

Clinical Pharmacokinetics of Systemically Administered Antimycotics

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Abstract: Systemic fungal infections are a major threat for immunocompromised patients. Beside the antimycotic spectrum, the pharmacokinetic properties of an antifungal drug are crucial for its clinical efficacy. Since patients with systemic mycoses frequently present with a significant co-morbidity, pharmacokinetics under special conditions such as renal insufficiency, renal replacement therapy or impaired liver function have to be considered.

Amphotericin B is eliminated unchanged by the liver and the kidney. Its plasma protein binding accounts for 95 to 99 percent. Conventional amphotericin B deoxycholate has a remarkable infusion related and renal toxicity. Therefore, lipid formulations have been developed. By now, three lipid formulations are therapeutically used: liposomal amphotericin B, amphotericin B colloidal dispersion and amphotericin B lipid complex. Striking differences in their plasma pharmacokinetics have been found. These differences can be attributed to the diverse disposition of the lipid moieties, while liberated amphotericin B displays a pharmacokinetic behavior which is independent from the lipid-formulation applied. The highest amphotericin B tissue concentrations have been found in the liver and in the spleen, followed by lung, kidney and heart. Concentrations in brain tissue are very low.

Flucytosine has no relevant protein binding and is eliminated by glomerular filtration.

Fluconazole, itraconazole, voriconazole, posaconazole and ravuconazole are triazoles, used for treatment of systemic fungal infections. Significant drug interactions have to be considered during therapy with triazoles, particularly in patients dependent on immunosuppression. These interactions are caused by the metabolism of triazoles in the liver where the cytochrome P450 (CYP) system is involved at a different extend as well as by their mechanisms of action. Triazoles display a favorable tissue distribution with high penetration into the central nervous system.

Echinocandins such as caspofungin and micafungin are rapidly taken up by peripheral tissues, particularly by the liver. In the first 24 hours this uptake appears to be the main route of elimination from plasma. Enzymatic degradation takes place, but is independent of CYP. Thus, drug interactions are a minor problem during echinocandin treatment. The highest tissue levels of caspofungin and micafungin have been measured in the liver. Moderate concentrations are achieved in lung, spleen and kidney. Penetration into the brain is relatively poor.

Key Words Amphotericin B, triazoles, echinocandins, drug interactions, elimination, tissue penetration, target site pharmacokinetics.

INTRODUCTION

Systemic fungal infections are a major cause of death in immunocompromised patients. Patients with hematologic malignancies are at a particularly high risk as well as patients who have undergone cytostatic chemotherapy, hematologic stem cell transplantation, solid organ transplantation, and critically ill patients at the intensive care unit (ICU). Inborn immune deficiencies or acquired immune deficiency syndrome (AIDS) and immunosuppression for auto-immune diseases are also predisposing for invasive mycoses. The increased incidence of systemic mycoses during the last two decades is attributed mainly to the administration of more aggressive myeloablative regimens in hematology and oncology and by the emergence of HIV infection [1].

Since systemic fungal infections are opportunistic infections, they are frequently accompanied by a poor clinical

condition that may end up with multi organ dysfunction syndrome. Renal failure, due to sepsis and co-administration of nephrotoxic medications as well as impaired liver function are common in patients at risk of invasive mycoses. In critically ill patients additional pathophysiological changes such as edema and altered tissue perfusion, may influence the absorption, distribution, metabolism and the elimination of antimycotic drugs [2]. Renal replacement therapy, which is required in a considerable number of patients suffering from invasive fungal infections, can also result in an altered drug elimination. On the other hand, the significant toxicity of several antimycotics can deteriorate an impaired organ function and thus contribute to the poor outcome of fungal infections [3]. Thus, pharmacokinetics established in healthy volunteers may often be of limited value in these patients. Moreover, the influences of co-morbidity on pharmacokinetic behavior of antimycotics has to be taken into account in order to warrant adequate dosage in clinical practice. Therefore, pharmacokinetic studies in special patient groups are of particular interest.

The high number of concomitant medications frequently required in patients suffering from systemic mycoses is prone to provoke numerous drug interactions resulting in

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toxicity or impaired efficacy of antifungal or concomitant therapy. The effects of several antimycotics, particularly azoles, on the cytochrome P 450 (CYP) system are well documented, though other metabolic pathways may play a role too.

The majority of pharmacokinetic investigations on antimycotics have been performed on plasma pharmacokinetics. For clinical efficacy, however, the concentrations at the site of infection may be more relevant. Data on tissue penetration of antimycotics are mainly derived from animal experiments.

This review focuses on human pharmacokinetics emphasizing pharmacokinetic changes in patients with comorbidity, such as renal failure, impaired liver function and critical illness. Dose recommendations, as far as available, are presented for these special clinical conditions and studies on tissue penetration and target site pharmacokinetics are discussed.

AMPHOTERICIN B

Amphotericin B has been in clinical use for half a century [4-8]. It is a polyene antimycotic comprising a monocyclic lactone ring which has a hydrophilic and a lipophilic moiety and is linked to mycosamine. Amphotericin B is nearly insoluble in water and poorly soluble in organic solvents. Its molecular weight is 924 Da. Conventional amphotericin B is a deoxycholate formulation forming a micellar solution in water.

The molecular target for amphotericin B is ergosterol, an essential constituent of fungal cell membranes. Eight amphotericin B molecules interact with eight ergosterol molecules forming a channel in the phospholipid bilayer membrane resulting in the leakage of essential small molecules from the cell [9-11].

Amphotericin B has a broad antimycotic spectrum. It is fungicidal to the majority of *Candida* species. *C. glabrata*, *C. lusitanae* and particularly *C. krusei* are less susceptible. Amphotericin B is also efficacious against the most common *Aspergillus* species, such as *A. niger* and *A. fumigatus*, against *Histoplasma capsulatum*, *Coccidioides immitis* and against *Leishmania donovani*. *Zygomycetes* are susceptible or intermediate [12]. Thus, amphotericin B still plays an important role in the treatment of suspected or proven invasive fungal infections, particularly in neutropenic patients [13]. Some *A. terreus* strains, *Fusarium* species, *Scedosporium* species and *Malassezia furfur* are resistant against amphotericin B.

The clinical use of amphotericin B is hampered by its infusion-related toxicity, such as chills, fever, nausea and hypotension, and by its nephrotoxicity [3, 14-22]. After a 1 mg test dose, the daily dose should be increased gradually up to a maintenance dose of 1 mg/kg and has to be infused over at least 4 hours. Continuous infusion appears to reduce adverse reactions [18].

Pharmacokinetics of Conventional Amphotericin B

Amphotericin B has to be administered intravenously. 95-99% of the drug are bound to plasma proteins, mainly to LDL, albumin and α 1 acid glycoprotein [23, 24].

In two patients, who had been on long-term amphotericin B treatment, the total clearance (CL) was 1,800 mL/h (about 25 mL/h/kg) and the mean terminal half-life, representing the elimination from the deep peripheral compartment ($t_{1/2\gamma}$) was 15 days. The renal clearance accounted for only 3% of the total body clearance (see Table 1) [25]. In both patients amphotericin B had obviously caused a remarkable renal damage. In another case report a peak concentration of 1.8 μ g/mL and a half-life ($t_{1/2\beta}$) of 21.5 hours was described after a dose of 0.5 mg/kg, which was given every other day. The sampling time was 48 h, because this patient was still on therapy [26]. In a study on healthy volunteers treated with low doses of amphotericin B, half-life was longer (30.8 to 50.0 h) and the amphotericin B clearance was slow (see Table 1) [27]. In eight patients with hematological malignancies, who had obtained a dose of 50 mg (0.78 mg/kg in average), amphotericin B was eliminated faster after the first dose (see Table 1). When amphotericin B had been dissolved in 20% intralipid solution instead of 5 % dextrose, amphotericin B concentrations were lower, the apparent volume of distribution at steady state (V_{ss}) was enhanced and CL was faster [28]. In five critically ill patients, who had been treated with a mean dose of 1.0 mg/kg, the mean amphotericin B peak concentration was lower (1.7 μ g/mL) and the mean half-life was 26.8 h, whereas the clearance turned out to be very slow (about 1 mL/h/kg, see Table 1) [29]. Bekersky and colleagues measured free and protein-bound amphotericin B separately in the plasma of five healthy volunteers, who had obtained a single dose of 0.6 mg/kg of amphotericin B (see Table 1). Twenty percent of labeled amphotericin B were detected in the urine and 43 % in the feces after 7 days [23, 30].

Three studies on pharmacokinetics of conventional amphotericin B were performed in children [31-33]. The detailed data is displayed in Table 1. In children aged below 9 years the clearance was higher than in elder children (34 vs. 14 mL/h/kg) [31], but there was a negative correlation between age and amphotericin B half-life [32].

