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CHEMOTHERAPY OF SYSTEMIC FUNGAL DISEASES

❖6713

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INTRODUCTION

After its discovery in 1953 (1), amphotericin B became the principal antifungal antimicrobic for systemic therapy in humans. Although toxicity proved to be formidable, until recently there were no alternatives for the treatment of systemic mycoses which offered comparable antifungal activity and greater safety.

The report of the antifungal activity of 5-fluorocytosine in 1963 (2) led to the availability of an orally administrable, less toxic agent. Unfortunately, the utility of this inhibitory antimicrobic may not extend beyond certain yeasts.

Most recently, the antifungally active imidazoles (e.g. miconazole) and the semisynthetic polyenes (e.g. amphotericin B methyl ester) have moved from in vitro and experimental in vivo investigations to trials in patients.

This review deals with four systemically applicable antifungal antimicrobics: amphotericin B, amphotericin B methyl ester, 5-fluorocytosine, and miconazole. Some properties of these drugs are summarized in Table 1, and the spectrum of activity against major groups of pathogens is presented in Table 2.

AMPHOTERICIN B

Characteristics

SOURCE AND PHYSICOCHEMICAL PROPERTIES Amphotericin B (AMB) is elaborated by selected strains of *Streptomyces nodosus* growing under defined and regulated conditions. The drug accumulates as a sludge on the mycelia and in the culture medium, as it is insoluble in water when the pH is above 2 and below 11: that is, it is amphoteric. Solutions at the extremes of pH are unstable. However, in the form of a dry powder, AMB is stable for long periods if stored at room temperature in the dark, in the absence of oxygen (3, 4).

The chemical and stereochemical absolute structure of AMB was deciphered in 1970 (5), and is depicted in Figure 1. Amphotericin B is a deep yellow-colored

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Table 1 Some properties of four antifungal antimicrobics[a]

Properties	Drug			
	Amphotericin B	Amphotericin B methyl ester	5-Fluorocytosine	Miconazole
Route of administration (physical state)	Intravenous (suspension)	Intravenous (solution)	Peroral (dry solid)	Intravenous (suspension)
Action	interaction with sterols and phospholipids of cell membranes and liposomes causing leakage of contents		enters pyrimidine anabolism to yield nonfunctional RNA	antimetabolic
Effect	fungicidal	fungicidal	fungistatic	fungistatic
Toxicity	++++	++	±	+
Peak concentration in serum	2.5	40.0	100.0	5.5
Geometric mean MIC (*C. albicans*)	2.9	2.9	14.2	0.6
Distribution	excluded from cerebrospinal fluid, central nervous system, urine	excluded from cerebrospinal fluid, central nervous system; present in urine	in all body water	excluded from cerebrospinal fluid, urine
Route of elimination	bile	bile, urine	urine	catabolized
Effect of renal dysfunction	none	none	accumulation	none
Development of resistance during therapy	rare	not reported	not uncommon	not reported

[a] Adapted from E. Goldstein, P. D. Hoeprich, 1977. Candidosis. In *Infectious Diseases*, ed. P. D. Hoeprich, Chap. 37. Hagerstown, Md.: Harper & Row. 1258 pp.

Table 2 Antibiotic spectrum of four antifungal antimicrobics

Pathogen group	Drug			
	Amphotericin B	Amphotericin B methyl ester	5-Fluorocytosine	Miconazole
Viruses	–	+[a]	–	–
Chlamydias	–	–	?	?
Mycoplasmas	+	+	?	?
Rickettsias	–	–	?	?
Bacteria	–	–	+[c]	+[c]
Fungi	+	+	+	+
Protozoa	+	+	–	–
Helminths	+	+[b]	–	–

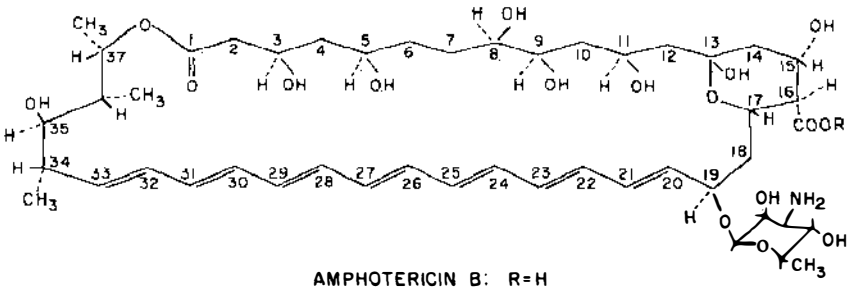
[a] Enveloped viruses.
[b] By analogy with amphotericin B.
[c] Only certain strains.

macrolide; it contains a chromophore made up of a rigid, heptaenic, planar, hydrophobic portion which is linked through an oxygen bridge to a flexible, polyhydroxylated, lipophobic residue (5, 6). It is also an aminoglycoside antimicrobic, as mycosamine, an amino sugar which is a component of several polyenes, is a glycosidically linked substituent to the hydroxyl at C-19 on the macrolactone ring. The amphoteric nature of the compound is contributed by the primary amine of mycosamine, and a carboxyl group at C-16 on the microlactone ring.

ANTIBIOTIC SPECTRUM

Mycoplasmas Mycoplasmas that require sterols for growth, for example, *Mycoplasma gallisepticum,* are susceptible to several polyenes including amphotericin B (7). *Acholeplasma laidlawii* are facultative with regard to preformed sterols and are resistant to polyenes when grown in the absence of sterols (8, 9).

Fungi By in vitro testing, most fungi that cause systemic mycoses are inhibited from growth by AMB at concentrations which are attainable in the blood after intravenous injection of a dose. That is, the minimal inhibitory concentrations (MICs) are usually less than 2.5 μg/ml with clinical isolates of *Aspergillus* spp., *Blastomyces* spp., *Candida* spp., *Coccidioides immitis, Cryptococcus neoformans, Histoplasma* spp., *Sporothrix schenkii,* and the Zygomyces (3, 10–15). However, there is variation, and some strains of a particular genus and species may be more resistant than others. Such variation may be of critical importance to therapy as evidenced by a statistically valid association between a favorable outcome in coccidioidomycosis treated with AMB, and MICs of the infecting strains of *C. immitis* that were equal to or less than 1.0 μg/ml (16).



AMPHOTERICIN B: R=H
m.w. 924.10

AMPHOTERICIN B METHYL ESTER: R=CH_3
m.w. 938.13

Figure 1 Amphotericin B and the semisynthetic derivative, amphotericin B methyl ester, are heptaenic polyene macrolides. The parent compound is insoluble whereas acid salts of the methyl ester are soluble in aqueous systems at physiologic pH. The primary amine of mycosamine—the amino sugar glycosidically linked to the lactone ring at C-19—appears to be essential to biological activity.

The relevance of in vitro assessment of minimal lethal concentrations (MLCs) is unknown. Measuring MLCs is fraught with even more technical variation than the determination of MICs. Moreover, the toxicity of AMB is so great that attainment of concentrations in the blood and body liquids that would be lethal to infecting organisms is quite unlikely.

