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Therapeutic Effect of the Triazole Bay R 3783 in Mouse Models of Coccidioidomycosis, Blastomycosis, and Histoplasmosis

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A new triazole, Bay R 3783, was compared with ketoconazole, itraconazole, and fluconazole, which were given via the alimentary tract at three dosages, and amphotericin B, which was given at 1 mg/kg intraperitoneally, in murine models of the systemic mycoses coccidioidomycosis, histoplasmosis, and blastomycosis. In a pulmonary coccidioidomycosis model, Bay R 3783, fluconazole, and itraconazole were essentially equally efficacious and more active than ketoconazole in protecting mice against death; but they were inferior to amphotericin B. In a short-term organ load experiment, Bay R 3783 and amphotericin B were equally effective and were more effective than the other drugs in reducing the amount of *Coccidioides immitis* in the lungs. Against meningocerebral coccidioidomycosis, Bay R 3783, itraconazole, and fluconazole at 25 mg/kg and amphotericin B prevented death only during therapy, with mortalities ensuing shortly thereafter. In mice with systemic histoplasmosis, Bay R 3783 and itraconazole at 25 mg/kg and amphotericin B prevented death in all mice through a 44-day observation period. Clearance of *Histoplasma capsulatum* from organs was similar in mice treated with Bay R 3783 and itraconazole; this clearance was greater than that in mice treated with ketoconazole and fluconazole but less than that in mice treated with amphotericin B. In mice with systemic blastomycosis, Bay R 3783 at 25 mg/kg yielded 90% survivors at 60 days, which was greater than that achieved with amphotericin B (60%) or itraconazole (30%). Clearance of *Blastomyces dermatitidis* from the lungs was greatest with Bay R 3783, followed by that with amphotericin B, itraconazole, fluconazole, and ketoconazole, in that order. Therefore, Bay R 3783 showed effectiveness comparable to or exceeding those of itraconazole and fluconazole and exceeding that of ketoconazole against these systemic mycoses in mice.

The chemotherapy of systemic infections caused by dimorphic fungi has relied on amphotericin B for three decades, and in recent years this polyene has been supplemented or supplanted by flucytosine and by the antifungal azoles. Whereas miconazole has found some utility by the parenteral, particularly intrathecal and intraventricular, routes (15), other azoles (ketoconazole, itraconazole, and fluconazole) have the advantage of being effective even when given by the oral route. The newer triazoles itraconazole and fluconazole additionally appear to have the advantages of less toxicity and apparently greater potency than ketoconazole against some systemic pathogens and greater activity than ketoconazole against meningocerebral infections (1–5, 12, 13, 16, 17).

Previous in vitro studies with Bay R 3783 and several other azoles against *Coccidioides immitis* (7) and fluconazole and ketoconazole against *Histoplasma capsulatum* (14) demonstrated the activity of this class of drug against the dimorphic fungal pathogens. This lead to the present study, in which Bay R 3783 (Fig. 1) was evaluated in murine models of the systemic mycoses blastomycoses, coccidioidomycosis, and histoplasmosis. As described in this report, Bay R 3783 given by the oral route showed effectiveness comparable to or exceeding that of itraconazole or fluconazole.

MATERIALS AND METHODS

Drugs. Bay R 3783 was received as a powder from Bayer AG (Wuppertal, Federal Republic of Germany), fluconazole was received as a powder from Pfizer Inc. (Groton, Conn.), itraconazole was received as a powder from Janssen (Piscataway, N.J.), ketoconazole was purchased as Nizoral (200-mg tablets; Janssen), and amphotericin B was purchased as Fungizone (E. R. Squibb & Sons, Princeton, N.J.). For administration, Bay R 3783 was either prepared as a suspension in 0.1% agar (Difco Laboratories, Detroit, Mich.) with 0.5% glucose or dissolved with heating at 60°C in polyethylene glycol 200 (J. T. Baker Chemical Co., Phillipsburg, N.J.). Ketoconazole tablets were pulverized and suspended in glucose agar, and fluconazole was dissolved in glucose agar. Itraconazole was dissolved in polyethylene glycol 200. The concentrations of azoles were adjusted for delivery by oral gavage in 0.1-ml volumes. Amphotericin B was diluted in 5% glucose and was injected intraperitoneally (i.p.) in 0.1-ml volumes.

Animals. White CF-1 and CFW female mice (average weight, 20 to 24 g; Charles River Breeding Laboratories, Inc., Wilmington, Mass.) were used in both survival and organ load experiments.

