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Penetration of New Azole Compounds into the Eye and Efficacy in Experimental *Candida* Endophthalmitis

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We studied the penetration of three azole compounds, ketoconazole, itraconazole, and fluconazole, into the ocular tissues and fluids of rabbits in the presence and absence of ocular inflammation. Drug concentrations were compared with those found in serum and cerebrospinal fluid. The rank order of penetration into eye tissue was fluconazole > ketoconazole > itraconazole. Fluconazole penetrated freely into both inflamed and uninflamed eyes. The presence of inflammation improved penetration of all three compounds into ocular fluids and tissues. Penetration of these azoles into the anterior chamber of uninflamed eyes and into the cerebrospinal fluid was similar. All three azole compounds reduced the number of yeasts found in the eye in hematogenous *Candida albicans* endophthalmitis in rabbits when therapy was initiated within 24 h of inoculation. However, only ketoconazole significantly reduced yeast counts in the eye when therapy was postponed for 7 days.

The incidence of ocular fungal infections has increased (10, 11, 26) due to a number of factors: increased prevalence of immunosuppression associated with organ transplantation and malignancies; prolonged recovery from complex surgical procedures; and increasing use of antibiotics, immunosuppressive agents, intravenous catheters, and hyperalimentation fluids. Endogenous *Candida* endophthalmitis (ECE) also occurs in heroin addicts (2, 9; D. W. Vastine, W. Horsley, S. B. Guth, and M. F. Goldberg, Letter, Arch. Ophthalmol. **94**:1805, 1976), neonates (28, 32), and postpartum patients not exposed to these factors (7). The most common species causing ECE is *Candida albicans* (8, 12). Others are *Candida tropicalis* (20, 26, 28), *Candida stellatoidea* (12), *Candida parapsilosis* (20), and *Candida guillermondi* (26).

Optimal therapies for oculomycoses have not been defined. Amphotericin B is less than ideal: it penetrates poorly into ocular fluids, is toxic, and must be given intravenously. Another polyene, pimaracin, can only be given topically. Oral flucytosine penetrates well into the ocular fluids, but this drug is active against only a limited range of pathogenic fungi, and resistance can develop during therapy. The development of azole compounds with broad-spectrum activity against yeasts and dimorphic fungi has expanded the therapeutic options. Miconazole and ketoconazole have been available for several years, but reported experience in eye infections is limited (5, 15, 21, 23). The present study examined the concentrations of three azole compounds, ketoconazole, fluconazole, and itraconazole, in different compartments of inflamed and uninflamed eyes of New Zealand white (NZW) rabbits. These three agents were then compared for their in vivo efficacy in an established rabbit model (24) for hematogenous *Candida* infection of the eye.

MATERIALS AND METHODS

Animals. Seventy-two male NZW rabbits weighing 2 to 3 kg were used. All rabbits were housed in separate cages and given rabbit chow (Purina Co.) and water ad libitum. Ketamine (Ketaject; Bristol Laboratories, Syracuse, N.Y.), 100 to 150 mg intramuscularly, and xylazine (Rompun; Cutter Laboratories, Shawnee, Kans.), 15 to 25 mg intramuscularly, were used as anesthesia for all procedures. Animals were sacrificed with intravenous pentobarbital.

Organism. A clinical isolate of *C. albicans* (Carter strain) was used for the endophthalmitis experiments. To prepare the inocula, *C. albicans* was transferred from a stock culture onto a Sabouraud agar plate containing 100 μg of chloramphenicol per ml and allowed to grow overnight at 37°C. Yeasts were then taken up on cotton swabs and suspended in 0.015 M phosphate-buffered saline (PBS). The yeast suspension was adjusted by optical density with a spectrophotometer (Gilford Instruments, Oberlin, Ohio) to a final concentration of 10^6 CFU/ml (24). The final concentration was verified by a colony count of twofold dilutions of each inoculum plated onto Sabouraud agar.

