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Clinical Pharmacokinetics of Systemic Antifungal Drugs

T.K. Daneshmend and D.W. Warnock

Clinical Pharmacology Unit, University Department of Medicine, and Department of Microbiology, Bristol Royal Infirmary, Bristol

Summary

The currently available drugs for the treatment of systemic fungal infections are amphotericin B, flucytosine, miconazole and ketoconazole.

Amphotericin B has to be given intravenously in the treatment of deep mycoses. The dose is gradually increased following a small initial dose, though this may delay the attainment of therapeutic concentrations. Amphotericin B serum concentrations are proportional to dose but only up to doses of 50mg. The serum pharmacokinetics fit a 3-compartment model, while cerebrospinal fluid pharmacokinetics fit a 2-compartment model. The precise identities of these compartments have not been determined. In the serum there is a relatively rapid initial half-life of 1 to 2 days, and a slower elimination phase of 15 days. Amphotericin B penetrates poorly into other body tissues, and concentrations are usually well below those in serum. This may partly be due to its high protein binding. The routes of amphotericin B elimination in man are unknown. Amphotericin B invariably causes dose-related renal damage, but this does not markedly alter its pharmacokinetics; mannitol infusions do not reduce this nephrotoxicity. Concurrent gentamicin administration and sodium depletion may enhance amphotericin B nephrotoxicity.

Flucytosine may be given orally or intravenously. It has a high (greater than 80%) oral bioavailability, but this is lower in patients with renal failure. Flucytosine absorption is delayed in renal failure and by antacids. The serum pharmacokinetics fit a 1-compartment model, and the apparent volume of distribution approximates to body water. Flucytosine has low protein binding and good tissue penetration. There is minimal metabolism in man; conversion to 5-fluorouracil may be the basis of flucytosine toxicity. Since flucytosine is largely eliminated by renal excretion, serum concentrations are markedly increased in the presence of renal impairment. The renal clearance of flucytosine closely parallels creatinine clearance, and in renal failure the half-life is considerably prolonged. Toxicity can be avoided by therapeutic monitoring of serum concentrations and reducing the dose when renal function is impaired.

Miconazole is poorly absorbed from the gut; therefore intravenous administration is required for treatment of systemic fungal infections. Its serum pharmacokinetics fit a 3-compartment model with a short initial half-life of less than 1 hour, an intermediate half-life of 2 hours, and a terminal half-life of 20 hours. Despite this long terminal half-life, miconazole has to be given every 8 hours. It has a high apparent volume of distribution and is highly bound to plasma proteins. Adequate penetration only occurs into certain body tissues. Pen-

etration into cerebrospinal fluid is poor and intrathecal injection may be required. Miconazole is oxidised in man and the inactive metabolites are excreted mainly in urine. Serum concentrations of miconazole are higher in renal failure, but dosage adjustment is rarely necessary. Miconazole toxicity is not related to pharmacokinetics, and the need for therapeutic monitoring of serum concentrations is unclear. Miconazole enhances the anticoagulant effect of warfarin.

Ketoconazole is well absorbed from the gut. Food has been reported to both enhance and reduce ketoconazole absorption. Absorption is decreased in renal failure and when gastric acidity is reduced. Its pharmacokinetics fit a 2-compartment model. The initial half-life is between 1 and 4 hours and the terminal half-life ranges between 6 and 10 hours; both elimination phases are dose-dependent. Ketoconazole is almost completely protein bound, and penetration into body tissues is variable. It is extensively metabolised, mainly by oxidation, to metabolites without antifungal activity which are excreted in urine and faeces. Renal and hepatic disease do not appear to affect ketoconazole kinetics. Therapeutic failure is associated with low serum concentrations of the drug, therefore therapeutic monitoring is of use in such patients. Cimetidine, and presumably other H_2-receptor antagonists, reduce ketoconazole serum concentrations by reducing absorption.

Antifungal drugs fall into three major groups. The first of these groups, the *polyene* antifungals, includes amphotericin B, natamycin and nystatin. These 3 agents are all effective topically for the treatment of superficial forms of candidiasis, but amphotericin B is the only member of this group which can also be given intravenously, and despite its many side effects remains the most important drug in managing the majority of systemic fungal infections. *Flucytosine* is a synthetic nucleotide analogue and the sole member of the second important group of antifungal drugs. It has a limited antifungal spectrum, but is useful in the management of certain patients with systemic candidiasis and cryptococcosis. Flucytosine is ineffective against most infections caused by filamentous fungi and another disadvantage is the emergence of resistant strains if it is used alone.

The third group of major antifungals is the *imidazoles*. Five imidazole derivatives are currently available for topical use: clotrimazole, miconazole, econazole, isoconazole and tioconazole. Of these, miconazole is also available as an intravenous preparation; it is better tolerated than amphotericin B, but thrombophlebitis is a significant problem. These imidazoles are poorly absorbed from the gut. With oral administration of miconazole therapeutic concentrations are difficult to attain without the use of large doses which cause gastric side effects. Clotrimazole induces its own metabolism and serum concentrations are barely detectable after a few days of oral therapy. However, a newer imidazole, ketoconazole, is active systemically after oral administration.

Certain other agents have been useful for specific fungal infections, e.g. griseofulvin, which has a spectrum limited to the agents of dermatophytosis. It is absorbed from the gut and concentrated in the outer stratum corneum.

The currently available drugs useful in the treatment of systemic fungal infections (so-called 'deep mycoses') are: amphotericin B, flucytosine, miconazole and ketoconazole. The pharmacokinetic characteristics of these drugs are the subject of the present review. Their pharmacology and therapeutic use have been reviewed by Bennett (1974), Cartwright (1978), Hoeprich (1978), Meade (1979), Sarosi et al. (1979), Heel et al. (1980), Medoff and

Kobayashi (1980), Stranz (1980), Bell (1981), Heel et al. (1982), Levine (1982), and Utz (1982). One review has dealt specifically with the complications of amphotericin B therapy (Maddux and Barriere, 1980). Potential future agents have been discussed by Ryley et al. (1981), and two recent monographs, one on antifungal chemotherapy in general (Speller, 1980) and the other on fungal infection in the compromised patient (Warnock and Richardson, 1982), deal with the clinical and laboratory aspects of treating fungal disease.

1. Amphotericin B

1.1 Physicochemical Properties and Activity

Amphotericin A and B are produced together during fermentation of *Streptomyces nodosus*, but only amphotericin B is used clinically. It is a polyene antibiotic containing both hydrophilic and lipophilic sites. Amphotericin B is not soluble in water and is also unstable. Its antifungal activity is greatest between pH 6.0 and 7.5, and diminishes as the pH falls.

Amphotericin B is active against most fungi pathogenic in man, including *Blastomyces dermatitidis, Candida* species, *Coccidioides immitis, Cryptococcus neoformans, Histoplasma capsulatum* and *Sporothrix schenckii. Aspergillus* species are the most frequently resistant fungi while the Mucorales show variable resistance. Apart from these exceptions however, resistant strains are seldom encountered among fungi susceptible to the drug. Amphotericin B acts by binding irreversibly to the sterol component of the fungal cell membrane. This causes deterioration in cell membrane function and ultimately leads to cell death.

Amphotericin B is available as a topical cream and ointment, pessaries, lozenges, oral suspension and tablets, and as a powder for intravenous use. The latter is formulated in vials containing 50mg amphotericin B, sodium phosphate buffer, and sodium desoxycholate (41mg), a bile salt which helps solubilise amphotericin B by forming a colloidal dispersion.

1.2 Absorption

Amphotericin B is poorly absorbed following oral administration. Serum amphotericin B concentrations were only 0.04 to 0.5 mg/L in 13 patients given oral doses of 1.6 to 5g per day for 2 days. In some of these patients oral administration produced extremely low and often undetectable amphotericin B concentrations in cerebrospinal fluid (CSF) [Louria, 1958]. The non-absorbability of amphotericin B from the gut and consequent absence of systemic side effects make it a suitable agent for the treatment of oral and gastrointestinal fungal infections.

In animals, absorption from intramuscular sites of administration is also poor. Amphotericin B is extremely irritant when injected into muscle and this route should not be used in man. Consequently, it needs to be given intravenously for the treatment of systemic fungal infections, but when given by this route it invariably causes side effects. These may be minimised by initially giving small doses which are then increased over 3 to 5 days.

1.3 Serum Concentrations after Intravenous Administration

In 15 patients without previous renal disease, intravenous doses of 5 to 70mg daily produced serum concentrations between 0.14 and 2.39 mg/L 4 hours after the start of the infusion (Bindschadler and Bennett, 1969). In the same study, alternate-day doses of 25 to 105mg gave serum concentrations between 1.00 and 2.40 mg/L at the end of the 4-hour infusion. In comparison with daily administration, alternate-day therapy with double the daily dose gave higher peak concentrations, but minimum serum concentrations of am-

photericin B were not significantly different with the 2 regimens (Bindschadler and Bennett, 1969). Also in this study, there was a proportionality between dose and serum levels at doses between 5 and 50mg, but at higher doses this relationship was lost. Peak concentrations tended to plateau at doses above 50mg (Bindschadler and Bennett, 1969).

In 20 patients given repeated 50mg intravenous doses of amphotericin B, mean serum concentrations were 1.21, 0.62 and 0.32 mg/L after 1, 18 and 42 hours from the end of the infusion (Fields et al., 1970). Detectable levels of the drug were still present at 7 weeks but not at 13 weeks after the end of treatment (Fields et al., 1970).

Amphotericin B is usually given as a slow intravenous infusion over 4 to 6 hours. Fields et al. (1971) have examined the effects of rapid infusion in 3 patients. The mean serum concentration was 2.02 mg/L 1 hour after rapid (45 minute) infusion of a 50mg dose, and 1.18 mg/L 1 hour after a slow (5 hour) infusion of the same dose. However, mean serum concentrations at 18 and 42 hours post-infusion were not significantly different after rapid and slow infusion. It was therefore suggested that rapid infusion may be more effective (and possibly without any more side effects) than slow infusion in seriously ill patients, although this has not yet been confirmed clinically.

The usual method of starting amphotericin B treatment, i.e. beginning with a small dose, leads to a delay in achieving therapeutic levels. On the basis of a pharmacokinetic model, daily doses of 1, 5, 10 and 50mg given on days 1, 2, 3 and 4 respectively, would result in therapeutic amphotericin B concentrations (between 0.2 and 0.5 mg/L) on day 4, and these would be maintained for about 10 hours (Atkinson and Bennett, 1978). Using the same model, an alternative regimen of 25mg on days 1 and 2, and 30mg on day 3 would result in therapeutic concentrations on day 1 which would be maintained from day 2 (Atkinson and Bennett, 1978). The latter regimen has therefore been recommended for seriously ill patients, although it should be pointed out the pharmacokinetic model used was based on data derived from a single patient.

1.4 Distribution

The apparent volume of distribution of amphotericin B in man is about 4 L/kg (Atkinson and Bennett, 1978). Detailed pharmacokinetic data from 2 patients suggest a 3-compartment model: a central compartment and 2 peripheral compartments, 1 fast and 1 slow. The volumes of the central and the fast and slow peripheral compartments are 0.44, 0.35 and 3.20 L/kg, respectively (Atkinson and Bennett, 1978). The central compartment probably represents blood volume but the identity of the peripheral compartments has not yet been determined.

Amphotericin B concentrations in body fluids other than serum are generally quite low. Urine contains only 3% of a dose given 24 hours earlier. Samples of peritoneal, pleural and synovial fluid usually contain less than half the simultaneous concentration in serum (Polak, 1979). In a patient with Candida peritonitis, the amphotericin B concentration in peritoneal fluid ranged between 0.44 and 0.78 mg/L, while the simultaneous serum concentrations were 0.52 and 1.5 mg/L (Peterson et al., 1978). Higher concentrations may be achieved in peritoneal fluid by giving amphotericin B intraperitoneally (Bayer et al., 1976).

Penetration of amphotericin B into bronchial secretions is poor. In the dog, an intravenous dose of 1.2 mg/kg bodyweight produced a serum concentration of 1.36 mg/L and a concentration in bronchial secretions of 0.16 mg/L just after the infusion, but subsequent bronchial specimens were less than 0.1 mg/L (Pennington et al., 1974).

In non-human primates, 24 hours after intravenous administration of tritiated amphotericin B the highest concentrations were found in the kidney, followed by the liver, spleen, adrenal glands, lung, thyroid, heart, skeletal muscle, pancreas, brain and bone in decreasing order. In these animals poor

penetration was noted into the cerebrospinal fluid (CSF), eye and urine (Hoeprich, 1978). However, in rabbits with experimental uveitis, good penetration into the aqueous humour has been noted (Green et al., 1965).

