Comparative Activities of UK-49,858 and Amphotericin B against 
Blastomyces dermatitidis Infections in Mice

CARON A. LYMAN, ALAN M. SUGAR,* AND RICHARD D. DIAMOND

Evans Memorial Department of Clinical Research and the Department of Medicine, Boston University Medical Center, Boston, Massachusetts 02118

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UK-49,858, a new antifungal triazole derivative, was compared with amphotericin B in the treatment of pulmonary infections by Blastomyces dermatitidis in male BALB/cByJ mice. Administration of UK-49,858 in daily doses of 25 or 50 mg/kg for 21 days gave 30 and 100% survival rates, respectively. These results compared with 100% mortality in infected controls and 100% survival among mice treated with amphotericin B. UK-49,858 did not eradicate the fungus from the lungs of surviving animals, while amphotericin B effected sterilization of the lungs in 66% of the survivors.

UK-49,858 [2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)-2-propanol] has been found to be effective in the treatment of candidiasis, aspergillosis, and dermatophytosis in mice and guinea pigs (3; data on file, Pfizer, Inc.). Compared with ketoconazole, this triazol is much more water soluble and gives rise to higher serum levels and broader areas under the curve when administered orally (K. Richardson, M. S. Marriott, and P. F. Troke, Int. Soc. Hum. Anim. Mycol., R2-1, 1985; S. Jevesnes, M. H. Tarbit, Int. Soc. Hum. Anim. Mycol., R2-3, 1985; data on file, Pfizer, Inc.). In this investigation, we examined the therapeutic efficacy of UK-49,858 in mice inoculated intranasally with Blastomyces dermatitidis.

The yeast form of B. dermatitidis ATCC 26199, a strain previously shown to be virulent in mice (1), was maintained in a synthetic medium at 37°C on a gyratory shaker. A 1-ml sample of the yeast suspension was subcultured onto enriched blood agar (GIBCO Laboratories, Grand Island, N.Y.) and incubated for 3 to 5 days at 37°C. Organisms were harvested by being washed twice in 0.154 M NaCl. Yeasts were counted with a hemacytometer and adjusted to the desired numbers by dilution in normal saline. Since the meaning and reliability of in vitro susceptibility testing of antifungal agents is unclear and preliminary experience with this drug has shown that in vivo testing of UK did not reliably indicate the potential of the drug for treating fungal infections in animal models (data on file, Pfizer, Inc.), we did not determine the in vitro susceptibility of the isolate to UK-49,858.

Four-week-old male BALB/cByJ mice weighing 15 to 20 g were obtained from Jackson Laboratories, Bar Harbor, Maine, and were inoculated intranasally by established techniques with 0.8 × 10⁴ to 1.0 × 10⁵ blastospores of B. dermatitidis (2). This inoculum was fatal to 100% of untreated animals within 15 days of inoculation. Animals were randomly divided into five groups, and treatment was initiated 5 days postinoculation. Two separate experiments were performed. Each experimental group contained 10 mice.

Amphotericin B (Fungizone Intravenous; E. R. Squibb & Sons, Inc., Princeton, N.J.), at a concentration of 0.2 mg/ml, was prepared fresh daily in a 5% glucose solution. One group of animals received intraperitoneal injections of 0.1 ml once daily for a total daily dosage of 1 mg/kg per day. UK-49,858 (obtained as a powder from Pfizer, Inc.) was dissolved in 0.15 M phosphate-buffered saline, pH 7.4, at final concentrations of 0.5, 2.5, and 5 mg/ml. Three randomized groups of mice received subcutaneous injections of this agent in 0.1-ml volumes twice daily for total dosages of 5, 25, or 50 mg/kg per day. Untreated control animals were injected twice daily at approximately 10-h intervals with an equal volume of 0.15 M phosphate-buffered saline. Subcutaneous administration was used, rather than gastric gavage, to ensure complete delivery of predetermined doses of active drug to each animal.

Untreated animals inoculated with 0.8 × 10³ to 1.0 × 10⁵ blastospores of B. dermatitidis developed a fulminating infection within 7 to 10 days, evidenced by gross evidence of weight loss, lethargy, and respiratory distress, and they died in 13 to 15 days. In contrast, all mice treated once daily with 1 mg of amphotericin B per kg survived and remained outwardly healthy and active. Of the lungs cultured from these amphotericin B-treated mice, 66% were sterile, and those still harbored viable organisms (<50 CFU per lung) displayed no gross evidence of pathology (Table 1).

Administration of UK-49,858 in daily doses of 5 mg/kg per day did not affect survival rate or time of survival. Survival was increased markedly by the administration of daily doses of 25 and 50 mg/kg for 21 days. Despite the improved survival rates, even the 50-mg/kg doses did not eradicate the...
fungus from the lungs or block the appearance of lethargy and respiratory distress. The lungs of UK-49,858-treated mice that survived to time of sacrifice were enlarged, displayed multiple large white nodules (lesions characteristic of pulmonary blastomycosis [2]), and yielded confluent growth on culture (Table 1).

These studies showed that the new triazole, UK-49,858, was less effective than amphotericin B in the treatment of murine blastomycosis. In contrast to amphotericin B, UK-49,858 failed to sterilize Blastomyces-infected lungs. To this point, the accomplishments of UK-49,858 are comparable to those reported for the related imidazole, ketoconazole (2). It should be possible to evaluate UK-49,858 at daily doses higher than 50 mg/kg, since the acute 50% lethal dose of this agent for rats and mice is >1,000 mg/kg. Assessments of the efficacy and toxicity of doses larger than 50 mg/kg and treatment for more than 21 days are needed.

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LITERATURE CITED