injection and before enucleation of eyes. Rabbits were sacrificed with a lethal cardiac injection of pentobarbital sodium and phe- nytin sodium (Beuthanasia-D; Schering Animal Health, Kenilworth, NJ). Four eyes per time interval up to 48 h and both eyes of an additional rabbit were enucleated on the same day and immediately frozen at −80°C. The eyes were dissected while frozen, and the entire vitreous was isolated according to the technique described by Abel and Boyle (21). The vitreous of the control eyes was isolated to obtain standardization curves for HPLC analyses. Assays of caspofungin concentrations in vitreous and aqueous humor samples were performed with high-performance liquid chromatography (HPLC).

HPLC. Caspofungin concentrations of vitreous and aqueous humors were determined using HPLC. Analysis of the samples was performed in a blinded fashion. The HPLC method of Spriet et al. was adapted (22). The rabbit vitreous samples and caspofungin standard (150 μl) were each pretreated with the addition of 600 μl of 100% methanol followed by vortex mixing at high speed for 1 min at room temperature. The mixtures were centrifuged in a microcentrifuge (CS 120 GX; Hitachi, Japan) at 45,000 rpm for 30 min at 4°C. A 450-μl portion of supernatant was transferred to a clean tube and dried in a centrifugal vacuum concentrator (Speed Vac Plus SC110; Savant Instruments, Inc., Holbrook, NY). The injection samples were redisolved in 120 μl of 20% methanol containing 0.1% trifuluoroacetic acid (TFA) followed by 1 min of vortex mixing. Insoluble particles were removed by ultracentrifugation at 45,000 rpm for 30 min at 4°C. The samples of aqueous humor (90 μl) were extracted with 450 μl of 100% methanol, and 450 μl of supernatant was discarded for drying after ultracentrifugation. After drying, the samples were redis- solved in 90 μl of 20% methanol containing 0.1% TFA.

The samples were analyzed with an HPLC system including a gradient HPLC pump (Allinteg 1100; Alltech Technologies, Germany) and a UV-VIS detector (S-3702; Soma, Japan) interfaced to a Chromato-integrator (D-2500, Hitachi, Japan). The gradient eluting system consisted of 0.1% TFA in deionized water (mobile phase A) versus 0.1% TFA in methanol (mobile phase B) with a flow rate of 1.5 ml/min. A 20-μl volume of each sample was injected onto a reverse-phase (RP) column (LiChrospher 100RP-18e; 250 mm by 4 mm, 5 μm; Alltech Technologies, Germany; column temperature of 35°C), which was pre-equilibrated with 20% mo- bile phase B. Caspofungin was eluted with a linear gradient of methanol (20% to 60% containing 0.1% TFA).

Caspofungin was monitored by absorbance at 215 nm and identified by coinjection with standard. The area of the caspofungin peak after baseline subtraction was calculated and compared with the area-versus-mass curve for the standard to quantify the amounts of caspofungin in the samples. The standard curve was linear to 20 μg/ml (correlation coeffi- cient = 0.9997 for the range 0.2 to 20.0 μg/ml), and the detection limit was estimated to be approximately 0.1 μg/ml (signal-to-noise ratio > 2). Samples with caspofungin outside the linear range were properly diluted with 20% methanol for further HPLC analysis.

Electroretinogram and histopathologic analysis. Sixteen New Zea- land White albino rabbits were given an intravitreal injection of one of four caspofungin doses: 15, 75, 130, or 300 μg in 0.1 ml. Caspofungin solutions were serially diluted with balanced salt solution (BSS) (Alcon Labs, Inc.) so that the final intravitreal concentrations were 10 μg/ml, 50 μg/ml, 100 μg/ml, and 200 μg/ml, based on the data that adult rabbit vitreous volume is about 1.4 ml. Each animal’s non-caspofungin-treated eye served as a control and was injected intravitreally with 0.1 ml of BSS instead of caspofungin. After the injections, all eyes were examined weekly by ophthalmoscopy. Animals were kept under ambient light on a 12-hour light/dark schedule. Four weeks after injection, animals were processed for electroretinogram recordings and subsequent retinal histologic exami- nations.