Organisms and conditions of culture. *C. immitis* Silveira ATCC 28868, *H. capsulatum* G217B, and *Blastomyces dermatitidis* 1389 were used for all experiments. Arthroconidia of *C. immitis* were obtained by culturing the fungus on 2% glucose–1% yeast extract (Difco) agar at 35°C for several weeks, dislodging the arthoconidia into sterile water with a magnetic stirring bar, and storing them in liquid suspension at 4°C until they were needed. Yeast-phase *B. dermatitidis* was maintained by weekly passage at 37°C on the agar described by Kelley (8) that was modified by substitution of glucose for starch and hemoglobin (equivalent to 0.5% [vol/vol] sheep blood) in place of serum. Inocula for experiments with the yeasts were prepared by culturing fresh slants 72 h before the experiments. *H. capsulatum* was maintained in the yeast phase on brain heart infusion (BHI)

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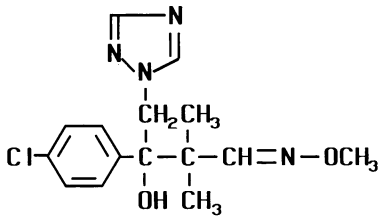

FIG. 1. Structure of Bay R 3783.

blood slants at 37°C by weekly transfer, with fresh slants cultured 72 to 96 h before initiation of the experiments.

Susceptibility testing. Yeast-phase *B. dermatitidis* and *H. capsulatum* were propagated on slants of BHI agar (Difco) at 37°C for 72 h before susceptibility testing. Bay R 3783, itraconazole, and ketoconazole were first dissolved in 95% ethanol and then subsequently diluted in BHI broth. Fluconazole and amphotericin B were diluted directly into BHI broth. Duplicate dilution series were done in microdilution plates by using 100-μl volumes of BHI broth. The inocula were standardized to 2×10^4 cells per ml of BHI broth by using a hemacytometer, and 100-μl volumes were added to each well. The plates were incubated at 37°C, and the MICs were determined at 96 h. The MICs for *C. immitis* have been reported previously (7).

Experimental design. The therapeutic efficacies of the compounds were examined by determining their effects on the survival of infected mice and on the number of viable fungi in the target organs.

(i) Survival experiments. All survival experiments were designed to follow an acute course of infection, with deaths generally starting in 5 to 12 days. The purpose of this approach was to provide a rigorous test of the antifungal agent, with the outcome essentially being determined before an active immune response could influence the results. Pulmonary and systemic coccidioidomycosis was induced by intranasal inoculation of *C. immitis*. Mice were first anesthetized with pentobarbital (50 mg/kg i.p.), and then 30 μl of inoculum (5×10^3 to 10×10^3 arthroconidia) was placed on the nares, from which it was inhaled. Meningocerebral coccidioidomycosis was induced by inoculating 60 to 90 *C. immitis* conidia in 30 μl intracranially with a 27-gauge needle. Blastomycosis of the lungs was induced by intravenous injection of 5×10^4 yeast-phase *B. dermatitidis* cells in 0.2 ml. For the histoplasmosis model, mice were infected intravenously with approximately 5×10^6 yeast-phase *H. capsulatum* cells in 0.2 ml. Therapy was begun 48 h after inoculation, and drugs were administered orally once daily for the periods indicated in Fig. 2 through 6. All animals were observed daily for deaths. There were 10 mice per group.

(ii) Short-term organ load experiments. Groups of eight mice each were infected by the appropriate routes with sublethal to lethal challenges (3×10^3 CFU of *C. immitis*, 8×10^5 CFU of *H. capsulatum*, 1×10^5 CFU of *B. dermatitidis*), and twice-daily (b.i.d.) therapy was initiated 48 h later. Therapy was given for 4 days; and after a 48-h washout period, target organs were removed, weighed, and then homogenized in 10 ml of sterile phosphate-buffered saline with a tissue homogenizer (Brinkmann Instruments, Inc., Westbury, N.Y.). Serial dilutions were made and plated in a quantitative fashion on the surface of Sabouraud glucose agar containing 0.05 mg of chloramphenicol per ml and 0.5 mg of cycloheximide per ml for *C. immitis* and *B. dermatitidis* and on BHI agar with chloramphenicol and cycloheximide for *H. capsulatum*. Cultures for *C. immitis* were incubated at 35°C, and cultures for *B. dermatitidis* and *H. capsulatum* were incubated at room temperature. Colonies were enumerated, and the results are expressed as the $\log_{10}$ CFU per gram of tissue.