Although resistance to AMB can be induced in vitro, there is concomitant loss of pathogenicity, and there is return of susceptibility after growth in AMB-free culture medium (17–20). Development of resistance to AMB during therapy has seldom been documented [see summary in reference (21)] and in one well-studied instance (22) resistance was associated with (*a*) disappearance of ergosterol from the cell membrane, (*b*) appearance of sterols with reduced affinity for AMB in the cell membrane, and (*c*) decreased pathogenicity as tested in hypercorticoid mice. That is, persistence of AMB-resistant fungi arising during therapy may be possible only in hosts with deficiencies of phagocytic function and/or cell-mediated immunity.

Protozoa By testing in vitro, amphotericin B is active against *Leishmania brasiliensis, L. donovani,* and *L. tropicalis; Trypanosoma cruzi; Trichomonas vaginalis; Entamoeba histolytica;* and *Naegleria* spp. (23–26). Clinical utility has been demonstrated in leishmaniasis (27–29).

Helminths Planaria are susceptible to amphotericin B (30). Observations on helminths parasitic in humans have not been reported.

MECHANISM(S) OF ACTION Amphotericin B, like other polyenes, interacts with sterols in cell membranes (31–32). The resultant destabilization is manifested in loss of intracellular metabolites. Leakage of potassium is detectable within minutes after susceptible cells are exposed to amphotericin B (33); such injury can be reversed by supplying extracellular potassium. When larger, essential molecules are lost, e.g. nucleic acids, the cell dies. Resting cells, as well as growing cells, are affected.

Although sterols are typically present in the cell membranes of eucaryotic cells, the kind of sterol varies. Ergosterol, the principal sterol of fungi, appears to be a more suitable ligand for AMB than does cholesterol, the sterol characteristic of human cells. This difference may provide the margin essential to therapeutic utility.

Clinical Pharmacology

ROUTES OF ADMINISTRATION Topical application and parenteral injection are employed in the clinical use of AMB. Oral administration and inhalation of aerosols have not proved to be of value in humans.

PREPARATIONS

Topical For topical use, AMB is admixed in a concentration of 3% (w/w) as a cream, a lotion, or as an ointment.

Parenteral For parenteral use, AMB is supplied in glass vials under nitrogen as a dry powder consisting of 50 mg of amphotericin B, 41 mg of sodium deoxycholate,

and 25.2 mg of sodium phosphates. After addition of 10 ml of sterile distilled water, vigorous shaking results in a clear, yellow "solution" which is in fact a suspension —a stable colloidal dispersion of micelles of AMB. The particles are too large to dialyze through cellophane; however, filtration through membranes of 0.45 μm average pore size apparently does not reduce the bioactivity of such suspensions (author's unpublished observations). The clinical correlates may be meager entry into the urine (34) and inconsequential loss during hemodialysis (35).

Before injection, the initial suspension must be diluted in sterile 5% glucose solution for injection to a final concentration that should not exceed 0.1 mg/ml. The pH should be $\geqslant$4.2 but $\leqslant$6.5 in order to minimize spontaneous decomposition (low pH) and agglomeration (neutral and higher pH). Sodium-containing dilutents must be avoided as they will cause precipitation. Such diluted "solutions" are appropriate for injection intravenously, or into the subarachnoid space, the joint spaces, serous cavities, abscesses, the bladder, and the eye.

DOSAGE

Topical Preparations for topical use are rubbed into lesions two to four times daily for several days to several months.

Parenteral It is generally recommended that intravenous therapy (*a*) commence with 0.10–0.25 mg/kg of body weight, (*b*) be advanced slowly by increments of the daily dose to 1.0–1.5 mg/kg, and (*c*) take 4–6 hr per injection (36). In this way, the patient may develop some tolerance to adverse reactions. However, such schedules have the disadvantage of providing subtherapeutic treatment for the first one to two weeks without insuring avoidance of adverse reactions. In many patients, and especially in those patients in whom therapy is urgent, treatment can be started at 0.5 mg/kg with the second dose advanced to 0.75 mg/kg if the initial injection was well tolerated. Further increments should be related to the peak concentrations attained in the serum (i.e. within five minutes of completion of injection of a dose) as the proper dose for a given patient is that quantity of AMB that yields peak concentrations of 2.0–2.5 μg/ml. When that dose is determined, shift to every-other-day, or thrice weekly, treatment is reasonable in view of (*a*) the slow elimination of AMB—the half-life in the serum of humans was reported to be about 24 hr (37), whereas in the nonhuman primate, *Macaca mulatta,* it was 17 hr (38) with a whole body half-life in *M. mulatta* of 275 hr; (*b*) the relatively slow growth of most fungi; and (*c*) the need to reduce the burden of adverse reactions. The total dose of AMB is determined by the clinical response, by surveillance by cultures and serologic studies, and by the damage inflicted on the patient by the drug. With regard to nephropathy, the rule of thumb holds that if renal function was normal at the outset, virtually all patients who are given 2 g or less will have no lasting renal dysfunction, fewer than 50% of patients who receive up to 4 g will have persistently diminished renal function, and about 80% of patients whose total dose exceeds 5 g will have some degree of permanent renal insufficiency (39). Measures such as alkalinizing the urine (40) or administration of mannitol (41) have either not been critically evaluated or were not preventive of nephropathy by controlled trial (42).

Intrathecal therapy with AMB is usually begun with injection of 0.025 mg (0.10 ml of a "solution" containing 0.25 mg of amphotericin B/ml in either 5% or 10% glucose solution). As tolerated by the patient, the dose is increased every two days to a maximum of 0.50 mg (e.g. 0.05 mg, 0.10 mg, 0.20 mg, 0.30 mg, 0.40 mg, 0.50 mg). The maximal tolerated dose is then injected two or three times weekly for a total dose which is determined by the clinical response, resolution of abnormalities of the cerebrospinal fluid (particularly, the disappearance of complement-fixing antibody in coccidioidal meningitis, and polysaccharide antigen in cryptococcal meningitis), and the patient's ability to abide the treatment (43).

The doses injected into body spaces and cavities, and the urinary bladder are quite arbitrary. In view of the possibility of absorption and transfer via the blood to the kidneys and other organs, the doses should not exceed 1 mg/kg of body weight. Smaller doses are generally used, e.g. 5 mg in 100 ml instilled into the bladder. Intraocular injection of doses as high as 30 μg has been reported (44).

DISTRIBUTION From studies with ^{3}H-labeled amphotericin B complexed with ^{14}C-labeled deoxycholate (45), the complex dissociates after injection into *M. mulatta* (46). Twenty-four hours after injection of a single dose of 1 mg/kg of body weight intravenously, AMB attained maximal concentrations in the kidneys with lesser concentrations present in (decreasing order) liver, spleen, adrenal, lung, thyroid, heart, somatic muscle, pancreas, brain, and bone. There was quite meager entry into the cerebrospinal fluid, the eye, and the urine.

