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Efficacy of UK-109496, a New Azole Antifungal Agent, in an Experimental Model of Invasive Aspergillosis

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The efficacy of UK-109496, a new azole antifungal agent, was evaluated in an immunosuppressed, temporarily leukopenic rabbit model of invasive aspergillosis. Oral therapy with UK-109496 at a dosage of 10 or 15 mg/kg of body weight every 8 h was begun 24 h after a lethal or sublethal challenge, and results were compared with those for amphotericin B therapy and untreated controls. UK-109496 eliminated mortality and also reduced the tissue burden of *Aspergillus fumigatus* 10- to 100-fold in liver and kidney tissues and to a lesser degree in lung tissue, and at the higher dose, no viable organisms were recovered from brain tissue from these animals. Both dosages of UK-109496 decreased or eliminated circulating antigen. The half-life of UK-109496 in rabbits was 2.5 to 3 h, and no accumulation of drug was seen even after 15 doses in either uninfected or infected animals. Thus, UK-109496 shows activity in this rabbit model of invasive aspergillosis. Additional studies are needed to determine the potential of the drug for use in the treatment of this infection.

Invasive aspergillosis is a common infection in immunocompromised patients and is associated with significant morbidity and mortality despite therapy with amphotericin B, which remains the drug of choice for this infection (1, 3, 4, 10, 12). Newer antifungal therapies with improved efficacy and reduced toxicity are needed to improve the treatment of invasive aspergillosis.

The recent development of newer azoles has been one approach to improving antifungal therapies (1, 5, 6, 12–14). These agents offer potential advantages over amphotericin B, including oral as well as intravenous administration, reduced toxicity, and a broad therapeutic index (1, 5, 6, 11, 13). One of the newer azoles is UK-109496, a monotriazole antifungal agent (Fig. 1) which has potent activity against the primary opportunistic fungal pathogens *Candida*, *Cryptococcus*, and *Aspergillus* species and excellent absorption after oral administration (8).

We developed a rabbit model of invasive aspergillosis 10 years ago and have used this model to evaluate the efficacy of antifungal therapy against this infection (1, 17). In our model, rabbits are immunosuppressed, develop leukopenia, and are further immunocompromised with steroid therapy. The disease in our model is similar to the clinical dissemination of invasive aspergillosis in humans with extensive infection in the lung, liver, kidney, and brain (1, 5, 11–14, 17). Efficacy of therapy is assessed by mortality, semiquantitative organ cultures, and serial measurement of *Aspergillus* antigen concentrations in serum (1). In the present study, we evaluated the pharmacokinetics and efficacy of UK-109496 in our rabbit model of invasive aspergillosis to assess the antiaspergillus activity of this compound in an experimental model of lethal infection.

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MATERIALS AND METHODS

Pharmacokinetics. Six female New Zealand White rabbits (1.5 to 2.5 kg) were each immunosuppressed with a single intravenous dose of 200 mg of cyclophosphamide (Bristol-Myers Pharmaceutical Research and Development, Evansville, Ind.) on the first day (day 1). Triamcinolone acetonide was given subcutaneously at 10 mg per rabbit beginning on day 1 and administered daily for the duration of the experiment. With this immunosuppressive regimen, the rabbits have reduced total leukocyte counts through day 7, with nadir on day 4. Therapy with UK-109496 (Pfizer Research, Sandwich, England) was initiated 48 h after administration of cyclophosphamide (day 3). UK-109496 was dissolved in dimethyl sulfoxide (DMSO) (40 mg of DMSO per ml) and then diluted to 1 mg/ml with distilled water (final DMSO concentration, 2.5%). The drug was prepared from powder just prior to use. UK-109496 was administered at 10 mg/kg of body weight by gastric gavage every 8 h for 5 days, for a total of 15 doses. Blood was obtained from central ear vessels at 1, 3, 6, and 8 h after the first dose and at 1, 3, 6, and 8 h after the final dose. Samples were taken at 8-h troughs and 1-h peaks for all other doses. These samples were used to determine single- and multiple-dose pharmacokinetics as well as mean peak levels of UK-109496.