Thus, plasma pharmacokinetics of amphotericin B deoxycholate is variable with a elimination half-life ($t_{1/2\beta}$) of about 10 to 24 h and a CL of about 10 to 30 mL/h/kg.

Acute renal failure is a contraindication for treatment with conventional amphotericin B. Patients with irreversible, terminal renal failure requiring renal replacement therapy, however, may of course obtain amphotericin B deoxycholate. During hemodialysis with cuprophane or cellulose membranes amphotericin B clearance was 240 to 720 mL/h (about 3.4 to 10 mL/h/kg, n=4) [34]. In a more recent report on two cases, the amphotericin B clearance was also slow using high-flux dialyzers and elimination of amphotericin B by hemodialysis was poor (see Table 1) [35]. In another study on 25 patients, amphotericin B doses between 25 and 50 mg, infused during dialysis, three times per week were well tolerated [36]. Considering that renal elimination of amphotericin B accounts for only 20% of total clearance the risk of accumulation is anticipated to be low in patients on hemodialysis. Thus, the doses administered in these three studies appear to be relatively modest in comparison with the standard dosage of 1 mg/kg daily. In dialysis patients suffer-

Table 1. Plasma Pharmacokinetics of Conventional Amphotericin B

Diagnosis/ Population	n	Dose (mg/kg)	Day of therapy	T _{inf}	C _{max} (µg/mL)	AUC (µg·h/mL)	t _{1/2β} (h)	CL (mL/h/kg)	V _{ss} (L/kg)	Reference
Histoplasmosis	2	1.1/d 0.9/2d	50/ 136	4 h	1.8	Not shown	Not shown ^a	25	Not shown	Atkinson & Bennett 1978 [25]
Coccidioido- mycosis	1	0.5/2d	13/25/39	1 h	1.7	Not shown	21.5	Not shown	Not shown	Hoeprich 1990 [26]
Healthy volun- teers	8 8	0.10 0.25	1/2/5	0.25 mg/kg/h	0.55 0.89		30.8 50.0	10	0.50 ± 0.05 0.74 ± 0.13	Kan <i>et al.</i> 1991 [27]
Neutropenic patients	8	0.78	1	1 h	2.8 ± 1.2	29 ± 15	15 ± 5	33	0.56 ± 0.15	Ayestaran 1996 [28]
Critically ill	5	1	Not shown ^b	1 h	1.7 (1.5- 2.1)	18.7 (9.7- 28.3)	26.8 (10- 37)	1	2.41 (1.12- 4.32)	Heinemann 1997 [29]
Healthy volun- teers	free 5 total	0.6	1	2 h	0.06 1.43	1.22 ± 0.13 46.6 ± 7.2	6.8 Not shown	94 ± 15 13 ± 2	1.8 ± 0.2	Bekersky <i>et al.</i> 2002 [23,30]
Children (17 days– 15 years)	10	0.75–1.0	≥ 5	2-6 h	0.1-1.2	Not shown	202 (7- 693)	10 – 828	1.2-9.4	Starke <i>et al.</i> 1987 [33]
Children (3 weeks – 18 years, median 11 years)	11	0.5 (d1) 1	1/3/7-10	4-6 h	1 ± 0.5 3 ± 2	Not shown	10 ± 1.5 6-21	26 ± 5 (7.7-44.2)	0.378 ± 0.025 (0.08-1.28)	Koren <i>et al.</i> 1988 [32]
Children (4 m – 14 a, mean 6.6 years)	9	0.25 - 1	1-7	2-4.5 h	0.78-10.2	Not shown	12–33	2-88	0.23-1.91	Benson & Nahata 1989 [31]
Hemodialysis	4	0.7-1.2	Not shown	Not shown ^c	Not shown	Not shown	Not shown	3.4–10 ^d	Not shown	Block <i>et al.</i> 1974 [34]
High effi- ciency-high flux hemo- dialysis	2	30-40 mg at dialysis	10	Not shown ^c	2.3	Not shown	Not shown	12-17 ^e	Not shown	Gussak <i>et al.</i> 2001 [35]
Critically ill on hemofiltration	2	1.0	10	4 h	0.54	6.6	9	349	4.18	Bellmann <i>et al.</i> 2003 [37]
off hemofiltration	2	1.0	10	4 h	1.10	42.4	30	68	1.73	

n, number of subjects enrolled; T_{inf}, infusion time; AUC, total area under the concentration-time curve, AUC₀₋₂₄; CL, amphotericin B clearance; V_{ss}, apparent volume of distribution at steady state; data is displayed as mean ± SD and/or (range); ^a t_{1/2}, γ was 15 d, ^b pharmacokinetic assessment was performed at "presumed steady state"; ^c amphotericin B was administered during each hemodialysis, therefore it can be assumed, that it was given 3 times a week and T_{inf} was about 4 h; ^d amphotericin B clearance by hemodialysis; ^e amphotericin B clearance by hemodialysis calculated for a standard body weight of 70 kg.

ing from life threatening invasive fungal infections, however, higher doses may be required.

In two critically ill patients with terminal renal failure, who required hemofiltration instead of intermittent hemodialysis because of hemodynamic instability, amphotericin B clearance appeared to be faster than in patients at the ICU

with normal renal function (349 vs. 68 mL/h/kg, see Table 1). Therefore a daily dose of 1 mg/kg or even 1.5 mg/kg may be appropriate [37].

Systematic investigations on amphotericin B pharmacokinetics in patients with impaired liver function are lacking. In a preclinical study on dogs, complete biliary obstruc-

tion lead to enhanced amphotericin B plasma levels [38]. However, by the manufacturer no dose adjustment is recommended for patients with hepatic failure.

Since no metabolites of amphotericin B have been identified, pharmacokinetic interaction can be expected to play a minor role in amphotericin B therapy [30, 39, 40]. However, a delayed elimination of antipyrine has been demonstrated. This was ascribed to the inhibition of CYP enzyme synthesis by an unspecific damage of hepatocytes [41, 42, 43].

Tissue distribution of amphotericin B displayed a high variability in animal experiments, even within the same species. The highest tissue levels were detected in the spleen (24.8 $\mu\text{g/g}$ after administration of 1 mg/kg of amphotericin B; the plasma level was 0.08 $\mu\text{g/mL}$ under identical conditions) and in the liver, followed by kidney and lung. Amphotericin B concentrations in brain were very low [44-53].

Two studies on amphotericin B distribution in human autopsy material confirmed the amphotericin B accumulation in liver and spleen. Amphotericin B concentrations in lung and kidney were intermediate (mean levels 11 and 5 $\mu\text{g/g}$, respectively, in the lung and 11 to 16 $\mu\text{g/g}$ in the kidney). In myocardium and brain tissue the amphotericin B concentrations were low (3.7 and 1.33 $\mu\text{g/g}$ in the myocardium [54, 55] and 1.0 ± 1.8 in the brain [55]). No plasma concentrations are available for comparison in these two autopsy studies.

LIPID-FORMULATED AMPHOTERICIN B

Lipid formulations of amphotericin B have been developed to overcome nephrotoxicity and infusion-associated adverse effects. Liposomal amphotericin B (AmBisome[®], Gilead, Dublin, Ireland), amphotericin B colloidal dispersion (Amphotec[®], Amphocil[®], Three Rivers Pharmaceuticals, Cranberry Township, PA) and amphotericin B lipid complex (Abelcet[®], The Liposome Company Incorporation, Princeton, NJ.) are in clinical use.

Liposomal amphotericin B consists of spherical liposomes, 45 to 80 nm in size. The liposomal bilayer membrane contains hydrogenated soy phosphatidylcholine, cholesterol, distearoylphosphatidylglycerol and amphotericin B in a molecular ratio of 2:1:0.8:0.4 [56]. Amphotericin B colloidal dispersion is a cholesteryl sulfate complex of amphotericin B (in a molecular ratio of 1:1), forming disk-like structures with a diameter of about 115 nm and a thickness of about 4 nm [57]. Amphotericin B lipid complex comprises L- α -dimyristoylphosphatidylcholine, L- α -dimyristoylphosphatidylglycerol and amphotericin B forming ribbon-like structures, 1,600 to 11,000 nm in length [58, 59].

