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Treatment of Exogenous *Candida* Endophthalmitis in Rabbits with Oral Fluconazole

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We investigated the efficacy of oral fluconazole, alone or in combination with oral flucytosine (5FC), in treating *Candida* endophthalmitis using a rabbit model. Albino rabbits were infected with an intravitreal inoculation of 1,000 CFU of susceptible *Candida albicans* and randomized 5 days later to receive treatment with oral fluconazole alone (80 mg/kg of body weight per day), a combination of fluconazole and 5FC (100 mg/kg/12 h), or no treatment. The treatment effect was assessed at 2 and 4 weeks after therapy by funduscopy, quantitative vitreous culture, and histopathology. Intravitreal levels of fluconazole, 2 to 24 h after the first dose, were measured to be >10 times the MIC of the drug for *C. albicans*. Among rabbits treated with fluconazole for 2 weeks, 67% had a >90% reduction in fungal load ($P < 0.05$) and 33% were sterile. After 4 weeks, all had a >99% reduction in fungal load ($P < 0.05$) and 75% were sterile ($P = 0.01$). This treatment effect was unchanged 4 weeks after discontinuation of fluconazole. Among rabbits treated with fluconazole and 5FC for 2 weeks, 67% died during therapy. Among the surviving rabbits, 75% had a >90% reduction in fungal load ($P < 0.05$) and 25% were sterile. We conclude that oral fluconazole may be useful for treatment of *Candida* endophthalmitis. Addition of 5FC was associated with high toxicity and minimal additional antifungal effect in our rabbit model.

Intraocular fungal infection can result from an exogenous inoculation of the microorganism, as in posttraumatic or postoperative endophthalmitis, or from an endogenous source, as in patients with fungemia. Fungal endophthalmitis accounts for 12% of all cases of infectious endophthalmitis and is a leading cause of endogenous infectious endophthalmitis (29). The most common cause of fungal endophthalmitis is *Candida albicans.*

Traditionally, the commonly used therapy for fungal endophthalmitis consists of intravenous amphotericin B, used alone or in combination with vitrectomy and intravitreal injection of amphotericin B (1, 8, 14–16, 20, 22, 23). Although intravenous amphotericin B therapy is often effective for treatment of chorioretinitis associated with fungal endophthalmitis, treatment failure can occur in eyes with advanced endophthalmitis with marked vitreous infiltrates due to the poor penetration of the drug into the vitreous (8). In addition, systemic administration of the drug requires prolonged hospitalization and is associated with unpleasant and potentially dangerous side effects. Treatment efficacy for advanced endophthalmitis may be enhanced by combining systemic amphotericin B therapy with vitrectomy and intravitreal amphotericin B injections, but such procedures are associated with potential morbidity.

For these reasons, the current advocated treatment for fungal endophthalmitis is controversial, and the therapy often is individualized on the basis of the severity of the endophthalmitis (8). In patients with endogenous *Candida* endophthalmitis without evidence of systemic infection, vitrectomy alone or vitrectomy combined with intravitreal injections of amphotericin B successfully treated the ocular infection (9). Some of these patients were given concurrent systemic oral antifungal therapy with ketoconazole or flucytosine (5FC) to treat possible subclinical systemic infection. Despite the reported successful outcome, the relative efficacies of these alternative therapies remain to be determined.

Fluconazole, a triazole derivative, is a new antifungal agent that has a broad spectrum of activity against most *Candida* species and other fungal organisms (13, 34, 35). It can be administered orally or intravenously and is associated with minimal systemic side effects. Originally, it was released for treatment of mucosal candidiasis and *Candida* peritonitis. In recent years, however, it has been noted to have excellent tissue penetration, especially in the central nervous system and ocular tissue, when administered orally (7, 32, 38). Presently, it has been used successfully for treatment of cryptococcal meningitis in AIDS patients intolerant of or unresponsive to amphotericin B (35). In a murine model, this treatment effect of fluconazole was enhanced by the addition of 5FC (2). In this study, we used a rabbit model to investigate the role of oral fluconazole, alone or in combination with 5FC, in the treatment of exogenous *Candida* endophthalmitis.