UK-109496 levels. Levels of UK-109496 in serum were measured by bioassay as previously described (11). Briefly, *Candida kefyr* was grown overnight in Sabouraud dextrose broth at 30°C and diluted with saline to a concentration of 5×10^5 cells as determined with a hemacytometer. A 1:50 dilution of cells was made with high resolution medium (Pfizer Central Research, Groton, Conn.) prepared according to the manufacturer's specifications. A 45-ml sample of the inoculated medium was poured into plates (150 by 25 mm), and wells were cut with a 4-mm punch. A standard curve was made by using known concentrations of drug in normal rabbit serum ranging from 1.56 to 0.01 μg/ml. Standards and samples were placed in the wells in duplicate and incubated for 24 h at 30°C. Inhibition zones were then measured, and the serum samples were compared with known standards. This method could detect 0.01 μg of UK-109496 per ml in serum.

Rabbit model. Our rabbit model has been described in detail previously (1, 5, 11–17). Rabbits were immunosuppressed on day 1 as described above. On day 2 (24 h after immunosuppression with cyclophosphamide), rabbits were challenged intravenously with 10^6 *Aspergillus fumigatus* conidia (lethal model) or 10^5 *A. fumigatus* conidia (sublethal model). Untreated, lethally challenged rabbits succumb with disseminated aspergillosis within 8 days. Rabbits were given 100 mg of ceftazidime (SmithKline Beecham, Philadelphia, Pa.) per day and 20 mg of gentamicin (Schering-Plough Research, Bloomfield, N.J.) per day intramuscularly to prevent opportunistic bacterial infection. Therapy with UK-109496, given by gastric gavage, was initiated 24 h after challenge and continued every 8 h for 6 days for a total of 18 doses. Groups of 10 rabbits, lethally or sublethally challenged, were treated with either 30 or 45 mg of UK-109496, which was prepared and administered as described above, per kg per day. Two untreated, infected controls were used with each group of 10 UK-109496-treated rabbits along with one rabbit treated with amphotericin B (Fungizone) in a dose of 1.5 mg/kg. Amphotericin B was diluted with 5% dextrose in sterile water at a ratio of 1 mg of drug to 10 ml of diluent and was given intravenously over 30 to 60 min, once daily for 6 days. Amphotericin B was used only with the lethally challenged rabbits. Surviving rabbits were killed 72 h after the last dose of UK-109496 (day

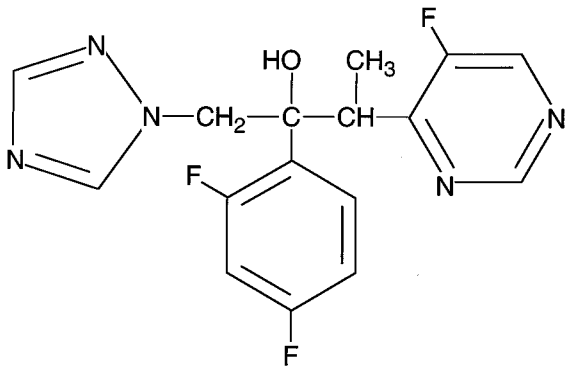

FIG. 1. Chemical structure of UK-109496.

11) or amphotericin B by overdose of ketamine (100 mg; Bristol Laboratories, Syracuse, N.Y.) and xylazine (20 mg; Mobay, Shawnee, Kans.). Tissue samples were cultured at the time of autopsy or sacrifice. Cultures were obtained by placing minced organ samples directly on blood agar and on Sabouraud dextrose agar plates. Samples were considered positive when more than one colony of *A. fumigatus* was present on ≥1 g of minced organ tissues plated directly on Sabouraud dextrose or blood agar plates or when semiquantitative cultures of tissue homogenates contained >10 CFU/g of tissue (5). The tissue burden of *A. fumigatus* was evaluated with a modification (5, 15, 16) of the semiquantitative culture technique of Graybill and Kaster (7). Samples of liver, kidney, lung, and brain tissues were manually chopped, weighed, diluted 1:10 (wt/vol) with sterile saline, and homogenized for 25 s with an electric tissue homogenizer (TRI-R Instruments, Rockville Center, N.Y.). Then 1.0- and 0.1-ml samples of each organ homogenate were plated in duplicate on Sabouraud dextrose and blood agar plates. The plates were incubated for 48 h at 37°C, and colonies were counted. The combination of these methods detected 2 to 20,000 CFU/g of tissue. Blood was collected at intervals and assayed for circulating levels of UK-109496 by bioassay and for circulating *A. fumigatus* antigen by our competition-inhibition enzyme-linked immunosorbent assay (ELISA) (17), and leukocyte counts were monitored.