ELIMINATION About 5% of a dose of AMB is excreted in antifungally active form in the urine during the 24 hr following intravenous injection in humans (34). When nonhuman primates, *M. mulatta,* were studied, the urinary excretion of AMB was similarly meager (38). Subsequently, the major route of excretion was identified as the bile in studies using ^{3}H-labeled AMB injected intravenously into *M. mulatta* (46).

Adverse Reactions

TOPICAL Topical application of AMB is virtually always well tolerated.

INTRAVENOUS Unfortunately, intravenous injection of AMB almost always causes adverse reactions. Thrombophlebitis is quite common and may be diminished by (*a*) giving "solutions" containing no more than 0.1 mg of amphotericin B per ml; (*b*) adjusting the pH of the "solution" for infusion to the range of 6.0–6.5; (*c*) adding heparin (0.5–1.0 units/ml) but never glucosteroids as they interact with AMB; (*d*) infusing slowly, over 4–6 hr; (*e*) treating every other day; (*f*) injecting into the venous side of a surgically created peripheral arteriovenous fistula—the rapid, turbulent flow assures rapid mixing. Because AMB so commonly eliminates readily accessible veins through thrombophlebitis, we routinely create a surgical arteriovenous fistula (e.g. radial artery-vein) at the outset of treatment as three weeks of maturation are required before a fistula may be used.

Some of the troublesome systemic reactions may be reduced in severity by premedication: for chills, fever, and headache—aspirin or acetaminophen; for nausea and vomiting—prochlorpromazine, an antihistamine, or trimethobenzamide; for hypokalemia—increased peroral intake of potassium. Anorexia, malaise, weight loss, anemia, azotemia, hyposthenuria, renal tubular acidosis, eighth cranial nerve dysfunction, and seizures are among the interrelated consequences of nephrotoxicity, bone marrow suppression, and neurotoxicity; cessation of treatment with AMB is the only effective antidote.

Certain life-threatening adverse reactions occur but rarely: renal shutdown, cardiac arrhythmias, hypotension, profound bone marrow suppression, gastrointestinal hemorrhage, acute liver failure, and anaphylactoid reactions. As these cannot be anticipated, alertness and prompt application of appropriate emergency measures are necessary.

INTRATHECAL The adverse effects of intrathecal administration of AMB are to some extent related to the site of injection. Lumbar subarachnoid injection may cause an arachnoiditis and a lumbosacral peripheral neuritis. If the dose is prepared in 10% glucose solution and the patient is placed head down immediately after injection, adverse effects in the lumbosacral area appear to be avoided (47). Headache may still occur.

Intracisternal injection may lead to an arachnoiditis that may contribute to hydrocephalus through involvement of the adjacent foramina (Luschka, Magendie). Decreased hearing, tinnitus and vertigo, blurred vision, and diplopia may also occur. Headache is common, fever may occur, and there is often nausea and vomiting.

Intraventricular injection may cause headache and fever. Some decrease in hearing may occur but other adverse reactions are uncommon as the amphotericin B is promptly diluted in cerebrospinal fluid.

OTHER SITES The capability of amphotericin B to irritate tissues may become clinically evident wherever it is injected. For example, injection into the eye will cause inflammation and interfere with vision.

Therapeutic Uses

TOPICAL Cutaneous and mucocutaneous candidal infections may respond to topical application of amphotericin B. However, the usual dermatophytic infections are resistant.

PARENTERAL Systemic infections caused by succeptible fungi are usually improved by treatment with amphotericin B. Not uncommonly, however, treatment with AMB is noncurative because both individual doses and the total dosage are limited by the severity of adverse reactions. Also, involvement of organs or compartments that exclude bloodborne amphotericin B may either foreclose effective therapy (e.g. the eye), or require protracted treatment by direct injection of the drug (e.g. fungal meningitis)—an alternative at once uncomfortable and hazardous.

AMPHOTERICIN B METHYL ESTER

Characteristics

SOURCE AND PHYSICOCHEMICAL PROPERTIES Esterification of AMB was first reported in 1972 when the preparation of the methyl ester was described (48). Interest has centered on amphotericin B methyl ester (AME) because (*a*) acute, lethal toxicity was markedly decreased with only slight decrease in antifungal potency, as compared with AMB and (*b*) increasing the length of the alkyl ester chain from methyl through butyl diminished concurrently both acute toxicity for mice and antifungal potency (49).

As one consequence of esterification, the amphotericin B molecule is no longer amphoteric but is cationic through the primary amine of mycosamine (Figure 1). Acid salts are readily prepared and are soluble in water attaining a near molecular dispersion (50); AME hydrochloride (in 5% glucose solution) dialyzes through cellophane (author's unpublished observation). Aggregation leading to precipitation is favored at neutrality and higher pH, whereas AME is unstable at low pH; that is, solubility and stability are favored at pH 5.5–6.5 (C. P. Schaffner, personal communication). Both as the free base and as acid salts AME has a yellow color that is indistinguishable from that of AMB.

AME base is stable for long periods if stored as a dry powder under refrigeration. Although acid salts may be less stable than the free base, the aspartate appears to survive storage under refrigeration for six months (P. A. Diassi, personal communication). In aqueous systems, AME appears to be slightly less stable than AMB as judged by the persistence of antifungal activity (51). Possibly spontaneous degradation of AME can proceed more readily as it is more highly dispersed than the colloidal AMB.

ANTIBIOTIC SPECTRUM

Viruses Several strains of herpes simplex virus were reported to be inactivated by AME in 1975 (52). More recently, the activity of AME against herpes simplex viruses (types 1 and 2) was confirmed (53); in addition, AME at concentrations of 1–5 μg/ml was shown to bring about a 50% plaque reduction with vaccinia virus, Sindbis virus, and vesicular stomatitis virus. Adenovirus type 4 and echovirus type 11 were not affected.

Mycoplasmas AME causes leakage of potassium from *Mycoplasma mycoides* subspecies *capri,* a strain that requires sterols (e.g. ergosterol, cholesterol) for growth (54). It is probable that other mycoplasmas requiring sterols for growth will also be susceptible to AME.

Fungi AME was nearly as active against fungi as AMB by in vitro testing of laboratory strains (48, 49, 55–57), and recent clinical isolates (58).

In experimental murine candidosis, AME was slightly less active than AMB when either a five-day regimen of intravenous injections (55) or daily intraperitoneal injections for 21 days was used (59). However, in another study, AME was substan-

tially less effective than AMB when the drugs were given intravenously on four consecutive days (57).