1.4.1 Cerebrospinal Fluid Concentrations

In man, CSF concentrations of amphotericin B are usually only 2 to 4% of the serum concentration following intravenous administration. Therefore patients with fungal meningitis may require intrathecal administration of amphotericin B, which may be facilitated by the use of a subcutaneous reservoir (Diamond and Bennett, 1973). A 2-compartment model has been used to describe the pharmacokinetics of amphotericin B in the CSF following intrathecal administration (Atkinson and Bindschadler, 1969). Since the CSF half-life of amphotericin B increases following repeated administration, it is thought to accumulate in the second compartment whose site is unknown (Atkinson and Bindschadler, 1969).

1.4.2 Protein Binding

Amphotericin B is highly protein bound in serum, mainly to β-lipoproteins (Bindschadler and Bennett, 1969). At serum concentrations of 0.75 and 1.60 mg/L the mean protein binding was 91 and 95% respectively (Block et al., 1974). This in part accounts for the poor penetration of amphotericin B into other body compartments and also its poor dialysability (Block et al., 1974).

1.5 Elimination

The metabolic fate of amphotericin B in man is unknown and no metabolites have been identified. Animal data are also sparse. In rhesus monkeys, high concentrations of amphotericin B have been noted in bile following intravenous administration (Lawrence et al., 1980). In dogs, serum amphotericin B concentrations were about 20% higher during periods of biliary obstruction (Craven et al., 1979). Metabolites were not identified in either study. It is possible that amphotericin B does not undergo metabolism, but is stored in various body tissues for prolonged periods.

The routes of elimination of amphotericin B in man are also unknown. Although only 3% of an administered dose appears in the urine after 24 hours (Atkinson and Bennett, 1978; Louria, 1958), a greater percentage can be accounted for in the urine after prolonged monitoring (Atkinson and Bennett, 1978). In animals, combined biliary and renal excretion accounted for less than half the dose administered (Craven et al., 1979; Lawrence et al., 1980). The fate of the rest is unknown. This may partly be due to limitations of assay methods, such that very low concentrations of amphotericin B excreted over a prolonged period may be undetectable.

In man, the total clearance of amphotericin B is low; values of 24.0 and 36.1 ml/min were noted in 2 patients (Atkinson and Bennett, 1978).

Half-life: Amphotericin B has a comparatively rapid initial serum half-life of about 24 to 48 hours, followed by a second elimination phase with a half-life of about 15 days (Atkinson and Bennett, 1978). Consequently, steady-state serum levels may not be achieved for some months after starting amphotericin B. In rhesus monkeys, a terminal elimination half-life of over 11 days had previously been noted by Jagdis et al. (1977).

1.6 Pharmacokinetics in Renal and Hepatic Disease

Amphotericin B almost invariably causes deterioration in renal function; however, this does not alter its pharmacokinetics. Therefore, amphotericin B dosage does not require alteration in patients with renal dysfunction (Bindschadler and Bennett, 1969; Block et al., 1974; Feldman et al., 1973). Pre-existing renal disease does not alter peak and trough amphotericin B levels (Bindschadler and Bennett, 1969), though it may be prudent to employ some-

what reduced dosages in such patients to reduce the extent of further renal damage. A correlation was, however, noted in 14 patients between serum creatinine and peak serum amphotericin B concentrations, but not trough levels (Bindschadler and Bennett, 1969).

Renal disease has a variable but modest effect on the renal excretion of amphotericin B (Bindschadler and Bennett, 1969). Amphotericin B behaves as a colloid in aqueous solution and is poorly dialysable. Its poor dialysability and high protein binding result in only negligible amounts being cleared by haemodialysis: in 4 patients amphotericin B clearance was between 3 and 5% of the simultaneous creatinine clearance (Block et al., 1974). There was no evidence of accumulation of the drug in an anephric patient given a total dose of 180mg over 16 days (Feldman et al., 1973). However, because of the long terminal half-life of amphotericin B, the effect of renal disease on steady-state levels may only be apparent after several months of therapy.

The effects of liver disease on amphotericin B pharmacokinetics are unknown. Ligation of the bile duct produces some increase in serum amphotericin B concentrations in animals (Craven et al., 1979), though such a change in patients with biliary obstruction has not been reported.

1.7 Amphotericin B Pharmacokinetics and Toxicity

The renal toxicity of amphotericin B is related to the total dose of the drug rather than to any specific pharmacokinetic parameter. In treatment, the total dose of amphotericin B and therefore its renal toxicity may be reduced by the concurrent administration of flucytosine (Bennett et al., 1979).

A normochromic normocytic anaemia almost always occurs in patients on prolonged amphotericin B treatment. It is possible that amphotericin B depresses the bone marrow directly or causes anaemia secondary to its renal damage. Amphotericin B-induced depression of erythropoietin production is the probable mechanism of the anaemia, though the relationship between drug kinetics and anaemia was not examined (MacGregor et al., 1978).

1.8 Therapeutic Monitoring

A number of microbiological methods for amphotericin B estimation in serum, CSF and other body fluids are available (Bannatyne et al., 1977; Bindschadler and Bennett, 1969; Cosgrove and Fairbrother, 1977; Gale, 1974; Green et al., 1965; Shadomy et al., 1969). These are time consuming and interference from other drugs is a problem. Freezing of the serum samples produces variable discrepancies in assay results (Bannatyne and Cheung, 1977). Assay by a radiometric method may be less time consuming (Hopfer and Groschel, 1977). A more rapid, specific and sensitive high performance liquid chromatographic (HPLC) method therefore offers considerable advantages (Nilsson-Ehle et al., 1977).

Therapeutic monitoring of amphotericin B serum and CSF concentrations is of limited clinical value. Optimum serum concentrations for specific fungal infections are not known. In addition, it is not clear in which pharmacokinetic compartment amphotericin B concentrations are crucial (Atkinson and Bennett, 1978). A 1-hour post-infusion serum concentration of twice the minimum inhibitory concentration of fungal isolates is thought desirable (Drutz et al., 1968).

1.9 Drug Interactions

Amphotericin B is a comparatively unstable compound but the precaution of protecting the infusion from light appears unnecessary (Block and Bennett, 1973). The drug is stable in 5% dextrose in water with or without added heparin or hydrocortisone sodium phosphate (Block and Bennett,

1973; Gotz et al., 1981; Jurgens et al., 1981). Parenteral amphotericin B preparations contain phosphate buffer which is incompatible with calcium-containing intravenous solutions, and the drug is also precipitated by other electrolyte solutions (Jurgens et al., 1981).

Antagonism between amphotericin B and miconazole has been recorded clinically (Schacter et al., 1976) and confirmed experimentally (Cosgrove et al., 1978). Possible antagonism between ketoconazole and amphotericin B has also been suspected (Brass et al., 1980), though not confirmed experimentally (Odds, 1983).

The combination of amphotericin B and gentamicin may produce synergistic nephrotoxicity. Churchill and Seely (1977) reported 4 patients with leukaemia who developed such an interaction. Within a few days the serum creatinine rose very sharply. Two of the patients died and autopsy showed renal tubular necrosis in both.

Amphotericin B causes hypokalaemia and this effect is potentiated by corticosteroids. Combined administration of these drugs may also result in reversible cardiac enlargement (Chung and Koenig, 1971). The hypokalaemia also potentiates digoxin toxicity (Cushard et al., 1969; Miller and Bates, 1969) and may cause rhabdomyolysis (Drutz et al., 1970). Hypokalaemia is the basis of an interaction between amphotericin B and skeletal muscle relaxants, resulting in enhancement of the effect of non-depolarising (curariform) drugs. Sodium depletion was noted to enhance the nephrotoxicity of amphotericin B in 2 patients (Feely et al., 1981).

Mannitol infusions have been given to patients receiving amphotericin B in the hope of reducing nephrotoxicity (Olivero et al., 1975; Rosch et al., 1976). However, this was not confirmed by a clinical trial; indeed there was some suggestion that mannitol contributed to amphotericin B-induced renal vascular pathology (Bullock et al., 1976). More recently, studies in dogs showed antagonism of amphotericin B-induced renal damage by dopamine and saralasin (Reiner and Thompson, 1979).

2. Flucytosine

2.1 Physicochemical Properties and Activity

Flucytosine (5-fluorocytosine; 5-FC) is a synthetic fluorinated pyrimidine, similar to fluorouracil, and was initially developed for use in cancer chemotherapy. It is slightly soluble in water and readily soluble in alcohol. Flucytosine has a narrow spectrum of activity limited to *Cr. neoformans, Candida* species and *Cladosporium* species. There is marked variability in sensitivity of different isolates, especially *Candida* species of which half may be resistant. Resistance to flucytosine may develop during therapy for cryptococcosis and for candidiasis (Scholer, 1980). For this reason flucytosine is seldom given alone, but rather in combination with amphotericin B. However, as it attains high concentrations in the urine, flucytosine may be useful when given alone in the treatment of lower urinary tract candidiasis, provided the infecting strain remains sensitive.

Flucytosine enters the fungal cell, a process aided by cytosine permease, and in the cytoplasm is incorporated into RNA after deamination to 5-fluorouracil and undergoing phosphorylation. This interferes with the normal synthesis in the fungal cell. Cellular protein synthesis may also be interrupted by the direct inhibition of DNA synthesis by flucytosine metabolites. The selective action of flucytosine on fungi depends upon the host's cells not converting flucytosine to 5-fluorouracil.

Flucytosine is available as oral tablets and as an infusion for intravenous use.

2.2 Absorption

Flucytosine is rapidly and completely absorbed after oral administration in normal (healthy) adults (Cutler et al., 1978; Dawborn et al., 1973; Koechlin et al., 1966; Schonebeck et al., 1973). Food and encapsulation of the dosage form delay but do not

Table I. Summary of studies reporting pharmacokinetic parameters of flucytosine. Data are given as mean or mean ± SEM. Range is given in parentheses

Reference	Assay	Subjects			Diagnosis	Dose (mg)	Route	Half-life (h)	Apparent volume of distribution (L/kg)	Plasma clearance (ml/min)	Urinary recovery (%)	Bio-availability (%)
		no.	sex	age (y)								
Koechlin et al. (1966)	Radio-labelled flucytosine	2	F	57	Hypertension; diabetes mellitus	2000	Oral	4.9 and 8.2				
Wade and Sudlow (1972)	Spectro-fluoro-metric	8	7M/1F	19-48	Normal	930-2000	Intra-venous	3.9 ± 0.4 (2.7-6.0)	0.78 ± 0.05 (0.67-0.97)	166 ± 16 (109-235)	76-107 (in 48h)	
Dawborn et al. (1973)	Bioassay	5			Normal	2000	Oral	5.6 ± 0.6 (4.2-6.7)	0.60 ± 0.02 (0.53-0.67)	106 ± 4.6 (83-117)	63-84 (in 24h)	
		12			Renal failure	2000	Oral	93.8 ± 57 (13.7- > 100)	0.56 ± 0.03 (0.43-0.66)	16.2 ± 2.8 (< 1.0-29)		
Schonebeck et al. (1973)	Bioassay	10	5M/5F	20-30	Normal	2000	Oral	2.89 (2.36-3.99)	0.88 ± 0.29 (mean for normals and patients)			
		39	32M/ 7F	19-88	Varying renal failure *Serum creatinine (mg/dl):*							
		13			1-2	2000	Oral	5.37 (2.80-7.98)			87 (in 24h) (6 patients)	
		8			22-4.5	2000	Oral	16.8 (8.99-37.7)				
		14			4.5-15.3	2000	Oral	38.6 (12.3-83.0)			18 (in 24h) (7 patients)	
		5			Nephrec-tomised	2000	Oral	85.0 (29.9-250)				

Cutler et al. (1978)	HPLC	4		Normal	500	Intra-venous	4.2 ± 0.3	0.68 ± 0.04	134 ± 7	99 ± 3 (in 48h)			
		5	4M/1F	18-40	Normal	500 (as solution)	Oral	3.1 ± 0.1	0.62 ± 0.04		88 ± 5 (in 48h)	83 ± 5	
						500 (as capsule)	Oral	3.4 ± 0.5	0.76 ± 0.11		81 ± 11 (in 48h)	87 ± 6	
						500 (as capsule + breakfast)	Oral	2.6 ± 0.85	0.46 ± 0.03		76 ± 9 (in 48h)	78 ± 2	
						500 (as capsule + antacid)[1]	Oral	3.5 ± 0.54	0.68 ± 0.09		82 ± 7 (in 48h)	89 ± 10	
		3	2M/1F		End-stage renal failure	500-1000	Oral and intra-venous	68-543	0.41-0.71	0.2-4			40-76
		6			Haemo-dialysis	500-1000	Intra-venous	28.5-430	0.55 ± 0.02	5.1 ± 1.6			

1 Aluminium hydroxide gel/magnesium hydroxide suspension.

decrease absorption. In normals, a single oral dose of 500mg resulted in peak serum concentrations of 11.2, 8.7 and 9 mg/L at 0.6, 1 and 1.5 hours when the dose was given as a solution, capsule and capsule with food, respectively (Cutler et al., 1978).