Pharmacokinetics of Lipid-Formulated Amphotericin B

Liposomal Amphotericin B

After infusion of a single dose of 2 mg/kg of liposomal amphotericin B over 2h, pharmacokinetic parameters were calculated using a non-compartmental method in 5 healthy volunteers. C_{max} was 22.9 ± 10 $\mu\text{g/mL}$, the area under the concentration-time curve from zero to infinity ($\text{AUC}_{0-\infty}$) was 288 ± 209 $\mu\text{g}\cdot\text{h/mL}$, $t_{1/2}$ 6.0 ± 2.1 h, V_{ss} 0.8 ± 0.6 mL/kg and CL amounted 9.7 ± 5.4 mL/h/kg. One week after administra-

tion, only 4.5% of the drug were recovered from urine and only 4.0% from the feces. [30]. After infusion of a dose of 3 mg/kg (infusion time [T_{inf}] = 1 h) liposomal amphotericin B pharmacokinetics were investigated in 10 patients [60]. Mean C_{max} was similar (29 $\mu\text{g/mL}$), V_{ss} was smaller (0.37 L/kg) and $t_{1/2}$ β was longer (23.6 h). The mean $\text{AUC}_{0-\infty}$ was 423 $\mu\text{g}\cdot\text{h/mL}$ and CL was 23 mL/h/kg. In another study, 36 patients with febrile neutropenia obtained 1.0, 2.5, 5.0 or 7.5 mg/kg/d for empiric treatment. The mean duration of therapy comprised 9.2 ± 0.8 days (T_{inf} = 1 h) [61]. Above a dose of 2.5 mg/kg an over-proportional increase in AUC was observed (doubling the dose lead to a 4 fold increase in AUC). Mean half-life was about 6-10 h, which is shorter than in the study mentioned before. The $\text{AUC}_{0-\infty}$ was 213 ± 196 $\mu\text{g}\cdot\text{h/L}$ after 2.5 mg/kg at steady state. After administration of 5 mg/kg, C_{max} was about 90 $\mu\text{g/mL}$ and $\text{AUC}_{0-\infty}$ 621 ± 371 $\mu\text{g}\cdot\text{h/L}$ during steady state. V_{ss} declined from about 0.2 L/kg (about 0.4 L/kg in the two low-dose groups) after the first infusion to about 0.1 L/kg after the last infusion and the amphotericin B clearance also decelerated during the treatment period, e.g. from 21 ± 14 mL/h/kg to 11 ± 6 mL/h/kg in the group treated with 5 mg/kg. This pharmacokinetic characteristics of liposomal amphotericin B were attributed to a saturable uptake by reticulo-endothelial cells [61]. In another study on 12 patients with suspected or documented invasive fungal infections, the mean half-life amounted 17.2 h [62]. During high-dose treatment (7.5-15.0 mg/kg/day) pharmacokinetics of liposomal amphotericin B was investigated in 44 immunocompromised patients. The mean half-life was 5.0-10.5 h, the amphotericin B clearance was also comparable with that in healthy subjects (5-25 mL/h/kg, declining with increasing duration of treatment). V_{ss} was between 0.13 and 0.23 L/kg. On day 7 of treatment with 15 mg/kg (T_{inf} = 2 h), a C_{max} as high as 178.6 ± 49.0 $\mu\text{g/mL}$ and an $\text{AUC}_{0-\infty}$ of $1,355 \pm 693$ $\mu\text{g}\cdot\text{h/mL}$ were achieved. After a single dose of 7.5 mg/kg, the values were 75.9 ± 58.4 $\mu\text{g/mL}$ and $815 \pm 1,068$ $\mu\text{g}\cdot\text{h/mL}$, respectively [63].

The first reports on pharmacokinetics of liposomal amphotericin B during renal replacement therapy were published in 1994. Peak and trough levels were measured in one patient on hemofiltration [64] and in one on hemodiafiltration [65]. C_{max} was 4.24 $\mu\text{g/mL}$ and C_{min} was 1.11 $\mu\text{g/mL}$ after 3 mg/kg on day 3 of AmBisome treatment during hemofiltration. No amphotericin B was detectable in the ultrafiltrate [64]. In the patient on hemodiafiltration, who had obtained 2 mg/kg of liposomal amphotericin B (T_{inf} = 1 h), C_{max} was 4.88 $\mu\text{g/mL}$ and the amphotericin B sieving coefficient was 0.07-0.45 [65]. In 16 critically ill patients Heinemann and colleagues [66] found a median C_{max} of 14.4 $\mu\text{g/mL}$ after a dose of 3 mg/kg (T_{inf} = 1 h). Median $t_{1/2}$ β was 13.5 h, V_{ss} was 0.37 L/kg and the median CL was as low as 0.23 mL/h/kg. In one patient pharmacokinetics was determined during hemodialysis as well as during a period of continuous venovenous hemofiltration. C_{max} , $t_{1/2}$, and CL were similar on and off renal replacement therapy [66]. In a more recent study on 9 critically ill patients (6 on hemofiltration, 3 off hemofiltration) lipid-formulated and liberated, plasma protein bound amphotericin B were separately determined after administration of a dose of 4 mg/kg during steady state [37]. The infusion time was 4 h. For total liposomal amphotericin B, the C_{max} values were 2.66 and 3.44 $\mu\text{g/mL}$ on and off hemofil-

tration, respectively. The low peak levels can be probably explained by the longer infusion time (4 h instead of 1 h). The mean $AUC_{0-\infty}$ values were 42.2 $\mu\text{g}\cdot\text{h}/\text{mL}$ and 49.5 $\mu\text{g}\cdot\text{h}/\text{mL}$, half-lives 13.6 and 14.9 h, CLs 140 and 61 $\text{mL}/\text{h}/\text{kg}$ and V_{ss} values 2.27 and 1.12 L/kg on and off hemofiltration, respectively. The difference in clearance was statistically significant. For liberated amphotericin B, peak levels amounted 0.60 $\mu\text{g}/\text{mL}$ and 0.51 $\mu\text{g}/\text{mL}$, half-lives 50 and 22 h and CLs 437 and 263 $\text{mL}/\text{h}/\text{kg}$, respectively, on and off hemofiltration (differences not significant). Despite a slightly enhanced elimination probably no dose adjustment is required since AUC was similar on and off hemofiltration [37]. Similar data was obtained from a patient on liposomal amphotericin B who was treated with albumin dialysis for cholestatic liver failure [67].

Thus, there are remarkable differences in pharmacokinetic parameters between the different study populations reflecting the influence of a variety of pathophysiological changes. In critically ill patients obviously lower plasma levels are achieved.

Amphotericin B Colloidal Dispersion

In healthy volunteers low single doses of 0.25, 0.5, 1.0 and 1.5 mg/kg of amphotericin B colloidal dispersion have been administered at a rate of 0.5 $\text{mg}/\text{kg}/\text{h}$ [68]. The half-life was much longer than that of liposomal amphotericin B and increased with the dose form 86 \pm 20 h after 0.25 mg/kg to 244 \pm 49 h after 1.0 mg/kg (235 \pm 74 h after 1.5 mg/kg). The clearance was rather constant and amounted about 26 $\text{mL}/\text{kg}/\text{h}$. The apparent volumes of distribution at steady state were 3.4 \pm 0.7 L/kg after infusion of 0.25 mg/kg and 7.9 \pm 1.0 L/kg after 1.5 L/kg . In the group that had obtained 1.5 mg/kg , a C_{max} of 2.5 \pm 1.0 $\mu\text{g}/\text{mL}$ was measured. The $AUC_{0-\infty}$ increased in a linear fashion with the escalation of the dosage (from 9.4 \pm 1.8 $\mu\text{g}\cdot\text{h}/\text{mL}$ to 57.3 \pm 14.3 $\mu\text{g}\cdot\text{h}/\text{mL}$). Population pharmacokinetics of amphotericin B colloidal dispersion was calculated from data of 51 bone marrow transplant recipients [69]. The mean V_{ss} was 4.21 L/kg (4.57 L/kg in children) the total clearance was as high as 111 $\text{mL}/\text{h}/\text{kg}$ (144 $\text{mL}/\text{h}/\text{kg}$ in children), $t_{1/2}$ β was 32 h and the dose normalized AUC (AUC/dose) was 9.6 $\mu\text{g}\cdot\text{h}/\text{mL}$ per 1 mg/kg in adults and 7.1 $\mu\text{g}\cdot\text{h}/\text{mL}$ per 1 mg/kg in children. The daily doses were highly variable (0.5 – 8.0 $\text{mg}/\text{kg}/\text{d}$, T_{inf} = 4 h). So far, pharmacokinetics of amphotericin B colloidal dispersion has not been investigated in patients suffering from chronic renal insufficiency or impaired liver function. The influence of intermittent hemodialysis is unknown. Critically ill patients on continuous veno-venous hemofiltration displayed C_{max} - and $AUC_{0-\infty}$ values that were slightly below those measured in critically ill patients off hemofiltration (0.73 $\mu\text{g}/\text{mL}$ vs. 0.82 $\mu\text{g}/\text{mL}$ and 8.7 $\mu\text{g}\cdot\text{h}/\text{mL}$ vs. 18.4 $\mu\text{g}\cdot\text{h}/\text{mL}$; T_{inf} = 4 h). CL and V_{ss} appeared to be slightly but not significantly enhanced by hemofiltration. Therefore, probably no dose adjustment is required during continuous hemofiltration [37].

In comparison with liposomal amphotericin B, total amphotericin B levels were much lower, whereas V_{ss} and CL were much higher in patients treated with amphotericin B colloidal dispersion. However, when liberated amphotericin B (bound to lipoproteins in plasma) was analyzed, ampho-

tericin B pharmacokinetics were similar for treatment with amphotericin B colloidal dispersion and for treatment with liposomal amphotericin B [37].