Antifungal agents. Itraconazole (Janssen Pharmaceutica, New Brunswick, N.J.) was administered orally in 50-mg capsules containing polyethylene glycol. Fluconazole (Pfizer Inc., Groton, Conn.) was dissolved in sterile water to a final concentration of 10 mg/ml. The fluconazole solution was warmed to resolubilize the drug before each treatment and injected intravenously. Ketoconazole (Janssen Pharmaceutica) was administered orally as 200-mg tablets. Amphotericin B was prepared by dissolving the standard parenteral preparation (E. R. Squibb and Sons, Princeton, N.J.) in sterile distilled water to a concentration of 5 mg/ml and injected intravenously.

Antifungal assay. A bioassay was used to determine azole levels in the serum, cerebrospinal fluid (CSF), aqueous humor, and vitreous body of each animal. The assay used the agar-well diffusion method of Bennett et al. (4), modified by the method of Jorgensen et al. for assaying azole compounds (25). The standard concentrations were dissolved in serum or normal saline. In preliminary experiments we found no differences in zone sizes between azole compounds in saline, CSF, and aqueous humor. The reproducibility of this assay when samples are run in triplicate is ±7%. The lower limit of sensitivity of the bioassay for ketoconazole and itraconazole was 0.078 μg/ml. For fluconazole, the lower limit ranged between 1.56 and 3.13 μg/ml.

To assay drug in rabbit corneas, 6-mm disks of tissue trephined from corneas were assayed by the trephine disk method (3, 35). Standards for this assay were prepared in

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TABLE 1. Concentrations of azoles in rabbits with and without eye inflammation, 4 h after a single dose

Drug and dose (mg/kg)	Concn (mean ± SEM)							
			Inflamed eye			Uninflamed eye		
	Serum (μg/ml)	CSF (μg/ml)	Cornea (μg/g)	Aqueous humor (μg/ml)	Vitreous body (μg/ml)	Cornea (μg/g)	Aqueous humor (μg/ml)	Vitreous body (μg/ml)
Fluconazole (80, i.v.)	77.6 ± 2.7	33.2 ± 2.5	6.2 ± 1.0	50.2 ± 6.2	21.5 ± 0.1	2.1 ± 0.3	21.9 ± 3.4	16.0 ± 5.3
Ketoconazole (~80, p.o.)	58.3 ± 4.5	3.1 ± 0.2	1.4 ± 0.1	33.6 ± 8.0	16.4 ± 2.7	0.7 ± 0.2	7.4 ± 5.1	2.9 ± 1.2
Itraconazole (~80, p.o.)	2.13 ± 0.58	ND[a]	0.05 ± 0.01	0.92 ± 0.01	0.22 ± 0.04	0.03 ± 0.01	ND	ND

[a] ND, Not detectable.

PBS, absorbed onto 6-mm filter paper disks, and plated as described previously (3, 35). *Candida pseudotropicalis* was used as the assay organism.

In vitro susceptibility testing. A broth dilution test adapted from the turbidimetric method of Galgiani and Stevens (18) was used. Briefly, to measure MICs or $IC_{1/2}$, an overnight growth of *C. albicans* Carter strain on Sabouraud slants was suspended in PBS and then adjusted by optical density to a final concentration of 10^5 CFU/ml. Serial twofold dilutions of antifungal agents were prepared in a buffered synthetic amino acid medium for fungi (SAAMF) (18). One hundred microliters of the inoculum (final concentration, 0.5×10^4 CFU/ml) was added to 2-ml plastic tubes with drug diluted in SAAMF, mixed, and incubated for 16 to 18 h at 30°C. Growth was read by a spectrophotometer (Gilford Instruments). The MIC was determined as the antibiotic concentration which inhibited the growth of the yeast by one-half compared with a drug-free control ($IC_{1/2}$).