Absorption of flucytosine is also delayed in the presence of impaired renal function. In terminal renal failure, peak flucytosine concentrations of 48.0 ± 4.7 mg/L (mean ± SEM) occurred at 10 hours after a 2g oral dose (Dawborn et al., 1973). Following a 1g oral dose, peak concentrations between 22.6 and 31.7 mg/L were seen in patients on haemodialysis (Cutler et al., 1978). In a group of patients with mild to moderate renal insufficiency, peak flucytosine concentrations of 46.3 ± 7.2 mg/L and 37.8 ± 5.3 mg/L were noted following single oral doses of 1.5 and 2g, respectively (Block and Bennett, 1972). The lower peak concentrations at the higher dose level cannot be explained, especially as detailed information on time of sampling and degree of renal dysfunction is not available.

Flucytosine absorption is delayed by concomitant administration of aluminium hydroxide/magnesium hydroxide suspension in normals (Cutler et al., 1978). The rate of absorption may also be decreased by neomycin (Bruckner and Creasey, 1974). Lack of absorption of flucytosine is extremely unusual and has been documented in only a single patient with Sjögren's syndrome (Scholer, 1980).

The oral bioavailability of flucytosine is above 80% in normal subjects but lower in patients with renal failure (see table I).

2.3 Serum Concentrations after Oral Administration

Following an oral dose of 1.5g flucytosine, peak serum concentrations of 45.8 ± 7.1 mg/L were seen in patients with cryptococcal meningitis who had normal renal function (Block and Bennett, 1972). In normal adults, a single oral dose of 2g gave peak concentrations of 30 ± 2.8 mg/L at 2 hours (Daw-

born et al., 1973), while a similar dose in patients with cryptococcal meningitis resulted in peak concentrations of 48.5 ± 2.5 mg/L between 1 and 2 hours after administration (Block and Bennett, 1972).

Flucytosine serum concentrations are increased by renal insufficiency. In normal adults without renal dysfunction, single oral doses of 2g resulted in peak serum concentrations between 30 and 40 mg/L (Dawborn et al., 1973; Schonebeck et al., 1973; Wade and Sudlow, 1972), while a dose of 2g given 4 times per day to patients with cryptococcal meningitis and varying degrees of renal function resulted in steady-state serum concentrations between 50 and 120 mg/L (Block and Bennett, 1972). In patients with cryptococcosis and normal renal function (serum creatinine less than 120 μmol/L), repeated oral doses of 150 mg/kg bodyweight per day (given in divided doses 4 times per day) resulted in a mean flucytosine serum concentration of 78 mg/L between 1 and 2 hours after administration and this fell to 60 mg/L at 6 hours (Bennett et al., 1979). In comparison, the same dose of flucytosine given to patients with cryptococcosis and a serum creatinine between 120 and 160 μmol/L gave serum concentrations of 119 mg/L between 1 and 2 hours and 99 mg/L at 6 hours after administration (Bennett et al., 1979).

In a single patient, long term oral therapy with flucytosine 100 mg/kg bodyweight per day for 2 weeks produced serum concentrations between 20 and 35 mg/L 4 hours after administration. This increased to between 55 and 72 mg/L at a dose of 200 mg/kg bodyweight per day for 2 weeks, and then fell to between 30 and 42 mg/L when the dose was reduced to 150 mg/kg bodyweight per day for 5 months (Morison et al., 1974).

2.4 Distribution

The apparent volume of distribution of flucytosine approximates to body water (see table I). Flucytosine is only 4% bound to plasma proteins over serum concentrations between 2 and 55 mg/L (Block et al., 1974), though higher protein binding had previously been reported (Davies and Reeves, 1971). CSF concentrations of flucytosine are usually 75% of serum concentrations (Block and Bennett, 1972; Fass and Perkins, 1971; Shadomy, 1970); however, the range is wide (see table II).

Flucytosine penetrates well into the peritoneal cavity after oral or intravenous administration (Bennett, 1977; Drouhet et al., 1973) and also into inflamed joints (Levinson et al., 1974). In dogs, flucytosine concentrations in bronchial secretions were found to be 76% of serum concentrations 3 hours after an intravenous dose (Pennington et al., 1974). Saliva concentrations of flucytosine in man are half or less than half the serum level (Scholer, 1980). Penetration into the eye occurs, though there is little information on intraocular flucytosine concentrations in man.

The good penetration of flucytosine into most body tissues has been ascribed to its high water solubility, low molecular weight and low protein binding.

2.5 Elimination

2.5.1 Metabolism

Less than 1% of a dose of flucytosine is believed to be metabolised in man, though more occurs in other species (Scholer, 1980). This is thought to be deamination to 5-fluorouracil or dihydrofluorouracil (Koechlin et al., 1966; Polak et al., 1976). Using sensitive methods (gas chromatography-mass spectrometry), Diasio et al. (1978a) found 5-fluorouracil serum concentrations between 10 and 400 μg/L in normal volunteers after a 2g oral dose of flucytosine. Similarly, in patients with cryptococcal meningitis being treated with flucytosine and amphotericin B, 5-fluorouracil concentrations of between 2 and 3060 μg/L were found (Diasio et al., 1978a). Conversion of flucytosine to 5-fluorouracil may be one mechanism in the development of flucytosine-associated toxicity.

Table II. Summary of studies reporting flucytosine serum and cerebrospinal fluid concentrations

Reference	No. of patients	Diagnosis	Dose (mg/kg)	Sampling time after dose (h)	CSF conc. (mg/L) [mean and range]	Serum conc. (mg/L) [mean and range]	CSF/serum (%) [mean and range]
Shadomy (1970)	5; CSF from 3	Cryptococcal meningitis	100	3-4	14.8 (8.5-28)	16.8 (1.8-33.0)	88
	4; CSF from 3	Cryptococcal meningitis	150	3-4	27.8 (18.3-40)	43.9 (23-86)	63
Fass and Perkins (1971)	5	Cryptococcal meningitis	50-140	1-2	41.1 (17-62)	58.5 (23-101)	74 (33-100)
Block and Bennett (1972)	2	Cryptococcal meningitis	4 g/day (oral)		78.2 (43-123)	91 (88-94)	79 (69-89)

2.5.2 Excretion and Half-life

Flucytosine is principally eliminated by renal excretion and the plasma clearance of the drug very closely parallels creatinine clearance (Cutler et al., 1978; Dawborn et al., 1973; Schonebeck et al., 1973). The half-life of flucytosine is usually between 3 and 6 hours in adults with normal renal function (see table I). The half-life is only slightly prolonged in premature neonates (Drouhet et al., 1974).

The half-life of flucytosine increases as the plasma creatinine concentration rises, and flucytosine clearance decreases as creatinine clearance falls (see table I). This close relationship has been variously expressed as follows:

$$t_{1/2}\ (h) = [6.8 \times \text{plasma creatinine (mg/dl)}] - 2.7$$

(Dawborn et al., 1973)

$$t_{1/2}\ (\text{min}) = \frac{0.55 \times \text{bodyweight (kg)}}{\text{Creatinine clearance (L)}}$$

(Wade and Sudlow, 1972)

$$t_{1/2}\ (h) = [5.2 \times \text{plasma creatinine (mg/dl)}] + 0.4$$

(Cutler et al., 1978)

In view of its renal route of excretion, high flucytosine concentrations are present in urine (Cutler et al., 1978; Davies and Reeves, 1973; Dawborn et al., 1973; Holt and Newman, 1973; Speller, 1974). In a patient with urinary candidiasis a daily flucytosine dose of 2.5g gave urinary concentrations between 300 and 1500 mg/L, and in another patient a daily dose of 4g resulted in urinary concentrations varying between 50 and 660 mg/L (Davies and Reeves, 1971). In adults and children given oral flucytosine at dosages between 25 and 200 mg/kg bodyweight per day, the serum flucytosine concentrations ranged between 0.9 and 66 mg/L and urinary concentrations between 18 and 2000 mg/L (Holt and Newman, 1973). In 2 diabetic patients with urinary infection with *Torulopsis glabrata*, a daily flucytosine dose between 50 and 150 mg/kg bodyweight resulted in serum concentrations between 26 and 94 mg/L and urinary concentrations ranging from 900 mg/L to 5800 mg/L (Speller, 1974).

2.6 Pharmacokinetics in Renal and Hepatic Disease

As mentioned above, renal disease markedly influences flucytosine pharmacokinetics, resulting in a slower rate of absorption, prolongation of the

serum half-life and decreased clearance (Cutler et al., 1978; Dawborn et al., 1973; Schonebeck et al., 1973); details of these changes are given in table I. The apparent volume of distribution of flucytosine is not significantly altered by renal failure. Dosage adjustment is usually required in the presence of renal impairment and various recommendations have proved useful (Scholer, 1980; Schonebeck et al., 1973). Our current recommendations are shown in table III.

In patients undergoing haemodialysis, the clearance of flucytosine is similar to creatinine clearance (Block et al., 1974; Cutler et al., 1978) and increases linearly with blood flow through the dialyser (Block et al., 1974). The clearance of flucytosine by peritoneal dialysis is not as good as haemodialysis but equals creatinine clearance (Polak, 1979).

Liver disease in laboratory animals does not significantly alter the pharmacokinetics of intravenous flucytosine (Block, 1973). In man, the available data are limited to a single patient with biopsy proven cirrhosis and cryptococcal meningitis who achieved serum flucytosine concentrations after oral administration which were similar to patients without hepatic or renal disease (Block, 1973).

The effects, if any, of severe liver disease on flucytosine pharmacokinetics have not been determined.

Table III. Recommendations for flucytosine dosage in renal insufficiency

Creatinine clearance (ml/min)	Individual dose (mg/kg)	Dose interval (h)
>40[1]	(25–) 50	6
40-20	(25–) 50	12
20-10	(25–) 50	24
<10	50	>24[2]

1 Renal function is considered to be normal when creatinine clearance is greater than 40 to 50 ml/min or concentration of creatinine in serum is less than 180 mol/L; concentration of creatinine in serum is not reliable unless renal function is stable.

2 Dose interval must be based on serum drug concentration measurement at frequent intervals. Maximum concentration in serum must not exceed 80 mg/L.

2.7 Flucytosine Pharmacokinetics and Toxicity

Although gastrointestinal, hepatic and haematological side effects of flucytosine are uncommon (Scholer, 1980), there is some evidence to suggest that in certain patients these may be related to serum concentrations rather than to idiosyncracy (Kaufmann and Frame, 1977). Bone marrow toxicity is likely when serum flucytosine concentrations are 125 mg/L or more, and this is more likely in the presence of renal impairment (Kaufmann and Frame, 1977). The bone marrow depression is usually reversible following reduction of serum flucytosine concentrations; however, over 10 fatal instances of bone marrow suppression have been noted (Scholer, 1980). Conversion of flucytosine to 5-fluorouracil in man has been proposed as the mechanism of bone marrow toxicity (Diasio et al., 1978b). In one study (Bennett et al., 1979), flucytosine toxicity was associated with serum concentrations greater than 100 mg/L in 6 out of 7 patients. In the same study, 5 other patients had serum flucytosine concentrations greater than 100 mg/L but did not develop toxicity.

The relationship between gastrointestinal and hepatic side effects and serum concentrations is even less well established. Present evidence suggests that the likelihood of toxicity is reduced if serum flucytosine concentrations do not exceed 100 to 125 mg/L. This is well above the mean steady-state concentration range of 35 to 70 mg/L recommended for effective antifungal chemotherapy (Scholer, 1980).

2.8 Therapeutic Monitoring

Monitoring of serum concentrations is necessary in order to avoid toxicity (see above) or to adjust dosage in the face of changing renal function. A number of microbiological (bioassay) methods for the determination of flucytosine have been described (Schiavone et al., 1973; Schonebeck et al., 1973; Shadomy, 1969) and some can measure flucytosine in the presence of amphotericin B (Kaspar and Drutz, 1975; Kaufmann et al., 1976). Flucytosine has also been measured by spectrofluorometry (Wade and Sudlow, 1972) and gas-liquid chromatography (Harding et al., 1976; Wee and Anhalt, 1977). Greater precision and accuracy has been achieved by measuring flucytosine by HPLC (Blair et al., 1975; Bury et al., 1979; Diasio et al., 1978b; Minors et al., 1980; Warnock and Turner, 1981).