Amphotericin B Lipid Complex

A single dose study was performed in healthy volunteers treated with 0.10 mg/kg (n=3), 0.25 mg/kg (n=7) or 0.50 mg/kg (n=8) of amphotericin B lipid complex (T_{inf} = 0.25 $\text{mg}/\text{kg}/\text{h}$). Mean C_{max} values were 0.116, 0.214 and 0.272 $\mu\text{g}/\text{mL}$, respectively. Thus, a 5 fold increase in the amphotericin B dose lead to an elevation of its mean plasma level by a factor of 2.25. The mean $t_{1/2}$ was between 19 h (after 0.1 mg/kg) and 45 h (after 0.50 mg/kg). The mean clearance amounted about 80 $\text{mL}/\text{h}/\text{kg}$ and the mean V_{ss} increased from 1.71 (after 0.1 mg/kg) to 3.93 L/kg (after 0.5 mg/kg) [27]. Different groups of patients were included in pharmacokinetic investigations by Adedoyin and colleagues, who used whole blood samples [70]: Asymptomatic HIV infected patients obtained single doses of 0.6 and 1.2 mg/kg of amphotericin B lipid complex respectively (T_{inf} = 18 minutes). Like in healthy volunteers, there was an increase in half-life (107 to 144 h), CL (31 to 67 $\text{mL}/\text{h}/\text{kg}$) and V_{ss} (4.6 to 7.9 L/kg) with increasing doses. The mean C_{max} was 2.72 $\mu\text{g}/\text{mL}$ after 1.2 mg/kg . In patients receiving antineoplastic chemotherapy, maximum concentrations were 1.14 $\mu\text{g}/\text{mL}$ and 1.62 $\mu\text{g}/\text{mL}$ after a 7 d treatment with 2.5 or 5.0 $\text{mg}/\text{kg}/\text{d}$ (T_{inf} = 2 h). The steady state appeared to be reached on day 2 or 3 of therapy in spite of the long half-life of amphotericin B lipid complex. In neutropenic patients with suspected or proven fungal infection, a C_{max} of 2.4 \pm 0.9 $\mu\text{g}/\text{mL}$ was measured after a single dose of 5 mg/kg (T_{inf} = 2 h). Similar data was obtained in patients suffering from mucocutaneous Leishmaniasis [70]. Another study was performed on 17 patients with proven or suspected fungal infection by the same authors' group. The patients obtained 5 mg/kg of amphotericin B lipid complex for 10 to 17 d (T_{inf} = 2 h) [71]. The results of the former investigations were confirmed: No significant amphotericin B accumulation took place. The half-life was as long as 393 \pm 486 h after the last dose. In 3 children with hepatosplenic candidiasis, who had obtained 2.5 mg/kg , pharmacokinetics was determined on day 1, 7 and 42 of treatment [72]. Mean C_{max} was 2.05 $\mu\text{g}/\text{mL}$ on day 7 and 1.69 on day 42 (T_{inf} = 1 h). Thus, there was a slight decline in plasma levels during therapy rather than an accumulation.

Pharmacokinetics of amphotericin B lipid complex in 4 healthy subjects was compared with that in 2 patients suffering from renal failure (one patient had a severely and the other one a moderately impaired renal function). The dose was 2.5 mg/kg , the infusion time 2 h. In the healthy volunteers $t_{1/2}$ was 140 h, the clearance about 70 $\text{mL}/\text{h}/\text{kg}$ and V_{ss} was about 10 L/kg . The patient with moderately impaired renal function displayed an increase in half-life (385 h) and in V_{ss} , while CL was reduced. However, in the patient with a creatinine clearance below 30 $\text{mL}/\text{min}/1.73 \text{ m}^2$ body surface area, CL was only slightly reduced and the other parameters were unchanged. Therefore the influence of renal function on amphotericin B lipid complex clearance could not be clarified by this study [70]. In two critically ill patients on continuous veno-venous hemofiltration, who had obtained a dose of 5 mg/kg , plasma concentrations of amphotericin B

lipid complex were lower (C_{max} was 0.39-0.74 $\mu\text{g/mL}$) and the half-life was shorter (14-19 h) than in the previous studies. The clearance was 377-729 mL/h/kg which is similar to the clearance measured in patients treated for leishmaniasis [70]. V_{ss} amounted 6-12 L/kg. In one of the two patients amphotericin B plasma levels were measured on and off hemofiltration revealing nearly identical time-concentration profiles [73].

Lipid-Formulated Amphotericin B in Liver Failure

Systematic trials assessing the pharmacokinetics of lipid-formulated amphotericin B in patients with impaired liver function are lacking. One liver transplant recipient with graft failure presented enhanced plasma and lung amphotericin B concentrations after AmBisome treatment [74].

Tissue Distribution of Lipid-Formulated Amphotericin B

In animal experiments, the highest amphotericin B concentrations were found in the spleen (up to 400 $\mu\text{g/g}$ in rats treated with liposomal amphotericin B) and the liver, followed by lung and kidney [75].

Results of three small autopsy studies on liposomal amphotericin B and amphotericin B lipid complex revealed a very high variability in tissue concentrations [76, 77]. The highest amphotericin B concentrations were measured in the liver (92.8-291.3 $\mu\text{g/g}$ after treatment with a cumulative dose of 820-3,428 mg of liposomal amphotericin B and 196-868 $\mu\text{g/g}$ after 1,200-22,200 mg of amphotericin B lipid complex) and the spleen. Intermediate amounts were recovered from the lung (0.55-45.39 $\mu\text{g/g}$ after liposomal amphotericin B and 222-1,019 $\mu\text{g/g}$ after amphotericin B lipid complex) and from the kidneys. Penetration of lipid formulated amphotericin B into the brain was found to be low (1-2 $\mu\text{g/g}$ for liposomal amphotericin B and for amphotericin B lipid complex) [76, 77]. In a patient who had died from graft dysfunction after liver transplantation amphotericin B liver concentration was 105.7 $\mu\text{g/g}$ and lung concentration was 69.4 $\mu\text{g/g}$ after a cumulative dose of 1,200 mg liposomal amphotericin B [74]. Because of the great differences in cumulative doses and duration of treatment, amphotericin B tissue concentrations are hardly comparable and do not support superiority of either liposomal amphotericin B or amphotericin B lipid complex concerning their tissue penetration.

In autopsy material obtained from 13 patients, who had been on therapy with amphotericin B colloidal dispersion, the mean amphotericin B lung concentration exceeded that measured in samples derived from 7 patients on liposomal amphotericin B significantly by a factor of three. No significant differences between the two treatment groups were detected in liver, spleen, myocardium and brain. The cumulative doses had been 2.91 $\text{g} \pm 3.68 \text{ g}$ and 2.74 $\pm 3.75 \text{ g}$, respectively [78]. In lung tissue samples taken from patients with lung cancer during surgery, tissue pharmacokinetics of liposomal amphotericin B were investigated after a single dose of 1.5 mg/kg [79]. Samples were taken between 10 and 25 hours after the end of infusion. Plasma concentrations decreased during the observation period from 3.54 to 0.98 $\mu\text{g/mL}$, whereas tissue levels increased from 0.95 to 2.58 $\mu\text{g/g}$.

Dosage and Active form of Lipid-Formulated Amphotericin B

The impressive differences in pharmacokinetics between the three lipid formulations, liposomal amphotericin B, amphotericin B colloidal dispersion and amphotericin B lipid complex, have been ascribed to their different particle size and - shape [59, 66, 68, 80, 81]. Because of this pharmacokinetic diversity, their clinical equivalence has been questioned [82]. The clinical efficacy of lipid-formulations has been compared with that of conventional amphotericin B using standard doses. These studies suggest that the three lipid-formulations are as effective as conventional amphotericin B [83]. Only liposomal amphotericin B and amphotericin B lipid complex were compared directly using similar daily doses and the outcome was also comparable [84, 85]. Equivalence to conventional amphotericin B was assessed *in vitro*, by animal experiments and in clinical trials for liposomal amphotericin B [86-88] and for amphotericin B colloidal dispersion [89-91]. A comparable efficacy of lipid-formulations and conventional amphotericin B is achieved, if the dose of lipid-formulated amphotericin B is about five times higher.

Liberation of Amphotericin B from its Lipid-Encapsulation

The mechanisms underlying the reduced toxicity along with preserved antimycotic efficacy are still a matter of discussion. Accumulation of liposomal amphotericin B at the sites of fungal infection was observed *in vitro* and is supposed to be responsible for efficacy in spite of the absence of free amphotericin B in plasma [55, 58, 81, 91, 92]. However, a significant amount of amphotericin B is obviously liberated in the plasma and bound to plasma proteins [23, 37, 93].