Drug pharmacokinetics. To produce ocular inflammation, 0.1 ml of 20% proteose was injected intravitreally into the right eye of 12 NZW rabbits. Approximately 36 h later, the rabbits were randomized into four groups of three rabbits each, and treatment was started. The groups received the following treatments: group I—fluconazole, 80 mg/kg intravenously (i.v.); group II—itraconazole, 80 mg/kg orally (p.o.); group III—ketoconazole, 80 mg/kg p.o. Between 3 and 4 h following therapy, the rabbits were anesthetized, and blood and CSF samples were aspirated. CSF was obtained with a 25-gauge needle on a 3-ml syringe which was introduced into the cisterna magna. Approximately 0.5 to 1.0 ml of CSF can be removed safely without blood contamination. Then, aqueous humor was withdrawn from both eyes. Animals were sacrificed, and the eyes were enucleated, rinsed in sterile water, and immediately frozen in liquid nitrogen. Tissues were dissected while still frozen and kept at −70°C until assayed to determine the tissue concentrations of the drugs (1).

Production and quantitation of *Candida* endophthalmitis. Sixty NZW rabbits were anesthetized, and a 1-ml suspension containing 10^6 blastospores of *C. albicans* was injected intravenously into a marginal ear vein. Approximately 24 h later, four rabbits were sacrificed, and both eyes from each animal were enucleated, rinsed in sterile PBS, and placed in a sterile petri dish for dissection. The cornea, lens, and iris were excised and discarded. The vitreous body was removed and transferred to a preweighed volumetric flask. Sclerae were opened by three radial incisions. The retina and choroid tissues were placed in a preweighed petri dish. Samples were weighed, diluted in 1 ml of PBS, and homogenized in a tissue homogenizer (Eberbach Corp., Ann Arbor, Mich.). One hundred microliters of the homogenate or 10-fold dilutions was plated on Sabouraud agar plates containing 100 μg of chloramphenicol per ml and allowed to grow overnight at 37°C. Colonies were counted on the following day; final concentrations were expressed as CFU per gram of tissue.

Fifty-six NZW rabbits were evaluated for eye lesions by indirect ophthalmoscopy. Both eyes were examined, and the mean number of foci per rabbit was recorded. Rabbits were randomized into several treatment regimens to achieve equal distribution of rabbits with various numbers of eye lesions in each group.

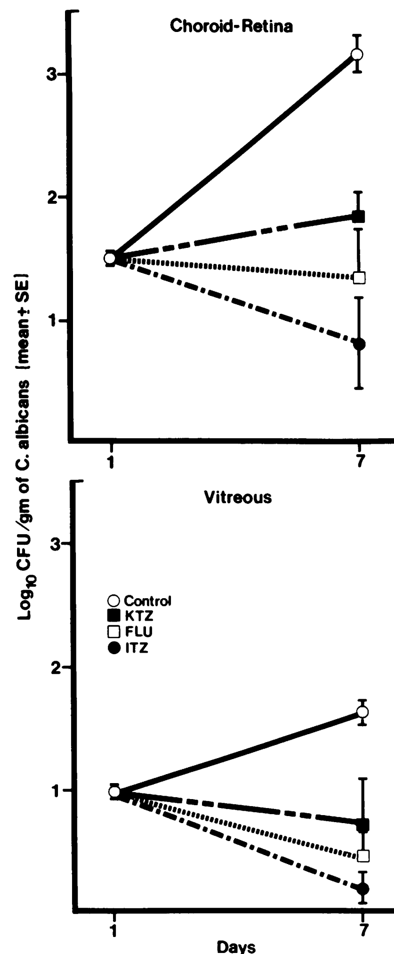

FIG. 1. Mean quantitative counts of *C. albicans* in the choroid-retina and vitreous body from average values for each rabbit after no treatment, ketoconazole (KTZ, 80 mg/kg per day p.o.), itraconazole (ITZ, 80 mg/kg per day p.o.), and fluconazole (FLU, 80 mg/kg per day i.v.) are shown. Treatment was started on day 1 of infection and maintained for 7 days.