2.9 Flucytosine Drug Interactions

For the treatment of various systemic fungal diseases flucytosine is combined with amphotericin B to advantage (Bennett et al., 1979). However, amphotericin B invariably causes a deterioration in renal function thereby increasing flucytosine serum concentrations and half-life (see above). This is probably the most common important drug interaction with flucytosine, although any drug which impairs renal function will similarly cause flucytosine toxicity. Though 5-fluorouracil absorption may be diminished by oral neomycin (Bruckner and Creasey, 1974) there is little evidence to suggest that flucytosine is similarly affected.

As already mentioned, concomitant administration of aluminium hydroxide/magnesium hydroxide suspension delays flucytosine absorption (Cutler et al., 1978) but has little effect on its bioavailability. Flucytosine is competitively inhibited by cytarabine (cytosine arabinoside) [Cartwright, 1978] and should therefore not be used in patients receiving the latter drug.

3. Miconazole

3.1 Physicochemical Properties and Activity

Miconazole is a relatively stable synthetic imidazole derivative which is sparingly soluble in water, but readily soluble in most organic solvents. It has a broad spectrum of antifungal activity against most clinically important fungi causing systemic infection, including *Aspergillus* species, *Candida* species, *Co. immitis*, *Cr. neoformans*, and *Paracoccidioides brasiliensis*. It is also active against the agents of dermatophytosis. Its therapeutic efficacy in systemic fungal infections has been reviewed by Heel et al. (1980), Holt (1980) and Bennett and Remington (1982). The mechanism of action of miconazole is not fully understood, but probably involves an alteration in fungal cell wall permeability, or alteration of RNA and DNA metabolism, or an intracellular accumulation of peroxides which are toxic to the fungal cell.

Miconazole is available as a topical cream, lotion and tincture, oral gel, vaginal tablets and cream, oral tablets, and as ampoules for parenteral use (containing 200mg base in 20ml of solution which includes 10% of 'Cremophor EL' as solvent).

3.2 Absorption

Miconazole is poorly absorbed from the gastrointestinal tract after oral administration. Serum miconazole concentrations show wide interindividual variation and are generally too low to be therapeutic (Boelaert et al., 1976; Mannisto et al., 1983). Oral doses of 522 and 1000mg produced mean peak serum concentrations of 0.37 and 1.16 mg/L respectively, 2 to 4 hours after administration (Boelaert et al., 1976). Simultaneous oral and intravenous administration of 522mg in 4 healthy adults gave a mean oral bioavailability of 27% (Boelaert et al., 1976). The low oral bioavailability may be due to both incomplete absorption (Brug-

mans et al., 1972), and hepatic first-pass metabolism (Plempel, 1979).

Absorption from other body sites, e.g. skin, vagina and buccal mucosa, is negligible (Brugmans et al., 1972; Scheijgrond, 1978). Therefore, therapy of systemic fungal infection requires parenteral administration of miconazole, usually by intravenous infusion. The following sections deal largely with the pharmacokinetics of the intravenous preparation.

3.3 Serum Concentrations after Intravenous Administration

Intravenous infusion of 522mg to 4 normal adults, 4 patients with mild renal impairment, and 4 patients undergoing haemodialysis, resulted in mean concentrations 15 minutes after infusion of 6.18 (range 2.02-9.10), 21.85 (range 3.28-32.95), and 13.98 (range 2.36-31.78) mg/L, respectively. Mean concentrations 1 hour after the infusion were 1.90, 6.76 and 4.55 mg/L; after 4 hours the mean concentrations were 0.44, 0.90 and 0.77 mg/L in the above 3 groups, respectively (Boelaert et al., 1976; Lewi et al., 1976).

Data on serum miconazole concentrations in patients with fungal disease are limited. Miconazole given intravenously in doses of 85 to 300mg, 400 to 550mg, 600 to 800mg and 1000 to 1200mg resulted in mean serum concentrations of 0.8, 1.2, 2.6 and 2.2 mg/L, respectively, in the first hour after administration; these concentrations fell to 0.5, 0.4, 0.5 and 0.8 mg/L, respectively, between 1 and 4 hours after the infusion (Levine, 1977). Intravenous infusion of 12.5 to 50 mg/kg bodyweight produced miconazole serum levels 5 minutes post-infusion between 5.0 and 13.4 mg/L in 6 patients with coccidioidomycosis (Hoeprich et al., 1980).

In another study, Stevens et al. (1976) noted peak serum concentrations of 2.5 and 2.0 mg/L in 2 patients given 352 and 585 mg/m^2, respectively, by the intravenous route. Doubling the frequency of administration from 3 to 6 times per day without changing the total daily dose considerably reduced the peak concentrations from 2.35 and 3.70 in 2 patients to 1.56 and 1.08 mg/L, respectively. However, there was only minor elevation in the trough levels from 0.16 and 0.57 to 0.27 and 0.65 mg/L, respectively (Stevens et al., 1976). In 10 patients with systemic mycoses, maximum serum concentrations of 7.5, 7.5, 2.3 and 1.8 mg/L were noted 15 minutes after intravenous infusion of 1000, 800, 600 and 400mg of miconazole, respectively (Sung et al., 1977).

Information on serum levels in children is also sparse (Clarke et al., 1980; Sung et al., 1979). In 1 neonate with candidiasis and poor renal function, an intravenous dose of 6 mg/kg bodyweight resulted in serum levels of 0.65 and 0.18 mg/L at 2 and 6 hours post-infusion, respectively; reduction of the dose to 4 mg/kg body weight resulted in serum concentrations of 0.71 mg/L after 1 hour and 0.23 mg/L after 4 hours (Sung et al., 1979). In another neonate, an intravenous dose of 3.8 mg/kg bodyweight produced serum levels of 0.53 and 0.19 mg/L at 2 and 6 hours after administration. Increasing the dose to 6.9 mg/kg bodyweight resulted in a 2-hour concentration of 1.26 mg/L and a 6-hour concentration of 0.27 mg/L (Sung et al., 1979).

3.4 Distribution

The mean apparent volume of distribution of miconazole was 1474L in normals, 809L in patients with renal disease, and 1388L in patients undergoing haemodialysis (Lewi et al., 1976). The mean volumes of the central compartment were 105, 57 and 64.2L in the above 3 groups, respectively (Lewi et al., 1976). Similar pharmacokinetic data are not available from patients with systemic mycoses.

In man, miconazole appears to penetrate well into certain body tissues, while other sites achieve negligible tissue concentrations. In 3 patients with joint and bone coccidioidomycosis, peak miconazole concentrations in synovial fluid were 0.9, 0.5

and 1.35 mg/L with intravenous doses of 200, 600 and 1200mg, respectively. In 2 of these patients, trough synovial fluid concentrations of 0.32 and 0.60 mg/L were seen with doses of 600 and 800mg (Deresinski and Stevens, 1979). Currently, there is no information on penetration into bone and muscle.

Studies in rabbits showed good intraocular penetration of miconazole when the drug was given intravenously, or by subconjunctival or topical application (Foster and Stefanyszyn, 1979). Combined topical and subconjunctival miconazole has been successful in treating keratomycosis (Foster, 1981), but candidal endophthalmitis was treated successfully only after the intravenous dose of miconazole was doubled to 2400mg per day (Gallo et al., 1982).

3.4.1 Cerebospinal Fluid Concentrations

Penetration of miconazole into CSF is poor, concentrations less than half the simultaneous serum level being achieved after intravenous administration. Following an intravenous dose of 30 mg/kg bodyweight per day, serum levels were between less than 0.5 and 4.35 mg/L, but CSF levels were virtually undetectable (Fisher et al., 1978). In 1 patient without meningitis, an intravenous dose of 585 mg/m^2 produced a miconazole concentration in lumbar CSF of 0.1 mg/L, while the serum concentration was 2.0 mg/L (Stevens et al., 1976). In another patient in remission, a dose of 352 mg/m^2 resulted in a serum concentration of 2.5 mg/L, and lumbar and cisternal CSF concentrations of 0.27 and 0.4 mg/L, respectively. Sung et al. (1978) found concentrations of 0.1 to 0.3 mg/L about an hour after an intravenous infusion of 800mg in 12 patients. In comparison, intrathecal injection of 20mg of miconazole at the lumbar region gave cisternal CSF concentrations of 6.2, 2.4, 0.7 and 0.24 mg/L at 12, 24, 48 and 72 hours, respectively (Sung et al., 1977, 1978). This route of administration achieves higher concentrations which are maintained longer than those following intravenous administration. Cisternal administration has also been used but may cause fatal subarachnoid haemorrhage (Sung et al., 1977).

3.4.2 Protein Binding

Miconazole is largely bound to plasma proteins, particularly albumin. At serum concentrations between 10 and 100 mg/L, protein binding of 93.1% was found by equilibrium dialysis and 90.7% by ultrafiltration (Stevens et al., 1976). This in part explains the poor penetration of miconazole into CSF and other fluids such as sputum. No miconazole was detectable in the sputum of 1 patient despite peak serum concentrations of 6.7 and 4.5 mg/L on 2 occasions (Stevens et al., 1976).

3.5 Elimination

3.5.1 Metabolism

In man, miconazole is thought to be rapidly metabolised by hepatic microsomal enzymes (Brugmans et al., 1972). The major metabolite is produced by oxidative N-dealkylation, and a secondary metabolite is produced by oxidative O-dealkylation. Breakdown of the imidazole ring produces a number of lesser metabolites. None of the metabolites possess antifungal activity.

There are 2 major and 3 minor miconazole metabolites excreted in faeces, but only 2 major and 1 minor metabolite in urine (Brugmans et al., 1972). Miconazole metabolism is not altered by repeated administration (Brugmans et al., 1972) and the drug is probably not an inducer of hepatic microsomal enzymes.

3.5.2 Excretion

Miconazole is eliminated largely in the faeces and urine as inactive metabolites. Between 14 and 22% of an intravenous dose and 10% of an oral dose is excreted in the urine; however, only 1% of this is present as unchanged miconazole. About 50% of an oral dose can be recovered in faeces, a large amount being present as unchanged drug (Brugmans et al., 1972).

3.5.3 Half-life

Following an oral dose of 250mg after an overnight fast, the mean serum miconazole half-life in 10 subjects was 1.68 hours (Mannisto et al., 1983). An intravenous dose of 522mg in healthy adults and patients with renal impairment produced a triphasic elimination pattern with a rapid initial half-life of about 0.4 hours, an intermediate half-life of about 2.5 hours, and a terminal half-life of about 24 hours (Lewi et al., 1976). In patients with fungal diseases, Stevens et al. (1976) noted a biphasic decay in serum concentrations with initial and terminal elimination half-lives of 0.5 and 20 hours, respectively. Sung et al. (1977) also noted a rapid initial half-life of 1 hour and a much slower terminal half-life.

Despite its slow terminal half-life miconazole has to be given at least 3 times per day in order to achieve effective serum concentrations. However, it has been suggested that serum concentrations continuously in excess of the minimum inhibitory concentrations may not be needed to treat mycotic infections with miconazole (Symoens, 1977).

3.6 Pharmacokinetics in Renal and Hepatic Disease

Miconazole kinetics are unchanged in patients with end-stage renal failure undergoing haemodialysis when compared with normal adults (Lewi et al., 1976). However, a significantly smaller apparent volume of distribution of miconazole was found in patients with moderate renal insufficiency, and this resulted in higher serum concentrations of the drug (Lewi et al., 1976). Currently, there is no information on the pharmacokinetics of miconazole in patients with fungal and renal disease. Miconazole is not removed by haemodialysis.

The effects of liver disease on miconazole kinetics have not been examined, but in view of its degradation by hepatic microsomal enzymes and possible first-pass metabolism, liver disease would be expected to influence miconazole disposition pharmacokinetics.

3.7 Miconazole Pharmacokinetics and Toxicity

Phlebitis, pruritus, rashes, haematological complications and other toxic and adverse effects caused by intravenous miconazole are not dose-related and appear reversible on stopping the drug. The vehicle solution, 'Cremophor EL' (polyethoxylated castor oil), causes hyperlipidaemia (Bagnarello et al., 1977; Barr et al., 1978; Naito et al., 1980; Sung et al., 1978) but this is also not dose-related. It is possible that some of the adverse reactions seen with miconazole (Stevens, 1977), particularly cardiorespiratory toxicity (Fainstein and Bodey, 1980), are related to rapid intravenous infusion, but pharmacokinetic data have not been published in these reports. It is therefore unclear whether a relationship exists between the toxicity and the pharmacokinetics of miconazole.