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MATERIALS AND METHODS

Inocula. A strain of *C. albicans* for which the MIC of fluconazole was ≤1.25 μg/ml and the MIC of 5FC was ≤10 μg/ml was isolated from a patient with fungal endophthalmitis. The organism was plated on *Brucella* agar with 5% horse blood at 35°C for 24 h. The organism was harvested and suspended in sterile saline at a turbidity equal to a McFarland turbidity standard of 1. The suspension was diluted serially to achieve a final concentration of 1,000 CFU/0.1 ml just prior to inoculation.

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Animal model. New Zealand albino rabbits, 2 to 2.5 kg in weight, were obtained from the same rabbitry throughout this experiment. Institutional guidelines regarding animal experimentation were followed. All procedures were performed on the right eye after adequate anesthesia was achieved. The rabbits were anesthetized with 1-ml intramuscular doses of a solution containing an equal mixture of ketamine (100 mg/ml; Parke-Davis, Morris Plains, N.J.) and xylazine (20 mg/ml; Mobay Corp., Shawnee, Kans.). Proparacaine 0.5% ophthalmic solution (Allergan) was used for topical anesthesia. Mydriasis was achieved with phenylephrine hydrochloride 2.5% ophthalmic solution and tropicamide 1% ophthalmic solution (Bausch and Lomb).

Anterior chamber paracentesis was performed just prior to fungal inoculation, using a 30-gauge needle attached to a tuberculin syringe. About 0.1 ml of aqueous fluid was aspirated. With a 30-gauge needle, 0.1 ml of the suspension of *C. albicans* (1,000 CFU) was injected directly into the vitreous cavity at the pars plana, about 2 mm posterior to the limbus.

Antifungal agents. Fluconazole was supplied as a powder by Pfizer Inc. (Groton, Conn.). It was suspended in 0.3% agar (Sigma) just prior to use and administered to rabbits orally with a 3-ml syringe and simple restraint. The dose was 80 mg/kg of body weight per day (which is equivalent to about 5.6 g/day in an adult human); the volume of each dose was ≤2 ml.

5FC was obtained as a capsule (Roche Laboratories, Nutley, N.J.), and the powder within the capsule was suspended in 0.3% agar just prior to use. The dose was 100 mg/kg of body weight every 12 h (which is equivalent to about 7 g every 12 h in an adult human); the volume of each dose was 1 ml.

Intraocular levels of fluconazole and 5FC. The rabbits ($n = 12$) were given a single oral dose of fluconazole and 5FC 5 days after intravitreous inoculation of fungus. After 2, 4, 8, and 24 h, the rabbits were sacrificed with a 5-ml intracardiac dose of pentobarbital (50 mg/ml; Abbott). There were three rabbits sacrificed per time point. Anterior chamber paracentesis was performed as previously described. The aqueous fluid (0.1 ml) was aspirated and collected from both the infected and contralateral uninfected eyes. Both eyes were enucleated. After the cornea, iris, and lens were surgically removed, the vitreous humor was aspirated and collected. The samples of aqueous and vitreous humors were stored at −70°C. Fluconazole levels were determined by a gas-liquid chromatography assay as previously described (21). 5FC levels were determined by a bioassay as previously described (5).

In vivo studies. Endophthalmitis was confirmed 5 days after fundus inoculation by indirect ophthalmoscopy. Endophthalmitis was defined as moderate to severe vitreous haze with partial or complete obscuration of >50% of the retinal and choroidal vasculature. Vitreous turbidity was graded with a scheme for *Candida* exogenous endophthalmitis outlined by Coats and Peyman (10). After the fundus appearance was graded and documented by fundus photography (Canon Fundus CV-6-ZA), rabbits were randomized to the following treatment conditions: group A, oral fluconazole alone for 2 weeks ($n = 10$); group B, oral fluconazole for 4 weeks ($n = 10$); group C, oral fluconazole alone for 4 weeks followed by no treatment for 4 weeks ($n = 10$); group D, oral fluconazole and 5FC for 2 weeks ($n = 12$); group E, no treatment for 2 weeks ($n = 10$); and group F, no treatment for 4 weeks ($n = 10$). After 2 weeks, all eyes were reexamined by indirect ophthalmoscopy and the fundus appearance was regraded and documented by fundus photography. Because some rabbits died during the first 2 weeks of the study (see Fig. 2), the number of rabbits surviving at the end of the period of study for each treatment group was somewhat unequal. There were nine eyes in group A, nine eyes in group B, nine eyes in group C, four eyes in group D, nine eyes in group E, and eight eyes in group F. Thus, at the end of 2 weeks, funduscopy was performed in 27 eyes that were treated with fluconazole alone (groups A, B, and C), 4 eyes treated with a combination of fluconazole and 5FC (group D), and 17 eyes that were untreated (groups E and F) (see Table 2). Similarly, after 4 weeks, there were 18 eyes treated with fluconazole (groups B and C) and 8 eyes without treatment (group F). After 8 weeks, there were nine eyes that had been treated with fluconazole for 4 weeks and off treatment for 4 weeks (group C). The clinical impression of improvement based on funduscopic examination was reconfirmed by comparing the fundus photographs taken before and after treatment. The examiner (S. S. Park) was blinded to the treatment condition of the eyes at the time of funduscopy and photographic evaluation.