TABLE 1. MICs of antifungal agents for spherule-endospore or yeast phase of dimorphic fungi in vitro[a]

Antifungal agent	MIC (μg/ml) at 96 h		
	C. immitis	*B. dermatitidis*	*H. capsulatum*
Bay R 3783	0.25[b]	0.5	0.06
Itraconazole	1.0[b]	<0.003	<0.003
Ketoconazole	8.0	0.012	0.003
Fluconazole	>64.0[b]	4.0	4.0
Amphotericin B	0.08–0.16	0.125	0.012

[a] Spherules or endospores of *C. immitis* and the yeast phases of *B. dermatitidis* and *H. capsulatum* were used.

[b] Results reprinted from the *Journal of Clinical Microbiology* (7) with permission.

Bioassay. Mice were dosed with Bay R 3783 via oral gavage at 25 mg/kg and bled via cardiac puncture in groups of five mice each at intervals over a 24-h period. The bioassay with *Candida pseudotropicalis* was performed as described previously (2).

Statistical analyses. Results from short-term organ load experiments were analyzed by the Duncan multiple-range test, with significance determined at the $P = 0.05$ level. Survival data were analyzed by the Cox proportional hazards estimation by using one-sided tables in comparisons of control group with treatment group values and two-sided tables in comparisons of the Bay R 3783 group with other treatment group values. Significance was determined at the $P = 0.05$ level. Data inappropriate for Cox analysis were compared in a pair-wise fashion using the log-rank method, with significance determined at the $P = 0.05$ level. Analyses were made only for the groups treated with 25 mg of azole per ml and 1 mg of amphotericin B per ml for all experiments.

RESULTS

Susceptibility testing. Results of MIC testing with the parasitic phases of the fungal isolates and drugs used in this study are presented in Table 1 (results for *C. immitis* are, in part, from the previous report of Hector et al. [7]).

Coccidioidomycosis. With the pulmonary model of coccidioidomycosis, three dosage levels of the four azoles were compared with a single dosage level of amphotericin B in animals infected with a large inoculum. At 2.5 mg/kg, none of the azoles was particularly effective, although the itraconazole-treated group had the best outcome (data not shown). At 10 mg/kg only ketoconazole was without effect, and itraconazole was superior to Bay R 3783 and fluconazole (Fig. 2A). Treatment with 25 mg of the azoles per kg and 1 mg of amphotericin B per kg resulted in a significant delay in deaths in comparison with controls for all drugs except ketoconazole ($P = 0.06$) (Fig. 2B). Among the azoles, Bay R 3783 forestalled the onset of deaths the longest, but ultimately, the onset of death in mice treated with Bay R 3783 was not statistically different from that in the itraconazole- and fluconazole-treated groups. Only amphotericin B completely prevented deaths through day 60.

In a meningoencephalitis model of coccidioidomycosis, 75 arthroconidia of *C. immitis* injected intracranially established a rapidly fatal infection. Therapy was begun after a

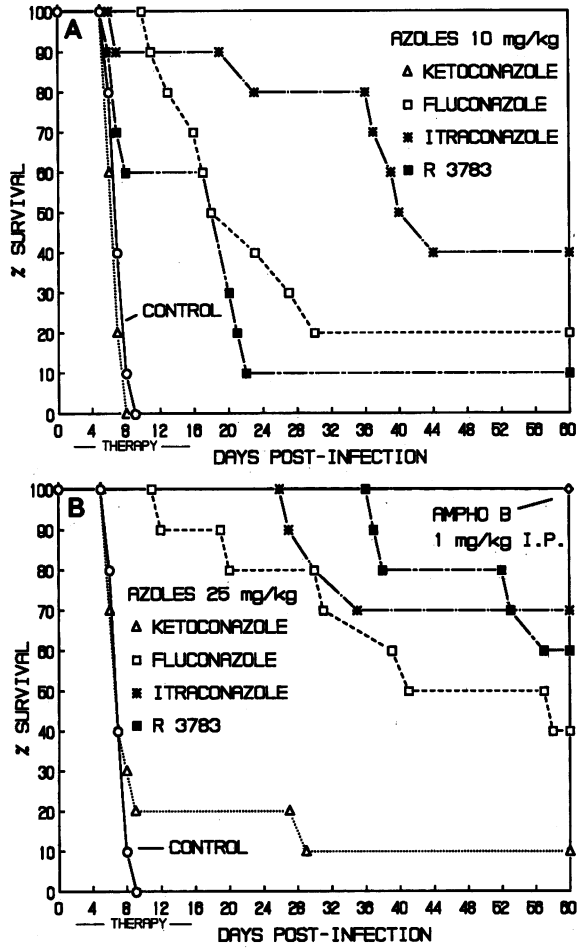

FIG. 2. Survival study in pulmonary coccidioidomycosis model in mice infected intranasally with 9.3×10^3 CFU by comparing control mice with mice treated with ketoconazole, fluconazole, itraconazole, and Bay R 3783 at 10 mg/kg (A) and 25 mg/kg (B) and with amphotericin B at 1 mg/kg (B). The periods of therapy are indicated under the *x* axes.