3.8 Therapeutic Monitoring

Miconazole concentrations in serum and other body fluids may be determined by bioassay (Espinel-Ingroff et al., 1977; Odds and Macdonald, 1981), gas-liquid chromatography (Mannisto et al., 1983) or HPLC (Brodie et al., 1978; Turner and Warnock, 1982). However, the need for regular monitoring of serum miconazole concentrations during prolonged treatment is unclear. As noted above (section 3.5.3), it has been suggested that serum levels continuously in excess of the minimum inhibitory concentrations of the infecting fungal organism may not be necessary for successful therapy (Symoens, 1977), and it is unclear whether therapeutic failures with miconazole (Bennett and Remington, 1982; Fisher et al., 1978) are related to low serum concentrations of the drug. Also, the side effects of miconazole appear to be

unrelated to specific pharmacokinetic parameters; consequently, therapeutic monitoring would not be useful in this context.

3.9 Miconazole Drug Interactions

The antagonism between miconazole and amphotericin B (Schacter et al., 1976) has been referred to earlier, and the 2 drugs should not be given together. Miconazole may prolong prothrombin time in patients on warfarin and other coumarin anticoagulants, though the mechanism for this interaction is unclear (Deresinski et al., 1977; Vanbreuseghem, 1977; Watson et al., 1982).

4. Ketoconazole

4.1 Physicochemical Properties and Activity

Ketoconazole is a synthetic imidazole derivative structurally similar to earlier imidazoles such as miconazole and clotrimazole. It is a weak dibasic compound and almost insoluble in water except at a pH lower than 3. Despite this, it is active systemically when given by the oral route. Ketoconazole has a spectrum of antifungal activity similar to that of miconazole. The present status of ketoconazole as an antifungal drug has recently been reviewed (Heel et al., 1982; Levine, 1982). Its efficacy in treating systemic fungal infections in man is currently being evaluated.

At present, ketoconazole is available only as tablets (of 200mg).

4.2 Absorption

Ketoconazole is well absorbed after oral administration, producing peak serum concentrations after usual single doses which should be clinically useful against many fungi. Absorption may be decreased in some patients with markedly reduced stomach acidity. Mean peak ketoconazole concentrations of about 6.5, 4.5, 1.3 and less than 0.5 mg/L were noted after administration of 400mg cimetidine followed by 200mg ketoconazole in acidified solution, 200mg ketoconazole alone, 400mg cimetidine followed by 200mg ketoconazole, and 400mg cimetidine followed 2 hours later by 200mg ketoconazole with bicarbonate (van der Meer et al., 1980); these studies were performed after an overnight fast.

Food has been reported both to enhance and reduce absorption. In one study, serum concentrations were higher and more consistent at 1 and 2 hours after administration when ketoconazole 200mg was taken during a standard breakfast in 30 patients with onychomycosis (Gascoigne et al., 1981). In normal subjects given oral doses of 200mg and 400mg with breakfast, mean peak ketoconazole concentrations of 3.6 and 6.5 mg/L occurred at 2 and 2.5 hours after administration, respectively (Daneshmend et al., 1981). More recently, Brass et al. (1982) found a reduction in mean AUC when single doses of ketoconazole were taken with meals or with antacid (aluminium hydroxide/magnesium hydroxide), but these reductions were not significant when compared with the fasting state. However, Mannisto et al. (1983) found that breakfast significantly reduced the absorption of ketoconazole: the mean peak concentration was 4.1 mg/L in the fasting state and only reached 2.3 mg/L when the 200mg dose was taken after breakfast. Ingestion of ketoconazole with orange juice produced an intermediate mean peak concentration of 3.6 mg/L (Mannisto et al., 1983).

Daily administration of 200mg ketoconazole for up to 28 weeks resulted in relatively stable ketoconazole concentrations between 3 and 5 mg/L (Gascoigne et al., 1981). However, allogenic bone marrow transplant recipients showed a steady decline in serum ketoconazole concentrations after 2 weeks, and this was associated with therapeutic failure (Hann et al., 1982). This decline was ascribed to bone marrow transplant related impairment of gastrointestinal function.

4.3 Serum Concentrations after Oral Administration

In single-dose studies, serum ketoconazole concentrations 2 hours after a 200mg oral dose have been variously reported as follows: 1.54 to 3.12 mg/L in 56 patients (Negroni et al., 1980); 1.6 to 7.0 mg/L in 21 patients (Robertson et al., 1980); 2.5 mg/L in 10 patients, and less than 0.4 mg/L in 2 patients (Hay et al., 1980). Galimberti et al. (1980) noted a 2-hour serum concentration range of 1.56 to 3.12 mg/L in 75% of their patients, while the remainder had concentrations below 0.78 mg/L. After the first dose of 200mg ketoconazole, the 2-hour serum concentration was between 0.03 and 15 mg/L in 7 patients with systemic and deep mycoses; this changed to between 0.62 and 3.5 mg/L after 3 to 12 weeks on the same dose (Drouhet and Dupont, 1980).

Ketoconazole concentrations 12 hours after a *200mg* dose are about 0.1 mg/L (Daneshmend et al., 1981; Gascoigne et al., 1981). Long term oral therapy with 200mg daily for 28 weeks produced steady-state serum levels between 3 and 5 mg/L (Gascoigne et al., 1981). Similar concentrations were seen for up to 5 weeks in immunocompromised patients (Hann et al., 1982). After a single oral dose of 400mg, mean peak ketoconazole concentrations were 6.5 mg/L (Daneshmend et al., 1981) and 5.5 mg/L (Gascoigne et al., 1981), though a lower concentration of 3.42 mg/L has been reported on repeated dosing (Espinel-Ingroff et al., 1981). 12 hours after a *400mg* dose, mean ketoconazole concentrations ranged between 0.3 and 0.4 mg/L in normal subjects (Daneshmend et al., 1981; Gascoigne et al., 1981). There is limited information on serum concentrations of ketoconazole after 600 and 800mg doses. Peak concentrations between 30 and 50 mg/L were noted in 2 patients on a 600mg dose. Interestingly, in 2 other patients, peak concentrations initially rose when the dose was increased from 400 to 800 mg/day, but were less than half the original value after 3 to 4 months on the higher dose (Brass et al., 1982).

Ketoconazole 400mg per day for 10 to 12 months in 4 patients resulted in serum concentrations 2 hours after administration between 1 and 4 mg/L; drug accumulation did not occur in 1 patient with moderate liver impairment (Hawkins et al., 1981).

4.4 Distribution

Information on tissue distribution of ketoconazole in man is limited. Following a 200mg oral dose, ketoconazole is detectable in urine, saliva, sebum and cerumen (Heel, 1982). The extent of its penetration into skin is not yet known. Uninfected bone, soft tissue and infected bone in amputated material from a patient with coccidioidomycosis had no detectable ketoconazole, while tendon and infected skin had concentrations of 2 and 10.7 mg/L, respectively (Brass et al., 1982). In excised tissue from a patient with paraspinal coccidioidomycosis, Graybill et al. (1980) found ketoconazole concentrations of less than 0.4 mg/L in bone and muscle. In joint fluid, concentrations of 0.06, 0.12 and 2.50 mg/L were present at 2, 2.6 and 8 hours after a 200mg oral dose (Brass et al., 1982).

No ketoconazole was detectable in saliva after a 50mg oral dose (Brass et al., 1982). After 100mg, a saliva concentration of 0.59 mg/L was detected only at 45 minutes after administration. A 200mg dose produced saliva levels of 2.43 and 0.30 mg/L after 1 and 2 hours, respectively (Brass et al., 1982).

4.4.1 Cerebrospinal Fluid Concentrations

In 4 patients with meningeal disease, CSF concentrations of ketoconazole ranged between undetectable levels and 0.24 mg/L 60 to 130 minutes after a 200mg oral dose, and were between undetectable levels and 0.85 mg/L (mean 0.39 mg/L) 60 to 225 minutes after a 400mg dose (Brass et al., 1982). No ketoconazole was detectable in the CSF of patients without meningitis. Brass et al. (1982) also found no correlation between simultaneous

serum and CSF concentrations. These workers had previously noted (Brass et al., 1980) a ketoconazole concentration of 0.85 mg/L in CSF and 13 mg/L in serum in a patient with meningeal disease given 200mg, then 400mg per day for some months.

In a patient with candidal meningitis given ketoconazole 400mg twice daily for 1 week, a peak CSF concentration of 3 mg/L was seen at 6 hours; after 30 days' treatment the peak concentration was 2.2 mg/L at 8 hours (Fibbe et al., 1980). Substantially lower values for peak CSF ketoconazole concentrations in meningeal coccidioidomycosis (0.3 mg/L) have been noted on a daily dose of 800mg (Craven et al., 1981). In unpublished studies (quoted by Heel, 1982) higher CSF concentrations of 2 and 7 mg/L were noted 3 to 4 and 1 to 2 hours after oral doses of 200 and 400mg, respectively.

4.4.2 Protein Binding

In plasma, only 1% of ketoconazole exists as the free drug. The remainder is bound to plasma proteins, particularly albumin. In whole blood, 84% of ketoconazole is bound to plasma proteins, 15% to blood cells and 1% is present as free drug (Heel et al., 1982).

4.5 Elimination

4.5.1 Metabolism

Heel (1982) has summarised the unpublished data on ketoconazole metabolism. In 3 males given tritiated ketoconazole, 70% of the dose was excreted over 4 days (57% in faeces and 13% in urine). Extensive metabolism appears to occur after absorption. Between 20 and 65% of faecal radioactivity was due to unchanged drug, but only 2 to 4% of urinary radioactivity consisted of unchanged ketoconazole. Separation and analysis of urinary and faecal extracts has identified the major metabolites. In man, the important metabolic pathways appear to be oxidation of the imidazole ring, degradation of the oxidised imidazole, oxidative O-dealkylation, oxidative degradation of the piperazine ring, and aromatic hydroxylation. However, none of the identified metabolites possess antifungal activity.

After oral administration, ketoconazole may undergo first-pass metabolism (presystemic elimination). Peak concentrations after oral doses to mice showed a disproportionate increase in serum levels with increasing doses (Borelli et al., 1979). In man, a similar disproportionate increase in AUC has been noted following oral doses of 100, 200 and 400mg (Daneshmend et al., 1981; Gascoigne et al., 1981). This has been interpreted as first-pass metabolism during absorption with transient saturation of hepatic metabolic capacity (Heel, 1982). Interestingly, this relationship has not been found to persist at higher doses, and suggests either better absorption, non-linear elimination, saturable first-pass metabolism or a change in the apparent volume of distribution of ketoconazole (Brass et al., 1982).

Preliminary evidence suggests that the metabolism of ketoconazole is inducible by other drugs and by ketoconazole itself at daily doses greater than 400mg per day (Brass et al., 1982). This and other aspects of ketoconazole pharmacokinetics (e.g. clearance) are hampered by the lack of an intravenous preparation.

4.5.2 Excretion

Ketoconazole is excreted in the faeces as metabolites and unchanged drug in variable proportions in healthy subjects (Heel, 1982). Following extensive metabolism, the metabolites are excreted into the gut, probably in bile (see above). Urinary excretion of ketoconazole is small and an unimportant route of elimination.

Graybill et al. (1980) found a urinary concentration of only 0.4 mg/L in 24-hour collections from 8 patients with fungal disease given 200 or 400mg orally.

4.5.3 Half-life

Ketoconazole half-life appears to be dose-dependent (see table IV), the half-life increasing with

Table IV. Summary of studies reporting mean serum half-life of ketoconazole following oral administration

Reference	Assay	Subjects		Dose (mg)/conditions	Half-life (h)	
		no.	diagnosis			
Brass et al. (1980)	Bioassay	11	Coccidioidomycosis	200 tab; fasting	4.0	
Brass et al. (1982)	Bioassay	15	Patients	200 tab	3.0	
Daneshmend et al. (1981)	Bioassay	6	Normals	200 tab; breakfast	2.0	
				400 tab; breakfast	2.7	
Mannisto et al. (1982)	HPLC	10	Normals	200 tab; fasting	1.75	
				200 tab; breakfast	1.92	
				200 tab; orange juice	1.80	
Gascoigne et al. (1981)	GLC	12	Normals		$t_{\frac{1}{2},1}$	$t_{\frac{1}{2},2}$
				100 tab; breakfast	1.44	6.5
				200 soln; breakfast	1.51	6.6
				200 tab; breakfast	1.75	8.1
				400 tab; breakfast	2.21	9.6
Maksymiuk et al. (1982)	Bioassay and HPLC	9	Leukaemia	200 tab every 6h	day 1	5.1
					day 8	5.4
					day 15	3.9
				200 tab every 12h	day 1	3.0
					day 8	2.4
					day 15	3.0

increasing dosage (Daneshmend et al., 1981; Gascoigne et al., 1981). With an oral dose of 200mg the range of mean ketoconazole half-lives has been 1.51 to 4 hours. At the higher dose of 400mg, half-lives of 2.21 and 2.7 hours have been noted. In other studies, a mean half-life of 3.7 hours (range 1.3 to 11.6) has been reported in cancer patients on 400 to 800mg per day (Maksymiuk et al., 1982). In contrast, a half-life of 55 minutes has been noted in severely immunocompromised patients given 400mg per day (Hann et al., 1983).