At the end of the period of study, the rabbits were anesthetized with an intramuscular dose of ketamine and xylazine and sacrificed with an overdose of intracardiac pentobarbital (5 ml). The infected eyes were enucleated for histopathologic analysis or quantitative fungal culture.

Histopathology. Among eyes in each treatment group that did not show funduscopic improvement at the end of the treatment period, representative eyes were selected for histologic studies. For histopathologic analysis, whole eyes were fixed in formalin and embedded in plastic. Representative 5-μm sections of the eye were obtained and stained with hematoxylin-eosin or Gomori's methenamine silver. The sections were examined by light microscopy by an examiner (S. S. Park) who was blinded to the treatment condition of the eyes and were evaluated for the presence of inflammation, fibrous organization, and fungal elements.

Quantitative culture. The rabbits were sacrificed at the end of the study period. After selection of representative eyes in each treatment group for histopathology, there were nine eyes in group A, eight eyes in group B, eight eyes in group C, four eyes in group D, seven eyes in group E, and seven eyes in group F available for quantitative vitreous culture. The infected eyes were enucleated and surgically dissected in a sterile manner. The cornea, iris, and lens were removed, and the whole vitreous was aspirated and weighed. The whole retina-choroid layer was separated from the sclera with a metal spatula, collected separately from the vitreous, and weighed. The samples were homogenized, and a weighed fraction of the samples was cultured on brucella agar–5% horse blood plates undiluted or after 10- and 100-fold dilutions with sterile normal saline. The plates were incubated for 48 h at 35°C in 5 to 10% CO_2. The colonies were counted on each plate by an examiner (B. Paton) who was blinded to the treatment conditions of the eyes. The total CFU in the eye (vitreous and retina-choroid) was calculated on the basis of the growth yielded from culture of measured fractions of the samples. Treatment effect was assessed in terms of reduction in vitreous fungal colony count, which was defined in this study as a total intraocular fungal burden (vitreous and retina-choroid) of <100 CFU. "Sterility" was defined as no growth in the plates of undiluted vitreous and retina-choroid samples after 5 days of incubation.

Statistical analysis. Treatment effect was determined by comparing the rate of fundus improvement, reduction in intraocular fungal load, and sterilization in treated versus control eyes. The statistical significance of the treatment effect was determined with Fisher's analysis. The quantitative vitreous culture results were analyzed in terms of the rate of reduction in intraocular fungal burden as defined by our study rather than by absolute counts of the CFU of candidas, since the absolute colony counts of the treated eyes did not fit a Gaussian curve. Given this condition, the mean and standard deviation values of the absolute colony count were thought to be misleading.

TABLE 1. Intraocular fluconazole concentrations in infected and uninfected eyes of three rabbits

Time after dose (h)	Fluconazole concn (μg/ml [mean + SEM]) in:			
	Aqueous fluid of:		Vitreous of:	
	Infected eyes	Uninfected eyes	Infected eyes	Uninfected eyes
2	27.86 ± 17.88	34.50 ± 3.30	30.37 ± 2.48	28.31 ± 4.65
4	42.23 ± 17.86	42.06 ± 9.69	41.56 ± 9.70	34.77 ± 2.85

RESULTS

Intraocular levels of fluconazole and 5FC. The aqueous and vitreous concentrations of fluconazole were similar in infected and contralateral uninfected eyes (Table 1). Intravitreal levels of fluconazole measured 2 to 24 h after the first oral dose were >10 times the MIC for our strain of *C. albicans* (Fig. 1). Intravitreal 5FC levels measured 2 to 24 h after the first oral dose were within the lowest detectable range of the bioassay, i.e., <20 μg/ml. Although absolute values could not be determined by this assay, the levels were in the same range as the MIC of 5FC.

