ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1986, p. 579–583
0066-4804/86/040579-05$02.00/0

Vol. 29, No. 4

Comparison of Itraconazole and Fluconazole in Treatment of Cryptococcal Meningitis and Candida Pyelonephritis in Rabbits

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Itraconazole and fluconazole, two new triazoles, were examined for their antifungal activity in rabbits. Fluconazole easily crossed the blood-cerebrospinal fluid barrier, and active drug was eliminated in high concentrations in the urine. On the other hand, itraconazole did not cross the blood-cerebrospinal fluid barrier in measurable amounts, and urine concentrations were variable. Despite differences in pharmacokinetics at the site of infection, both agents were equally effective in treating cryptococcal meningitis and candida pyelonephritis in animals. By using a ketoconazole-resistant strain of *Candida albicans*, we showed that there was cross-resistance in vivo between these two new triazole compounds.

For over 25 years, amphotericin B has provided the standard treatment for most systemic mycotic infections (13, 14). However, this drug is less than ideal in many respects, especially with regard to toxicity. In the search for alternative therapies, the azole compounds represent an important development. Imidazoles, such as clotrimazole and miconazole, have proven very effective for treating superficial dermatophyte and yeast infections. An intravenous preparation of miconazole had some success against disseminated mycoses (4, 11), but lack of clinical experience has limited its use for systemic disease. Ketoconazole is the most recently licensed addition to the meager stockpile of systemic antifungal drugs. It has proven to be effective against both superficial dermatophyte and yeast infections (9, 10), and some disseminated mycoses such as paracoccidioidomycosis, blastomycosis, histoplasmosis, and coccidioidomycosis (5, 19, 21).

In the quest for new antifungal agents with lower toxicity, broader spectrum, and better pharmacokinetic profiles, the progressive development of azole compounds has produced the triazoles. These include itraconazole and fluconazole.

In this study, we compared the pharmacokinetics, in vitro activity, and in vivo efficacy of these two agents in two animal model infections: cryptococcal meningitis in cortisone-treated rabbits and candida pyelonephritis in rabbits. In the first model, we evaluated the effect of these agents on a central nervous system infection in a compromised host. In the second model, we examined the treatment of the most common pathogenic yeast in the urinary tract (6).

MATERIALS AND METHODS

Animals. New Zealand White rabbits (2 to 3 kg) were housed in separate cages and given rabbit chow (Purina) and water ad libitum. They were anesthetized with 100 to 150 mg of ketamine (Ketaject; Bristol Laboratories, Syracuse, N.Y.) plus 15 to 25 mg of xylazine (Rompun; Cutter Labs, Shawnee, Kans.) intramuscularly (i.m.) for all procedures.

Antifungal agents. Itraconazole (Janssen Pharmaceutica, Inc., New Brunswick, N.J.) was administered orally in 50-mg capsules containing polyethylene glycol. Fluconazole powder (Pfizer Inc., Groton, Conn.) was dissolved in sterile water at 10 mg/ml. The solution was heated gently to resolubilize the drug before each treatment regimen. Ketoconazole (Janssen) was used in 200-mg tablets.

Organisms. A human cerebrospinal fluid (CSF) isolate of *Cryptococcus neoformans* (DP strain) was used in the meningitis experiments. This isolate was used in our previous studies (18). A clinical isolate of *Candida albicans* (Carter strain) was used for the pyelonephritis experiments. A second isolate used in the pyelonephritis experiments was *C. albicans* MCV7220 (a strain supplied by S. Shadomy, also known as the Dittmore isolate from C. Kirkpatrick). This strain is resistant to ketoconazole in vitro and in vivo (20). Yeasts were maintained by serial transfer on Sabouraud slants.

Antimicrobial assays. A bioassay was performed on sera, CSF, and urine from treated animals. The assay was a combination of the agar well diffusion method of Bennett et al. (2) and the method of Jorgensen and Drutz (12) for the assay of ketoconazole. The assay organism was a strain of *Candida pseudotropicalis*. The antifungal standards used in each plate were diluted in the appropriate fluid: CSF, serum, or urine. The lower limit of sensitivity of the bioassay for itraconazole lay between 0.078 and 0.156 μg/ml. The lower limit for fluconazole lay between 1.56 and 3.13 μg/ml.