Using a sensitive gas-liquid chromatographic method of measuring ketoconazole concentrations and prolonged sampling (48 hours), Gascoigne et al. (1981) found that ketoconazole has a slow elimination phase with terminal half-lives in normal subjects of 6.5, 8.1 and 9.6 hours after doses of 100, 200 and 400mg, respectively. In contrast to the other pharmacokinetic studies, this study clearly shows that ketoconazole kinetics after oral administration fit a 2-compartment model. This slower elimination phase is also dose-dependent.

4.6 Pharmacokinetics in Renal and Hepatic Disease

Renal disease causes non-significant decreases in the rate of absorption and peak serum concentrations of ketoconazole. Urinary elimination of ketoconazole is normally small and this is further diminished in renal failure (Heel, 1982). In 2 patients with renal failure undergoing haemodialysis, there was no change in ketoconazole half-life or peak concentrations, and the drug did not appear to be dialysable (Brass et al., 1982). Dosage adjustment is therefore not required in renal failure.

Mild liver dysfunction does not appear to affect ketoconazole kinetics (Heel, 1982; Heel et al., 1982). However, in 1 patient with liver disease given single oral doses of 200 and 400mg, ketoconazole serum concentrations remained elevated up to 8 hours later and half-life could not be calculated (Brass et al., 1982). This suggested impairment of ketoconazole metabolism in liver disease, but long term administration in the same patient showed no accumulation. The influence of liver disease on ketoconazole kinetics requires further study.

4.7 Ketoconazole Pharmacokinetics and Toxicity

Numerous mild and reversible side effects have been observed with ketoconazole (Heel et al., 1982). Though as many as 10% of patients treated with ketoconazole show transient abnormalities of liver function (Heel et al., 1982), ketoconazole-induced hepatitis is uncommon (Horsburgh et al., 1982). However, some severe cases of hepatitis and a few deaths possibly caused by ketoconazole-induced hepatotoxicity have occurred. Currently, there is no information on the relationship between the pharmacokinetics and toxic or idiosyncratic reactions to ketoconazole.

4.8 Therapeutic Monitoring of Ketoconazole

Most studies have employed microbiological methods for measuring ketoconazole in various body tissues and various bioassay techniques have been described (Clayton and Wingfield, 1981; Daneshmend et al., 1981; Jorgenson et al., 1981; Van Cutsem et al., 1980); these methods have a lower limit of sensitivity between 0.05 and 0.125 mg/L. Gas-liquid chromatographic measurement of ketoconazole is more sensitive (lower limit down to 0.001 mg/L) [Gascoigne et al., 1981] but this method has been employed only by the manufacturers. More recently, a number of HPLC methods have been described but most do not offer any greater sensitivity over bioassay (Alton, 1980; Andrews et al., 1981; Mannisto et al., 1983; Swezey et al., 1982).

Peak serum ketoconazole concentrations after a 200mg dose did not correlate with clinical response in 86 patients with superficial infections or in 74 patients with deep mycoses (Heel, 1982). Similarly, the rate of clinical response in patients with dermatophyte infections was not related to serum ketoconazole concentrations (Robertson et al., 1980). However, Negroni et al. (1980) found that therapeutic failure in 3 patients with paracoccidioidomycosis was associated with ketoconazole concentrations below 0.19 mg/L. Also, Hay et al. (1980) found that in 2 patients who achieved serum concentrations of less than 0.4 mg/L at 2 hours on a 200mg dose, doubling the dose led to higher and possibly more therapeutic concentrations. Recently, it has been shown that therapeutic failure in both immunocompetent and immunocompromised patients is often associated with low serum levels (Graybill et al., 1982; Hann et al., 1982). For this reason it is important to monitor serum ketoconazole concentrations in all cases of apparent therapeutic failure.

4.9 Ketoconazole Drug Interactions

Therapeutic failure in 1 patient was ascribed to an interaction between cimetidine and ketoconazole, and pretreatment of normal adults with cimetidine led to a 65% reduction in the AUC of ketoconazole (van der Meer et al., 1980). Therefore cimetidine should be given about 2 hours after ketoconazole to reduce this interaction. In contrast, pretreatment with a proprietary antacid ('Maalox') did not significantly reduce ketoconazole absorption (Brass et al., 1982). Similarly, concurrent administration of neomycin sulphate, colistin and co-trimoxazole do not appear to affect ketoconazole absorption (Hann et al., 1982).

Possible antagonism between ketoconazole and amphotericin B was suspected in 2 patients (Brass et al., 1980). This is a theoretical possibility in view of the antagonism between amphotericin B and miconazole (Cosgrove et al., 1978). However, there have been no other reports of this suspected antagonism and *in vitro* work suggests some synergy between ketoconazole and amphotericin B (Odds, 1983).

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References

Alton, K.B.: Determination of the antifungal agent, ketoconazole, in human plasma by high performance liquid chromatography. Journal of Chromatography 221: 337-344 (1980).

Andrews, F.A.; Peterson, L.R.; Beggs, W.H.; Crankshaw, D. and Sarosi, G.A.: Liquid chromatographic assay of ketoconazole. Antimicrobial Agents and Chemotherapy 19: 110-113 (1981).

Atkinson, A.J. and Bennett, J.E.: Amphotericin B pharmacokinetics in humans. Antimicrobial Agents and Chemotherapy 13: 271-276 (1978).

Atkinson, A.J. and Bindschadler, D.D.: Pharmacokinetics of intrathecal administered amphotericin B. American Review of Respiratory Disease 99: 917-924 (1969).

Bagnarello, A.G.; Lewis, L.A.; McHenry, M.C.; Weinstein, A.J.; Naito, H.K.; McCullough, A.J.; Lederman, R.J. and Gavan, T.L.: Unusual serum lipoprotein abnormality induced by the vehicle of miconazole. New England Journal of Medicine 296: 497-499 (1977).

Bannatyne, R.M. and Cheung, R.: Discrepant results of amphotericin B assay on fresh versus frozen serum samples. Antimicrobial Agents and Chemotherapy 12: 550 (1977).

Bannatyne, R.M.; Cheung, R. and Devlin, H.R.: Microassay for amphotericin B. Antimicrobial Agents and Chemotherapy 11: 44-46 (1977).

Barr, R.J.; Fujita, W.H. and Graham, J.H.: Eruptive xanthomas associated with intravenous miconazole therapy. Archives of Dermatology 114: 1544-1545 (1978).

Bayer, A.S.; Blumenkrantz, M.J.; Montgomerie, J.Z.; Galpin, J.E.; Coburn, J.W. and Guze, L.B.: Candida peritonitis: report of 22 cases and review of the English literature. American Journal of Medicine 61: 832-840 (1976).

Bell, W.E.: Treatment of fungal infections of the central nervous system. Annals of Neurology 9: 417-422 (1981).

Bennett, J.E.: Chemotherapy of systemic mycoses. New England Journal of Medicine 290: 30-32 and 320-323 (1974).

Bennett, J.E.; Flucytosine. Annals of Internal Medicine 86: 319-322 (1977).

Bennett, J.E.; Dismukes, W.E.; Duma, R.J.; Medoff, G.; Sande, M.A.; Gallis, H.; Leonard, J.; Fields, B.T.; Bradshaw, M.; Haywood, H.; McGee, Z.A.; Cate, T.R.; Cobbs, C.G.; Warner, J.F. and Alling, D.W.: A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis. New England Journal of Medicine 301: 126-131 (1979).

Bennett, J.E. and Remington, J.S.: Miconazole in cryptococcosis and systemic candidiasis: a word of caution. Annals of Internal Medicine 94: 708-709 (1982).

Bindschadler, D.D. and Bennett, J.E.: A pharmacologic guide to the clinical use of amphotericin B. Journal of Infectious Diseases 120: 427-436 (1969).

Blair, A.D.; Forrey, A.W.; Meijsen, B.T. and Cutler, R.E.: Assay of flucytosine and furosemide by high-pressure liquid chromatography. Journal of Pharmaceutical Sciences 64: 1334-1339 (1975).

Block, E.R.: Effect of hepatic insufficiency on 5-fluorocytosine concentrations in serum. Antimicrobial Agents and Chemotherapy 3: 141-142 (1973).

Block, E.R. and Bennett, J.E.: Pharmacological studies with 5-fluorocytosine. Antimicrobial Agents and Chemotherapy 1: 476-482 (1972).

Block, E.R. and Bennett, J.E.: Stability of amphotericin B in infusion bottles. Antimicrobial Agents and Chemotherapy 4: 648-649 (1973).

Block, E.R.; Bennett, J.E.; Livoti, L.G.; Klein, W.J.; MacGregor, R.R. and Henderson, L.: Flucytosine and amphotericin B: hemodialysis effects on the plasma concentration and clearance. Annals of Internal Medicine 80: 613-617 (1974).

Boelaert, J.; Daneels, R.; Van Landuyt, H. and Symoens, J.: Miconazole plasma levels in healthy subjects and in patients with impaired renal function. Chemotherapy 6: 165-169 (1976).

Borelli, D.; Bran, J.L.; Fuentes, J.; Legendre, R.; Leiderman, E.; Levine, H.B.; Restrepo-M. A. and Stevens, D.A.: Ketoconazole an oral antifungal: laboratory and clinical assessment of imidazole drugs. Postgraduate Medical Journal 55: 657-661 (1979).

Brass, C.; Galgiani, J.N.; Blaschke, T.F.; Defelice, R.; O'Reilly, R.A. and Stevens, D.A.: Disposition of ketoconazole, an oral antifungal, in humans. Antimicrobial Agents and Chemotherapy 21: 151-158 (1982).

Brass, C.; Galgiani, J.N.; Campbell, S.C. and Stevens, D.A.: Therapy of disseminated or pulmonary coccidioidomycosis with ketoconazole. Reviews of Infectious Diseases 2: 656-660 (1980).

Brodie, R.R.; Chasseaud, L.F. and Walmsley, L.M.: High-pres-

sure liquid chromatographic determination of the antimycotic agent, econazole in plasma. Journal of Chromatography 155: 209-213 (1978).

Bruckner, H.W. and Creasey, W.A.: The administration of 5FU by mouth. Cancer 33: 14-18 (1974).

Brugmans, J.; van Cutsem, J.; Heykants, J.; Schuermans, V. and Thienpont, D.: Systemic antifungal potential, safety, biotransport and transformation of miconazole nitrate. European Journal of Clinical Pharmacology 51: 93-99 (1972).

Bullock, W.E.; Luke, R.G.; Nuttall, C.E. and Bhathena, D.: Can mannitol reduce amphotericin B nephrotoxicity? Double-blind study and description of a new vascular lesion in the kidneys. Antimicrobial Agents and Chemotherapy 10: 555-563 (1976).

Bury, R.W.; Mashford, M.L. and Miles, H.M.: Assay of flucytosine (5-fluorocytosine) in human plasma by high-pressure liquid chromatography. Antimicrobial Agents and Chemotherapy 16: 529-532 (1979).

Cartwright, R.Y.: Use of antibiotics: Antifungals. British Medical Journal 2: 108-111 (1978).

Chung, D.K. and Koenig, M.G.: Reversible cardiac enlargement during treatment with amphotericin B and hydrocortisone. American Review of Respiratory Diseases 103: 831-841 (1971).

Churchill, D.N. and Seely, J.: Nephrotoxicity associated with combined amphotericin B-gentamicin therapy. Nephron 19: 176-181 (1977).

Clarke, M.; Davies, D.P.; Odds, F. and Mitchell, C.: Neonatal systemic candidiasis treated with miconazole. British Medical Journal 281: 354 (1980).

Clayton, Y.N. and Wingfield, H.J.: Bioassay of ketoconazole in human serum. Clinical Research Reviews 1: 189 (1981).