Survival on fluconazole and 5FC. Among 12 rabbits treated with a combination of oral fluconazole and oral 5FC, 8 (67%)

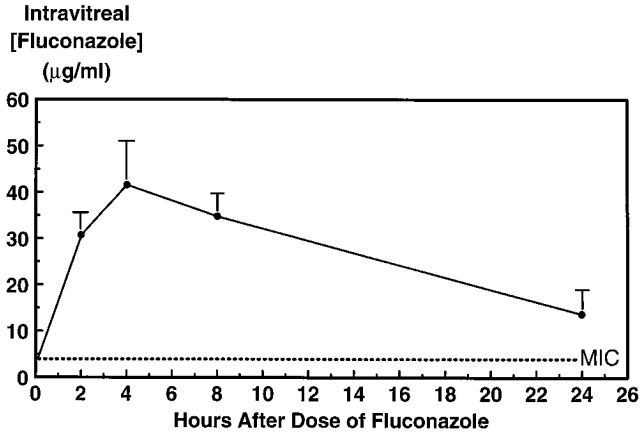

FIG. 1. Intravitreal fluconazole concentrations after an oral dose of fluconazole (80 mg/kg) compared with the MIC of this drug for the strain of *C. albicans* used in the study (three rabbits per time point).

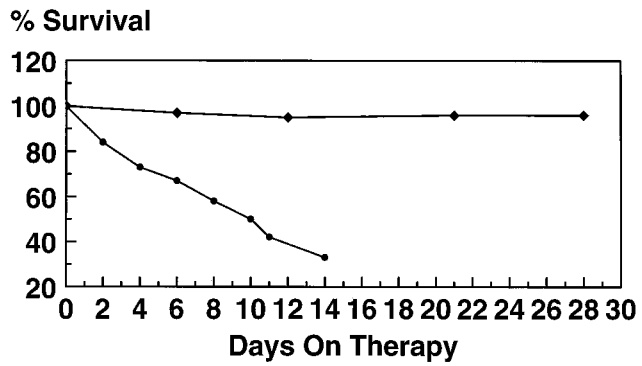

FIG. 2. Rate of survival of the rabbits treated with oral fluconazole either alone (◆) or with 5FC (●). The percentage of rabbits surviving after each day of treatment is reported. There were 30 rabbits treated with fluconazole alone and 12 rabbits treated with combination therapy at the start of the treatment period.

TABLE 2. Summary of treatment effect after therapy with oral fluconazole

Result	Duration of therapy (wk)	% of eyes (*n*) in group treated with:		
		Nothing (control)	Fluconazole	Fluconazole + 5FC
Fundus improvement	2	0 (17)	44[a] (27)	50[a] (4)
	4	0 (8)	28 (18)	
	4 on, 4 off		44 (9)	
Reduction of vitreous and retinachoroid fungal burden	2	0 (7)	67[a] (9)	75[a] (4)
	4	43 (7)	100[a] (8)	
	4 on, 4 off		100 (8)	
Sterilization of vitreous and retinachoroid	2	0 (7)	33 (9)	25 (4)
	4	0 (7)	75[b] (8)	
	4 on, 4 off		88 (8)	

[a] Statistically significant difference from the control group result ($P \leq 0.05$).
[b] Statistically significant difference from the control group result ($P = 0.01$).

died during the first 2 weeks of therapy (Fig. 2). Because of the high toxicity associated with this combination therapy, the effect of longer treatment was not studied. Among 30 rabbits treated with oral fluconazole alone, only 2 (7%) died during the first 2 weeks of therapy. A similar survival rate was noted in untreated animals; among 20 untreated rabbits, 3 died during the first 2 weeks after infection. No additional mortality was noted between the second and fourth weeks of study among 18 remaining rabbits treated with oral fluconazole and among 9 remaining untreated rabbits. The only noted side effect of treatment with oral fluconazole alone was mild diarrhea which occurred in 30 to 50% of the rabbits.