Criteria for evaluation of efficacy. Three criteria were used to evaluate efficacy of therapy in the lethally challenged rabbits compared with the lethally challenged, untreated controls: mortality, tissue burden of *A. fumigatus* of the target organs, and antigenemia as determined by our ELISA. Only the last two criteria were used to evaluate efficacy in the sublethally challenged rabbits.

Statistical analysis. The Fisher exact test, the Wilcoxon rank sum test, and the Kruskal-Wallis analysis were used when appropriate. Statistical significance was defined as $P < 0.05$.

RESULTS

Pharmacokinetics. The mean peak level of UK-109496 in serum (± standard deviation) after a single dose of 10 mg/kg for three rabbits was 1.26 ± 0.25 μg/ml 1 h after oral administration (Fig. 2). At 3 h, the mean level of UK-109496 in serum (± standard deviation) had fallen to 0.5 ± 0.1 μg/ml, which was approximately 40% of the 1-h peak level. Drug was detectable in all three rabbits at 6 h, but at 8 h only one rabbit had a detectable level of 0.04 μg/ml. The half-life of UK-109496 was 2.5 to 3 h in this group of rabbits given a single dose.

The mean peak level of UK-109496 in serum (± standard deviation) after the 15th dose of 10 mg/kg in six rabbits was 0.69 ± 0.22 μg/ml approximately 1 h after oral administration (Fig. 3). Also, the mean levels of UK-109496 in serum after the 15th dose were 0.28 ± 0.07 μg/ml at 1.5 h, 0.12 ± 0.03 μg/ml at 2 h, and 0.12 ± 0.13 μg/ml at 3 h after administration. No drug was detectable in any rabbit at 6 and 8 h after administration of 10 mg of UK-109496 per kg. We also determined the peak and trough levels of UK-109496 in serum at 1 and 8 h after administration for each of the 15 doses in each of the six rabbits studied. The means for six rabbits for each of the 15 peak levels in serum are shown in Fig. 4 and ranged between 0.7 and 1.3 μg/ml. The mean of these 15 mean peak levels in serum was 0.94 μg/ml. There was no significant accumulation

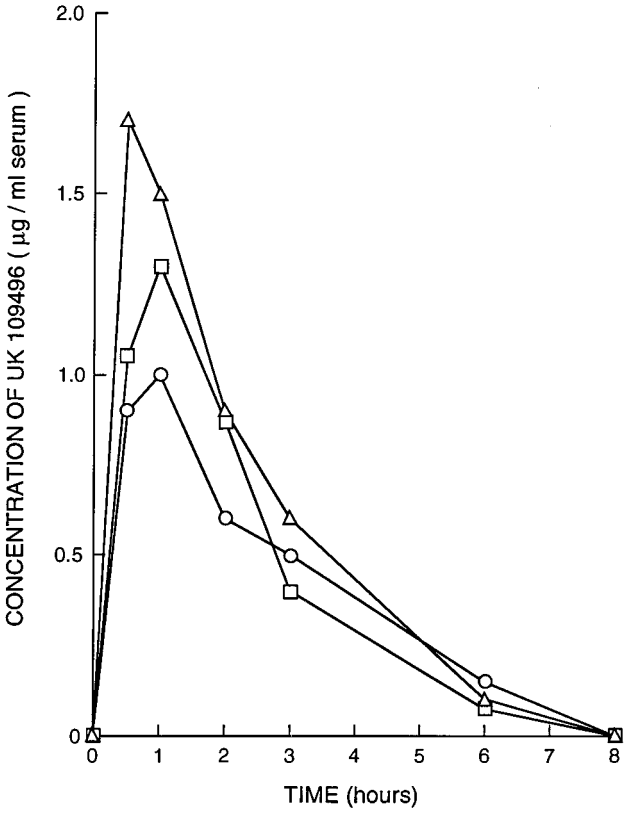

FIG. 2. Single-dose pharmacokinetics: levels of UK-109496 in serum in three immunosuppressed rabbits as a function of time after a single dose of 10 mg of UK-109496 per kg.

of drug even after 15 doses. Furthermore, drug was undetectable in 51 of 57 trough serum samples obtained at 8 h after drug administration. Also, all animals appeared healthy at the end of treatment, and no pathology was seen in any organs at autopsy.