Cosgrove, R.F.; Beezer, A.E. and Miles, R.J.: *In vitro* studies of amphotericin B in combination with the imidazole antifungal compounds clotrimazole and miconazole. Journal of Infectious Diseases 138: 681-685 (1978).

Cosgrove, R.F. and Fairbrother, J.E.: Bioassay method for polyene antibiotics based on the measurement of rubidium efflux from rubidium-loaded yeast cells. Antimicrobial Agents and Chemotherapy 11: 31-33 (1977).

Craven, P.C.; Graybill, J.R.; Jorgensen, J.H. and Dismukes, W.E.: High dose ketoconazole for human fungal meningitis. 21st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, 4-6 November (1981).

Craven, P.C.; Ludden, T.M.; Drutz, D.J.; Rogers, W.; Haegele, K.A. and Skrdlant, H.B.: Excretion pathways of amphotericin B. Journal of Infectious Diseases 140: 329-341 (1979).

Cushard, W.G.; Kohanim, M. and Lantis, L.R.: Blastomycosis of bone treated with intramedullary amphotericin B. Journal of Bone and Joint Surgery 51A: 704-712 (1969).

Cutler, R.E.; Blair, A.D.; Kelly, M.R.: Flucytosine kinetics in subjects with normal and impaired renal function. Clinical Pharmacology and Therapeutics 24: 333-342 (1978).

Daneshmend, T.K.; Warnock, D.W.; Turner, A. and Roberts, C.J.C.: Pharmacokinetics of ketoconazole in normal subjects. Journal of Antimicrobial Chemotherapy 8: 299-304 (1981).

Davies, R.R. and Reeves, D.S.: 5FC and urinary candidiasis. British Medical Journal 1: 577-579 (1971).

Dawborn, J.K.; Page, M.D.; Schiavone, D.J.: Use of 5-fluorocytosine in patients with impaired renal function. British Medical Journal 4: 382-384 (1973).

Deresinski, S.C.; Galgiani, J.N. and Stevens, D.A.: Miconazole treatment of human coccidioidomycosis: status report; in: Ajello (Ed.) Coccidioidomycosis: Current Clinical and Diagnostic Status. Proceedings of the Third International Coccidioidomycosis Symposium, Tucson, Arizona, November, 1976, pp.267-292 (Symposia Specialists, Miami 1977).

Deresinski, S.C. and Stevens, D.A.: Bone and joint coccidioidomycosis treated with miconazole. American Review of Respiratory Diseases 120: 1101-1107 (1979).

Diamond, R.D. and Bennett, J.E.: A subcutaneous reservoir for intrathecal therapy of fungal meningitis. New England Journal of Medicine 288: 186-188 (1973).

Diasio, R.B.; Lakings, D.E. and Bennett, J.E.: Evidence for conversion of 5-fluorocytosine to 5-fluorouracil in humans: possible factor in 5-fluorocytosine clinical toxicity. Antimicrobial Agents and Chemotherapy 14: 903-908 (1978a).

Diasio, R.B.; Wilburn, M.A.; Shadomy, S. and Espinel-Ingroff, A.: Rapid determination of serum 5-fluorocytosine levels by high-performance liquid chromatography.. Antimicrobial Agents and Chemotherapy 13: 500-504 (1978b).

Drouhet, E.; Babinet, P.; Chapusot, J.P. and Kleinknecht, D.: 5-Fluorocytosine in the treatment of candidiasis with acute renal insufficiency; its kinetics during haemodialysis and peritoneal dialysis. Biomedicine 19: 408-414 (1973).

Drouhet, E.; Borderon, J.C.; Borderon, E. and Boulard, P.: Evolution des concentrations serique de 5-fluorocytosine chez les prematures. Bulletin de la Societe Francaise de Mycologie Medicale 3: 37-40 (1974).

Drouhet, E. and Dupont, B.: Chronic mucocutaneous candidosis and other superficial and systemic mycoses successfully treated with ketoconazole. Rev. Inf. Dis. 2: 606-619 (1980).

Drutz, D.J.; Fan, J.H.; Tai, T.Y.; Cheng, J.T. and Hsieh, W.C.: Hypokalaemic rhabdomyolysis and myoglobinuria following amphotericin B therapy. Journal of the American Medical Association 211: 824-826 (1970).

Drutz, D.J.; Spickard, A.; Rogers, D.E.; and Koenig, M.G.: Treatment of disseminated mycotic infections. A new approach to amphotericin B therapy. American Journal of Medicine 45: 405-418 (1968).

Espinel-Ingroff, A.; Shadomy, S. and Fisher, J.F.: Bioassay for miconazole. Antimicrobial Agents and Chemotherapy 11: 365-368 (1977).

Espinel-Ingroff, A.; Shadomy, S.; Porter, D.; Stelz, M.; Dismukes, W.E. and CMSC Group: Ketoconazole: serum levels as determined by bioassay. 21st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, 4-6 November (1981).

Fainstein, V. and Bodey, G.P.: Cardiorespiratory toxicity due to miconazole. Annals of Internal Medicine 93: 432-433 (1980).

Fass, R.J. and Perkins, R.L.: 5-Fluorocytosine in the treatment of cryptococcal and Candida mycoses. Annals of Internal Medicine 74: 535-539 (1971).

Feely, J.; Heidemann, H.; Gerkens, J.; Roberts, L.J. and Branch, R.A.: Sodium depletion enhances nephrotoxicity of amphotericin B. Lancet 1: 1422-1423 (1981).

Feldman, H.A.; Hamilton, J.D. and Gutman, R.A.: Amphotericin B therapy in an anephric patient. Antimicrobial Agents and Chemotherapy 4: 302-305 (1973).

Fibbe, W.E.; van der Meer, J.W.M.; Thompson, J. and Moreton, R.P.: CSF concentrations of ketoconazole. Journal of Antimicrobial Chemotherapy 6: 681 (1980).

Fields, B.T.; Bates, J.H. and Abernathy, R.S.: Amphotericin B serum concentrations during therapy. Applied Microbiology 19: 955-959 (1970).

Fields, B.T.; Bates, J.H. and Abernathy, R.S.: Effect of rapid intravenous infusion on serum concentrations of amphotericin B. Applied Microbiology 22: 615-617 (1971).

Fisher, J.F.; Duma, R.J., Markowitz, S.M.; Shadomy, S.; Espinel-Ingroff, A. and Chew, W.H.: Therapeutic failures with miconazole. Antimicrobial Agents and Chemotherapy 13: 965-968 (1978).

Foster, C.S.: Miconazole therapy for keratomycosis. American Journal of Ophthalmology 91: 622-629 (1981).

Foster, C.S. and Stefanyszyn, M.: Intraocular penetration of miconazole in rabbits. Archives of Ophthalmology 97: 1703-1706 (1979).

Gale, E.F.: The release of potassium ions from *Candida albicans* in the presence of polyene antibiotics. Journal of General Microbiology 80: 451-465 (1974).

Galimberti, R.; Negroni, R.; Iglesia de Elias Costa, M.R. and Casala, A.M.: The activity of ketoconazole in the treatment of onychomycosis. Reviews of Infectious Diseases 2: 596-598 (1980).

Gallo, J.; Grunstein, H.; Clifton-Bligh, P.; Billson, F.A. and Tarr, K.H.: Miconazole in fungal endophthalmitis. Lancet 1: 53 (1982).

Gascoigne, E.W.; Barton, G.J.; Michaels, M.; Meuldermans, W. and Heykants, J.: The kinetics of ketoconazole in animals and man. Clinical Research Reviews 1: 177-187 (1981).

Gotz, V.P.; Mar, D.D. and Roche, J.J.: Compatibility of amphotericin B with drugs used to reduce adverse reactions. American Journal of Hospital Pharmacy 38: 378-379 (1981).

Graybill, J.R.; Craven, P.C.; Donovan, W. and Matthew, E.B.: Ketoconazole therapy for systemic fungal infections: inadequacy of standard dose regimens. American Review of Respiratory Diseases 126: 171-174 (1982).

Graybill, J.R.; Lundberg, D.; Donovan, W.; Levine, H.B.; Rodriguez, M.D. and Drutz, D.J.: Treatment of coccidioidomycosis with ketoconazole: clinical and laboratory study of 18 patients. Reviews of Infectious Diseases 2: 661-673 (1980).

Green, W.R.; Bennett, J.E. and Goos, R.D.: Ocular penetration of amphotericin B. Archives of Ophthalmology 73: 769-775 (1965).

Hann, I.M.; Prentice, H.G.; Corringham, R.; Blacklock, H.A.; Keaney, M.; Shannon, M.; Noone, P.; Gascoigne, E.; Fox, J.; Boesen, E.; Szawatkowski, M. and Hoffbrand, A.V.: Ketoconazole versus nystatin plus amphotericin B for fungal; prophylaxis in severely immunocompromised patients. Lancet 1: 826-829 (1982).

Hann, I.M.; Prentice, H.G.; Keaney, M.; Corringham, R.; Blacklock, H.A.; Fox, J.; Gascoigne, E. and van Cutsem, J.: The pharmacokinetics of ketoconazole in severely immunocompromised patients. Journal of Antimicrobial Chemotherapy (In press, 1983).

Harding, S.A.; Johnson, G.F. and Solomon, H.M.: Gas-chromatographic determination of 5-fluorocytosine in human serum. Clinical Chemistry 22: 772-776 (1976).

Hawkins, S.S.; Gregory, D.W. and Alford, R.H.: Progressive disseminated histoplasmosis: favourable response to ketoconazole. Annals of Internal Medicine 95: 446-449 (1981).

Hay, R.J.; Wells, R.S.; Clayton, Y.M. and Wingfield, H.J.: Treatment of chronic mucocutaneous candidosis with ketoconazole: a study of 12 cases. Reviews of Infectious Diseases 2: 599-605 (1980).

Heel, R.C.: in Levine (Ed.) Ketoconazole in the Management of Fungal Disease (ADIS Press, Sydney 1982).

Heel, R.C.; Brogden, R.N.; Carmine, A.; Morley, P.A.; Speight, T.M. and Avery, G.S.: Ketoconazole: a review of its therapeutic efficacy in superficial and systemic fungal infections. Drugs 23: 1-36 (1982).

Heel, R.C.; Brogden, R.N.; Pakes, G.E.; Speight, T.M. and Avery, G.S.: Miconazole: a preliminary review of its therapeutic efficacy in systemic fungal infections. Drugs 19: 7-30 (1980).

Hoeprich, P.D.: Chemotherapy of systemic fungal diseases. Annual Review of Pharmacology and Toxicology 18: 205-231 (1978).

Hoeprich, P.D.; Lawrence, R.M. and Goldstein, E.: Treatment of coccidioidomycosis with miconazole. Journal of the American Medical Association 243: 1923-1926 (1980).

Holt, R.J.: The imidazoles; in Speller (Ed.) Antifungal Chemotherapy, pp.107-147 (Wiley, Chichester 1980).

Holt, R.J. and Newman, R.L.: The antimycotic activity of 5-fluorocytosine. Journal of Clinical Pathology 26: 167-174 (1973).

Hopfer, R.L. and Groschel, D.: Radiometric determination of the concentration of amphotericin B in body fluids. Antimicrobial Agents and Chemotherapy 12: 733-735 (1977).

Horsburgh, C.R.; Kirkpatrick, C.H. and Teutsch, C.B.: Ketoconazole and the liver. Lancet 1: 860 (1982).

Jagdis, F.A.; Hoeprich, P.D.; Lawrence, R.M. and Schaffner, C.P.: Comparative pharmacology of amphotericin B and amphotericin B methyl ester in the non-human primate, *Macaca mulatta*. Antimicrobial Agents and Chemotherapy 12: 582-590 (1977).

Jorgensen, J.H.; Alexander, G.A.; Graybill, J.R. and Drutz, D.J.: Sensitive bioassay for ketoconazole in serum and cerebrospinal fluid. Antimicrobial Agents and Chemotherapy 20: 59-62 (1981).

Jurgens, R.W.; DeLuca, P.P. and Papadimitrou, D.: Compatibility of amphotericin B with certain large volume parenterals. American Journal of Hospital Pharmacy 38: 377-378 (1981).

Kaspar, R.L. and Drutz, D.J.: Rapid, simple bioassay for 5-fluorocytosine in the presence of amphotericin B. Antimicrobial Agents and Chemotherapy 7: 462-465 (1975).

Kaufmann, C.A.; Carleton, J.A. and Frame, P.T.: Simple assay for 5-fluorocytosine in the presence of amphotericin B. Antimicrobial Agents and Chemotherapy 9: 381-383 (1976).