After administration of liposomal amphotericin B to healthy subjects, amphotericin B is slowly released from liposomes. More than 90% of the liberated amphotericin B fraction are bound to plasma proteins [23, 94]. The lower toxicity of liposomal amphotericin B has been ascribed to smaller amounts of unbound amphotericin B in the plasma. It has been postulated that its antifungal effectiveness is maintained by its accumulation at target site, particularly at fungal cell membranes. Deposition of liposomes on fungal surfaces and amphotericin B uptake by fungal cells after treatment with liposomal amphotericin B could be visualized by *in vitro* experiments [56]. It was hypothesized that amphotericin B is cleaved from liposomes by phospholipases [94]. The liposomes are obviously removed from the circulation by cells of the RES *via* endocytosis. Therefore an efficacy against intra-cellular parasites has been assumed.

In vitro experiments on amphotericin B colloidal dispersion revealed that amphotericin B dissociates from its lipid moiety at therapeutic concentrations (0.1 $\mu\text{g/mL}$). After dissociation, amphotericin B is bound mainly to HDL. Amphotericin B colloidal dispersion is rapidly taken up by cells of the mononuclear phagocytic system resulting in comparably low plasma levels and reduced toxicity [89].

For amphotericin B lipid complex it is supposed, that amphotericin B is liberated from its lipid-encapsulation at the target site by fungal or host phospholipases [95]. Ex-

periments with knock-out mutants, however, could not confirm the role of fungal phospholipases [96]. After incubation of plasma with amphotericin B lipid complex, amphotericin B was found to bind to high density lipoprotein (HDL 3), whereas it bound to lipoprotein-deficient fractions (LPDP) after incubation with amphotericin B deoxycholate [97].

FLUCYTOSINE

Flucytosine (5-fluorocytosine, Ancotil[®], ICN Pharmaceuticals Ltd., Cedarwood, Chineham Business Park, Hampshire, UK) is in therapeutic use since 1968 [98]. It is taken up by susceptible fungal cells *via* the enzyme cytosine permease, which is localized in the cell membrane. Inside the fungal cell flucytosine is desaminated to its active form 5-fluorouracil (5FU). Its antimycotic activity is based on two molecular mechanisms: firstly, 5FU is converted into 5-fluorouridine monophosphate (FUMP), 5-fluorouridine diphosphate (FUDP) and finally 5-fluorouridine triphosphate (FUTP), which is incorporated into the fungal RNA instead of uridylic acid thus inhibiting protein synthesis. Secondly, 5FU is converted into fluorodeoxyuridine monophosphate (FdUMP) by the uridine monophosphate pyrophosphorylase, which inhibits the fungal thymidylate synthetase, a key enzyme in DNA synthesis. The main adverse effects of 5FU, hepatotoxicity and myelotoxicity, have been ascribed to the occurrence of significant plasma levels of 5FU during treatment with flucytosine. Flucytosine may convert to 5FU spontaneously or under the influence of the gut flora [99].

The antimycotic spectrum of flucytosine comprises *Candida* species, *Cryptococcus neoformans*, *Cladophialophora carionii*, *Fonsecaea* species and *Phialophora verrucosa* [100]. Because of frequently occurring resistance, flucytosine is usually administered in combination with amphotericin B. This therapeutic approach has been effective against several *Candida* species such as *C. tropicalis*, *C. parapsilosis* and *C. guilliermondii*, as well as against *Aspergillus* species [99].

After oral intake flucytosine is well absorbed, its bioavailability accounts for 76-89% [101]. It is highly water-soluble and only about 3-4% are bound to plasma proteins [102]. After oral administration, about 90% of flucytosine are eliminated unchanged through the kidneys *via* glomerular filtration [102-104]. In healthy volunteers, the half-life amounts 3-4 hours and V_{ss} 0.4-0.8 L/kg. The recommended daily dose is 150-200 mg/kg (37.5-50.0 mg/kg q.i.d.), the infusion time about 30 minutes, resulting in C_{max} and C_{min} values of 50-100 µg/mL and 25-50 µg/mL, respectively [99, 105]. The clearance of flucytosine is similar to the creatinine clearance. In patients with renal failure half-life can be as long as 85 h [106]. Therefore a dose reduction according to creatinine clearance is recommended: patients with a creatinine clearance of 20-40 mL/min/1.73 m² body surface area should obtain 37.5-50.0 mg/kg b.i.d., if the creatinine clearance is 10-20 mL/min/1.73 m² this dose should be administered once daily [106].

The favorable tissue penetration of flucytosine is ascribed to its small molecular size and its high solubility in water. In human cerebrospinal fluid (CSF) its concentrations reached 71-85% of the respective serum levels. In bronchial secretion 76%, in saliva 50% and in ascites 25-40% of the respective

serum concentrations were measured. Even in tissues, that are not easily accessible, significant amounts of flucytosine could be determined: in bone 3 µg/mL (30% of the respective serum level), 26 µg/mL (41% of serum concentration) in synovial fluid and in aqueous humour 10 µg/mL (20% of serum levels). More than 10 fold serum concentrations are measured in urine [107, 108]. Target site pharmacokinetics of flucytosine in bronchial secretion was investigated in the dog. Its concentration was rather constant (about 20 µg/mL) during a 3 h sampling period [109].

Flucytosine is efficiently removed by hemodialysis - its clearance during dialysis is identical with that of creatinine [34]. Therefore it should be administered after dialysis [34, 102, 106, 107, 110, 111]. For patients requiring continuous veno-venous hemofiltration different dose recommendations can be found in the literature. This may be due to different hemofiltration protocols, particularly different ultrafiltration rates, which influence flucytosine elimination. Ittel *et al.* recommended a dose of 25 mg/kg every 14 h [112]. A much higher dosage interval of 48-72 h was proposed by Thomson and co-workers [113]. Hepatic metabolism plays a minor role in elimination of flucytosine [101, 107, 111, 114]. Thus, probably no dose reduction is required in patients with impaired liver function. Data on flucytosine pharmacokinetics, however, are very sparse in this group.

An increased hematotoxicity has to be expected when flucytosine is administered together with cytostatic and immunosuppressive drugs. Cytarabine, however, competitively inhibits flucytosine uptake by the fungal cell resulting in an impaired antimycotic efficacy [99].

AZOLES

Azole antimycotics include two subclasses of drugs: the imidazoles and the triazoles. Imidazoles contain an imidazole ring, which is a heterocyclic five-member ring with 2 nitrogen atoms. The triazole group has 3 nitrogens. Most imidazole derivatives are locally applied. Only ketoconazole can be administered systemically. The majority of azoles for systemic use are triazoles. Beside fluconazole and itraconazole, new broad spectrum triazoles such as voriconazole, posaconazole and ravuconazole were introduced in therapy during the last years. Azole antimycotics inhibit C14 α desmethylase by binding to the hem group of CYP. C14 α desmethylase is required for the conversion of lanosterol into ergosterol. This molecular mechanism is in part responsible for the clinically relevant drug interactions of this class of antifungals. The extent of drug interactions, however, varies between the different azoles depending on their hepatic metabolism.

Ketoconazole

Ketoconazole (Nizoral[®], Janssen-Cilag, Beerse, Belgium) is an imidazole dioxolane derivative. It is active against *Candida* species, *Cryptococcus immitis*, *Histoplasma capsulatum*, *Malassezia furfur*, *Paracoccidioides brasiliensis* and against dermatophytes. But it is inactive against *Aspergillus* species and *Zygomycetes* [100]. Beside its antimycotic efficacy it decreases the synthesis of corticosteroids and testosterone synthesis [115]. It is also used in androgen independent prostate cancer [116]. Beside local application, it was

orally administered for skin and mucosal infections which failed to respond to topical therapy. Its bioavailability is highly variable. Enteral absorption is improved by food and acidic pH. In plasma, 84% of ketoconazole are bound to protein, mainly to albumin, and 15 % to erythrocytes. Only 1% exists as free drug [117].

The standard dose is 200 mg - 400 mg once per day. CYP3A4 is involved in its hepatic metabolism. CYP2C8 and CYP2C9 are probably also inhibited by ketoconazole. Furthermore, ketoconazole is an inhibitor of P-glycoprotein (PGP). Accordingly, numerous drug interactions have been described and ketoconazole is used as a model substance for CYP3A4 inhibition in pharmacokinetic studies e.g. [118-120]. For example, ketoconazole has been demonstrated to enhance plasma levels of cyclosporine A [121, 122] clarithromycin, telithromycin [123], everolimus [119], antihistamines [124], rosiglitazone [125] and many other drugs which are metabolized by the CYP system or eliminated by PGP. The metabolites of ketoconazole are inactive. Ketoconazole is eliminated mainly by the feces [117]. The plasma elimination is biphasic and dose dependent. The half-life during the first 10 h is about 2 h, the terminal half-life is 8 h. Ketoconazole has been reported to penetrate well into the urine, the saliva, the synovial fluid, into sebum and cerumen, but not sufficiently into the cerebrospinal fluid [117].