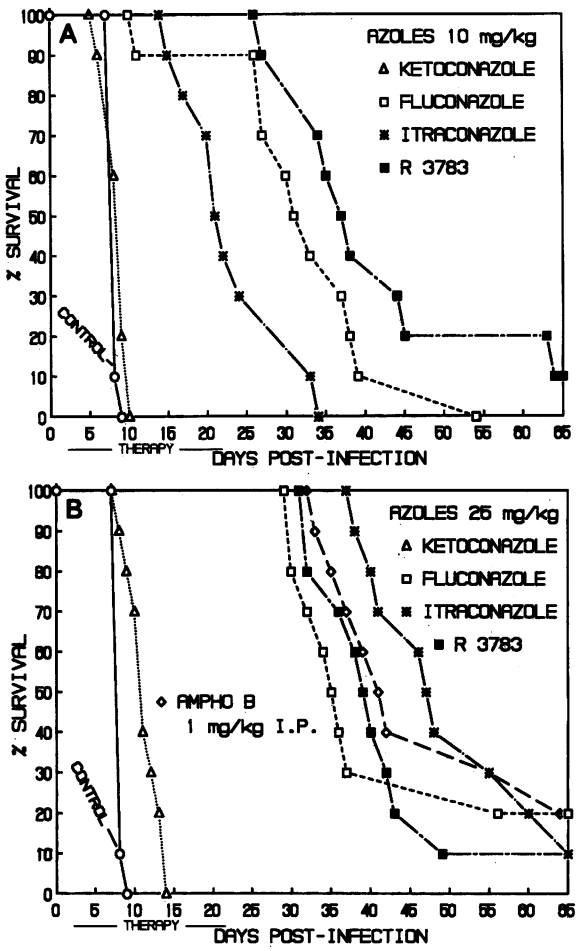

FIG. 3. Survival study in meningocerebral coccidioidomycosis model in mice infected intracranially with 75 CFU by comparing control mice with mice treated with ketoconazole, fluconazole, itraconazole, and Bay R 3783 at 10 mg/kg (A) and 25 mg/kg (B) and with amphotericin B at 1 mg/kg (B). The periods of therapy are indicated under the *x* axes.

48-h delay with azoles at 10 or 25 mg/kg and amphotericin B at 1 mg/kg i.p. Drugs were given for 21 days. As shown in Fig. 3A, the azoles differed greatly in their ability to protect the animals, with Bay R 3783 being somewhat superior to fluconazole. Ketoconazole was without effect in this model. At the 25-mg/kg level (Fig. 3B), although all treatment groups were statistically different from the control, only ketoconazole did not prevent deaths during the duration of therapy. Discontinuation of therapy, however, was followed by death of most of the mice. There were no statistical differences among the groups treated with Bay R 3783, itraconazole, fluconazole, and amphotericin B. Cultures from surviving mice sacrificed at 65 days after infection (42 days after the cessation of therapy) showed that *C. immitis* disseminated from the brain and meninges to other organs in most mice. Interestingly, the liver was positive for *C. immitis* in all mice with extracranial dissemination, but in some mice in which the liver was affected, the lungs were not affected. One mouse each from the fluconazole- and amphotericin B-treated groups was free of *C. immitis*. Whether this was due to curative therapy or failure to achieve proper inoculation is uncertain.

A short-term organ load assay was conducted by using the pulmonary model in mice. Drugs were given for 5 days, and then the lungs were removed after a 48-h washout period for quantitative cultures. Bay R 3783 and amphotericin B were statistically superior to the other azoles under the conditions that we used, effecting a 5-log-unit reduction in CFU (Table 2). Ketoconazole was without effect at the doses we used,

TABLE 2. Short-term organ loads in lungs of mice infected with *C. immitis*[a]

Group	Dose (mg/kg)	Mean log CFU ± SEM	Statistical group[b]
Control		6.44 ± 0.11	A
Ketoconazole	25	6.46 ± 0.07	A
Fluconazole	25	3.78 ± 0.56	B
Itraconazole	25	2.54 ± 0.57	B
Bay R 3783	25	0.89 ± 0.44	C
Amphotericin B	1[c]	0.63 ± 0.63	C

[a] Animals were infected with 3,000 CFU intranasally.
[b] Groups with the same letter are not statistically different at the $P = 0.05$ level.
[c] Amphotericin B was given once daily only.