Treatment. The survival of rabbits treated with UK-109496 beginning 24 h after challenge is shown in Table 1. By day 9, all four untreated, lethally infected control animals (challenged with 10^6 *A. fumigatus* conidia) had died, compared with none of 10 rabbits treated with UK-109496 at 10 mg/kg every 8 h and none of 10 animals treated with UK-109496 at 15 mg/kg every 8 h ($P < 0.005$). Also, all amphotericin B-treated animals survived. Similarly, by day 9, mortality occurred in 2 of 4 sublethally infected control rabbits (challenged with 10^5 *A. fumigatus* conidia) compared with none of 10 animals treated with 10 mg and none of 10 rabbits treated with 15 mg of UK-109496 per kg every 8 h. However, as expected, the differences in mortality between the control and treated animals in the sublethally infected groups were not statistically significant.

The results of semiquantitative cultures of liver, kidney, lung, and brain tissues from lethally challenged animals are shown in Table 2. Extensive infection with *A. fumigatus* was present in the liver, kidney, and lung tissues of all untreated control rabbits. Treatment with UK-109496 at 10 mg/kg every 8 h reduced the tissue burden 10-fold in the livers and kidneys but to a lesser degree in the lungs, whereas treatment with 15 mg of UK-109496 per kg every 8 h reduced the tissue burden 100-fold in liver tissue and >10-fold in kidney tissue compared with that in untreated controls. In this experiment, cultures of

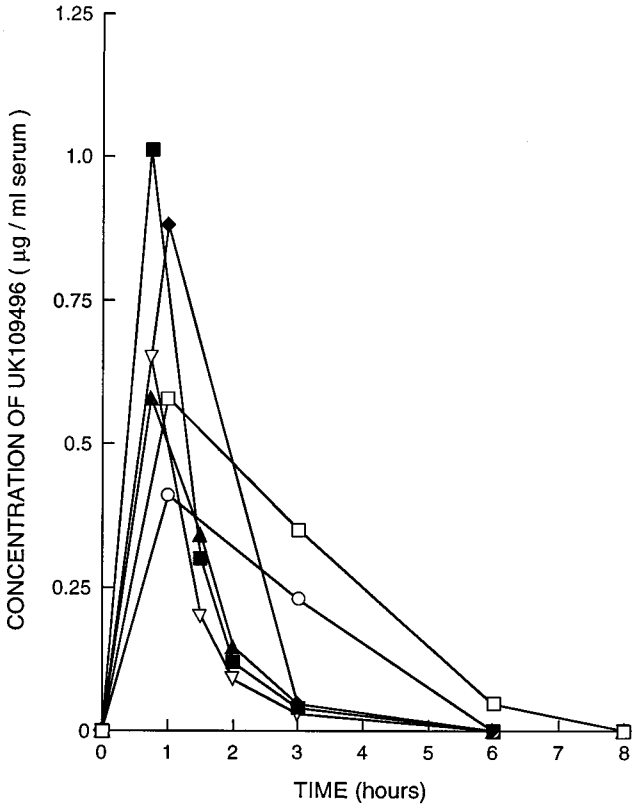

FIG. 3. Multiple-dose pharmacokinetics: levels of UK-109496 in serum in six immunosuppressed rabbits as a function of time after the 15th consecutive dose of 10 mg of UK-109496 per kg administered every 8 h.

lung tissues were contaminated with bacterial overgrowth and quantitative cultures could not be done. Treatment with amphotericin B produced the greatest reduction in the tissue burden and the fewest infection-positive organs for the kidneys, livers, and lungs.

TABLE 1. Mortality of *Aspergillus*-infected rabbits treated with UK-109496 or amphotericin B

Inoculum (no. of organisms)	Treatment (mg/kg/dose)[a]	No. dead/no. tested (%)
Lethal (10^6)	None	4/4 (100)
	UK (10)	0/10 (0)[b]
	UK (15)	0/10 (0)[b]
	AmB (1.5)	0/4 (0)[b]
Sublethal (10^5)	None	2/4 (50)
	UK (10)	0/10 (0)
	UK (15)	0/10 (0)

[a] UK, UK-109496; AmB, amphotericin B.
[b] $P < 0.005$ for lethal treatments compared with controls.

The numbers of positive organ cultures for treated rabbits and control animals given a lethal challenge of *A. fumigatus* are also shown in Table 2. Although UK-109496 at 30 and 45 mg/kg/day reduced the tissue burden of infection, there was no significant difference in the recovery of organisms from organs of treated animals compared with that from control rabbits except from the livers of animals treated with 45 mg/kg/day ($P < 0.05$ compared with treatment with 30 mg/kg/day).