Fundus appearance. When the eyes were examined 5 days after fungus inoculation, all eyes had significant vitreous inflammation and fit the criteria for endophthalmitis as defined in this study. Among untreated rabbits, all infected eyes showed progressive vitreous opacification (Table 2). After 4 weeks, 50% of untreated eyes had complete vitreous opacification with a loss of the red reflex and appeared phthisical. In contrast, after 2 weeks of therapy, progressive vitreous clearing, defined as any degree of reduction in severity grading by indirect ophthalmoscopy, was noted in 44% of eyes treated with fluconazole alone and 50% of eyes treated with combination therapy (Table 2). This difference was statistically significant ($P < 0.05$). After 4 weeks on fluconazole, a few eyes which had shown vitreous clearing during the first 2 weeks of treatment appeared slightly worse because of vitreous fibrous organization. However, 28% showed persistent progressive vitreous clearing. When eyes were reexamined 4 weeks after discontinuation of fluconazole, all eyes had a fundus appearance which was unchanged or slightly improved since the cessation of therapy. The overall rate of vitreous clearing among these eyes off therapy was 44%.

Quantitative fungal culture. Table 3 summarizes the absolute fungal colony count obtained by quantitative vitreous culture of each treatment group. Treatment effect in terms of reduction in absolute counts of CFU is noted after 2 and 4 weeks of treatment. However, because of a significant spontaneous reduction in the fungal colony count after 4 weeks in some untreated eyes, the values did not fit a Gaussian curve and resulted in a mean value which was smaller than the standard deviation. Thus, treatment was assessed, as summarized in Table 2, as the rate of reduction in intraocular fungal colony count in treated and control eyes as defined in our study. After 2 weeks of treatment, a reduction in fungal colony count, as defined in Materials and Methods in this study, was noted in 67% of eyes treated with oral fluconazole alone and in 100% of eyes treated with combination therapy. The treatment effect was statistically significant in both groups compared with results in untreated eyes, which had no reduction in fungal burden.

After 4 weeks of oral fluconazole alone, 100% of eyes had a reduction in fungal colony count. Among control eyes without treatment for 4 weeks, 43% had a spontaneous reduction in fungal colony counts; however, this spontaneous reduction in fungal burden was observed only in untreated eyes that became phthisical. The treatment effect of 4 weeks of fluconazole was statistically significant even if these phthisical control eyes were included in the analysis. In addition, when fluconazole was discontinued for 4 weeks, the fungal burden in all treated eyes remained decreased.

Overall, the fundus appearance of the treated eyes correlated poorly with the reduction in fungal colony count. Although all eyes that improved by funduscopy had reductions in fungal colony count, not all eyes that had reductions in fungal burden had clinical improvement by funduscopy. A few eyes showed progressive vitreous opacity during treatment and could not be readily differentiated from control eyes by funduscopy.

Rate of sterilization. Treatment effect was analyzed by comparing the rate of sterilization of the vitreous and retina-choroid in treated and control eyes. The results are summarized in Table 2. None of the untreated eyes were sterile at 2 or 4 weeks. In contrast, a progressive increase in the rate of sterilization was noted in eyes treated with oral fluconazole alone. After 4 weeks of fluconazole, 75% of the eyes were sterile. The remaining 25% of eyes that did not fit our definition of sterile had 1 or 2 CFU of fungus per eye. Similarly, when fluconazole was discontinued for the next 4 weeks, the rate of sterilization remained high at 88%.

Among the eyes that were treated with combination oral therapy for 2 weeks, 25% became sterile. This treatment effect was not statistically significant compared with results in untreated eyes because of the low number of surviving rabbits at the end of the treatment period.