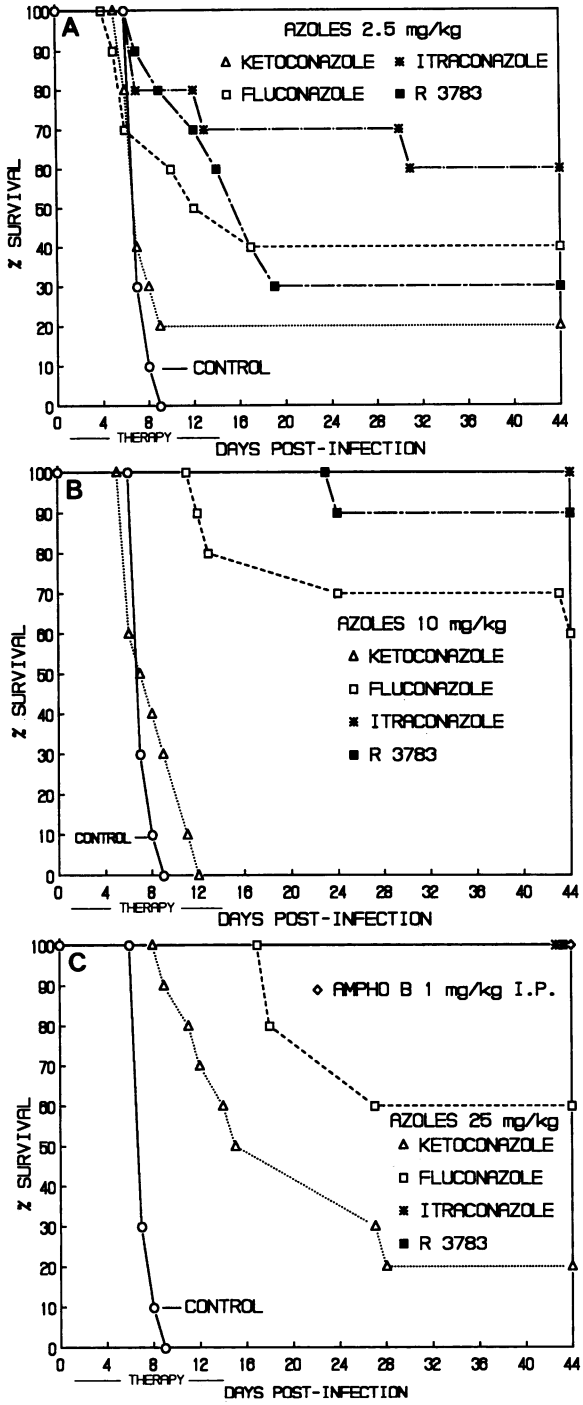

FIG. 4. Survival study in histoplasmosis model in mice infected intravenously with 5×10^6 CFU by comparing control mice with mice treated with ketoconazole, fluconazole, itraconazole, and Bay R 3783 at 2.5 mg/kg (A), 10 mg/kg (B), and 25 mg/kg (C) and with amphotericin B at 1 mg/kg (C). The periods of therapy are indicated under the *x* axes.

while itraconazole and fluconazole had a moderate degree of efficacy.

Histoplasmosis. In a survival experiment with the systemic model of histoplasmosis in mice infected intravenously with a highly lethal challenge of yeast-phase *H. capsulatum* G217B, three dose levels of the four azoles and amphotericin