Disagreement also arose as to the effectiveness of AME when compared with AMB in the treatment of experimental murine cryptococcosis and blastomycosis. One report (59) held AME to be slightly less effective than AMB when the drugs were injected intraperitoneally, daily, for 21 days (respective ED_{50} values of 2.0 and 0.2 mg/kg in cryptococcosis; 2.8 and 0.3 mg/kg in blastomycosis); the other (57) asserted that AME was markedly less active when the drugs were given intravenously, daily, for four days (respective ED_{50} values of 32 and 1.4 mg/kg in cryptococcosis; 15 and 0.4 mg/kg in blastomycosis).

AME was efficacious, but less active than AMB in experimental murine histoplasmosis treated with daily IP injections for 21 days (59), and in experimental murine coccidioidomycosis treated with daily IP injections for 30 days (60).

Protozoa Three clinical isolates of *Naegleria* spp. were inhibited by 0.15 μg/ml of AME by testing in vitro. However, lower concentrations of AMB (0.04 μg/ml) were inhibitory (author's unpublished observations).

Helminths There have been no reports of assessment of AME as an anthelmintic.

MECHANISMS OF ACTION Loss of intracellular potassium results from exposure of *Candida albicans* (54, 61) and *Mycoplasma mycoides* subspecies *capri* (54) to AME, an effect which is antagonized by sterols—zymosterol > ergosterol > cholesterol. Thus, it appears that AME affects susceptible cells in the same way as AMB and other polyenes; that is, interaction with sterols in the cell membrane damages the membrane causing increased permeability. As assessed by loss of intracellular potassium, human erythrocytes are much less susceptible to membrane damage from AME than from AMB although *C. albicans* are virtually as susceptible to both drugs (62). Apparently, esterification of AMB reduces the affinity of the molecule for cholesterol.

The antiviral activity of AME is intriguing in view of the (*a*) lack of antiviral activity from AMB; and (*b*) apparent restriction of AME to action against enveloped viruses (53). Two factors may be important: (*a*) the molecular or near molecular dispersion of AME provides polyene which is physically subviral in size; and (*b*) the viral envelope, as it is derived from the mammalian host cell, contains sterol receptors.

Clinical Pharmacology

ROUTES OF ADMINISTRATION Intravenous and intrathecal injection are the only routes of administration by which AME has been given to humans (63).

PREPARATIONS In most of the in vitro and nonhuman animal work, AME hydrochloride was used (38, 46, 48, 49, 51–56, 58–62).

The ascorbate has been used to treat humans (63). Each dose is prepared by adding the requisite amount of AME base to 50 ml of 0.2% ascorbic acid (w/v) in 5% glucose for injection. Vigorous shaking is necessary to achieve solution. After

membrane filtration (0.22 μm average pore size) the sterile AME ascorbate solution is diluted for use. For intravenous injection, the diluent is 5% glucose solution for injection in sufficient quantity to yield a final concentration of 0.5–0.6 mg/ml; heparin to provide 0.5 unit/ml of final solution is added and the mixture is stored in the refrigerator until injected (usually the same day, but no longer than 48 hr). For intrathecal injection, the filtered concentrate is diluted either in 5% or 10% glucose solution for injection to yield a final concentration of 0.5 mg/ml; 3 ml portions are conveniently distributed in sterile ampoules and stored frozen at –40°C.

AME aspartate has had limited experimental trial and may prove to be preferable for clinical use because of its stability in storage and ease of use. The aspartate dissolves virtually instantaneously in 5% glucose solution for injection.

DOSAGE AME was well tolerated when injected daily for 30 days into mice at 15 mg/kg intraperitoneally (60), into rats at 20 mg/kg intraperitonally (64), and into dogs at 10 mg/kg intravenously (64). *Macaca mulatta* were less tolerant: a single dose of 15 mg/kg intravenously caused death from intravascular hemolysis; 10 mg/kg caused detectable hemolysis without evident illness; and 5 mg/kg was well tolerated (38).

In humans, intravenous therapy with AME has commenced with a dose of 0.5 mg/kg given intravenously over a period of 30–45 min. If this dose is well tolerated, 1.0 mg/kg may be given on the second day, then 2.5 mg/kg on the third day, advancing to 5.0 mg/kg on the fourth day of treatment. Therapy may then be continued at 5.0 mg/kg injected every other day or thrice weekly. The peak concentrations in the serum (specimens obtained within 5 min after completion of an infusion over a period of 45 min) are 15–30 μg/ml, and the predose values are 0.5–2.5 μg/ml (63). Every-other-day therapy appears to be effective although AME is eliminated more rapidly than AMB—in the nonhuman primate, *M. mulatta,* the whole body half-life of AME was 97 hr and the serum half-life 2.5 hr (38). Total dosage remains to be determined. From the present limited experience, it appears that a total dose of 10 g is beneficial, and has not been provocative of serious renal damage.

For intrathecal therapy, AME in 5% glucose solution should be used for intracisternal or intraventricular injection. AME in 10% glucose solution should be used for lumbar injection followed by placing the patient in the head down position (47). Whatever the site of intrathecal injection, the dose should be advanced on an every-other-day regimen from an initial 0.1 mg to 2.5 mg by 0.25 mg increments, as tolerated by the patient. Thrice weekly injections have been given for periods as long as six months; optimal dosage remains to be determined.

DISTRIBUTION The distribution of AME was studied in mice using AME ascorbate with ^{14}C in the methyl ester (65). After a single intravenous dose of 66 mg/kg of body weight, the highest concentration was found in the lungs; 24 hr after injection, the distribution (in descending order) was lung, spleen, liver, kidney, stomach, heart, intestine, thymus, testis, and brain. The relevance of these ^{14}C data was confirmed by bioassay for AME extracted (dimethyl sulfoxide, methanol) from portions of lung, spleen, liver, and kidney. Also, there was correspondence of

bioautographic and radioactivity measurements of thin-layer chromatograms of butanol extracts of the urine.

With doubly radiolabeled AME hydrochloride—^{3}H in the chromophore and ^{14}C in the methyl ester (46)—the distribution of AME was studied in the nonhuman primate, *M. mulatta* (46). Twenty-four hours after a single intravenous dose of 5 mg/kg of body weight, the distribution (in descending order) was spleen, liver, kidneys, adrenal, lung, pancreas, heart, thyroid, skeletal muscle, bone, and brain. The high concentrations attained in the urine and the bile were confirmed as being of therapeutic potential by bioassay. There was meager entry of AME into the cerebrospinal fluid and the liquids of the eye.

ELIMINATION In *M. mulatta,* about 20% of a single intravenous dose of AME was excreted in the urine during the 4 hr following injection (38). With doubly radiolabeled AME (45), excretion in the bile was shown to be a major route of elimination (46).

Adverse Reactions

In general, adverse reactions to AME are qualitatively the same as those engendered by AMB. But the reactions to AME tend to be less severe, and on the average, doses that are five times higher can be tolerated.

INTRAVENOUS Thrombophlebitis is also caused by AME, and the measures helpful with AMB are also useful with AME.

