

AMPHOTERICIN B COMBINED WITH FLUCONAZOLE IS BETTER THAN ALL OTHER COMBINATIONS FOR CRYPTOCOCCAL MENINGITIS

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INTRODUCTION: Cryptococcal meningitis remains the most common life-threatening opportunistic infection of the central nervous system in persons with AIDS. Optimal treatment with existing drugs has been elusive with the most recent large clinical trial reporting a 52% success rate for 386 subjects treated with amphotericin B with or without flucytosine followed by azole maintenance. Management of this disease is complicated by the limited availability of flucytosine, particularly in countries most affected by the AIDS epidemic.

Both animal and in vitro studies have demonstrated that flucytosine plus either amphotericin B or fluconazole has significantly greater mycologic activity against cryptococcal meningitis compared to either drug alone. However, amphotericin B and fluconazole have not been tested together or in a three drug combination with flucytosine. Given the low cost and widespread availability of amphotericin B and fluconazole, we evaluated this combination in a murine model of cryptococcal meningitis.

METHODS: Meningitis was established in male BALB/c mice weighing 23-25 g by intracerebral injection of approximately 700 CFU of *C. neoformans*. Treatment was started on day 2 with fluconazole and flucytosine dissolved in the sole source of drinking water. Dose levels tested were: amphotericin B alone at 0.3 to 1.3 mg/kg i.v., fluconazole at 10-40 mg/kg/day + amphotericin B at 0.5 mg/kg i.v. daily for 14 days with or without flucytosine at 20-105 mg/kg/day for 14 days. Mice were sacrificed at 16 days and the numbers of fungal colonies in the brain quantified. Untreated control mice were sacrificed at predetermined times to estimate the growth curve of *C. neoformans* in the brain. Additional untreated controls were followed for survival. The association between response and dose combination was evaluated using local regression; 99% confidence intervals (CI) were used to evaluate antifungal effect.

RESULTS: 40% of mice treated with amphotericin B at 0.7 mg/kg and 80% treated with > 0.9 mg/kg died during or within 24 hours of the first dose. No untreated control mice survived beyond day 11. 95% of mice treated with fluconazole at > 16 mg/kg/day + flucytosine survived to the end of treatment. 100% of mice treated with amphotericin B survived to the end of the experiment, regardless of fluconazole or flucytosine dose.

Among mice not treated with amphotericin B, the greatest antifungal activity was seen at 40 mg/kg/day of fluconazole alone (99% CI: 1.9, 4.1 log₁₀ CFU). The addition of amphotericin B to fluconazole in the range 16-32 mg/kg/day, reduced the 99% CIs to 0.4 to 1.6 log₁₀ (p < 0.01). Adding flucytosine did not increase the antifungal activity of either fluconazole alone or fluconazole plus amphotericin B.

CONCLUSIONS: The addition of amphotericin B has a striking effect on the antifungal effect of fluconazole. Given this dramatic increase in antifungal activity and the widespread availability of these two drugs, the full potential of this two-drug combination deserves immediate evaluation in a randomized clinical trial. Although dose-limiting toxicity associated with amphotericin B prevents testing higher doses of the standard formulation, it would be worthwhile to explore the potential of liposomal formulations in combination with fluconazole.