NEW DRUGS FOR THE SYSTEMIC MYCOSES: FLUCYTOSINE AND CLOTRIMAZOLE*

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FOR the purposes of this occasion I shall limit my presentations to two drugs; both are available but only one is efficacious.

FLUCYTOSINE

Chemistry. Flucytosine (5-fluorocytosine or 5-FC) is a fluorinated pyrimidine. It is a white crystalline powder with a molecular weight of 129.1; it is slightly soluble in water and readily soluble in alcohol (Figure 1).

Mode of action. Flucytosine is incorporated by some yeasts and then interferes with subsequent pyrimidine metabolism at one or perhaps several enzymatic sites. Flucytosine enters the cell via permease enzymes located on the surface. Within the cell it is deaminated by cytosine deaminase to fluorouracil. Uracil is used preferentially by fungi and represses the internal synthesis of pyrimidines. Thus, flucytosine ultimately would seem to interfere with thymidylate synthetase.

Susceptibility. Only a few genera of fungi are susceptible: *Cryptococcus neoformans, Candida sp., Torulopsis sp.,* and *Cladosporium sp.* Even within these genera, however, there are marked differences among isolates—notably with *Candida sp.,* of which 50% of isolates may be resistant *de novo. C. neoformans* isolates are generally more sensitive, and the minimal inhibitory concentration (MIC) ranges from 0.39 to 12.5 μg./ml. The minimal fungicidal concentration (MFC) usually does not vary by more than one tube, although occasional exceptions show a marked discrepancy.

In *in vivo* studies—customarily performed in mice—with isolates of

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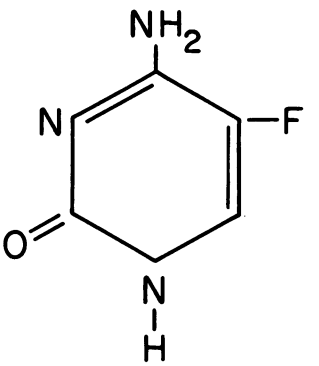

Fig. 1. Structural formula of flucytosine.

C. neoformans, *Candida sp.*, and *Cladosporium trichoides*—chemotherapeutic activity has been demonstrated and is proportionate to the *in vitro* values.

Resistance. Owing to the marked activity in the fungi just mentioned, other systemic pathogens—notably *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis*—have been studied repeatedly, but no activity has been demonstrated. *Asperqillus sp.* are most often resistant, although occasional species have been sensitive and activity has been reported in a few cases of natural disease in man. Only a minimal beneficial effect has been shown in experimental infections with *Sporothrix schenckii.* No activity has been demonstrated against the dermatophytes.

It is crucial to *in vitro* studies that the media be free of competitive pyrimidines which the fungi can use selectively in preference to flucytosine, with resulting values which are falsely indicative of resistance. Development of resistant organisms is a notable feature clinically. Almost two thirds of isolates cultured during or after therapy from patients receiving the drug have been resistant.

Absorption, distribution, and excretion. Despite its relative insolubility in water, flucytosine is well absorbed from the gastrointestinal tract after oral administration. The drug is detectable in serum after 30 minutes and reaches peak values in approximately four to six hours. With doses ranging from 15 to 150 mg./kg./day, levels have varied. However, at the presently recommended dosage (150 mg./kg./day) peak levels range from 50 to 75 μg./ml. The drug is detectable in serum

A DOSAGE SCHEDULE FOR FLUCYTOSINE ACCORDING TO CREATININE CLEARANCE

Creatinine clearance Vcr (ml./min.)	*Dose interval (hours)*
>40	6
40-20	12
20-10	24
<10	>24 according to serum levels

24 hours after the administration of a single dose, and the half life is approximately three hours.

The exact distribution of flucytosine in body fluids and organs is not known. The drug passes readily into the cerebrospinal fluid, producing levels 60 to 80% of those simultaneously present in serum. It has been difficult to correlate levels of drug and protein in the cerebrospinal fluid. In experimental studies, levels found in intrabronchial secretions after intravenous administration exceeded the MIC for up to 90% of *Candida sp.* isolates.

On oral administration approximately 90% of the quantity given can be found unchanged in the urine during a period of 24 hours. The drug is not metabolized in the body. With impaired renal function maximal serum concentrations that are 50% higher than those found with normal function have been recorded. Clearance by hemodialysis approximates that of creatinine. Contrariwise, impaired hepatic function was not shown to increase serum levels.

Administration. At present the optimal and maximal recommended dose is 150 mg./kg./day. It has been customary to administer this in four equally divided doses at intervals of six hours. The drug is available in tablets of 250 and 500 mg.

Because the drug is excreted to such a large extent by the kidney and because serum levels are increased when renal function is impaired, it has seemed reasonable to reduce the interval between doses. Although there are no established studies in this regard, it has been recommended that the interval be adjusted according to creatinine clearance (see accompanying table).