Some systemic reactions, such as chills, fever, headache, nausea, and vomiting, may also be reduced, if not prevented, by premedication as used with AMB: Anorexia, malaise, weight loss, anemia, azotemia, and eighth cranial nerve dysfunction also occur. Although generally less severe than with AMB, these reactions probably also reflect nephrotoxicity, bone marrow suppression, and neurotoxicity which will not resolve until treatment with AME is stopped.

Of the several life-threatening reactions associated with AMB, in the limited experience to date, only hypotension has been observed with AME. Thus far, the renal dysfunction caused by AME has reversed after treatment was terminated.

INTRATHECAL From limited clinical experience, it is evident that headache may be precipitated by the intrathecal injection of AME. Yet, doses as high as 2.5 mg per injection may be tolerated and given thrice weekly for treatment periods of several weeks when administered by the lumbar hyperbaric technique (47).

Therapeutic Uses

It is probable that AME will be useful in the same clinical situations in which AMB is now used. Because of lesser toxicity, larger doses of AME can be given and may be tolerated for longer periods of treatment. The greater urinary outfall may also be an advantage, as in recipients of a transplanted kidney who have a fungal urinary tract infection.

The potential of activity against nonfungal infectious agents has yet to be investigated.

5-FLUOROCYTOSINE

Characteristics

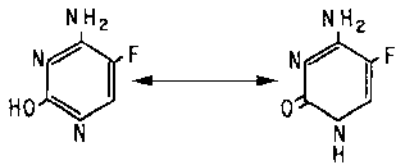
SOURCE AND PHYSICOCHEMICAL PROPERTIES 5-Fluorocytosine (flucytosine, 5FC) is one of several fluoropyrimidines that were synthesized in 1957 (66) as possible anticancer agents. Although 5FC has no anticancer activity, antifungal activity was reported in 1964 (2).

5FC is a white powder that melts with decomposition at about 295°C, and is soluble in water to the extent of about 0.12 M (15 g/liter). In aqueous systems at physiologic pH, 5FC exists in tautomeric form (Figure 2). Antifungal activity is retained undiminished for at least seven days in a variety of aqueous systems, including synthetic culture mediums and human serum (51).

ANTIBIOTIC SPECTRUM

Bacteria There are no reports of systematic evaluation of the susceptibility of bacteria to 5FC. However, from studies of the metabolism of pyrimidines and pyrimidine nucleosides by *Salmonella typhimurium* (67), it is clear that some bacteria are susceptible. Other kinds of bacteria, including other genera of the Enterobacteriaceae, may be susceptible as they are able to deaminate cytosine to produce uracil, that is, to convert 5FC to 5-fluorouracil (68, 69) (see section on mechanisms of action, below).

Fungi Until it was appreciated that conventional, complex, and undefined culture mediums antagonized the antifungal activity of 5FC (70, 71), susceptibility test results were often at variance with assessments of activity in fungal infections—either experimentally induced in nonhuman animals or as they occurred in humans. Comparison of results from different laboratories is made difficult by other variables in techniques of testing such as the size of inocula, period of incubation, and state of testing—liquid medium or gelled medium (using discs or wells). Despite such limitations, it appears that strains of *Candida albicans* newly isolated from humans vary widely in susceptibility to 5FC with as many as 15% resistant (70, 72–79); perhaps such variation is greater among non-*albicans* spp. (79, 80). According to Drouhet, 93% of serogroup A strains of *C. albicans* are inhibited by $\leqslant 25$ μg/ml whereas just 16.7% of serogroup B strains are similarly susceptible (81). Fungistasis is the typical effect of 5FC against *C. albicans* (82).



5-FLUOROCYTOSINE
m.w. 129.1

Figure 2 One of a series of synthetic fluoropyrimidines, 5-fluorocytosine is inhibitory to certain fungi and bacteria. It is soluble in water and is tautomeric at physiologic pH.

Clinical isolates of *Torulopsis glabrata* are usually susceptible to 5FC (76, 79), and generally the effect is fungicidal (82). Native resistance may occur in 5–7% of isolates.

As isolated from patients, *Cryptococcus neoformans* vary from quite susceptible to totally resistant to 5FC (70, 72, 77, 83, 84). Overall, about 3–5% of pretreatment isolates are resistant to concentrations of 5FC $\geqslant 25$ μg/ml.

The pathogenic molds are generally resistant to 5FC by in vitro and in vivo assessment. There may be exceptions among the *Phialophora* spp. (85), *Cladosporium* spp. (86), and *Sporothrix schenkii* (75). *Aspergillus* spp. have been reported to be resistant (70, 74, 87) in agreement with the author's experience, and susceptible (74, 88) to 5FC. As only a few strains of various species have been tested, perhaps what is needed is a study of several clinical isolates of each of the pathogenic species of *Aspergillus.*

MECHANISMS OF ACTION From work with bacteria and yeasts, it is clear that the 5-fluoropyrimidines are (*a*) not intrinsically toxic, (*b*) antibiotic only as a result of extensive metabolic interconversions, and (*c*) metabolized by the very enzymes that catalyze the metabolism of normal pyrimidines. That is, cells will be inhibited from growth only if they convert fluoropyrimidines into either fluorouridine triphosphate (89) or fluorocytidine triphosphate (90) which is then used to synthesize RNA. Cells with metabolic blocks to the formation of fluoronucleotide triphosphates from fluoropyrimidines will be resistant to these compounds (Figure 3).

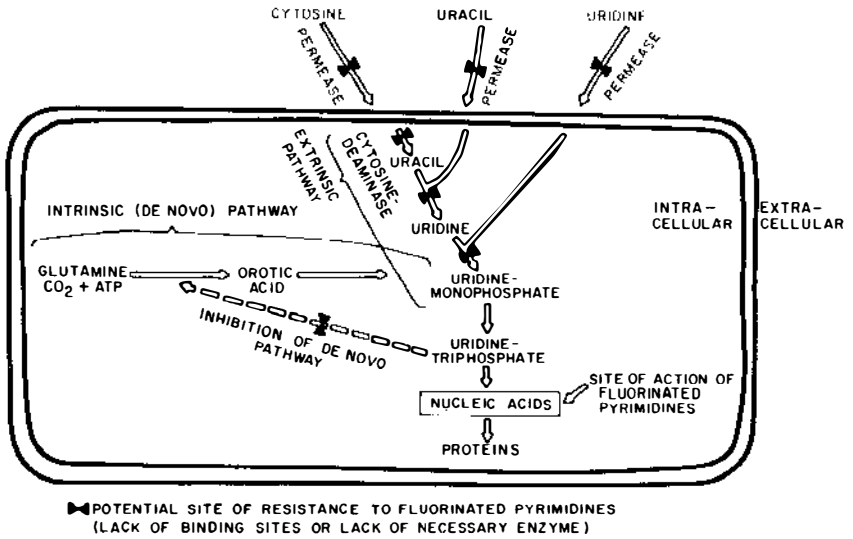


Figure 3 As fluoropyrimidines are metabolized exactly as are normal pyrimidines, resistance to the antibiotic action of fluoropyrimidines may arise at many sites. (Reproduced from A. G. Vandevelde, A. A. Mauceri, J. E. Johnson, III, *Ann. Int. Med.* 77:43–51, 1972.)