Prior to testing, rabbits were allowed to adapt to darkness overnight and were anesthetized with a solution of ketamine and xylazine. Several drops of 0.5% tropicamide (Mydracyl) and 2.5% phenoxyline for pupil dilatation and a drop of 0.5% paracaine hydrochloride for corneal anesthesia were applied. A single bright-flash electroretinogram (ERG) (UTAS-E 300; LKC Technology, Gaithersburg, MD, USA) was performed to assess safety and retinal function. A small amount (2.5%) of methylcel- lulose gel was applied to the eye, and a gold electrode was placed in contact with the center of the cornea. A reference electrode was attached to the shaven skin of the scalp and a ground electrode was clipped to the rabbit’s tail. For dark-adapted ERG, the luminance of the stimulus was 3 cd/m² with a duration of 10 ms. Five responses elicited by identical flashes ap- pamed at 10-s intervals were averaged. The amplitude and implicit time of the a and b waves were measured and averaged.

Following the electroretinogram tests, the animals were sacrificed. Both eyes from all animals were enucleated and fixed immediately in 4% formaldehyde in 0.1 M phosphate buffer (pH 7.4). The eye was cut along the cornea-optic nerve axis into halves after the lens was removed. Speci- mens were fixed further in 4% paraformaldehyde and 0.5% glutaralde- hyde in 0.1 M phosphate buffer (pH 7.4). Histological sections were ob- tained for light-microscopic examination after the tissues were embedded in paraffin, sectioned at a thickness of 6 μm, and stained with hematoxy- lin-eosin.

RESULTS

Indirect ophthalmoscopy of the rabbit eyes revealed no retinal damage, hemorrhage, or detachment after intravitreal injection of 50 μg/0.1 ml caspofungin. The mean caspofungin levels measured for vitreous and aqueous humors at all sampling times are listed in Table 1. The vitreous concentration declined rapidly with time. The mean vitreous concentration was 6.06 ± 1.76 μg/ml 1 h after injection and declined to 3.396 ± 0.42 μg/ml at 4 h and 0.47 ± 0.15 μg/ml at 24 h, respectively. An exponential decay model was used to fit the data, and a least-squares regression analysis was performed. The elimination half-life was calculated from the slope of the line of log concentration versus time. The vitreous caspofungin concentration showed an exponential decay with a half-life of 6.28 h. The mean aqueous concentration was much lower and showed undetectable levels in all samples after injection (Table 1).

To directly evaluate rod photoreceptor function, we measured the waves of ERG, which arises almost exclusively from the rod photoreceptors. The responses to an intense flash, which saturated
TABLE 1 Levels of caspofungin at different times after intravitreal injection of 50 µg/0.1 ml in rabbits

<table>
<thead>
<tr>
<th>Time</th>
<th>Caspofungin concn (µg/ml) in the vitreous (n = 4)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 min</td>
<td>13.98 ± 0.87</td>
</tr>
<tr>
<td>1 h</td>
<td>6.06 ± 1.76</td>
</tr>
<tr>
<td>2 h</td>
<td>4.71 ± 2.03</td>
</tr>
<tr>
<td>4 h</td>
<td>3.39 ± 0.42</td>
</tr>
<tr>
<td>8 h</td>
<td>2.98 ± 0.57</td>
</tr>
<tr>
<td>16 h</td>
<td>2.04 ± 0.94</td>
</tr>
<tr>
<td>24 h</td>
<td>0.47 ± 0.15</td>
</tr>
<tr>
<td>48 h</td>
<td>Undetectable</td>
</tr>
</tbody>
</table>

*Values are means ± standard deviations. Caspofungin in all aqueous samples was below the detection limit (0.1 µg/ml) after injection.