In vitro susceptibility testing. To measure MICs, an overnight growth of yeasts on Sabouraud slants was suspended in phosphate-buffered saline. The yeast suspension was adjusted by optical density to a final concentration of 10^5 CFU/ml in synthetic amino acid medium, fungal (SAAMF) (8). Doubling dilutions of the two antifungal agents in SAAMF were made. Yeasts were incubated for 18 to 24 h at 30°C, and growth was read by a spectrophotometer (Gilford Instruments Laboratories, Inc., Oberlin, Ohio). The MIC was determined as the antibiotic concentration that inhibited the growth of yeasts by one-half compared with that of a growth control, an adaptation of the turbidometric method of Galgiani and Stevens (7).

Production of cryptococcal meningitis. On Columbia blood agar plates containing 100 μg of chloramphenicol per ml, 4-day cultures of *C. neoformans* were taken up on cotton swabs, suspended in 0.015 M phosphate-buffered saline, and adjusted to approximately 5×10^7 CFU/ml. Rabbits, injected i.m. with 2.5 mg of cortisone acetate per kg (Merck Sharp & Dohme, West Point, Pa.) 24 h earlier, were sedated, and 0.3 ml of the yeast suspension was inoculated intracisternally.

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TABLE 1. Range of MICs[a] of intraconazole and fluconazole for three yeast strains

	MIC (μg/ml)	
	Intraconazole	Fluconazole
C. neoformans (DP strain)	0.025–0.05	3.12–6.25
C. albicans (Carter strain)	0.025	0.4–0.8
C. albicans (MCV7220 strain)	0.1–0.2	25–100

[a] Repeated three times.

Daily cortisone injections were continued for 18 days. At 4 days after inoculation, CSF was aspirated, and serial dilutions of CSF in phosphate-buffered saline were plated on Columbia blood agar. Rabbits were then randomized to treatment groups. CSF was withdrawn on days 7, 11, 14, and 18 of infection for quantitative counts.

Production of candida pyelonephritis. Rabbits were anesthetized, and 1 ml of candida suspension was injected intravenously into the marginal ear vein. For the Carter strain, the inoculum size was 10^6 CFU, and for the MCV7220 strain, the inoculum size was 10^7 CFU. The 10-fold increase in inoculum was necessary because the MCV7220 strain was less virulent than the Carter strain in our rabbits. Quantitative kidney cultures after an injection of either of these two inocula showed that similar concentrations of organisms were present in the kidney before treatment. At 1 week after inoculation, rabbits were sacrificed by the injection of pentobarbital. Kidneys were removed, and urine was aspirated from the bladder. Urine was also cultured quantitatively on Sabouraud agar plates. An incision was made to expose the renal pelvis; a swab was placed in this cavity and then streaked across a Sabouraud agar plate. A small piece of cortical tissue was removed from one pole of each kidney, minced, and diluted in phosphate-buffered saline for quantitative cultures on Sabouraud agar plates.

Treatment regimens. Rabbits were started on 50 or 200 mg of itraconazole orally, 200 mg of ketoconazole orally, or 10, 20, or 80 mg of fluconazole per kg intravenously each day. Treatment was started in rabbits with cryptococcal meningitis on day 4 of infection and continued daily for 2 weeks. Rabbits with candida pyelonephritis were started on therapy 24 h after inoculation and treated for 1 week. All cultures were obtained approximately 24 h after the last dose of antifungal drug.

Statistical analysis. For a comparison of yeast counts at the end of therapy, the Student *t* test for unpaired means was used. Fisher's exact test was used to compare the numbers of rabbits with sterile CSF or tissue in each group.

RESULTS

The in vitro activity of the two triazoles in SAAMF broth is shown in Table 1. Itraconazole was more active than fluconazole on a weight basis in vitro. In vitro, the ketoconazole-resistant strain of *C. albicans* (MCV7220) was approximately 10- to 100-fold less sensitive than the ketoconazole-susceptible strain (Carter) to both triazole compounds.