Some microorganisms have a quirk to their pyrimidine metabolism that makes them susceptible to 5FC. They require cytidine but cannot make it from cytosine [e.g. *S. typhimurium* (91) and *Saccharomyces cerevisiae* (90)] and they are endowed with cytosine deaminase, an enzyme that converts cytosine to uracil. Other microorganisms are resistant to 5FC apparently because they do not take up exogenous cytosine (90) or lack cytosine deaminase (author's unpublished observations). Mammalian cells lack cytosine deaminase (92, 93) and therefore 5FC is safe for use in the treatment of humans.

Native resistance through lack of cytosine deaminase is mimicked by the development of resistance (Figure 3) through mutational deletion of cytosine deaminase (94). In addition, loss of uridine monophosphate pyrophosphorylase activity has led to resistance in vitro with *C. albicans* (95). Other mechanisms of resistance to 5FC include (*a*) alterations of uridine monophosphate kinase (96), (*b*) overproduction of pyrimidines (95, 97), and (*c*) diminished entry of 5FC into cells (97).

Clinical Pharmacology

ROUTES OF ADMINISTRATION 5FC is usually administered perorally. It has been given intravenously in 0.9% NaCl solution for injection but the requirements of solubility oblige the administration of a significant load of water and NaCl; for example, a 75 kg patient given 5FC by intravenous injection of 200 mg/kg of body weight per day would receive 1.5 liter of a 1% solution of 5FC, obliging administration of 13.5 g of NaCl.

PREPARATIONS Tablets containing 0.25 and 0.50 g are commercially available for peroral therapy. For clinical investigational use, a sterile 1% (w/v) solution of 5FC in 0.9% NaCl solution for intravenous injection has been used.

DOSAGE As first used to treat systemic mycoses, the dosage of 5FC was too low. Indeed, the development of resistance to 5FC during therapy appeared to be favored by low doses (72, 79, 80, 83, 85, 98). For this reason, the author recommends 5FC be given in the dosage favored abroad (80, 99), namely 200 mg/kg of body weight per day, perorally, in patients with normal renal function. If this daily dose is divided into four equal portions taken every 6 hr, concentrations in the serum will generally fluctuate between 35 and 80 μg/ml (99). In the author's experience, administration as three equal portions every 8 hours, which is perhaps a more practical regimen for outpatients, yields concentrations of 25–100 μg/ml serum. These considerations may be important because development of resistance in vitro appeared to be favored at concentrations <25 μg/ml (80, 95), and the frequency of adverse reactions may be increased when concentrations in the serum exceed 120 μg/ml (99, 100).

In patients with reduced renal function, the dose must be lowered to compensate for the diminished excretory capacity (101–104). In the author's view, this is best accomplished by adherence to a normal interval of dosage, e.g. every 8 hr, with reduction of the total daily dose in direct proportion to the degree of renal impairment as assessed by a test of actual renal function, e.g. the creatinine clearance. In

this way, the advantage of steady state therapy, e.g. maintenance of concentrations of 5FC in the blood that are above 25 μg/ml but below 120 μg/ml, is gained, as contrasted with the wider excursions in concentrations of 5FC that usually result when the interval between doses is prolonged (103, 104). The appropriateness of any regimen of therapy must be judged by measurement (bioassay) of the low (immediate predose) and high [1 hr (normals) or 4 hr (uremia) after a peroral dose] concentrations in the serum.

As 5FC is readily removed by hemodialysis (35, 80, 102, 103, 105) and also to some extent by peritoneal dialysis (102), the loss should be replenished by giving a normal interval dose, according to the patient's body weight, on completion of the procedure, e.g. 50 to 67 mg/kg after hemodialysis (possibly half as much after peritoneal dialysis, although there is very little information on this point).

DISTRIBUTION After ingestion, at least 90% of a dose of 5FC is absorbed from the gut. It distributes apparently uniformly in extracellular body water and has a half-life in the serum that averages 2.9 hr (104, 106, 107). Special compartments are readily penetrated; expressed as percentage of the concentration of 5FC in concurrently obtained serum, peritoneal fluid was 100% (102), cerebrospinal fluid was 75% (108), synovial fluid was 60% (109), aqueous humor was 20% (110), and bronchial secretions were 76% (111).

ELIMINATION Over 90% of 5FC is eliminated in the urine as biologically active drug in concentrations 10 to 100 times higher than those in the serum (104, 106, 107). After peroral administration of ^{14}C-labeled 5FC to humans, as much as 1% of the dose was found in the urine as α-fluoro-β-ureido-propionic acid, a metabolite of 5-fluorouracil (107). Possibly, this metabolite arose from 5FC which was deaminated by enteric bacterial flora to yield 5-fluorouracil which was then absorbed and catabolized by the volunteer, a sequence with obvious potential for 5-fluorouracil toxicity.

Adverse Reactions

5FC engenders adverse reactions uncommonly. As summarized by Scholer (99), of patients treated with 5FC, some 6% develop gastrointestional symptoms (anorexia, nausea, vomiting, diarrhea, abdominal pain), 5% have evidence of disturbed hepatic function (elevations of transaminases, alkaline phosphatase; rarely, increased bilirubin, hepatic enlargement), and 5% manifest depression of bone marrow function (leukopenia, thrombocytopenia; rarely, agranulocytosis, anemia, or pancytopenia).

However, it is quite difficult to determine the true frequency of adverse reactions to 5FC. Patients who acquire systemic mycoses often have compromised function of the gut, liver, and bone marrow as a consequence of an underlying, nonmycotic disease, or caused by the treatment for the underlying disease, or both. Malfunction of the gut may result in decreased motility causing a shift of the colonic flora into the small bowel; absorption may become aberrant if the mucosa is injured or eroded. If renal function is also decreased, high concentrations of 5FC may be maintained in the blood and be reflected in unusually high concentrations in intestinal secre-

tions. The net effect might well be heightened toxicity as a consequence of increased elaboration of 5-fluorouracil by enteric bacterial flora, and increased absorption of this toxic metabolite.

Therapeutic Uses

5FC may be used to treat systemic mycoses caused by susceptible strains of *Candida* spp., *Cryptococcus neoformans, Torulopsis glabrata,* and chromomycosis caused by susceptible strains of *Phialophora* spp. or *Cladosporium* spp. Failures of treatment of systemic yeast infections do occur because resistance to 5FC develops during therapy, but the frequency of this event is unclear. When 5FC was first used (*a*) pretreatment susceptibility tests either were not done or were improperly carried out —some apparent treatment failures may have actually been infections caused by strains not recognized as natively resistant; (*b*) the dosage was inadequate both in daily quantity and in duration of treatment, conditions later recognized as favoring selection of resistant forms.

