

Chemotherapeutic Activity of 5-Fluorocytosine Against a Lethal *Candida albicans* Infection in Mice

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Received for publication 5 February 1969

Numerous strains of *Candida* were inhibited by low concentrations of 5-fluorocytosine in vitro. Marked increase in life span occurred in *C. albicans*-infected mice treated with 5-fluorocytosine.

5-Fluorocytosine has been reported to inhibit localized and chronic infections caused by *Candida albicans* in cortisone-stressed mice (1), although it has little biological activity when tested in a number of other systems (J. Malbica et al., Fed. Proc. 21a:384). The continuing problem of controlling microbial infections in cancer patients (2) prompted a re-evaluation of this compound for anti-*Candida* activity. Previously described paper-disc agar diffusion methods (3) were used to determine the in vitro anti-*Candida* activity of 5-fluorocytosine. Five strains of *C. albicans* were tested for in vitro sensitivity to 5-fluorocytosine. Four of the strains were sensitive to concentrations as low as 1 µg per disc (zone diameters ranging from 1.6 to 2.7 cm). One strain, *C. albicans* Duke 2548, was resistant to a concentration of 100 µg per disc. Other species of *Candida* were also sensitive to inhibition by 5-fluorocytosine.

C. albicans SRI 523, a strain sensitive to 5-

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TABLE 1. *In vivo* activity of 5-fluorocytosine against an experimental *C. albicans* (strain SRI 523; inoculum size, 10⁷ cells injected iv) infection in mice

Treatment ^a	Time after infection (day)				
	1	2	3-4	5	6-10
None.....	0/10 ^b	5/5	7/3	8/2	9/1
5-Fluorocytosine, 200 mg/kg, ip.....	0/10	0/10	0/10	0/10	1/9
Amphotericin B, 7.5 mg/kg, ip.....	0/10	0/10	0/10	0/10	0/10

^a All mice were treated 15 min after injection. No deaths were observed in control groups of mice receiving these doses of drugs.

^b Dead/living.

fluorocytosine inhibition in vitro, was selected for in vivo tests. The in vivo activity of 5-fluorocytosine was determined by injecting *C. albicans* SRI 523 intravenously (iv) into male, BALB/c

TABLE 2. *In vivo* activity of 5-fluorocytosine against an experimental *C. albicans* (strain SRI 523; inoculum size, 10⁶ cells injected iv) infection in mice

Treatment ^a	Day after infection (no. of mice dead)							No. of mice surviving on day 30	Mean day of death
	3	6	8	9	11	12	13		
None.....	3 (1)	6 (2)	8 (2)	9 (1)	11 (1)	12 (1)	13 (2)	0	9
5-Fluorocytosine, 165 mg/kg, ip.....	8 (1)	9 (1)	14 (1)	17 (1)	19 (2)	24 (1)	27 (1)	2	19
5-Fluorocytosine, 87.5 mg/kg, ip.....	12 (2)	13 (4)	19 (2)	22 (1)				1	13
Amphotericin B, 7.5 mg/kg, ip.....	9 (1)	14 (1)	22 (1)	24 (1)				6	24+

^a All mice were treated within 15 min after injection. No deaths were observed in control groups of mice receiving these doses of drugs.

mice (18 to 22 g). To approximate therapeutically realistic doses, the highest concentration of 5-fluorocytosine tested was 200 mg/kg which is $\frac{1}{6}$ th the reported intraperitoneal (ip) LD₅₀ for the drug (1). In all experiments, the mice were treated within 15 min after infection with *C. albicans*. Amphotericin B was used for comparative purposes. Our experience indicates that a single ip treatment with doses of 87.5 to 200 mg of 5-fluorocytosine per kg results in a prolongation of life as long as 7 to 10 days; after this time deaths attributable to *Candida*, as evidenced by autopsy, occur with increasing frequency, resulting in loss of most of the animals (Tables 1 and 2). Amphotericin B appears somewhat superior to 5-fluorocytosine in these limited experiments.

The need for effective, pharmacologically acceptable, anti-*Candida* agents and the in vivo effectiveness against a lethal *Candida* infection reported here appear to warrant a detailed in vivo evaluation of 5-fluorocytosine.

The mechanism by which 5-fluorocytosine

exerts its antifungal effect is not known. The compound is inactive against *Escherichia coli* (1) which is sensitive to inhibition by 5-fluorouracil. Since our strains of *Candida* are insensitive to 5-fluorouracil, it appears that the anticipated deamination (4) of 5-fluorocytosine to 5-fluorouracil does not occur.

This investigation was supported by contract PH43-65-594 from the Cancer Chemotherapy National Service Center (CCNSC), National Cancer Institute, Public Health Service.

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