Fluconazole

Fluconazole contains two azole rings and a phenyl ring which is substituted by two fluoride atoms in position 2 and 4. It is soluble in water. Fluconazole is active against *Candida albicans* and *Cryptococcus species* [126, 127].

The main side effects of fluconazole are hepatotoxicity and prolongation of the QT interval in ECG bearing the risk of ventricular arrhythmias such as torsades de point.

Fluconazole has a bioavailability of more than 90% after oral administration [128] that is uninfluenced by food or pH [129]. A bioavailability of approximately 100% was determined even in critically ill patients after recent gastro-intestinal surgery [130]. After intake of 100 mg of fluconazole, a C_{max} of 1.7 $\mu\text{g/mL}$ was measured in healthy volunteers. The $AUC_{0-\infty}$ was 93 $\mu\text{g}\cdot\text{h/mL}$. After intake of 400 mg C_{max} was 9.1 $\mu\text{g/mL}$. T_{max} after oral administration was 0.5 h - 1.0 h. The plasma protein binding of fluconazole amounts only 12% [129], the plasma half-life about 30 h. Thus, steady state conditions are not reached before the 6th day of treatment with the maintenance dose. The total fluconazole clearance in healthy volunteers was 15-24 mL/h/kg [129-131] and V_{ss} about 0.75 L/kg [132, 133]. 60% to 80 % of fluconazole are eliminated unchanged by the kidneys *via* glomerular filtration. Tubular re-absorption takes place.

Only small amounts of fluconazole are metabolized in the liver. Nevertheless, a variety of relevant drug interactions has to be taken into account in clinical practice as a result of its mechanism of action [129]. Fluconazole inhibits hepatic CYP 3A4 and CYP 2C9 [121]. Co-administration of cisapride and fluconazole even at low doses such as 200 mg per day led to an increase in cisapride levels and a significant prolongation of the QT-interval. Several cases of complex ventricular arrhythmias occurred [134]. Therefore the simul-

taneous treatment with cisapride and fluconazole is contraindicated and cisapride has been withdrawn from the market in many countries. Prolongation of the QT interval as well as hepatotoxicity was observed when fluconazole was given together with antihistamines, such as astemizole, terfenadine or desloratadine [135, 136]. Therefore, this combination should also be avoided. Fluconazole prescription together with warfarin can significantly affect the prothrombin time (enhance the international normalized ratio [INR]) bearing the risk of life threatening bleedings [137, 138]. Frequent monitoring of INR is therefore mandatory if the combination is unavoidable.

Phenytoin levels are significantly enhanced by concomitant fluconazole therapy, since phenytoin is metabolized by CYP2C. Neurological side effects, such as double vision, dizziness, nystagmus and impaired coordination have been recognized [139-141].

Sulfonylureas, such as tolbutamide display significantly enhanced C_{max} and $AUC_{0-\infty}$ values, if taken together with fluconazole, which can cause severe hypoglycemia [142]. Co-administration of fluconazole with benzodiazepines such as midazolam and triazolam resulted in a prolonged hypnotic effect and amnesia [121, 143]. Plasma levels of the contraceptive hormones ethinyl estradiol and levonorgestrel were enhanced by 40% and 24%, respectively, after 200 mg of fluconazole. C_{max} of celecoxib, which has affinity to CYP2C9, increased by 60% and the AUC by 130% [144]. After administration of 100 mg of fluconazole b.i.d. for 3 d, the theophylline clearance was reduced by 15-18% [145]. Thus, fluconazole may increase the arrhythmogenic effect of theophylline. The zidovudine metabolism is also reduced by fluconazole [146]. Its AUC was increased by 20% after 15 days of fluconazole 200 mg per day. When the fluconazole dose was 400 mg per day, the AUC was enhanced by 74% [121].

Rifampin as an inducer of CYP3A caused a 20% decrease in fluconazole half-life and AUC [147, 148]. In critically ill patients this effect appears to be much more pronounced and probably leads to an insufficient antimycotic activity [148]. On the other hand, fluconazole enhances the AUC of rifabutin increasing the risk of uveitis [149].

In patients stabilized on cyclosporine A after kidney-, kidney-pancreas- or bone marrow transplantation, cyclosporine A levels will usually rise, when fluconazole treatment is started, particularly when the dose exceeds 100 mg/d. Nephrotoxicity is the major concern in this setting [150-155]. Tacrolimus plasma levels were increased by concomitant fluconazole administration. When fluconazole was administered orally, the tacrolimus dose had to be reduced by 56%; after intravenous infusion of fluconazole a dose reduction of only 26% was required [156, 157]. Sirolimus levels are also enhanced, when fluconazole is applied at the same time [158].

A favorable tissue distribution of fluconazole has been demonstrated in rats [121] and in rabbits [159]. In humans, fluconazole concentrations were determined in saliva, sputum, cerebrospinal fluid, vagina, blister fluid, blister roof, skin scrapings and in urine. The highest fluconazole concentrations were present in urine, in skin scrapings and in blister

roof (2 to 12 times higher than in plasma). In the other tissues, fluconazole concentrations were similar to those measured in the plasma. Concentrations in the cerebrospinal fluid were even 50 to 90% of the respective plasma levels [160-162]. Fluconazole penetration into the human brain was studied by Thaler and co-workers in tissue samples obtained during resection of brain tumors [163]. The brain concentrations amounted $17.6 \pm 6.6 \mu\text{g/g}$ ($133 \pm 74\%$ of the respective plasma levels) [163]. Fluconazole pharmacokinetics in the extra-cellular space of brain tissue was determined in rats using microdialysis technique. The ratio $\text{AUC}_{\text{Brain}} / \text{AUC}_{\text{Plasma}}$ was 0.6 in this model. After administration of 10 mg/kg, the maximum concentration in brain tissue was $8 \mu\text{g/mL}$ [164].

The required dose of fluconazole depends on the underlying disease. For localized candidiasis, such as onychomycosis a dose as low as 150 mg once per week is sufficient. Doses of 800-1,200 mg per day are required in critically ill patients [165]. Peak plasma levels of 40-60 mg/mL are achieved then [166]. In patients with renal failure fluconazole elimination is markedly slowed. When the creatinine clearance was 35 mL/min/1.73 m² body surface area (normal range 70-100 mL/min/1.73 m²), the half-life was enhanced by a factor of 3 (96 h) and the fluconazole clearance was reduced by one half (about 10 mL/h/kg) [131]. Therefore the manufacturer recommends a dose reduction by 50%, if the creatinine clearance is between 11 and 50 mL/min/1.73 m² [144]. Because of its low protein binding, its water solubility and its relatively small molecular size, fluconazole is efficiently eliminated by renal replacement therapy. After a hemodialysis for 3 h, the fluconazole plasma concentration was reduced by $26 \pm 3\%$, after 4 hours by $39 \pm 2\%$ [167]. In patients on continuous ambulatory peritoneal dialysis, pharmacokinetic parameters are similar to those in patients with a creatinine clearance of 35 mL/min/1.73 m² ($t_{1/2}$ was 79 h, CL 8 mL/kg/h) [168, 169].

Very high amounts of fluconazole are obviously eliminated by continuous veno-venous hemofiltration and hemodiafiltration. This is of particular relevance since in critically ill patients high plasma levels should be achieved. In patients on hemodiafiltration a mean peak concentration of 25.9 $\mu\text{g/mL}$, a plasma half-life of 9 h, a CL of 60 mL/h/kg and a V_{ss} of 0.7 L/kg were found after an intravenous dose of 800 mg ($T_{\text{inf}}=2$ h). Therefore the authors recommended a dose of 500-600 mg twice daily for patients on hemodiafiltration [170]. Muhl *et al.* have proposed to administer 400-800 mg per day in this group of patients [171]. For patients on hemofiltration, 800 mg once daily have been recommended [172].

Fluconazole is the standard drug for the treatment of suspected or proven *C. albicans* infections. Since this species is still very common, fluconazole plays an important role in antifungal prophylaxis. The pharmacokinetic behavior of fluconazole is well characterized and its excellent tissue penetration is of clear advantage.

Itraconazole

Itraconazole (Sporanox[®], Janssen-Cilag, Beerse, Belgium) is a highly lipophilic triazole. It is active against numerous

dermatophytes, such as *Trichophyton*, *Microsporum* and *Epidermophyton floccosum*, against yeasts, such as *Candida albicans* and *C. krusei*, *Cryptococcus neoformans*, *Pityrosporum* and *Trichosporum*. It has also some activity against several *Aspergillus* species, *Paracoccidioides brasiliensis*, *Cladosporium* and *Pseudallescheria boydii* [173, 174]. Beside gastro-intestinal adverse effects and hepatotoxicity, congestive heart failure was associated with itraconazole treatment [175].

