Letters to the Editor

Is It Morphologic Type or Physiologic State That Governs Susceptibility of Candida albicans to Clotrimazole Kill?

At concentrations in the range of $10^{-5}$ to $10^{-4}$ M, certain antifungal imidazoles (e.g., clotrimazole [CTM] and miconazole) can exert a direct physicochemical cell-damaging lethal action (2-5, 8, 9), but others (e.g., ketoconazole) cannot or at best have a very limited capacity for such action (1-3, 8). All imidazoles, however, can inhibit synthetic reactions on metabolic pathways to essential fungal cell membrane components and can do so even at concentrations $<<10^{-5}$ M, resulting in an effect that is primarily fungistatic (8, 10, 11). The issue with which we are concerned here involves the direct physicochemical lethal action of CTM.

In a recent report, Niimi et al. (6) concluded that germ-tube-forming cells of Candida albicans, representing the initial stage in development of hyphal growth by this dimorphic organism, are much more susceptible to the rapid fungicial action of CTM in the 10- to 50-µg/ml range ($3 \times 10^{-5}$ to $1.5 \times 10^{-4}$ M) than are yeast cells. The basic design of experiments supporting this conclusion was as follows. Early-stationary-phase yeast cells were washed and suspended in 0.1 M phosphate buffer (pH 6.7) containing 1.0 mM L-proline. Suspensions were preincubated 3 h at either 37°C to promote germ tube production or at 25°C to maintain the organism in its yeast form. Growth, monitored turbidimetrically, was reportedly negligible during this preincubation period. When both suspensions were then treated with 30 µg of CTM per ml ($9 \times 10^{-5}$ M) at 37°C for 2 h, germ-tube-forming cells were killed more rapidly and to a greater extent than were yeast cells. Despite these findings, the conclusion that germ-tube-forming cells are more susceptible to CTM kill than yeast cells is questionable when an additional factor in the experimental design of Niimi et al. (6) is considered together with results of some recent miconazole studies in our laboratory (3).

Our work showed that yeast cells of C. albicans in early stationary phase were resistant to the direct lethal action of miconazole but budding yeasts were highly susceptible to such action in late lag and early logarithmic phases of the growth cycle (3), i.e., the period of so-called physiological youth (7) in which microorganisms are metabolically prepared for a maximal rate of cell proliferation. When Niimi et al. (6) suspended early-stationary-phase yeasts in buffer containing L-proline, incubation at 37°C was favorable for germ tube production. However, it is doubtful that yeast cell proliferation (i.e., budding) was similarly favored in the same menstrum at 25°C. Thus, at the end of the 3-h preincubation, it is quite likely that germ-tube-forming cells were in physiologic youth and therefore susceptible to CTM kill, whereas yeast cells were still essentially in stationary phase and resistant to such action.

The marked susceptibility of late-lag- to early-logarithmic-phase yeast cells of C. albicans to the direct lethal action of CTM is shown in Fig. 1. Details regarding conduct of the time-kill type of experiments shown were presented earlier (3). When either $8 \times 10^{-5}$ or $4 \times 10^{-5}$ M CTM was added together with early-stationary-phase cells to synthetic liquid medium and incubated at 37°C with rotary shaking, the drug was strictly fungistatic in effect. In contrast, when CTM was added after 3 h of incubation without drug, there was a precipitous 2- to 3-log reduction in CFU per milliliter within 3 additional h of incubation. On the basis of our findings and those of Niimi et al. (6), we conclude that the direct lethal action of CTM against Candida albicans is related to growth phase or physiologic state rather than to morphologic type.

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LITERATURE CITED

Acyclovir Prophylaxis for Herpes Simplex Virus Infection


We take exception to one sentence which states, “Oral ACV does not produce significant reduction in symptoms of recurrent genital HSV episodes but does decrease the duration of viral shedding and slightly reduces the time to healing.”

If this were true, there would be no sense in using intermittent dosage of ACV for recurrent genital HSV episodes. In our experiences, this is the commonest use of ACV. In fact, in an article published in 1986, Goldberg et al. (1) showed that oral ACV was effective in reducing time to healing and new lesion formation. If oral ACV is used early enough in an outbreak, the outbreak could occasionally be aborted altogether.

LITERATURE CITED


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Author’s Reply

In reply to the letter from Dr. Goldberg and J. Sperber, we offer the following.

The majority of studies evaluating oral acyclovir for the treatment of recurrent genital herpes have demonstrated a shortening of the duration of viral excretion from lesions and hastened healing of lesions. The effect of therapy on the symptoms of genital herpes have been more variable, some studies showing no effect and others showing some shortening of the duration of pain and itching (2–5). In the study of Goldberg et al. (1) in which they compared 800 mg of acyclovir twice daily versus the standard dosage of 200 mg five times a day, in physician-initiated therapy, acyclovir reduced the healing times of genital lesions by an average of 1.5 day in males and 0.5 day in females. Similar figures were a 1.5-day reduction in lesion duration with patient-initiated therapy. No data concerning the effect of this higher dose of acyclovir on symptoms were reported. The effect of acyclovir on aborting episodes remains controversial. Dr. Goldberg’s study suggested that early therapy was associated with a higher frequency of aborted episodes, although the differences between acyclovir and placebo recipients were not statistically significant. This effect has been shown in an additional study (5), while others have not demonstrated this (4).

Selective use of oral acyclovir for the early treatment of recurrent genital herpes is appropriate. Whether use of larger doses of acyclovir will enhance these therapeutic benefits requires further study.

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