Mean peak serum levels (± standard error) between 1 and 4 h for the lower doses of triazoles were 6.2 ± 1.1 μg/ml for 50 mg orally of itraconazole, 17.4 ± 2.4 μg/ml, and 9.5 ± 0.5 μg/ml for a 20- or 10-mg/kg intravenous bolus of fluconazole, respectively. Serum, CSF, and urine concentrations for the higher doses (i.e. 200 mg of itraconazole orally or 80 mg of fluconazole per kg intravenously) are shown in Table 2. One 200-mg capsule of itraconazole represents approximately 80 mg/kg per rabbit. This triazole was relatively well absorbed. The drug levels were detectable over 24 h; after multiple doses, accumulation occurred. This provided indirect evidence that induction of liver enzymes leading to increased metabolism did not occur. Serum levels of fluconazole increased predictably as the dose was raised. Its relatively long half-life in rabbits was reflected by the high concentrations measured at the end of 24 h. This triazole also accumulated in the serum of rabbits after multiple doses. The concentrations attained by the two triazoles in CSF and urine differed dramatically. Itraconazole could not be detected in the CSF of any rabbits, early or late in infection. By contrast, fluconazole passed freely into the CSF. The mean peak after dose 1 of 80 mg/kg was approximately 50 μg/ml; after daily dose 14, the drug had accumulated in the CSF. The mean peak level at 2 h after dose 14 was 207 ± 25 μg/ml. The percent penetration of fluconazole into CSF from serum ranged between 60 and 80%. Fluconazole persisted in CSF, being always present in this compartment 24 h after a dose. In the urine, itraconazole concentrations 24 h after dose 6 were variable. Over one-half of the rabbits had unmeasurable urine concentration (i.e., less than 0.08 μg/ml). However, several rabbits did have concentrations of greater than 10 μg/ml of urine measured. Fluconazole, on the other hand, appeared to be eliminated primarily by the kidneys in a biologically active form. High concentrations of fluconazole, between 159 and 599 μg/ml, were present in urine 24 h after the last dose of 80 mg/kg. Even at lower doses of 20 mg/kg, levels in the urine ranged from 93 to 266 μg/ml.

The effect of treatment with fluconazole and itraconazole on cryptococcal meningitis in rabbits was examined. In

TABLE 2. Itraconazole and fluconazole in serum, CSF, and urine from rabbits with cryptococcal meningitis or candida pyelonephritis

Drug	Dosage	No. of doses	Time after last dose (h)[a]	Concn (μg/ml)		
				Serum (mean ± SE)	CSF (mean ± SE)	Urine (median [range])
Intraconazole	200 mg/day orally	1	1–3	12.3 ± 0.7	<0.08	ND[b]
			24	10.7 ± 1.6	<0.08	ND
		6	24	6.2 ± 1.0	ND	<0.08 (<0.08–12.6)
		14	24	15.3 ± 1.6	<0.08	ND
Fluconazole	80 mg/kg per day intravenously	1	1–3	73.3 ± 6.8	45.1 ± 4.5	ND
			24	37.5 ± 3.0	30.8 ± 0.9	ND
		6	24	37.7 ± 3.6	ND	320 (159–599)
		14	24	65.2 ± 16.9	48.0 ± 11.4	ND

[a] Peaks (1 to 3 h) and troughs (24 h) were measured after 1, 6, or 14 days of treatment.
[b] ND, Not done.

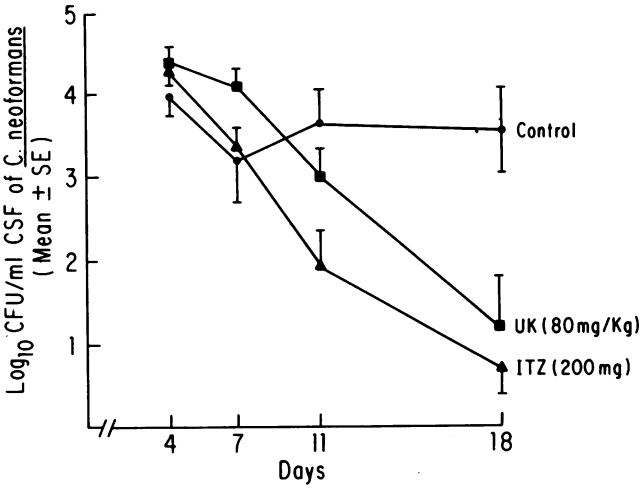

FIG. 1. This graph represents the mean yeast counts in CSF of rabbits receiving no treatment (control) (15), fluconazole (UK) at 80 mg/kg per day intravenously (19), or itraconazole (ITZ) at 200 mg/day orally po (18) for 2 weeks. Treatment was started on day 4 of infection after CSF withdrawal, and samples were cultured on days 7, 11, and 18 of infection.

preliminary experiments, we tested 10 mg of fluconazole per kg per day for 14 days and found no therapeutic effect. We therefore compared fluconazole treatment at 80 mg/kg per day and itraconazole at 200 mg per day, the oral dose which approximates 80 mg/kg per day. Figure 1 shows the effect of treatment on yeast counts in CSF. Despite high drug levels in the CSF, fluconazole had little effect on yeast counts early in infection. Itraconazole also had no significant effect on yeast counts in the CSF during the first few days of treatment. During the last 10 days of treatment, however, there was a consistent and similar drop in CSF yeast counts associated with treatment with either fluconazole or itraconazole. At the end of 2 weeks of therapy, yeast counts in both were significantly lower than in untreated animals ($P < 0.01$); there was no significant difference in outcome between the two treatment regimens. At the end of treatment, 11/15 rabbits in the itraconazole group and 4/7 in the fluconazole group had sterile CSF cultures. A group of these rabbits with sterile CSF was followed by serial CSF cultures for 2 weeks after treatment while continuing cortisone; no relapses occurred.