Treatment regimens. (i) Early therapy: 24 NZW rabbits were started on treatment 24 h after inoculation with *C. albicans* and maintained on daily treatment for 7 days. Four groups of six rabbits each received the following: group I—itraconazole, 80 mg/kg per day p.o.; group II—ketoconazole, 80 mg/kg per day p.o.; group III—fluconazole, 80 mg/kg per day i.v.; group IV—no treatment. (ii) Late therapy: 32 NZW rabbits were started on antifungal agents 7 days after inoculation with *C. albicans* and maintained on daily treatment for 7 days. Four groups of seven rabbits each received the same treatments as groups I through IV above. In this experiment an additional group of four rabbits received amphotericin B (1 mg/kg per day i.v.). Rabbits were sacrificed 24 h after the last dose in all groups, and quantitative cultures were performed as described above.

Statistical analysis. For comparison of yeast counts at the end of therapy, an analysis of variance of ranks, sequentially followed by pairwise comparison *t* tests, was used. Means were calculated from the average value for both eyes of each rabbit; n = number of animals. A Student *t* test was used to compare drug levels in inflamed and uninflamed eyes.

RESULTS

Concentrations in serum measured 4 h after a single dose are shown in Table 1. Both ketoconazole and itraconazole were relatively well absorbed. A 200-mg dose of ketoconazole and itraconazole p.o. per rabbit represents approximately 80 mg/kg, similar to the intravenous dose used for fluconazole.

The concentrations of the three azoles in the aqueous humor from inflamed and uninflamed eyes and in the CSF are shown in Table 1. There were striking differences among the three agents. Inflammation facilitated penetration of all azoles into the aqueous humor, but fluconazole crossed both blood-aqueous and blood-CSF barriers freely even in the absence of inflammation. Fluconazole was found in the aqueous humor at approximately 64% of the concentration in serum, comparable to the good penetration of flucytosine into the eye (27, 34). As we have reported previously, itraconazole could not be detected in the CSF by our bioassay (29), nor could itraconazole be detected in the aqueous humor of uninflamed eyes. However, for inflamed eyes, the percent penetration of itraconazole into the aqueous humor was about 45% of the simultaneous level in serum. Ketoconazole was present in both uninflamed and inflamed eyes by our assays, with the latter having significantly higher concentrations. Interestingly, significantly higher concentrations of ketoconazole were found in the aqueous humor than in CSF.

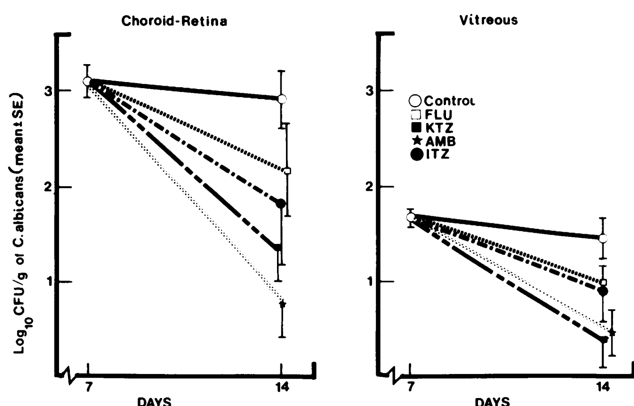

FIG. 2. Quantitative cultures of the choroid-retina and vitreous body after rabbits received no therapy, ketoconazole, itraconazole, fluconazole, or amphotericin B (AMB, 1 mg/kg i.v.) daily for 1 week. Therapy was started on day 7 of infection and maintained for 7 days. See the legend to Fig. 1 for other doses and abbreviations.

TABLE 2. Drug concentrations in serum of rabbits treated for *Candida* endophthalmitis

Drug	Dose (mg/kg)	No. of doses	Time concn measured (h after last dose)	Mean concn in serum (μg/ml) ± SEM
Amphotericin B	1	1	2	1.2 ± 0.04
		1	24	0.8 ± 0.01
		7	24	1.1 ± 0.03
Itraconazole	80	1	2	2.31 ± 0.4
		1	24	4.33 ± 0.3
		7	24	6.78 ± 0.5
Ketoconazole	80	1	2	72.09 ± 1.1
		1	24	14.29 ± 1.8
		7	24	11.63 ± 6.0
Fluconazole	80	1	2	65.36 ± 5.5
		1	24	33.90 ± 2.6
		7	24	53.85 ± 4.2

The concentrations of these three azoles in the vitreous body are shown in Table 1. These levels were approximately 20 and 5% of the concentrations in serum for fluconazole and ketoconazole, respectively. Intraconazole could not be detected in the uninflamed eye. Inflammation enhanced penetration of all azoles into this ocular compartment.