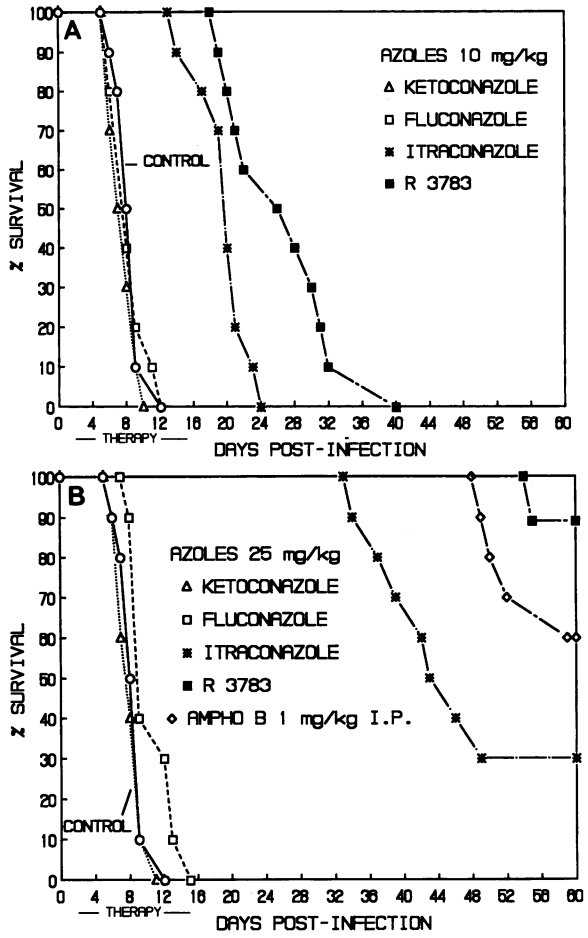

FIG. 5. Survival study in blastomycosis model in mice infected intravenously with 5×10^4 CFU by comparing control mice with mice treated with ketoconazole, fluconazole, itraconazole, and Bay R 3783 at 10 mg/kg (A) and 25 mg/kg (B) and with amphotericin B at 1 mg/kg (B). The periods of therapy are indicated under the *x* axes.

B at 1 mg/kg were compared. At 2.5 mg/kg, none of the azoles was able to prevent deaths completely, although the itraconazole-treated group had the best outcome (Fig. 4A). At 10 mg/kg, only ketoconazole was without effect, with itraconazole being slightly superior to Bay R 3783 and fluconazole (Fig. 4B). Itraconazole and Bay R 3783 at 25 mg/kg and amphotericin B at 1 mg/kg were able to prevent deaths completely through day 44 and were statistically superior to fluconazole, which was, in turn, statistically superior to ketoconazole (Fig. 4C). All treatment groups were statistically different from the control group.

In a short-term organ load assay, the various treatments resulted in a broad range of responses in the groups of mice (Table 3). All drugs resulted in significant reductions in viable fungal cells in livers and spleens in comparison with those in controls, with amphotericin B being significantly more active than any of the azoles, followed by Bay R 3783, itraconazole, and ketoconazole and fluconazole, which were the least active under these conditions.

Blastomycosis. Pulmonary blastomycosis was established by infecting the animals intravenously with the yeast phase of the causative organism, which established an infection with an acute course. Three dosage levels of azoles were compared with 1 mg of amphotericin B per kg in this model,

TABLE 3. Short-term organ loads in spleens and livers of mice infected with *H. capsulatum*[a]

Group	Dose (mg/kg)	Mean log CFU ± SEM		Statistical group[b]	
		Liver	Spleen	Liver	Spleen
Control		6.59 ± 0.19	6.10 ± 0.15	A	A
Fluconazole	25	5.87 ± 0.11	5.29 ± 0.07	B	B
Ketoconazole	25	5.76 ± 0.07	5.04 ± 0.14	B	B
Itraconazole	25	5.49 ± 0.11	4.35 ± 0.16	B,C	C
Bay R 3783	25	5.14 ± 0.09	3.66 ± 0.11	C	D
Amphotericin B	1[c]	1.76 ± 0.38	2.83 ± 0.44	D	E

[a] Animals were infected with 800,000 CFU.
[b] Groups with the same letter are not statistically different at the $P = 0.05$ level.
[c] Amphotericin B was given once daily only.

with therapy being initiated after a 48-h delay and then given for 14 days. At 2.5 mg/kg, none of the azoles was able to prolong survival in comparison with that in controls. At 10 mg/kg, however, both itraconazole and Bay R 3783 showed a delay in the onset of mortalities until after the cessation of therapy (Fig. 5A), while fluconazole and ketoconazole were without obvious therapeutic effect. The experiment was continued for 60 days because there were discernible differences in the appearance between the mice that received 25 mg of itraconazole and Bay R 3783 per kg at the end of the first 30 days. Therapy with Bay R 3783 resulted in the fewest deaths by day 60 (Fig. 5B). This was statistically different ($P = 0.11$) from the results obtained with the other azoles but not those obtained with amphotericin B. Treatment with ketoconazole did not result in a significant response in comparison with that in the controls, but treatment with fluconazole resulted in a response that was statistically different ($P = 0.03$) from that of the control.