Itraconazole is available as a capsule formulation. The bioavailability of the capsule formulation amounts about 55% and is highly variable. The absorption is improved by acidic gastric environment and by taking the capsule together with fatty food [176-178]. After bone marrow transplantation and in patients with HIV infection, a decreased bioavailability of the capsule formulation was found [179-181]. Two hydroxypropyl- β -cyclodextrin containing formulations have been developed: an oral solution with an improved bioavailability and a solution for i.v. administration. Unlike the capsule formulation, the oral solution should be taken without food.

In plasma, 99.8% of itraconazole are bound to proteins. Pharmacokinetics of itraconazole and its main metabolite were compared in healthy volunteers after intake of the conventional capsule formulation and the oral solution. The half-life is about 10-20 h after a single dose and about 30 h at steady state. After an oral dose of 200 mg C_{max} was 0.3 $\mu\text{g/mL}$ and the time to C_{max} (T_{max}) was 5 h. The peak concentration of the active metabolite hydroxy-itraconazole was about 0.5 $\mu\text{g/mL}$. No difference between the capsule formulation and the oral solution was found in itraconazole peak concentrations, T_{max} and $t_{1/2}$. However, the $\text{AUC}_{0-\infty}$ values for itraconazole and hydroxy-itraconazole were increased by about 30% when the oral solution had been taken [182]. In HIV infected patients, C_{max} was significantly higher (1.33 $\mu\text{g/mL}$) after the intake of the oral solution compared to the capsule formulation (0.74 $\mu\text{g/mL}$). Each formulation had been taken at a dose of 200 mg twice daily for 7 days [183]. The V_{ss} of itraconazole is relatively high (11 L/kg). Itraconazole is excessively metabolized by CYP3A4 in the liver. Thirty metabolites are known. The major active metabolite is hydroxy-itraconazole [184-186]. About 90% of itraconazole are eliminated as inactive metabolites within seven days (35% by the kidney and 54% *via* the feces). The unchanged drug can be recovered mainly from the feces [173].

Itraconazole concentrations in fat exceed plasma concentrations 17 fold and those in skin 19 fold. The ratio of tissue concentration to plasma concentration is about 4 in bone, about 3 in liver and about 2 in lung, kidney, spleen and muscle [183]. *In vitro* experiments revealed an itraconazole accumulation in alveolar macrophages [187].

The oral standard dose is 200 mg b.i.d. If i.v. administration is required, 200 mg b.i.d. should be given for the first two days followed by 200 mg once daily. Treatment should be continued orally with 200 mg b.i.d. as soon as possible to avoid accumulation of the solvent hydroxypropyl- β -cyclodextrin. Since itraconazole is keratinophilic and tends to accumulate in skin, hair and nail, a one-week oral pulse therapy at a daily dose of 200-400 mg is effective against

dermatophyte skin infections. Two pulses with 400 mg per day are required for treatment of onychomycosis of the fingers, three pulses for onychomycosis of the toes [174].

In critically ill patients intravenous administration of 200 mg b.i.d. for the first two days followed by 200 mg i.v. once daily over 5 days and then by 200 mg of the oral solution b.i.d. was reported to yield sufficient trough levels exceeding 0.25 µg/mL [188].

Itraconazole is hardly eliminated by hemodialysis. Hydroxypropyl-β-cyclodextrin, however, is dialyzable. Hemodiafiltration appears to require enhanced doses. An oral dose of 300 mg t.i.d. resulted in a C_{max} of only 0.28 µg/mL (about half of the C_{max} after 200 µg/mL given to subjects with normal renal function) [183, 189]. Since itraconazole is a strong inhibitor of CYP 3A4, co-administration of terfenadine, astemizole, cisapride, midazolam, triazolam, quinidine, simvastatin, lovastatin and atorvastatin must be avoided. Enhanced plasma levels of warfarin, immunosuppressants such as cyclosporine A, tacrolimus, sirolimus and everolimus, of anti HIV drugs such as ritonavir, indinavir, saquinavir, of digoxin, carbamazepine, rifabutin and of methylprednisolone have to be taken into account [121, 190]. Co-administration of negative inotropic drugs may enhance the risk of congestive heart failure and plasma levels of calcium antagonists are enhanced by itraconazole (see Table 2) [191-194].

Itraconazole has a broader antimycotic spectrum than fluconazole, which is advantageous in immunocompromised

patients. It has proven to be effective in antifungal prophylaxis in this group as well as in critically ill patients. In treatment of onychomycosis it was superior to fluconazole [174].

Voriconazole

The chemical structure of voriconazole (Vfend[®], Pfizer Limited, Sandwich, Kent, UK) is similar to that of fluconazole. But a methyl group has been introduced into the propanol back bone and one of the two triazole groups has been replaced by a fluoropyrimidine ring. Voriconazole has a broader antimycotic spectrum than fluconazole: It is active against non-albicans *Candida* species and against *Aspergillus* as well as against *Scedosporium*, *Fusarium*, *Histoplasma capsulatum*, *Blastomyces dermatitidis* and *Coccidioides immitis*. But voriconazole lacks activity against *Zygomycetes*.

Voriconazole has an intermediate plasma protein binding of 58 % and a bioavailability as high as 96 % after oral administration, which is independent from the gastric pH. It is available as a tablet form, as an oral solution and as an i.v. formulation. The half-life is dose-dependent. After administration of 3 mg/kg i.v. or 200 mg p.o. it is about 6 h. The peak levels rise in a non-linear fashion with the increase in the administered dose. The C_{max} was 3.01 µg/mL after an i.v. dose of 3 mg/kg b.i.d. (T_{inf} =1h) and 1.89 µg/mL after 200 mg b.i.d. given orally. The trough levels are 0.5-2.5 µg/mL, when standard dosage is applied. An increase of the i.v. dose

Table 2. Drug Interactions of Itraconazole

Drugs displaying enhanced levels during itraconazole therapy	Possible complications	Reference	Drugs that lower itraconazole levels	Reference
HMG-CoA-reductase inhibitors (lovastatin, simvastatin, atorvastatin)	Rhabdomyolysis	Lomaestro & Piatek 1998 [121]	Phenytoin	Lomaestro & Piatek 1998 [121]
Immunosuppressives (Cyclosporine A, tacrolimus, sirolimus, everolimus)	Over-immunosuppression, nephrotoxicity, CNS toxicity	Lomaestro & Piatek 1998 [121]	Carbamazepine	Lomaestro & Piatek 1998 [121], Sporanox package insert [173]
Antihistamines (terfenadine, astemizole)	Cardiac arrhythmias	Lomaestro & Piatek 1998 [121, Sporanox package insert [173]	Tuberculostatics (rifampin, rifampicin, isoniazid)	Lomaestro & Piatek 1998 [121] Sporanox package insert [173]
Midazolam, triazolam	Over-sedation	Lomaestro & Piatek 1998 [121]		
Warfarin	Bleedings	Lomaestro & Piatek 1998 [121]		
Quinidine	Arrhythmias, nausea	Sporanox package insert [173]	Drugs that enhance itraconazole levels	Reference
Calcium antagonists (felodipine, nifedipine)	Hypotension, edema	Jalava <i>et al.</i> 1997 [192], Neuvonen & Suhonen 1995 [193], Tailor <i>et al.</i> 1996 [194]	Macrolides (clarithromycin, erythromycin)	Sporanox package insert [173]
Anti HIV medication (ritonavir, indinavir, saquinavir)	Enhanced toxicity	Sporanox package insert [173]	Anti HIV medication (ritonavir, indinavir, saquinavir)	Sporanox package insert [173]

by a factor of 1.7 lead to a 2.4 fold C_{\max} value and elevated the AUC over the dosage interval (AUC_{τ}) by a factor of 3.1 [195, 196]. The peak level was reached 1.5-3 h after an oral dosage. V_{ss} is about 4.5 L/kg, the voriconazole clearance in healthy volunteers is about 7 L/h (100 mL/h/kg). About 80% of the administered dose are eliminated by the kidney after metabolization in the liver, 20% *via* the feces [196, 197]. Animal experiments revealed a non-linear decay of voriconazole plasma levels which was accelerated after 6-20 h depending on the administered dose [196].

Voriconazole is metabolized in the liver. The rate-limiting step in voriconazole degradation, the fluoropyrimidine-N-oxidation, depends on CYP2C9. CYP3A4 and CYP2C19 are also involved in voriconazole metabolisms but play a minor role. CYP2C9 displays a genetic polymorphism. Consequently, there are fast and slow voriconazole metabolizers. In slow metabolizers, a 4 fold elevation in voriconazole plasma levels has been described. In the Asian population the prevalence of slow voriconazole metabolizers is reported to be about 20% [195, 196].