Histopathology. Because some eyes failed to show fundus improvement after treatment with fluconazole, histopathologic analysis was used to determine the degree of inflammation and fibrous proliferation in these eyes compared with that in untreated eyes. In eyes that were not treated, the vitreous cavity was almost completely filled with inflammatory cells after 4 weeks. There was also evidence of fibrous proliferation and

TABLE 3. Summary of quantitative vitreous and retina-choroid fungal culture

Duration of therapy (wk)	Intraocular fungal burden (CFU) in group treated with:					
	Nothing (control)		Fluconazole		Fluconazole + 5FC	
	Absolute values (*n*)	Mean ± SEM	Absolute values (*n*)	Mean ± SEM	Absolute values (*n*)	Mean ± SEM
2	921, 842, 549, 605, 557, 676, 412 (7)	652 ± 177	705, 110, 0, 33, 57, 0, 17, 28, 0 (9)	116 ± 225	0, 22, 43, 605 (4)	223 ± 295
4	23, 450, 14, 15, 1,968, 130, 458 (7)	437 ± 703	1, 2, 0, 0, 0, 0, 0, 0 (8)	0 ± 1		
4 on, 4 off			0, 0, 0, 0, 0, 0, 0, 10 (8)	1 ± 4		

traction retinal detachment. With Gomori's methenamine silver stain, persistent fungal elements were seen in the midst of active inflammation. Similarly, in eyes that were treated with fluconazole for 4 weeks that did not have funduscopic improvement clinically, persistent vitreous inflammation was observed. However, the foci of inflammation showed more fibrous organization. Four weeks after the discontinuation of fluconazole, the fibrous organization was more marked. In addition, Gomori's methenamine silver staining failed to show fungal elements even in the midst of persistent foci of inflammatory cells.

DISCUSSION

Fluconazole is a difluorophenyl bis-triazole derivative that has been shown to have significant antifungal activity in several animal models (2, 18, 25, 42). Although preliminary in vitro studies showed the drug to be fungistatic and poorly effective in inhibiting growth of many strains of fungi, the in vivo activity of this drug following systemic administration is superior to those of other oral antifungal agents, such as ketoconazole, and rivals that of intravenous amphotericin B (25, 39).

Presently, there are anecdotal reports of patients who have been successfully treated for endogenous *Candida* endophthalmitis with fluconazole alone (6, 11, 12, 26, 28, 40, 43). In one of these cases, the endophthalmitis had been resistant to treatment with intravitreal amphotericin B and systemic ketoconazole but responded to treatment with oral fluconazole (6). In addition, an ongoing prospective multicenter clinical trial of patients with candidemia has thus far shown treatment with fluconazole to be as effective as treatment with amphotericin B (30). However, animal studies thus far have failed to show a significant antifungal effect of the drug in treating endogenous *Candida* endophthalmitis unless therapy is initiated within 24 h of intravenous fungus inoculation (17, 38).

In this study, we used a rabbit model of exogenous *Candida* endophthalmitis to determine the efficacy of this drug in treating intraocular *Candida* infection. Consistent with previous studies in rabbits which had shown excellent ocular tissue penetration of the drug when given orally or intravenously, our results show that oral fluconazole administration is well tolerated and results in intraocular concentrations of the drug which remain greater than 10 times the MIC of the drug for our strain of *C. albicans* (32, 38). In addition, intravitreal penetration of the drug was unaffected by the presence of active inflammation induced by the fungal infection. However, it is worth noting that the dose of drug used in this animal study is equivalent to an about 5.6-g daily dose for an adult human, much higher than the dose thus far used clinically in patients with candidal or cryptococcal infections, i.e., $\leq$1.2 g/day (4).

In our model of exogenous *Candida* endophthalmitis, direct intravitreal inoculation with 1,000 CFU of *C. albicans* resulted in vitreous inflammation in all eyes. This intraocular fungal burden was chosen since it is comparable to that noted in previous studies of eyes of rabbits with late-stage endogenous *Candida* endophthalmitis (24). In our study, even though treatment was delayed until 5 days after fungus inoculation, when moderate to severe vitreous inflammation was observed, oral fluconazole reduced fungal burden by greater than 99% in all eyes after 4 weeks. Sterilization was achieved in 75% of these eyes. Despite the fact that the drug is fungistatic in in vitro studies, the treatment effect was unchanged when therapy was discontinued for 4 weeks in our rabbit model.