The tissue concentrations of the azole compounds obtained from corneal specimens are shown in Table 1. Measurable amounts of all three azoles were found in these tissues, with higher amounts in the inflamed eye ($P < 0.01$) for all three azoles.

The in vitro MICs of the azoles against *C. albicans* (Carter strain) determined in SAAMF for amphotericin B, ketoconazole, and fluconazole ranged between 0.4 and 0.8 μg/ml. The MIC of itraconazole was at least 10-fold lower than those of the other azoles and amphotericin B, which had an MIC of less than 0.025 μg/ml.

The efficacy of treatment with ketoconazole, itraconazole, and fluconazole for early *Candida* endophthalmitis in rabbits is shown in Fig. 1. All three azoles significantly inhibited the growth of *C. albicans* in the choroid-retina tissue (P = 0.0004) and vitreous body (P = 0.0007) when therapy was started 24 h postinoculation. The *F* test, examining pairwise *t* tests, showed that all three azoles were similar in effect and better than no treatment. Despite low drug levels in ocular fluids and tissue, early treatment with itraconazole was at least as effective as with ketoconazole and fluconazole.

We also examined the efficacy of therapy at a more advanced stage of infection when the number of organisms in the retina and choroid had peaked, a feature described by previous investigators (24). The results of late therapy, started on day 7 of infection, are shown in Fig. 2. The number of organisms in the choroid-retina of animals receiving amphotericin B or ketoconazole was significantly lower than the number in the control group after treatment ($P < 0.05$). Some decline of yeast counts in the vitreous body in rabbits receiving these two agents occurred, but the reductions were not statistically significant. Neither of the triazole compounds, itraconazole and fluconazole, reduced the num-

ber of yeasts found in the choroid-retina or vitreous body. Thus, these triazoles had little effect on the more established infection.

The various antifungal therapies were monitored by determining the concentrations of the corresponding drugs in serum during day 1 of treatment at 2 h and 24 h and during day 7 at 24 h after administration of the drugs (Table 2).

DISCUSSION

The rabbit provides a simple and convenient model for assessing the pharmacokinetics and efficacy of systemic antifungal antibiotics in hematogenous *Candida* endophthalmitis (24). The model is reproducible, is similar in natural evolution to human infection, and requires no interference with host defenses. Cultures can be obtained from different sites of the eye.

Intraocular penetration of most drugs depends largely on the permeability of the ocular structures, which varies in inflamed and uninflamed eyes (6). Little is known about the ocular penetration of antimycotic agents. Foster and Stefanyszyn (15) reported that intravenous infusion of a 30-mg/kg dose of miconazole nitrate in rabbits produced peak aqueous humor levels of 7.9 μg/ml at 1 h; no drug was detected in the vitreous body. Despite another initial report of good miconazole penetration into the eye (vitreous body concentration of 0.4 μg/ml 1 h after a 700-mg miconazole infusion and simultaneous serum concentration of 0.7 μg/ml [15, 23]), parenteral miconazole was not effective in preventing the development of hematogenous *Candida* endophthalmitis in the rabbit model (24). Also, Blumenkranz and Stevens noted progression of ECE in a 19-year-old female heroin addict during intravenous miconazole therapy (5).