For kidney infections, we determined the effect of treatment on the number of yeasts in the renal parenchyma. Results of both itraconazole and fluconazole therapy are shown in Table 3. There was a dose-related reduction in the numbers of yeasts in renal tissue for the Carter strain. This dose effect was also seen with both itraconazole (50 versus 200 mg) and fluconazole (10, 20, and 80 mg/kg). All treatment regimens were significantly better than no treatment ($P < 0.01$). The effect of treatment on other sites in the urinary tract was also examined. The collecting system and urine cultures appeared to parallel the kidney cultures: renal pelvis swabs from only 4 of 29 rabbits treated with fluconazole or itraconazole were positive for yeasts, compared with 13 of 15 of control rabbits ($P < 0.01$). Likewise, the number of positive urine cultures in rabbits receiving 20 mg of fluconazole per kg per day (1/9), 80 mg of fluconazole per kg per day (1/8), and 200 mg of itraconazole per day (1/9) was significantly lower than that of the controls (9/10; $P < 0.01$ for each). In summary, both itraconazole and fluconazole effectively treated *Candida* urinary tract infection at three sites when the strain appeared susceptible in vitro and the infection was recently established.

To examine the effect of these azole agents on the treatment of a candida strain that was resistant to ketoconazole, we established a model with the MCV7220 strain. Table 3 shows the effect of 200 mg of ketoconazole per day of treatment on the two strains (Carter and MCV7220) in the rabbit candida pyelonephritis model. While the azole-susceptible Carter strain responded to therapy ($P < 0.01$), ketoconazole had no effect on the azole-resistant MCV7220 strain. This result demonstrated its resistance to ketoconazole treatment in vivo ($P > 0.05$ compared with controls). Having established this model, we then compared the effect of 200 mg of itraconazole per day and 20 mg of fluconazole per kg per day on the two strains. The results for both itraconazole and fluconazole mirrored the effects of treatment with ketoconazole in this model (Table 3). Infection with MCV7220 strain is resistant to therapy with these two azoles ($P > 0.05$ compared with controls). This observation indicates that cross resistance in vivo exists among several of the azole compounds for this particular strain.

DISCUSSION

Recent experience with ketoconazole indicates that imidazoles can succeed in the treatment of some systemic mycoses. For example, ketoconazole has already become the drug of choice for paracoccidioidomycosis (10). It has also been used effectively in blastomycosis and histoplasmosis (5). Ketoconazole has proven to be very effective against mucosal candidiasis (9), but its potential value for the treatment of disseminated candidiasis is still unclear. In fact, even amphotericin B has not been well studied in this infection (14). In this study, we evaluated two new azole compounds, itraconazole and ketoconazole, in the treatment of fungal infections in animals. They possess important similarities and differences in animal infections, which may be of clinical relevance.

Although the route of infection is artificial, our cryptococcal meningitis model in rabbits resembles human disease in many ways: it follows a subacute course, is potentiated by immune suppression, and approximates the heavy burden of organisms found at the site of infection in humans (17). Candida pyelonephritis in rabbits is also a useful model to

TABLE 3. Quantitative counts of *C. albicans* in renal cortex, showing one azole-sensitive (Carter) and one azole-resistant (MCV7220) strain after treatment with itraconazole, fluconazole, or ketoconazole

Drug	Dose	Mean CFU/g ± SE (no.)	
		Carter strain[a]	MCV7220 strain[b]
Itraconazole	0	4.24 ± 0.45 (12)*	4.03 ± 0.53 (8)*
	50 mg	2.10 ± 0.38 (9)*†	
	200 mg	0.70 ± 0.30 (11)*†	4.65 ± 0.51 (4)*
Fluconazole	0	4.10 ± 0.36 (15)‡	3.01 ± 0.21 (3)†
	10 mg/kg	2.16 ± 0.20 (9)‡§	
	20 mg/kg	1.32 ± 0.27 (9)‡	2.72 ± 0.73 (5)†
	80 mg/kg	0.64 ± 0.44 (8)‡§	
Ketoconazole	0	4.17 ± 0.38 (6)‖	4.03 ± 0.53 (8)‡
	200 mg/kg	0.81 ± 0.37 (6)‖	3.87 ± 0.36 (5)‡

[a] $P < 0.01$, for groups with same symbol.
[b] $P > 0.05$, for groups with same symbol.

examine the efficacy of treatment regimens. The disease produced is subacute; this avoids the requirement for very early therapy or even prophylaxis to show any drug effect, as is the case in some murine models for candidiasis. Quantitative cultures can be made from several different sites in the urinary tract and evaluated in relation to the amount of drug present at the site.