The results of semiquantitative cultures of liver, kidney, lung, and brain tissues from sublethally challenged animals are also shown in Table 2. Treatment with UK-109496 at 30 mg/kg/day reduced the tissue burden more than 100-fold in the liver and to a lesser degree in the kidneys and brains but not in the lungs compared with the burden in untreated, sublethally challenged control animals. In addition, treatment with UK-109496 at the higher daily dose of 45 mg/kg further reduced the tissue burden of *A. fumigatus* in liver, kidney, and lung tissues, and no organisms were recovered from brain tissue from these treated animals.

The number of positive organ cultures for treated rabbits given a sublethal challenge of *A. fumigatus* was less than that observed for treated animals given a lethal challenge, particularly at the higher treatment dose of 45 mg/kg/day (Table 2).

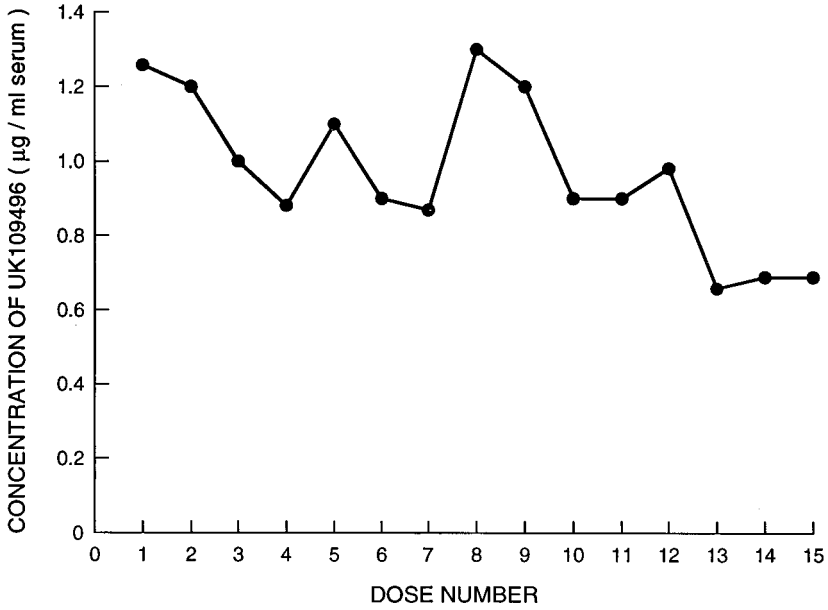

FIG. 4. Mean peak levels of UK-109496 in serum obtained at each dose for six immunosuppressed rabbits monitored over a 15-dose course. Drug was administered orally every 8 h. Mean values for doses 1, 11, and 14 are for three animals; the mean value for dose 10 is for five animals.

TABLE 2. Results of organ cultures with UK-109496 or amphotericin B begun 24 h after challenge

Inoculum	Treatment and mg/kg/dose (n)[a]	Colony count (mean $\log_{10}$ CFU/g of tissue ± SE)[b]				No. of positive cultures/no. of rabbits			
		Liver	Lung	Kidney	Brain	Liver	Lung	Kidney	Brain
Lethal	None (4)	3.3 ± 0.1	2.3 ± 0.2	3.1 ± 0.2	0.5 ± 0.5	4/4	4/4	4/4	1/4
	UK, 10 (10)	2.3 ± 0.3 (0.040)	1.9 ± 0.4 (0.9999)	2.3 ± 0.3 (0.0879)	0.3 ± 0.2 (0.9293)	10/10	8/10	9/10	3/10
	UK, 15 (10)	1.0 ± 0.3 (0.0038)	ND[c]	2.0 ± 0.7 (0.2558)	0.3 ± 0.1 (0.8440)	5/10[d]	10/10	7/10	2/10
	AmB, 1.5 (4)	0.3 ± 0.2 (0.0180) [0.0020]	0.7 ± 0.2 (0.0759) [0.1526]	<0.3 (0.0139) [0.0271]	0.6 ± 0.5 (0.8501) [0.9880]	1/4	2/4	0/4	1/4
Sublethal	None (4)	3.2 ± 0.2	1.8 ± 0.2	1.2 ± 0.7	0.5 ± 0.5	4/4	3/4	2/4	1/4
	UK, 10 (10)	0.8 ± 0.9 (0.0038)	1.9 ± 0.3 (0.7207)	0.9 ± 0.4 (0.8754)	0.2 ± 0.2 (0.4850)	5/10	8/10	4/10	1/10
	UK, 15 (10)	0.5 ± 0.2 (0.0032) [0.0043]	1.2 ± 0.4 (0.4182) [0.4950]	0.7 ± 0.4 (0.5085) [0.7801]	0 (0.1138) [0.3166]	4/10	5/10	3/10	0/10