Ketoconazole, an oral azole compound presently available for treatment of mycoses, is a potent inhibitor of ergosterol synthesis in *C. albicans*. It is soluble in organic solvents, absorbed well from the gastrointestinal tract, and metabolized by the liver; approximately 90% is protein bound. Ketoconazole has a half-life of 2 to 3 h in humans. In our study a single oral dose of 80 mg of ketoconazole per kg given to rabbits produced a 4-h mean concentration in serum of 58 ± 4.5 μg/ml, which is 10-fold higher than that routinely found in humans treated with standard doses of 200 to 400 mg/day. Although inflammation seems to be an important factor in ocular penetration of ketoconazole, we found measurable amounts of ketoconazole in all ocular sites tested, even in uninflamed eyes. Recently, O'Day et al. (27) reported detectable amounts of ketoconazole in the aqueous humor and vitreous body from a patient undergoing therapeutic vitrectomy for fungal endophthalmitis. We measured ketoconazole in the aqueous humor of two patients and found levels in this fluid which were approximately one-quarter of the concentrations found in simultaneous serum samples (unpublished data). Although the relationship between penetration and successful treatment of ECE is not clear, successful therapy with ketoconazole has been described for keratomycosis in both rabbits and humans (21). In a previous study, ketoconazole failed in a rabbit ECE model as determined by cultures done after 7 and 14 days of therapy. However, when ketoconazole was given for 28 days in this model, the number of organisms was significantly lower than in nontreated controls (24). In this study we were able to demonstrate a significant decrease in the number of yeasts in choroid-retina tissue in ketoconazole-treated rabbits with both early and late therapy. Although a difference in yeast counts was also seen in the vitreous fluid, the response to ketoconazole was not significant when therapy was initiated late. We did not examine the possibility that prolonged treatment with this azole would have successfully treated all sites of infection.

The ocular pharmacokinetics of the two triazoles described here are different. Itraconazole (M_r 705) is larger than fluconazole, very hydrophobic, and more than 90% bound to protein in serum. Fluconazole is a smaller molecule (M_r 306), soluble in water, and only 10 to 20% protein bound in serum. It has a long half-life and is excreted renally. Besides all these advantageous pharmacokinetic properties, fluconazole may be given either p.o. or i.v. While itraconazole in vitro has been shown to be very active against a variety of fungi, including *Aspergillus* species (19), fluconazole appears to have the better pharmacokinetic profile. However, despite the low drug levels found in the eye, itraconazole proved as effective as fluconazole in treating ECE when started early in infection. Efficacy despite poor drug availability at the site of infection recalls the effect of itraconazole in our cryptococcal meningitis rabbit model (30), in which this drug was active despite undetectable CSF concentrations. However, no significant responses to itraconazole or fluconazole were seen when therapy was attempted at a later stage of infection. It is disappointing that fluconazole also did not clear the vitreous body and choroid-retina of yeasts when therapy was initiated 7 days postinfection, in view of its high concentration at the site of infection. Outcome of treatment for ocular infection apparently is unpredictable despite excellent in vitro activity and the bioavailability of a drug at the site of infection. These results also suggest that the success of some azole compounds in endogenous *Candida* eye infections may depend on how early in the course of the infection they are started.

The ocular pharmacokinetics of i.v. amphotericin B have been partially defined. In animal model studies amphotericin B was detected only in the aqueous humor and not in the vitreous body (24). In the human eye (29), amphotericin B has been found in both the vitreous body and aqueous humor after i.v. infusion. In one study (13), 0.24 and 0.23 μg/ml were found in the aqueous humor and vitreous body, respectively, when the amphotericin B concentration in serum was 0.6 μg/ml. In this study, we did not attempt to study the ocular penetration of amphotericin B. However, because we felt the need for comparison with new triazole compounds and ketoconazole, we included amphotericin B in our late-therapy regimen. i.v. amphotericin B was effective following daily administration of 1 mg/kg for 7 days when therapy was initiated 7 days postinfection. Amphotericin B concentrations in rabbit serum were comparable to those found in humans. This polyene remains the standard for treatment of oculomycosis, unsurpassed by the newer azole compounds in this model.

Although caution is needed in extending the results of therapeutic trials from rabbits to humans, especially when a single dose regimen is used, our study shows that oral ketoconazole might be useful for some oculomycoses. The new triazole compounds itraconazole and fluconazole did not fulfill the expectations of being better options than ketoconazole for ECE in the rabbit model. However, their spectrum of antifungal activity and ocular pharmacokinetics in the rabbit make these agents worthy of further examination.

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