The pharmacokinetics of itraconazole and fluconazole are notably different. Itraconazole is larger than fluconazole, is very insoluble in aqueous fluids, and is highly protein bound (greater than 90%). Fluconazole is a relatively small molecule which is partially water soluble, with protein binding of only 15 to 20% in rabbit serum. We have previously shown that this drug easily passes into CSF in the presence or absence of inflammation, and that it persists and accumulates in the subarachnoid space (16). Its penetration into CSF is similar to that of flucytosine, but vastly different from other azole compounds such as ketoconazole, miconazole, vibunazole, and itraconazole (16). It also appears that fluconazole is excreted into the urine in a fully active form. Its solubility confers the potential for fluconazole to become the first imidazole offered in both oral and intravenous preparations for the treatment of disseminated mycoses. Itraconazole, on the other hand, does not cross the blood-CSF barrier in detectable amounts. Its excretion into the urine is erratic, resembling that of ketoconazole in this rabbit model. Thus, pharmacokinetic studies suggest that fluconazole could be an ideal drug for treating central nervous system and urinary tract infections, while itraconazole might be less successful.

Itraconazole has the edge in respect to direct antifungal activity in vitro, while fluconazole appears to have distinct advantages in bioavailability at sites of infection. When these agents were directly compared in our cryptococcal meningitis model, they appeared to have equivalent activity at similar doses. Despite our inability to detect drug in the CSF, itraconazole proved surprisingly effective. This finding recalls the effect of amphotericin B, which works reasonably well in both humans and animals with fungal meningitis, despite poor penetration into CSF (3). It is also surprising that fluconazole did not clear the CSF of yeasts more quickly, in view of its high concentrations at this site. While drug concentration at the site of infection is a crucial factor in the success of therapy for bacterial meningitis, our findings suggest that the eradication of yeasts from the central nervous system must involve other mechanism(s) that cannot be predicted by the simple measurement of drug concentration in CSF.

In the candida pyelonephritis model, both fluconazole and itraconazole effectively treated the azole-susceptible strain. Despite notable differences in pharmacokinetics between the two agents, they appeared similar in efficacy. Efficacy increased for both antifungals when doses were raised with activity in different parts of the urinary tract (cortex, pelvis, and bladder). While this model represents an established yeast infection with large numbers of organisms present, it should be noted that infection was present for only 24 h before treatment. The effects of these triazoles on chronic infection after the establishment of mature renal cortical abscesses might be different.

An azole-resistant *C. albicans* strain (MCV7220) was used to determine if cross resistance between ketoconazole and these triazoles occurred in vivo. Only a few such strains have been isolated from patients. Ryley et al. have shown in vitro and in vivo correlation by using several of these resistant strains in murine infections (20). These strains have abnormal ergosterol synthesis and can be identified by in vitro testing. Our strain had relatively higher MICs for both itraconazole (10-fold) and fluconazole (100-fold) than did the ketoconazole-susceptible strain. In the rabbit model of candida pyelonephritis, all three azole compounds were ineffective in treatment, demonstrating that in vivo cross resistance exists between imidazoles and triazoles for certain strains.

This paper does not include data on amphotericin B. Previous experiments in the same meningitis model suggest that any regimen containing amphotericin B is likely to be superior to treatment with azoles alone (15). However, combination therapy with triazoles plus a polyene or flucytosine or both might prove more effective than any single agent, including amphotericin B, in meningitis. Further investigation is needed.

Cryptococcal meningitis and candida pyelonephritis in rabbits are convenient and appropriate animal infections in which to examine the effect of antifungal agents. New treatments are needed for cryptococcal meningitis, because the 60 to 70% success rate of current therapy is disappointingly low (1). As new cases associated with the acquired immune deficiency syndrome continue to appear, this success rate may actually worsen. Better treatment for candidiasis in compromised hosts also would be desirable. Properly controlled studies of new and old agents are needed. These animal studies provide a stimulus to continued evaluation of triazoles against yeast infections.

ACKNOWLEDGMENTS

We thank Janet Routten and Sharon Coward for help in preparation of the manuscript.

This work was supported in part by a grant from Pfizer Inc.

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