The rod photoreceptors, were recorded. The saturated a-wave and b-wave amplitudes and implicit time for the eyes with intravitreal caspofungin injection of 10, 50, 100, and 200 µg/ml and measurements from control eyes are summarized in Table 2. There were no statistical differences in a-wave and b-wave responses between control eyes and any caspofungin-injected eyes using an unpaired t test. The statistical comparison of the amplitudes and the implicit times of a waves and b waves from electroretinograms between control eyes and the eyes with injection of various concentrations of caspofungin are shown in Table 2 and Fig. 1.

Gross examination of eye specimens showed no retinal hemorrhages or signs of infection in any caspofungin-injected or control eyes. Histologic examination with light microscopy did not reveal any retinal abnormality in the eyes injected with BSS as controls. In eyes injected with caspofungin at intravitreal concentrations of 10 µg/ml to 200 µg/ml, no focal necrosis or other abnormality could be observed in any layer of retina (Fig. 2).

DISCUSSION

Although fungus is a common causative organism of systemic infection, it is an unusual cause of endophthalmitis and often carries an ominous prognosis. The difficulty in treatment is due to a combination of the growth characteristics of fungi, a scarcity of effective antifungal agents, and poor tissue penetration. Severe fungal infections may result in extensive retinal damage, acute inflammation, and rapid vision loss. Despite current advances in antifungal therapy, the management of acute fungal endophthalmitis remains a formidable challenge.

The antifungal agent used most often for treatment of fungal endophthalmitis is amphotericin B. It was the first polycrystalline compound shown to be effective in treating systemic mycosis and was the treatment of choice against yeasts and natamycin-resistant filamentous fungi, notably Aspergillus (23, 24). In vitro activities of amphotericin B vary, with the MICs ranging from less than 0.5 to 6.37 µg/ml and, for Fusarium solani infections, from 1.56 to 100 µg/ml (25, 26). Intravitreal injection of 5 to 10 µg of amphotericin B is a widely used treatment for fungal endophthalmitis. While amphotericin B is an irritant, intravitreal liposomal amphotericin B is well tolerated in monkey and rabbit eyes and has been used in the treatment of Candida endophthalmitis (16, 27, 28). Another broad-spectrum antifungal agent administered intravitreally for treatment of fungal endophthalmitis is voriconazole, which inhibits the fungal enzyme cytochrome P450 demethylase. In vitro studies have shown that voriconazole MICs range from 0.06 to 0.25 µg/ml for Candida species, 0.5 µg/ml for Aspergillus species, and 2 to 8 µg/ml for Fusarium oxysporum and Fusarium solani (29–32). Clinically, intravitreal voriconazole injections have been effective in treating fungal endophthalmitis caused by Aspergillus flavus, Scedosporium apiospermum, and Fusarium species and Candida albicans (33). However, amphotericin B can induce intraocular inflammation, and voriconazole has a rapid clearance in the vitreous. In addition, both agents can cause retinal necrosis at lower concentrations. Fluconazole is highly effective against Candida spp., but it shows high MICs (>100 µg/
ml) against *Aspergillus* (34). Fluconazole has excellent penetration into the vitreous (35). A case of endogenous *Candida albicans* endophthalmitis in a newborn refractory to intravenous amphotericin B that responded to fluconazole has been reported (14). Itraconazole is active against a variety of fungi and is well absorbed orally in doses of 50 to 400 mg daily. However, systemically administered itraconazole penetrates poorly into noninflamed aqueous or vitreous. Caspofungin is fungicidal *in vitro* and *in vivo* against a broad range of *Candida* spp., including species that are intrinsically resistant to azoles (*Candida krusei* and *Candida glabrata*) or amphotericin B (*Candida lusitaniae*) and emerging species (e.g., *Candida famata* and *Candida rugosa*) (36–38). Caspofungin MIC<sub>90</sub> range between 0.06 and 1 µg/ml (39–42).