A second experiment was initiated in which mice infected in a similar fashion were not treated until the first deaths occurred (day 6), at which time the azoles were administered at 25 mg/kg and amphotericin B was administered at 1 mg/kg for a total of 10 days. Interestingly, Bay R 3783 and amphotericin B appeared to be less effective than itraconazole initially, but all mice in the latter group ultimately died (Fig. 6). Once again, the response to Bay R 3783 at 25 mg/kg

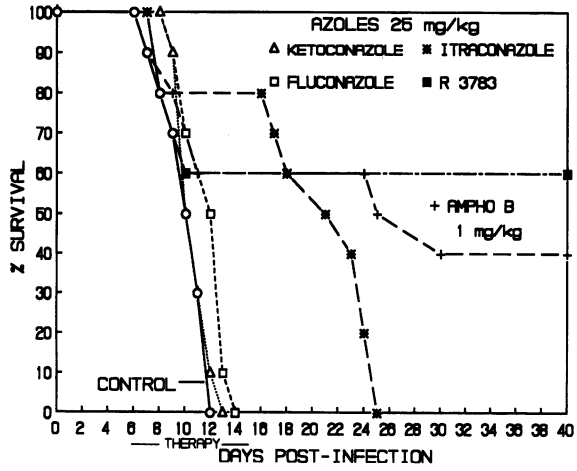

FIG. 6. Delayed therapy survival study in blastomycosis model in mice infected intravenously with 5×10^4 CFU by comparing control mice with mice treated with ketoconazole, fluconazole, itraconazole, and Bay R 3783 at 25 mg/kg and with amphotericin B at 1 mg/kg. The period of therapy is indicated under the *x* axis.

was not statistically superior to that to amphotericin B at 1 mg/kg ($P = 0.5$) but was superior to that to itraconazole ($P = 0.04$). Treatment with either ketoconazole or fluconazole did not result in a significant delay in deaths.

A short-term organ load assay in which the four azoles and amphotericin B at 1 mg/kg were compared was conducted with the same model, with the lungs cultured as the target organ. Treatment with Bay R 3783 resulted in a statistically superior response to infection with *B. dermatitidis* compared with the response to all the other drugs (Table 4). This was followed by the responses of the amphotericin B- and itraconazole-treated groups (Table 4). The responses of the ketoconazole- and fluconazole-treated groups were indistinguishable from those of the untreated controls.

Bioassay. A limited study of the pharmacokinetics of Bay R 3783 at a dose of 25 mg/kg was performed. The data are presented in Fig. 7 as the mean inhibition zone sizes of five samples per interval over 24 h rather than concentrations in serum because of the biphasic response that was seen. This is reflective of the known breakdown of the parent compound to multiple biologically active metabolites (K. A. Wright, J. R. Perfect, and W. Ritter, Program Abstr. 29th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 728, 1989; J. Lee, W. Ritter, J. Lecciones, P. Kelly, P. Pizzo, and T. J. Walsh, 29th ICAAC, abstr. no. 727, 1989). However, assuming that the initial peak was solely due to Bay R 3783, a peak concentration of 0.75 μg/ml for the sample obtained at 0.5 h was determined from the standard curve of a bioassay for this compound.

DISCUSSION

At the doses selected for use in mice, the triazole Bay R 3783 showed efficacy comparable to or exceeding those of the triazoles itraconazole and fluconazole against *C. immitis*,

TABLE 4. Short-term organ loads in lungs of mice infected with *B. dermatitidis*[a]

Group	Dose (mg/kg)	Mean log CFU ± SEM	Statistical group[b]
Control		6.19 ± 0.04	A
Ketoconazole	25	6.08 ± 0.12	A
Fluconazole	25	5.63 ± 0.12	A
Intraconazole	25	4.03 ± 0.23	B
Amphotericin B	1[c]	3.09 ± 0.23	C
Bay R 3783	25	2.29 ± 0.37	D

[a] Animals were infected with 100,000 CFU intravenously.
[b] Groups with different letters are statistically different at the $P = 0.05$ level.
[c] Amphotericin B was given once daily only.

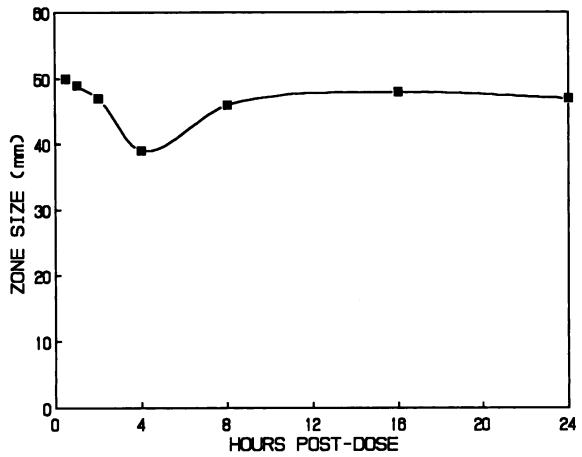

FIG. 7. Bioassay of serum from mice dosed with 25 mg of Bay R 3783 per kg via oral gavage. Results are presented as the mean zone size of inhibition from five samples per interval.