[a] UK, UK-109496; AmB, amphotericin B.
[b] Values in parentheses, P compared with controls (Wilcoxon rank sum); values in brackets, P for multiple-group comparisons (Kruskal-Wallis analysis).
[c] ND, not done (bacterial contamination).
[d] $P < 0.05$ compared with UK-109496 at 10 mg/kg (chi-square analysis).

TABLE 3. Serum *Aspergillus* antigen values for temporarily immunosuppressed rabbits infected with *A. fumigatus*

Inoculum (no. of organisms)	Treatment (mg/kg/dose)[a]	(No. of rabbits with >50 ng of antigen/ml)/(no. tested)	Median ng of antigen/ml[b] (range)
Lethal (10^6)		4/4	970 (230–2,500)
	UK (10)	3/10	17 (0–1,650)
	UK (15)	3/10	3 (0–172)
	AmB (1.5)	1/4	7 (0–60)
Sublethal (10^5)	None	4/4	370 (147–800)
	UK (10)	1/10	16 (0–46)
	UK (15)	0/10	13 (0–23)

[a] UK, UK-109496; AmB, amphotericin B.
[b] Median antigen levels were calculated from the final antigen concentration for each rabbit in its respective group.

Antigenemia was dramatically reduced or eliminated in rabbits treated with either 30 or 45 mg of UK-109496 or amphotericin B per kg per day compared with that of untreated controls, whether they received a lethal or sublethal challenge with *A. fumigatus* (Table 3). Every control animal had >50 ng of circulating aspergillus antigen per ml; median antigen values were 970 and 370 ng/ml for lethally and sublethally challenged animals, respectively. In contrast, only 7 of 40 UK-109496-treated rabbits had circulating antigen values of >50 ng/ml, and the median antigen values for all treated rabbits, both lethally and sublethally challenged, were ≤17 ng/ml (Table 3). These antigen values were similar to those observed for amphotericin B-treated animals.

The mean peak concentrations of UK-109496 in serum in infected animals on the first day (after the third dose) and toward the end of treatment (after the 15th or 18th dose) are shown in Table 4. The mean peak levels in serum were higher for animals treated with 15 mg/kg every 8 h than for rabbits treated with the 10-mg/kg dose on both the first and the fifth or sixth day of therapy ($P \leq 0.01$ and $P \leq 0.05$, respectively). However, the levels in serum in infected rabbits treated with 10 mg/kg every 8 h were similar to those observed in uninfected animals treated with the same dose on the first and last days of treatment (Fig. 2 and 3 and Table 4). Also, levels of UK-109496 in serum were undetectable at the time of sacrifice, which was 3 days after the animals received the last dose of UK-109496.

TABLE 4. Serum UK-109496 levels as measured by bioassay 1 h after oral dosing

UK-109496 dose (mg/kg)	*Aspergillus* inoculum	Mean level in serum (μg/ml) ± SE after therapy for[a]:	
		1 day	5 or 6 days
10	Lethal	0.83 ± 0.08 (10)	0.98 ± 0.08 (10)
	Sublethal	0.61 ± 0.07 (9)	0.73 ± 0.07 (9)
15	Lethal	1.37 ± 0.12 (9)[b]	1.36 ± 0.14 (10)[c]
	Sublethal	1.42 ± 0.15 (10)[b]	1.65 ± 0.19 (8)[c]

[a] Values in parentheses are the numbers of animals tested.
[b] $P < 0.01$ compared with 10 mg/kg every 8 h using Wilcoxon rank sum.
[c] $P < 0.05$ compared with 10 mg/kg every 8 h using Wilcoxon rank sum.

DISCUSSION

The prognosis for invasive aspergillosis in immunocompromised patients remains poor despite antifungal therapy (2, 4). Thus, newer antifungal agents with increased efficacy and decreased toxicity are needed to improve our ability to treat invasive aspergillosis. The newer azoles offer several potential advantages in the treatment of invasive fungal infections. These advantages include oral as well as intravenous administration, minimal acute toxicity, reduced nephrotoxicity, and an improved therapeutic index compared with that of amphotericin B (6).