Caspofungin is distributed well in tissue but penetrates minimally into the eye intravenously due to its high level of protein binding and high molecular weight. The high level of protein binding could limit the amount of caspofungin available for activity in plasma (38, 43, 44). Consequently, failure of intravenously administered caspofungin in treatment of fungal endophthalmitis has been reported (45). Caspofungin exerts its fungicidal effect against *Candida* spp. in a concentration-dependent manner over a broad concentration range *in vivo*. Furthermore, caspofungin also possesses prolonged postantifungal effects, remaining at a high concentration in tissue and maintaining antifungal efficacy even after the serum concentration falls below the MIC (46). Due to the characteristics of high-level protein binding and high molecular weight, the efficacy, toxicity, and residence times of caspofungin within the vitreous may change. Assuming that the protein binding in the vitreous is similar to that in plasma, only 3% of caspofungin will be present as a free drug. In such a case, an intravitreal concentration of 100 µg/ml of caspofungin will result in a free-drug level of 3 µg/ml, which is about 3 times the MIC of caspofungin against *Aspergillus* and *Candida* isolates. However, the protein level in the vitreous is low, and the caspofungin levels detected in the vitreous in this study were much higher than we expected. Therefore, a therapeutic level of caspofungin in the vitreous was achieved. Although the relationship between caspofungin concentration and antifungal activity in the vitreous has not been determined, caspofungin exhibits linear pharmacokinetics with a lower elimination rate than voriconazole in the vitreous and has a prolonged postantifungal effect, in which case a potent antifungal efficacy of caspofungin in vitreal cavities would be expected. In a study of experimentally induced *Candida* endophthalmitis, a single intravitreal injection of 100 µg of caspofungin produced a greater improvement in symptoms and a greater decrease in colony counts than 50 µg of voriconazole or 10 µg of amphotericin B (47).

The concentration of a drug in the vitreal cavity depends on its dosage, the volume of distribution, and the elimination rate. The elimination of a drug in the vitreal cavity may be affected by a variety of factors, including its molecular weight, protein binding, and tissue absorption. The clearance of a drug in the vitreal cavity can be via the anterior route passage into the aqueous humor and the posterior route by active transport across the retina. Generally, drugs eliminated from vitreous cavities using a retinal pump mechanism have shorter half-lives than drugs eliminated via the anterior chamber (28, 29). This study showed that caspofungin in the vitreous had an exponential decay and a half-life of 6.28 h. Therefore, its antifungal efficacy against *Candida* and *Aspergillus* species would persist up to 24 h. Given the elimination rate and low aqueous concentrations achieved, our data suggest that caspofungin is eliminated primarily via the posterior route. With the normal volume of the vitreal cavity in rabbits assumed to be 1.4 ml, the injected dose of 50 µg/0.1 ml in rabbit eyes resulted in an initial vitreous concentration of 33.33 µg/ml. The peak vitreous levels achieved were thus nearly 30 times greater than the MICs of caspofungin against most *Candida* and *Aspergillus* spp.

Some antifungal agents may be toxic to retinal structures. However, caspofungin has an excellent safety profile with reduced toxicities, compared to other antifungal agents applied intravitreally in the rabbit. Because electroretinograms measure a panretinal response, they are employed in monitoring retinal toxicity. Different ERG components are related to different retinal structures. Negative a waves and b waves reflect the function of photoreceptors and bipolar and Müller cells, respectively (48). Moreover, the ratio of b-wave to a-wave amplitude represents the response of a given stimulus in the inner and outer retina. It is difficult to standardize ERG responses, because they are influenced by a number of factors, such as pupil size, electrodes, stimulus intensity, dark adaptation time, age, and body temperature (49, 50). There were no significant differences in the values of amplitude and the implicit time, which suggests that the inner and outer retina were not functionally impaired by the dose of intravitreal caspofungin that was used in this study. In addition, there were no differences in the ratios of b-wave to a-wave amplitude between the eyes that were injected with caspofungin and control eyes, which suggests that intravitreal concentrations of up to 200 µg/ml of caspofungin do not cause the deterioration of retinal function.