One of the limitations of our study is that the treatment effect was observed in animal eyes with vitritis from exogenous *Candida* endophthalmitis while most cases of clinical fungal endophthalmitis present as chorioretinitis from endogenous infection. In fact, our results are in contrast to observations reported by Filler et al. (17). In their rabbit model of endogenous *Candida* endophthalmitis, intravenous fluconazole administration at the dose used in our study, i.e., 80 mg/kg/day, was ineffective in reducing the intraocular fungal colony count although therapy was started within 48 h of fungus inoculation and continued for 24 days. The lack of response to therapy in their model may be due to the high dose of fungal inoculum used to create the endophthalmitis. In their study, intravenous inoculation of 800,000 CFU of fungi was used to produce endophthalmitis with an intraocular fungal burden of 500 to 1,000 CFU. In their model, extraocular systemic fungal abscesses which did not sterilize after treatment with systemic fluconazole were formed. These abscesses may have resulted in continuous fungemia and reinfection of ocular tissue despite prolonged systemic fluconazole therapy.

Interestingly, Filler et al. noted that intravenous amphotericin B successfully sterilized the eye and other visceral organs in their rabbit model of endogenous *Candida* endophthalmitis (17). This result suggests that intravenous amphotericin B is superior to systemic fluconazole in sterilizing tissue infected with a high fungal burden. However, it is not clear whether this high fungal burden is representative of the level of infection seen clinically among patients with endogenous or exogenous *Candida* endophthalmitis.

When treatment effect in our study was assessed in terms of funduscopic improvement, a lower response rate was noted. This is in agreement with a previous work that has shown a poor correlation between funduscopic appearance and quantitative fungal culture in eyes that had been successfully treated for *Candida* endophthalmitis with amphotericin B (17). In our study, histopathologic analysis of those eyes that failed to improve funduscopically did show persistent inflammation in the absence of fungal elements. Although the inflammation appeared somewhat less prominent in eyes treated with fluconazole compared with that in untreated eyes, these observations suggest that successful antimicrobial therapy alone is inadequate in preserving ocular tissue. Concurrent anti-inflamma-

tory therapy has been advocated on the basis of animal models of both bacterial and fungal endophthalmitides (10, 27, 37).

In an effort to shorten the duration of oral antifungal therapy, we investigated the possibility of enhancing the antifungal activity of fluconazole by using a combination oral antifungal therapy. 5FC was chosen since it is an oral antifungal agent with excellent bioavailability and tissue penetration (3). Its use as a sole antifungal agent has been limited because of the rapid emergence of resistant strains of fungi. However, because of its excellent penetration into the central nervous system, it has been used successfully in combination with amphotericin B or fluconazole in treatment of cryptococcal meningitis (2, 19, 36).

Reported data on intraocular penetration of 5FC in human and rabbit eyes are consistent with our findings in infected rabbit eyes (33, 41). Our results show that an oral dose of 5FC can result in an intraocular level of the drug which is in the range of the MIC of 5FC for our *Candida* strain. Although the use of 5FC combined with fluconazole may have a slightly higher antifungal effect than fluconazole alone, it was associated with severe toxicity at doses used in our study in combination with fluconazole. The low survival rate noted with combination therapy is consistent with previously reported observations in rabbits in which 5FC alone, at doses as low as 75 mg/kg/day, was uniformly fatal after 3 to 5 days of administration because of hepatic necrosis (24). Although the drug is better tolerated in humans, leukopenia secondary to bone marrow suppression is a frequently encountered dose-limiting toxicity, and levels of the drug in serum need to be closely monitored among patients on this drug regimen (3, 19).

In summary, on the basis of our study, oral fluconazole may be an effective antifungal agent for treatment of exogenous *Candida* endophthalmitis. Although there are anecdotal clinical reports of cases of fungal endophthalmitis that have failed therapy with fluconazole alone (31), the dose of fluconazole that has been used clinically for endophthalmitis thus far is much lower than the doses that were used in this and other animal studies, as well as in patients with cryptococcal meningitis (4, 17). In addition, these cases may represent advanced infection which may have failed the more traditional therapy with systemically administered amphotericin B with or without vitrectomy and intravitreal amphotericin B. As a better understanding of the clinical efficacy and limitations of this drug emerges, it remains to be seen whether fluconazole will be as effective as amphotericin B clinically for treatment of endogenous or exogenous fungal endophthalmitis. However, the relative safety and ease of administration make fluconazole an appealing future treatment alternative, either as a sole antifungal agent or as an adjuvant antifungal therapy used in concert with intravitreal or intravenous amphotericin B.

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