Toxicity. In most patients flucytosine is tolerated remarkably well, especially in comparison with amphotericin B. Abdominal bloating and diarrhea have been noted occasionally. The most frightening finding thus far reported has been intestinal perforation, observed in two patients. Leukopenia and thrombocytopenia have been seen occasionally, but it has usually been difficult to exclude concurrent causes, such as underlying hematologic disorder, malignant disease, corticoids, antimetabolites, other drugs, or the underlying infection itself. Elevations of serum glutamic oxalacetic transaminase and alkaline phosphatase have been seen occasionally but histologic evidence of hepatoxicity is lacking. Toxicity has been encountered more frequently in azotemic patients. The decision to treat a woman of childbearing age should take into account teratogenic effects demonstrated in laboratory animals.

Indications. It seems justifiable at present to use flucytosine in preference to amphotericin B in any patient who can take the drug orally and is infected with a susceptible fungus. This includes the pulmonary form of cryptococcosis, in which the prognosis is such that the use of amphotericin B may not be indicated. Flucytosine has been effective in patients who have had relapses after treatment with amphotericin B. There is laboratory and newly accumulating clinical evidence that the optimal treatment may be a combination of flucytosine and eamphotericin B, especially in patients with meningitis.

It is much more difficult to define the indications in infections caused by *Candida sp*. *Candida sp*. septicemia is so quickly either fatal or self-limited that most patients die or get well before or despite treatment. Similarly, in *Candida sp*. meningitis the disease is relatively mild, and patients have recovered without specific antifungal therapy. It would seem prudent to treat such patients with a drug as innocuous as flucytosine. Experience with infections caused by *T. galbrata*, *S. schenckii*, *Aspergillus sp*, and *C. sp*. has been limited; hence the treatment should be undertaken only under special circumstances and after deliberate consideration of alternatives. One patient who died had no evidence at autopsy of continuing *C. trichoides* infection after treatment with flucytosine of a culturally proved brain abscess.

Clotrimazole

Chemistry. Clotrimazole is a new benzimidazole (O-chloro-alpha-alpha-diphenyl-benzimidazole) synthesized in the laboratories of Bayer

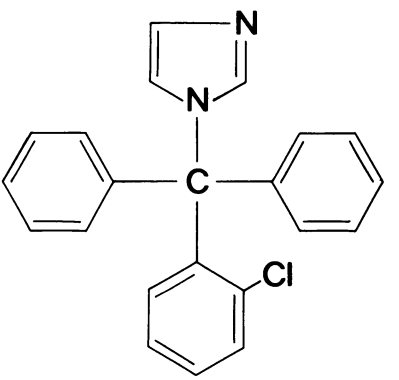

Fig. 2. Structural formula of clotrimazole.

in Germany. It is relatively insoluble in water but can be dissolved in such organic solvents as chloroform or polyethylene glycol (Figure 2).

Mode of action. Little is known about this drug. It has been suggested that relatively high concentrations preferentially damage the fungal cell membranes, making them permeable to intracellular phosphates and potassium and thus inhibiting intracellular macromolecular synthesis. This action is strikingly similar to that of polyenes, notably amphotericin B.

Extrapolation from studies of a related drug suggests that lower concentrations of clotrimazole may impede the uptake of glutamines and purines.

Susceptibility. In vitro a wide variety of fungi, both pure yeasts and filamentous fungi, both dermal and systemic pathogens, are susceptible. The latter group includes *Aspergillus sp.*, *Allescheria boydii*, *S. schenckii*, *Candida sp.*, *H. capsulatum*, *B. dermatitidis*, *C. neoformans*, and *C. immitis.*

Resistance. In vitro resistance has not been observed despite prolonged attempts to induce it in fungi. Among bacteria only *Staphylococcus sp.* appear to be sensitive, and these are only mildly sensitive. Gram-negative bacteria are almost completely resistant.

In vivo experience with fungi is another story. Workers in my laboratory could demonstrate no chemotherapeutic activity in laboratory animals infected with any of the pathogens referred to under *in vitro* susceptibility except for *A. boydii*, *C. neoformans*, and *C. immitis*, and only at dosages of greater than 100 mg./kg.

Absorption, distribution, and excretion. Clotrimazole is absorbed poorly from the gastrointestinal tract, and concentrations approximately 1,000 times that in the serum are present in the feces. Urinary levels are approximately four times those in the serum. Peak serum levels occur one to six hours after the first dose. Minute amounts have been detected in sputum.

Enzyme induction appears to occur in man as in the rat. After a few days none of the drug can be detected in the serum.

Administration. The drug has been supplied in capsules of 500 mg. for oral administration. The dosage in children has been 100 mg./kg./day. In adults, doses above 1.5 gm. every six hours (approximately 80 mg./kg./day) could not be tolerated.

Toxicity. Side effects are noted in virtually all patients and are usually disturbing enough to preclude a six-week drug trial, for example. Gastrointestinal symptoms—especially nausea, vomiting, and diarrhea, but also abdominal cramps and even midepigastric pain—are common. In one study "mental disturbances" were reported in one fourth of the patients. These disturbances have included hallucinations and disorientation.

Indications. On the basis of *in vivo* trials and limited clinical studies, all of which reveal little efficacy and much toxicity, there are no clinical indications for the use of clotrimazole preferentially in man. It is conceivable that in a desperately ill patient who has not responded to other antimycotics the use of clotrimazole could be justified. This pessimism applies to systemic use for serious disease and not to topical therapy for superficial infections.