Combined therapy using amphotericin B (AMB) with 5FC has been suggested not only to prevent emergence of resistance, but also to provide a therapeutic bonus in the form of additive or synergistic action. However, these good effects from the combination might not be realized with infections sequestered in body areas or compartments from which AMB is excluded, e.g. the urinary tract, the eye, and the central nervous sytem. The matter has been put to clinical trial.

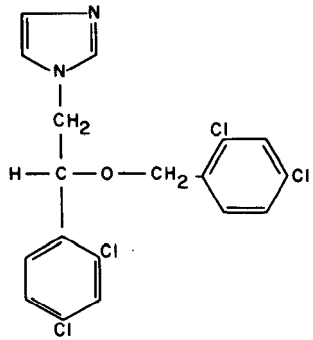
A six week regimen of therapy consisting of 5FC (150 mg/kg of body weight per day, perorally, as four equal portions every 6 hr) and AMB (0.3 mg/kg of body weight per day, intravenously) has had uncontrolled trial in the treatment of cryptococcal meningitis (112); the results appeared to be at least as good as attained with single agent therapy. The dose of AMB would, by itself, be subtherapeutic, particularly in view of the poor ingress of AMB into the central nervous system. However, the AMB might diminish renal function enough to cause retention of 5FC, providing the equivalent of higher dosage with 5FC. The relatively high rate of adverse reactions, attributed to 5FC (possibly due to 5-fluorouracil), might be explained in this way.

The methyl ester of amphotericin B may prove to be suitable for concomitant use with 5FC because it is excreted in the urine, attains low but detectable concentrations in the cerebrospinal fluid, and is less toxic than AMB (63).

MICONAZOLE

Characteristics

SOURCE AND PHYSICOCHEMICAL PROPERTIES Miconazole (Figure 4) is one of a series of β-substituted 1-phenethylimidazoles which were synthesized in the late 1960s in Belgium (113). It is a white powder that (*a*) melts at 75–83°C, (*b*) dissolves in a variety of organic solvents, but is insoluble in water, and (*c*) retains full antifungal activity for at least 7 days at 37°C as a colloidal suspension in a variety of aqueous systems (51).



MICONAZOLE
m.w. 416.14

Figure 4 Miconazole is one of several phenethylimidozoles which are inhibitory to many kinds of fungi and some bacteria. It is essentially insoluble in aqueous systems at physiologic pH.

ANTIBIOTIC SPECTRUM

Bacteria By testing in vitro, miconazole inhibited several different *Streptococcus* spp. (not *faecalis* or *faecium*), *Staphylococcus* spp. (some exceptions), *Bacillus* spp., *Corynebacterium diphtheriae, Listeria monocytogenes,* and *Erysipelothrix insidiosa* at concentrations $\leqslant$ 10 μg/ml (113–116); for lethal activity against these bacteria, concentrations 4 to 16 times higher than inhibitory levels were needed (116). More than 100 μg/ml was necessary for inhibition of gram-negative bacteria [various Enterobacteriaceae, *Pseudomonas aeruginosa, Pasteurella pseudotuberculosis, Bordetella bronchiseptica* (115, 116)].

Fungi The reported MICs of miconazole for pathogenic fungi including the dermatophytes (113–119) often exceeded greatly the concentrations attainable in humans after parenteral administration. Perhaps the MIC values were only apparently high, as testing was carried out in conventional, complex, undefined culture mediums. Such mediums, e.g. Sabouraud's glucose medium, are antagonistic to miconazole, reducing antifungal activity 30- to 50-fold as compared with results obtained in completely synthetic, totally defined mediums (120). The bases for such antagonism are not known, although no effect resulted from (*a*) extraction of Sabouraud's medium with diethyl ether and (*b*) the separate addition of orotic acid, and pyrimidines and purines (as free bases, nucleosides, or nucleotides) to a nonantagonistic, synthetic, defined medium (120).

With a nonobfuscatory, liquid culture medium, the susceptibility of clinical isolates of *Candida albicans* (100 isolates); *Candida parapsilosis* (8 isolates); *Candida tropicalis* (6 isolates); and *Torulopsis glabrata* (31 isolates) was determined (121). Accepting a 5 μg/ml as the peak concentration in the serum of patients given

tolerable doses of miconazole by intravenous injection (122, 123), MICs were categorized as susceptible, $\leq$1.25 μg/ml; indeterminate, 1.25–5.00 μg/ml; and resistant, $\geq$ 5.00 μg/ml. The results were as follows: *C. albicans*—65% susceptible, 28% resistant (7% indeterminate); *C. parapsilosis*—62% susceptible, 38% resistant; *C. tropicalis*—all susceptible; *T. glabrata*—all susceptible. These same criteria were also applied to the results of tests carried out under the identical conditions with *Cryptococcus neoformans* (19 isolates), *Coccidioides immitis* (65 isolates), and *Aspergillus* spp. (20 isolates) (124); the results were as follows: *C. neoformans*—95% susceptible, (5% indeterminate); *C. immitis*—all susceptible; *Aspergillus* spp. —30% susceptible; 20% resistant (50% indeterminate).

Miconazole is primarily fungistatic (82). With *C. albicans,* the numbers of colony forming units (CFUs) remaining from inocula of 6×10^4 CFU/ml were determined at intervals during a 48 hr period of incubation in liquid, synthetic medium containing either 0.6 or 10 μg/ml of miconazole. The CFUs increased slightly or were unchanged for 6 to 8 hr and then fell to a nadir of 2×10^2 to 10^4 CFU/ml by the end of the experiment.

MECHANISMS OF ACTION Relatively few studies on the mechanism(s) of action of miconazole have been reported. Morphologic evidence of effects on *C. albicans* was found by (*a*) transmission electron microscopy [injury to the cell wall, plasmalemma, and cytoplasmic organelles was clear at a concentration of 4.16 μg/ml (125)] and (*b*) scanning electron microscopy [roughened cell surfaces and altered budding sites at concentrations as low as 0.042 μg/ml (126)].

Adverse effects on the respiration and the permeability of *Candida* spp. were demonstrated at concentrations of miconazole $\geq$10 μg/ml (127). In another study with *C. albicans* (128), lower, actually subinhibitory, concentrations of miconazole (e.g. 0.004 μg/ml) interfered with the uptake of orotic acid, adenine, guanine, and hypoxanthine, increased the uptake of the corresponding purine nucleosides, and had no effect on the transport of glucose, glycine, or leucine.

The relevance of these studies (125–128) is difficult to assess because (*a*) most, if not all, of the work was carried out in culture mediums that antagonize miconazole; (*b*) the concentrations of miconazole required to achieve an observable effect sometimes exceeded the limits of clinical practicality (peak concentrations in the serum around 5 μg/ml); and (*c*) the miconazole was dissolved in organic solvents, whereas an aqueous suspension is used in therapy.

Clinical Pharmacology

ROUTES OF ADMINISTRATION Miconazole is used locally by topical application, and systemically by intravenous and intrathecal injection.