UK-109496 is a new oral monotriazole antifungal agent. This new compound has solubility characteristics which permit intravenous administration as therapy for systemic fungal infections, including those caused by *Aspergillus*, *Candida*, and *Cryptococcus* spp. (8). Although UK-109496 continues to undergo development for clinical trials to determine efficacy and toxicity in substantial numbers of patients, this new azole is currently in use in a preliminary pilot study in humans (18).

In previous animal studies, we observed that the therapeutic efficacy of some newer azoles, particularly saperconazole and SCH 39304, correlated with drug dosage and delivery (11, 13). Our studies with saperconazole suggested that levels in serum and therapeutic efficacy, as measured by mortality and CFU present in organ cultures after treatment, correlated directly with drug dosage and route of administration. Intravenous administration resulted in higher levels in serum and lower colony counts in tissues (13). Similar results were observed when we compared two oral doses of SCH 39304. The higher oral dose was more effective in reducing or eliminating both antigenemia and the burden of *A. fumigatus* in the tissues of treated rabbits (11). However, saperconazole and SCH 39304 have been removed from clinical trials because of toxicity. Other azoles (specifically, ketoconazole and itraconazole) have had limited clinical utility because only oral forms of these drugs are commercially available for clinical use. Suboptimal drug absorption has been associated with poor clinical outcome in some patients (4). These observations have led to the use of cyclodextrins to improve the solubility of these compounds in an attempt to improve both the delivery after oral administration and the clinical efficacy of these drugs (9).

In the present study, UK-109496 was dissolved in DMSO and administered in an aqueous solution with a final DMSO concentration of 2.5%, a nontoxic concentration in our animal model. This formulation resulted in reproducible levels of UK-109496 in serum in immunosuppressed infected animals, and therapeutic efficacy was shown to be dose related. The peak levels in serum were higher and the colony counts were lower for animals treated with 45 mg/kg/day than for animals treated with 30 mg of UK-109496 per kg per day. Although other formulations may possibly improve both the pharmacokinetics and the therapeutic efficacy of UK-109496, no others were tested in the present study.

Our experimental model, like all models of lethal infection, does not permit simultaneous culturing of organ tissues from untreated controls and from treated animals, since the untreated controls die before the final day of the experimental protocol. However, in previous studies, using a sublethal challenge, we have shown that untreated control animals surviving until sacrifice have a tissue burden virtually identical to that of untreated controls for which cultures were made at autopsy (12). It is important that UK-109496 at both doses studied eliminated mortality in both lethally and sublethally challenged animals, similar to the results observed with amphotericin B. Furthermore, both doses of UK-109496 reduced or eliminated antigenemia in rabbits receiving a lethal or sublethal challenge of *A. fumigatus*, which correlated with the reduced tissue burden of fungal organisms.

The results of our pharmacokinetic studies indicated that UK-109496 had a short half-life of a few hours in rabbits, frequently with no detectable levels in serum after 6 h. Nevertheless, 8-h dosing, even at the lower dose of UK-109496, eliminated mortality and reduced or eliminated antigenemia in our lethal model. However, a statistically significant reduction in tissue burden of organisms was observed only in livers from animals treated with 30 or 45 mg/kg/day and in kidneys from animals treated with 45 mg of UK-109496 per kg per day. These observations suggest persistence of *A. fumigatus* and possibly multiplication during periods when drug levels were inadequate because of the rapid metabolism of UK-109496 in rodents (8).

In this model, UK-109496 eliminated mortality, as did amphotericin B and SCH 39304, whereas fluconazole and saperconazole only reduced mortality compared with that of the controls (1, 5, 11–16). Also, UK-109496 reduced or eliminated antigenemia comparably to other antifungal agents previously tested in this model of invasive aspergillosis (1, 5, 11–16). However, the reduction in the tissue burden of organisms in animals treated with UK-109496, although comparable to that of other azole antifungal agents tested in this model, was not as complete as that observed with amphotericin B (1, 5, 11–16).

In conclusion, UK-109496, a new monotriazole antifungal agent, effectively prolongs survival, significantly reduces or eliminates *A. fumigatus* antigenemia, and reduces the tissue burden in an immunosuppressed rabbit model of invasive aspergillosis. Further studies are needed to determine the therapeutic potential of this drug in the treatment of invasive aspergillosis.

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