Kaufmann, C.A. and Frame, P.T.: Bone marrow toxicity associated with 5-fluorocytosine therapy. Antimicrobial Agents and Chemotherapy 11: 244-247 (1977).

Koechlin, B.A.; Rubio, F.; Palmer, S.; Gabriel, T. and Duschinsky, R.: The metabolism of 5-fluorocytosine-2^{14}C and of cytosine-^{14}C in the rat and the disposition of 5-fluorocytosine-2^{14}C in man. Biochemical Pharmacology 15: 435-446 (1966).

Lawrence, R.M.; Hoeprich, P.D.; Jagdis, F.A.; Monji, N.; Huston, A.C. and Schaffner, C.P.: Distribution of doubly radiolabelled amphotericin B methyl ester and amphotericin B in the non-human primate, *Macaca mulatta*. Journal of Antimicrobial Chemotherapy 6: 241-249 (1980).

Levine, H.B.: Miconazole levels in blood, CSF and joint fluid and minimal inhibitory concentrations to clinical isolates of fungi. Unpublished report, Janssen Pharmaceutica (1977).

Levine, H.B. (Ed.): Ketoconazole in the Management of Fungal Disease (ADIS Press, Sydney 1982).

Levinson, D.J.; Silcox, D.C.; Rippon, J.W. and Thomsen, S.: Septic arthritis due to non-encapsulated *Cryptococcus neoformans* with coexisting sarcoidosis. Arthritis and Rheumatology 17: 1037-1047 (1974).

Lewi, P.J.; Boelaert, J.; Daneels, R.; DeMeyere, R.; Van Landuyt, H.; Heykants, J.J.P.; Symoens, J. and Wynants, J.: Pharmacokinetic profile of intravenous miconazole in man: comparison of normal subjects and patients with renal insufficiency. European Journal of Clinical Pharmacology 10: 49-54 (1976).

Louria, D.B.: Some aspects of the absorption, distribution, and excretion of amphotericin B in man. Antibiotic Medicine and Clinical Therapy 5: 295-301 (1958).

MacGregor, R.R.; Bennett, J.E. and Erslev, A.J.: Erythropoietin concentration in amphotericin B-induced anemia. Antimicrobial Agents and Chemotherapy 14: 270-273 (1978).

Maddux, M.S. and Barriere, S.L.: A review of complications of amphotericin B therapy: recommendations for prevention and management. Drug Intelligence and Clinical Pharmacy 14: 177-184 (1980).

Maksymiuk, A.W.; Levine, H.B. and Bodey, G.P.: Pharmacokinetics of ketoconazole in patients with neoplastic diseases. Antimicrobial Agents and Chemotherapy 22: 43-46 (1982).

Mannisto, P.T.; Mantyla, R.; Nykanen, S.; Lamminsivu, U. and Ottoila, P.: Impairing effect of food on ketoconazole absorption. Antimicrobial Agents and Chemotherapy 21: 730-733 (1982).

Meade, R.H.: Drug therapy reviews: clinical pharmacology and therapeutic use of antimycotic drugs. American Journal of Hospital Pharmacy 36: 1326-1334 (1979).

Medoff, G. and Kobayashi, G.S.: Strategies in the treatment of systemic fungal infections. New England Journal of Medicine 302: 145-155 (1980).

Miller, R.P. and Bates, J.H.: Amphotericin B toxicity: a follow up report of 53 patients. Annals of Internal Medicine 71: 1089-1095 (1969).

Minors, J.O.; Foenander, T. and Birkett, D.J.: Liquid-chromatographic determination of 5-fluorocytosine. Clinical Chemistry 26: 117-119 (1980).

Morison, W.L.: Connor, B. and Clayton, Y.: Successful treatment of chromoblastomycosis with 5-fluorocytosine. British Journal of Dermatology 90: 445-449 (1974).

Naito, H.K.; McHenry, M.C. and Lewis, L.A.: Drug-induced dyslipoproteinaemia: a report of two cases. Clinical Chemistry 26: 163-168 (1980).

Negroni, R.; Robles, A.M.; Arechavala, A.; Tuculet, M.A. and Galimberti, R.: Ketoconazole in the treatment of paracoccidioidomycosis and histoplasmosis. Reviews of Infectious Diseases 2: 643-649 (1980).

Nilsson-Ehle, I.; Yoshikawa, T.T.; Edwards, J.E.; Schotz, M.C. and Guze, L.B.: Quantitation of amphotericin B with use of high-pressure liquid chromatography. Journal of Infectious Diseases 135: 414-422 (1977).

Odds, F.C.: Interactions between amphotericin B, 5-fluorocytosine, ketoconazole and miconazole against pathogenic fungi *in vitro*. Antimicrobial Agents and Chemotherapy (In press, 1983).

Odds, F.C. and Macdonald, F.: Persistence of miconazole in vaginal secretions after single applications. British Journal of Venereal Diseases 57: 400-401 (1981).

Olivero, J.J.; Lozano-Mendez, J.; Ghafary, E.M.; Eknoyan, G. and Suki, W.N.: Mitigation of amphotericin B nephrotoxicity by mannitol. British Medical Journal 1: 550-551 (1975).

Pennington, J.E.; Block, E.R. and Reynolds, H.Y.: 5-fluorocytosine and amphotericin B in bronchial secretions. Antimicrobial Agents and Chemotherapy 6: 324-326 (1974).

Peterson, L.R.; Kelty, R.H.; Hall, W.H. and Votava, H.J.: Therapy of Candida peritonitis: penetration of amphotericin B into peritoneal fluid. Postgrad. Med. J. 54: 340-342 (1978).

Plempel, M.: Pharmacokinetics of imidazole antimycotics. Postgraduate Medical Journal 55: 662-666 (1979).

Polak, A.: Pharmacokinetics of amphotericin B and flucytosine. Postgraduate Medical Journal 55: 667-670 (1979).

Polak, A.; Eschenhof, E.; Fernex, M. and Scholer, H.J.: Metabolic studies with 5-fluorocytosine-6-^{14}C in mice, rats, rabbits, dogs and man. Chemotherapy (Basel) 22: 137-153 (1976).

Reiner, N.E. and Thompson, W.L.: Dopamine and saralasin antagonism of renal vasoconstriction and oliguria caused by amphotericin B in dogs. Journal of Infectious Diseases 140: 564-575 (1979).

Robertson, M.H.; Hanifin, J.M. and Parker, F.: Oral therapy with ketoconazole for dermatophyte infections unresponsive to griseofulvin. Reviews of Infectious Diseases 2: 578-582 (1980).

Rosch, J.M.; Pazin, G.J. and Fireman, P.: Reduction of amphotericin B nephrotoxicity with mannitol. Journal of the American Medical Association 235: 1995-1996 (1976).

Ryley, J.F.; Wilson, R.G.; Gravestock, M.B. and Poyser, J.P.: Experimental approaches to antifungal chemotherapy. Advances in Pharmacology and Chemotherapy 18: 49-176 (1981).

Sarosi, G.A.; Armstrong, D.; Barbee, R.A.; Bates, J.H.; Campbell, G.D.; George, R.B.; Goldstein, R.A.; Schaffner, W. and Stevens, D.A.: Treatment of fungal diseases. American Review of Respiratory Disease 120: 1393-1397 (1979).

Schacter, L.P.; Owellen, R.J.; Rathbun, H.K. and Buchanan, B.: Antagonism between miconazole and amphotericin B. Lancet 2: 318 (1976).

Scheijgrond, H.: Buccal absorption of miconazole in tablet and gel formulation in 5 healthy volunteers. Unpublished report, Janssen Pharmaceutica (1978).

Schiavone, D.J.; Page, M.D. and Dawborn, J.K.; Rapid microbiological assay for 5-fluorocytosine. British Medical Journal 4: 380-382 (1973).

Scholer, H.J.: Flucytosine; in Speller (Ed.) Antifungal Chemotherapy, pp.35-106 (Wiley, Chichester 1980).

Schonebeck, J.; Polak, A.; Fernex, M. and Scholer, H.J.: Pharmacokinetic studies on the oral antimycotic agent 5-fluorocytosine in individuals with normal and impaired renal function. Chemotherapy (Basel) 18: 321-336 (1973).

Shadomy, S.: In vitro studies with 5-fluorocytosine. Applied Microbiology 17: 871-877 (1969).

Shadomy, S.: Further in vitro studies with 5-fluorocytosine. Infection and Immunity 2: 484-488 (1970).

Shadomy, S.; McCay, J.A. and Schwartz, S.I.: Bioassay for hamycin and amphotericin B in serum and other biological fluids. Applied Microbiology 17: 497-503 (1969).

Speller, D.C.E.: *Torulopsis glabrata* urinary tract infection treated with 5-fluorocytosine. Journal of Clinical Pathology 27: 50-52 (1974).

Speller, D.C.E. (Ed.): Antifungal Chemotherapy (Wiley, Chichester 1980).

Stevens, D.A.: Miconazole in the treatment of systemic fungal infection. American Review of Respiratory Disease 116: 801-806 (1977).

Stevens, D.A.; Levine, H.B. and Deresinski, S.C.: Miconazole in coccidioidomycosis. II. Therapeutic and pharmacologic studies in man. American Journal of Medicine 60: 191-202 (1976).

Stranz, M.H.: Miconazole. Drug Intelligence and Clinical Pharmacy 14: 86-95 (1980).

Sung, J.P.; Campbell, G.D. and Grendahl, J.G.: Miconazole therapy for fungal meningitis. Archives of Neurology 35: 443-447 (1978).

Sung, J.P.; Grendahl, J.B. and Levine, H.B.: Intravenous and intrathecal miconazole therapy for systemic mycoses. Western Journal of Medicine 126: 5-13 (1977).

Sung, J.P.; Rajani, K.; Chopra, D.R.; Grendahl, J.G.; and Haws, E.B.: Miconazole therapy for systemic candidiasis in a conjoined (Siamese) twin and a premature newborn. American Journal of Surgery 138: 688-691 (1979).

Swezey, S.F.; Giacomini, K.M.; Abang, A.; Brass, C.; Stevens, D.A. and Blaschke, T.F.: Measurement of ketoconazole, a new antifungal agent, by high performance liquid chromatography. Journal of Chromatography 227: 510-515 (1982).

Symoens, J.: Clinical and experimental evidence on miconazole for the treatment of systemic mycoses: a review. Proceedings of the Royal Society of Medicine 70 (Suppl. 1): 4-8 (1977).

Turner, A. and Warnock, D.W.: Determination of miconazole in human saliva using high-performance liquid chromatography. Journal of Chromatography 227: 229-232 (1982).

Utz, J.: Chemotherapy of the systemic mycoses. Medical Clinics of North America 66(1): 221-234 (1982).

Vanbreuseghem, R.: In round-table discussion and chairman's summing up. Proceedings of the Royal Society of Medicine 70 (Suppl. 1): 51-54 (1977).

Van Cutsem, J.; van der Flaes, M.; Thienpont, D.; Dony, J. and Horing, C.: Determination of ketoconazole in hairs from orally treated rats and guinea pigs. Mykosen 23: 418-425 (1980).

van der Meer, J.W.M.; Keuning, J.J.; Scheijgrond, H.W.; Heykants, J.; van Cutsem, J. and Brugmans, J.: The influence of gastric acidity on the bio-availability of ketoconazole. Journal of Antimicrobial Chemotherapy 6: 552-554 (1980).

Wade, D.N. and Sudlow, G.: The kinetics of 5-fluorocytosine elimination in man. Australian and New Zealand Journal of Medicine 2: 153-158 (1972).

Warnock, D.W. and Richardson, M.D. (Eds): Fungal Infection in the Compromised Patient (Wiley, Chichester 1982).

Warnock, D.W. and Turner, A.: High-performance liquid chromatographic determination of 5-fluorocytosine in human serum. J. Antimicr. Chemoth. 7: 363-369 (1981).

Watson, P.G.; Lochan, R.G. and Redding, V.J.: Drug interaction with coumarin derivative anticoagulants. British Medical Journal 285: 1045-1046 (1982).

Wee, S.H. and Anhalt, J.P.: Gas chromatographic determination of 5-fluorocytosine: a modified extraction method. Antimicrobial Agents and Chemotherapy 11: 914-915 (1977).

Wilson, R. and Feldman, S.: Toxicity of amphotericin B in children with cancer. American Journal of Diseases of Children 133: 731-734 (1979).

Author's address: Dr *T.K. Daneshmend,* Clinical Pharmacology Unit, University Department of Medicine, Bristol Royal Infirmary, *Bristol BS2 8HW, Avon* (England).