PREPARATIONS Only two preparations, both for topical use, are licensed for sale in the United States: 2% miconazole nitrate cream, and 2% miconazole nitrate lotion. Tablets, containing 0.250 g miconazole, have been used experimentally in topical oropharyngeal therapy.

The preparation for parenteral injection is also an investigational drug. It is an aqueous suspension which is stabilized by Cremophor El®—polyethoxylated castor oil (a mixture of ricinoleic acid polyglycol ester, glycerol polyglycol ethers, and polyglycols). Each milliliter of the presently used colorless, colloidal suspension contains miconazole, 10 mg; Cremophor EL, 0.115 ml; methylparaben, 1.62 mg; propylparaben, 1.18 mg. Prior to mid-1975, the composition was miconazole, 8.7 mg; Cremophor EL, 0.1 ml; sodium bisulfite, 0.5 mg; acetic acid, 0.004 ml; sodium acetate trihydrate, 0.4 mg; methylparaben, 1.62 mg; propylparaben, 0.18 mg.

DOSAGE

Topical Miconazole cream is applied to areas of dermatophytosis, cutaneous candidosis, and onychomycosis twice daily for periods as long as four to six weeks (129–136). For vaginal candidosis, 5–6 g of miconazole cream is inserted intravaginally once daily for 14 days (137–143).

Oropharyngeal candidosis may be treated four times each day by allowing a tablet to dissolve in the mouth before swallowing; the treatment is continued for at least two days after oropharyngeal lesions have disappeared (144).

Systemic Clinical experience with systemic use of miconazole is limited, and there is as yet no general agreement as to dosage. The author has used 25 mg/kg body weight per day injected intravenously as two equal portions, every 12 hours (122, 123). The drug was diluted in 5% glucose solution for injection to give a final concentration of 2.0–2.5 mg/ml, and each dose was delivered over a period of 1 hr. The peak/valley concentrations in the serum (specimens obtained about 15 min and 11.5 hr after a dose, respectively) were 5.0–13.4 μg/ml and 0.3–0.8 μg/ml.

Other workers have reported that (*a*) doses $\geqslant$9 mg/kg of body weight generally produce peak concentrations $\geqslant$1.0 μg/ml of serum regardless of 6 or 8 hr dosage interval (119) and (*b*) doses of 800 mg injected every 8 hours yielded peak/valley concentrations of 7.5 and 0.4 μg/ml of serum (145).

Because renal dysfunction has no effect on the concentrations attained in the blood and does not influence the rate of disappearance of the drug from the blood (122, 123, 146, 147), the dose need not be altered when there is renal failure. Hemodialysis does not remove significant quantities of miconazole (146, 147).

Miconazole has been injected intrathecally into the lumbar subarachnoid space in doses as high as 20 mg, and into the cervical and cisternal subarachnoid spaces and lateral ventricles in doses as high as 15 mg (145). As the suspension of miconazole is hyperbaric, patients should be placed in a head down position after lumbar injection. Intrathecal injections have been given at three- to seven-day intervals.

DISTRIBUTION When ^{3}H-labeled miconazole was used, there was virtually no absorption after topical application to the skin or in the vagina (148). About 27% of an orally administered dose of miconazole was absorbed (147).

After intravenous injection, the half-life of miconazole in the blood was 24 to 25 hr (146); essentially no antifungally active drug appeared in the urine (122, 123,

146–148). There was meager entry into the cerebrospinal fluid with concentrations ranging from 0.10–0.27 μg/ml (119, 122, 123, 145). The drug penetrated into pus and synovial fluid [achieving respective concentrations which were about 50% and 25% of those in concurrently obtained serums (123)], but not into sputum (119).

Following lumbar subarachnoid injection of 20 mg of miconazole in a patient with coccidioidal meningitis, the concentration in cerebrospinal fluid obtained from the cisternal space fell from 6.5 to 0.24 μg/ml over a period of 72 hr (145).

ELIMINATION Catabolism of miconazole probably occurs in the liver, without augmentation of catabolic capacity as treatment is continued (122, 123). Several metabolites of miconazole, e.g. 2,4-dichloromandelic acid and 2-[(2,4-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)-acetic acid appear in the urine and account for 10–14% of the dose (146, 148). About 12% of the dose is excreted in the feces as an antifungally active drug (146).

Adverse Reactions

Burning, itching, and irritation occur uncommonly after topical application of miconazole.

Intravenous administration of miconazole has been associated with giddiness, light-headedness, abnormalities of vision, itching, arthralgias, nausea, and vomiting during, and in the hour after, infusion, whereas skin rash, hyperlipidemia, aggregation of erythrocytes and rouleaux formation, anemia, thrombocytosis, and thrombophlebitis are adverse reactions that may persist for several days (119, 122, 123, 145, 149–152). The transient reactions are clearly dose dependent and may be diminished to some extent by premedication with an antihistamine. Thrombophlebitis occurred in almost every patient when the original preparation for parenteral use was injected into relatively small peripheral veins as solutions containing $\geqslant$ 2.5 mg of miconazole/ml. The newer preparation appears to be less irritating; also, injection via a central vein avoids thrombophlebitis (119, 145). Hyperlipidemia, as manifested by elevations of the concentrations of cholesterol, triglycerides, and lipoproteins, disappears over a period of months after treatment with miconazole is discontinued; its occurrence has been attributed to the colloid stabilizer, Cremophor EL (151, 152). In association with the hyperlipidemia (152), erythrocyte aggregation with rouleaux formation and poor adherence of blood to glass may prevent preparation of smears suitable for microscopic examination.

Intrathecal injection of miconazole may engender arachnoiditis (145).

Therapeutic Uses

TOPICAL Dermatomycosis, onychomycosis, cutaneous candidosis, and candidal vulvovaginitis respond satisfactorily to topical treatment with miconazole (129–143). Oropharyngeal candidosis may also be benefited (144).

INTRAVENOUS It would appear that systemic mycoses might respond to treatment with miconazole given intravenously if the causative fungi are susceptible and neither the central nervous system, eye, nor the urinary tract is involved. Only a few

patients with candidosis, cryptococcosis, sporothricosis, aspergillosis, histoplasmosis, or parococcidioidomycosis have been treated with miconazole (149, 152–155). Many more patients with coccidioidomycosis have received the drug. Initial results appeared to be favorable (119, 122, 145); however, with additional experience and the long-term follow-up which is essential to evaluation of therapy in coccidioidomycosis (123, 156) there is considerable doubt that the course of disseminated disease is favorably influenced.

Indeed, therapeutic failures should not be unexpected. Miconazole is primarily fungistatic—particularly at the concentrations attainable in patients with doses that are safe. The limitation of fungistasis is important because so many patients with systemic mycoses have coexisting, predisposing immunodeficiencies and/or other inadequacies of host defenses.

INTRATHECAL Too few patients have been treated with miconazole given by intrathecal injection to allow evaluation of therapy by this route.

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