Although intravitreal injection of caspofungin does not lead to electrophysiological changes in the rabbit retina based on ERG, focal damage to the retina may occur, because full-field ERG is a mass effect of light stimulation on the retina (51, 52). In our results, there was no evidence of histologic damage to the retina with intravitreal concentrations of up to 200 µg/ml. This nontoxic dose of caspofungin in the retina is more than 200 times the MIC<sub>90</sub> for *Candida* spp. and *Aspergillus* spp. The tolerance doses of caspofungin in the retina should be safe and sufficient for the treatment
of fungal endophthalmitis, even with cumulative doses in retinal tissue after repeated injections. Based on the results of our ERG tests and retinal histopathologic studies, intravitreal concentrations of up to 200 μg/ml of caspofungin do not cause photoreceptor functional impairment or structural changes in the rabbit retina. However, intravitreal concentrations of caspofungin caused retinal toxicity among some animal species. Mojumder et al. showed that vitreal concentrations from 0.41 to 4.1 μM in mice did not significantly alter their ERG waveforms. However, at a concentration of 41 μM (50 μg/ml), the a-wave and b-wave amplitudes were reduced, and a decrease in the number of cells in the ganglion cell layer was observed (53). Kernt and Kampik reported that caspofungin did not cause significant toxic effects in human retinal pigment epithelium (RPE) cells after 24 h treatment at vitreal concentrations between 5 and 75 μg/ml in a cell culture study, but doses of caspofungin above 150 μg/ml led to a rapid and significant reduction of viability in RPE cells (54). In a study of experimentally induced Candida endophthalmitis in rabbit eyes, 100 μg/0.1 ml of intravitreally injected caspofungin had no toxic effect on the retinal layers when evaluated histopathologically under light microscopy (47). In addition to the different levels of tolerance among species, the characteristics of tissue absorption and protein binding may result in higher concentrations in the mouse retina than in the white rabbit retina even at the same vitreous concentrations, which means that caspofungin is more toxic in the mouse retina.

The results of this study indicate that intravitreal injection of caspofungin may be an alternative in the treatment of fungal endophthalmitis. In comparison with the current antifungal agents, caspofungin has several advantages. (i) Caspofungin is less toxic to the retina than amphotericin B and voriconazole in the rabbit, though it is known to cause local irritation at the site of injection. Intravitreal concentrations of amphotericin B between 4.1 and 8.3 μg/ml have been found to produce retinal toxicity, and voriconazole at a concentration of 50 μg/ml also results in retinal focal necrosis. In addition, amphotericin B is proinflammatory. (ii) Caspofungin has a lower elimination rate and exhibits prolonged postantifungal effects, perhaps because of its high molecular weight and high rate of tissue abstraction (39). Synergistic action with the azole group of antifungals and amphotericin B and the biofilm-eradicating effect are other advantages of caspofungin, although there is, as yet, no evidence to suggest that these will improve efficacy in endophthalmitis. As a result of caspofungin’s unique mechanism of action and the high morbidity of fungal endophthalmitis, there is considerable interest in using this antifungal agent as an alternative or as part of a combination antifungal therapy. Caspofungin is also a promising agent as first-line therapy for endophthalmitis and as salvage therapy for damage caused by Candida spp. and Aspergillus spp. However, caspofungin has limitations in the antifungal spectrum, including its limited efficacy against two significant ophthalmic pathogens, Fusarium and Scedosporium spp. More clinical data are needed to define caspofungin’s role as primary therapy for fungal endophthalmitis and its role in antifungal combination therapy.

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