B. dermatitidis, and *H. capsulatum* infections. At the doses selected, Bay R 3783 was superior to ketoconazole. However, by adjusting the dosages for any of the azoles tested, it may be possible to increase the efficacy of the drugs within a range of safe dosages. Indeed, it is evident from previously published data (11) on experimental coccidioidomycosis that ketoconazole at 10 and 20 mg/kg b.i.d. is only partially effective, while at 40 mg/kg b.i.d. or higher it is fully protective, against lethal challenge with *C. immitis*. Having established in preliminary experiments the efficacy of Bay R 3783 at 25 mg/kg, the purpose of the present study was to determine the lower limits of efficacy of this compound and to use these dosages for comparative evaluation with other azoles as well as a standard dosage of amphotericin B.

In the pulmonary model of coccidioidomycosis, the azoles itraconazole, fluconazole, and Bay R 3783 resulted in similar levels of efficacy up to dosages of 25 mg/kg but were inferior to amphotericin B when it was used at 1 mg/kg. Thus, the results of the in vitro susceptibility tests for this fungus were not predictive of therapeutic outcome. In the model of meningoencephalitis, none of the drugs tested was able to prevent deaths once therapy was discontinued. These findings are similar to the previous findings of Graybill et al. (5), in which fluconazole, which was used in the model of coccidioidal meningoencephalitis at 20 mg/kg b.i.d., did not prevent deaths even during therapy, whereas 60 mg/kg b.i.d. fluconazole prevented death in 90% of mice during therapy; but deaths occurred within a few days of the cessation of therapy.

In the experimental histoplasmosis model, itraconazole and Bay R 3783 were superior to the other azoles and comparable to amphotericin B. The incomplete survival of the mice treated with fluconazole is in contrast to the 100% protection shown by Polak and Dixon (14), who used fluconazole at 10 mg/kg over a 20-day observation period. However, the experimental conditions differed in particular in that Polak and Dixon (14) commenced therapy 6 h after infection of the mice, whereas in the present study medication was not started until 48 h after infection. Polak and Dixon (14) observed that the reduction in CFU in the spleen following treatment with fluconazole at 25 mg/kg was >2 log units compared with that following treatment with amphotericin B at 0.5 mg/kg; and at 50 mg/kg, fluconazole reduced the viable count by 2 log units more than that with amphotericin B at 1.0 mg/kg. Previously, Kobayashi et al. (9, 10) found that 50% protective doses of fluconazole ranged from 6.2 to 47.3 mg/kg, varying with the strain of mouse and the size of the infective inoculum. In our experiments amphotericin B exceeded the effectiveness of fluconazole. In the present study the CFU per gram of liver regularly exceeded the count in the spleen, as Polak and Dixon (14) observed previously.

In the experimental blastomycosis model, 2 weeks of therapy with Bay R 3783 at 25 mg/kg was as effective as that with amphotericin B at 1 mg/kg in preventing deaths and was superior to itraconazole. The fact that Bay R 3783 excelled in the treatment of blastomycosis was also evident from its greater reduction in the number of viable organisms recovered from the lungs that was brought about by itraconazole and amphotericin B. Under the conditions of our experiments, neither fluconazole nor ketoconazole enhanced survival. However, the efficacy of itraconazole at the higher doses of 50 and 150 mg/kg per day were demonstrated previously by Arathoon et al. (E. Arathoon, E. Brummer, and D. A. Stevens, Abstr. Annu. Meet. Am. Soc. Microbiol. 1987, F-18, p. 392) by using 60 and 75% lethal dose challenges with *B. dermatitidis*. Even at 80 mg/kg, ketoconazole failed to prevent death in mice infected intranasally with 74 CFU, which produced death in 90% of untreated mice and 80% of treated mice in 40 days (90% of treated mice in 55 days). In larger (25-g) mice, ketoconazole at 160 mg/kg provided for the survival of all mice infected with 60 CFU, which produced only 25% deaths in 30 (and 60) days (6). Similarly, in a recent report by Tucker et al. (16), who used a highly lethal model of pulmonary blastomycosis, ketoconazole at 100 mg/kg failed to prevent deaths during therapy, whereas the newer triazole ICI 195,739 was curative at 50 mg/kg.

The results of this study indicate that Bay R 3783, like the other triazoles, shows promise as a useful compound against the deep mycoses.

ACKNOWLEDGMENT

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LITERATURE CITED

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