The mechanism of action of voriconazole comprises inhibition of CYP3A4 and CYP2C10. On the other hand, CYP3A4 and CYP2C19 are involved in its metabolism. Therefore, numerous drug interactions are observed during treatment with voriconazole. In particular, plasma levels of immunosuppressants are enhanced. Thus, the dose of cyclosporine A has to be reduced by 50 % and the dose of tacrolimus to one third, if voriconazole is co-administered. Frequent monitoring of plasma levels of immunosuppressants is necessary to prevent nephrotoxicity and over-immunosuppression. Co-administration of sirolimus has to be avoided, since C_{\max} of sirolimus is enhanced by 556% and AUC_{τ} by 1,014% [198]. Plasma concentrations of histamine blockers (e.g. terfenadine and astemizole or cimetidine), cisapride, pimozone and quinidine are also enhanced by voriconazole. As mentioned, this can provoke QT prolongation and torsades de point. In patients on warfarin or coumarin an increased bleeding risk by voriconazole has to be considered. Therefore, a dose adaptation and frequent controls of INR are required. An increased and prolonged effect of benzodiazepines with over-sedation has to be anticipated. Co-administration of voriconazole together with sulfonyleureas may cause hypoglycemia. Prednisolone levels are moderately enhanced by voriconazole. *In vitro* experiments on liver microsomes suggest, that levels of HMG-CoA reductase inhibitors are also elevated by voriconazole. The omeprazole dose should be reduced by 50% under concomitant voriconazole treatment [199]. Enzyme inducers, particularly rifampicin, carbamazepine and phenobarbital, excessively reduce voriconazole concentrations and co-administration is therefore contraindicated. If the combination of rifabutin and voriconazole is inevitable, voriconazole dosage should be increased to 5 mg/kg i.v. or 350 mg p.o. twice a day [198]. Complex interactions are faced with phenytoin. Therefore, frequent phenytoin level controls are mandatory and voriconazole dosage has to be enhanced up to 5 mg/kg i.v. twice daily or 400 mg p.o. twice daily. *In vitro* experiments suggest that the voriconazole metabolism is delayed by HIV protease inhibitors such as saquinavir, amprenavir and nelfinavir. On the other hand, voriconazole may inhibit the me-

tabolism of these drugs [198]. *In vitro* experiments suggest, that the voriconazole disposition is also delayed by the non-nucleoside HIV reverse transcriptase inhibitors delaviridine and efavirenz [195, 198, 200]. Long-term intake of St. Johns wort enhanced the voriconazole clearance and reduced the $AUC_{0-\infty}$ and the C_{\max} significantly [201]. Co-administration of anidulafungin had no effect on voriconazole pharmacokinetics [202].

The tissue distribution of voriconazole has been investigated in animals. Five minutes after administration of a dose of 10 mg/kg to rats, the following tissue concentrations were measured: 21.1 $\mu\text{Eq/g}$ in the liver, 10.4 $\mu\text{Eq/g}$ in the adrenal cortex, 5.8 $\mu\text{Eq/g}$ in the lungs and 8.1 $\mu\text{Eq/g}$ in the brain [195]. In guinea pigs concentrations of voriconazole in cerebrospinal fluid (CSF) amounted 68 % of the simultaneously determined plasma concentration after the same dose, given orally over 5 days [203].

Published data on the penetration of voriconazole into human tissue are sparse. In CSF specimens drawn from 14 patients, median voriconazole levels of 0.65 $\mu\text{g/mL}$ (range 0.08 to 3.93 $\mu\text{g/mL}$) were measured by Lutsar *et al.* [203]. Plasma concentrations ranged from < 0.1 $\mu\text{g/mL}$ to 7.23 $\mu\text{g/mL}$ (median 1.08 $\mu\text{g/mL}$) at the same time. The median penetration ratio (CSF / plasma) amounted 0.46 (range 0.22 – 1.00). Lower CSF concentrations (0,08-0.17 $\mu\text{g/mL}$) were recovered through a ventricular drainage by Denes *et al.* [204]. The T_{\max} in CSF was 6 h. No plasma concentrations are displayed in this report. In pulmonary epithelial lining fluid (ELF) of 12 lung transplant recipients, who had taken 200 mg of voriconazole orally once to twice daily (mean number of doses 66 ± 44), concentrations between 0.29 $\mu\text{g/mL}$ and 83.32 $\mu\text{g/mL}$ were found. The simultaneously determined plasma levels were 0.15 to 4.56 $\mu\text{g/mL}$. Bronchoscopies had been performed 0.5 - 13.5 h after voriconazole administration. The ELF concentrations had their maximum at 5 h- 6 h after voriconazole intake. The average ratio of ELF concentration to plasma concentration ($C_{\text{ELF}}/C_{\text{Plasma}}$) was 11 ± 8 [205]. In pleural empyema, voriconazole concentrations of 0.8 $\mu\text{g/mL}$ to 1.4 $\mu\text{g/mL}$ were measured. The ratio empyema to plasma ($C_{\text{empyema}}/C_{\text{Plasma}}$) amounted 0.45 to 0.95 [206].

When voriconazole is administered intravenously, a loading dose of 6 mg/kg b.i.d. should be given, followed by a maintenance dose of 4 mg b.i.d. The oral standard dose recommended for adults is 400 mg at the first day followed by 200 mg b.i.d. Adult patients with a body weight below 40 kg should obtain a loading dose of 200 mg b.i.d and a maintenance dose of 100 mg b.i.d. Children (aged 2 to 12 years) should obtain an oral dose of 200 mg twice daily or 7 mg /kg i.v. twice daily. A loading dose is not recommended for pediatric patients [207].

Patients with impaired renal function can be treated with the standard dosage. The solvent sulfobutylether- β -cyclodextrine (SBECD), which is added to the i.v. formulation, however, accumulates and has a potential nephrotoxicity [195]. During a hemodialysis of 8 h, 8% of voriconazole and 46% of SBECD were removed [195]. In patients suffering from liver cirrhosis (stage Child-Pugh A and B), the voriconazole clearance has been found to be reduced by about 50% [195].

Therefore a 50% reduction of the maintenance dose is recommended for this group [207]. For patients with advanced liver cirrhosis at Child-Pugh C stage, pharmacokinetic data are lacking so far. Plasma levels were measured in one patient undergoing continuous veno-venous hemodiafiltration. Pharmacokinetic parameters were similar to those in patients off hemodiafiltration. The sieving coefficient was 0.53 and the hemodiafiltration clearance was below 10 % of the total voriconazole clearance [208].

Considering the complex pharmacokinetics and the numerous interactions of voriconazole, therapeutic drug monitoring is certainly advisable, particularly in patients with impaired liver function and in the critically ill.

Voriconazole has a very broad spectrum comprising most of the relevant pathogenic fungi (*Zygomycetes*, however, are not in its spectrum). It is available for i.v. and for oral use. Published data on its tissue distribution suggests a satisfying penetration, particularly into the CNS and into the lung.

Posaconazole

Posaconazole (Noxafil[®], Schering Plough, Hérouville St Clair, France), a new broad spectrum triazole, has recently been launched. It bears chemical resemblance to itraconazole. Its antimycotic spectrum is similar to that of voriconazole but includes *Zygomycetes* in addition. Posaconazole is available as a tablet formulation and as an oral suspension. No i.v. formulation is available at the time. The enteral absorption is improved by the intake of food, particularly high fat nutrition, or by nutritional supplements (e.g. 360 Kal of Boost Plus resulted in a 3.4 fold increase in C_{max} and a 2.6 fold increase in AUC) [209-211]. Its bioavailability has been studied in mice, rats, dogs and Cynomolgus monkeys. When the hydroxy- β -cyclodextrin containing oral solution was used, it amounted 52-100%. For the methylcellulose formulation, the bioavailability was between 14% and 48% [212]. Posaconazole has a plasma protein binding of 98-99% [213]. After a single dose of 400 mg, C_{max} was 0.6 $\mu\text{g/mL}$, T_{max} 6.3 h, $AUC_{0-\infty}$ 19.4 $\mu\text{g}\cdot\text{h/mL}$, and the clearance (CL/F) was 230 to 300 mL/h/kg in healthy subjects [213, 214]. The half-life is about 20 h resulting in a time of 7-10 d to reach steady state [214]. Under steady state conditions, on day 14 of treatment with 400 mg of posaconazole b.i.d., the mean C_{max} was 4.15 $\mu\text{g/mL}$, T_{max} 5 h, $t_{1/2}$ 31 h, the posaconazole clearance (CL/F) 11.5 L/h (about 150 mL/h/kg) and the apparent volume of distribution Vd/F was about 6.5 L/kg. Despite the long $t_{1/2}$, splitting the daily dose of 800 mg led to an enhanced AUC by improved absorption. Obviously, the oral absorption is saturable. Thus, 200 mg four times a day, followed by 400 mg b.i.d. appear to be the optimal dosage [209, 215]. Renal clearance of unchanged posaconazole is negligible. In patients with mild or moderate renal impairment as well as in patients on intermittent hemodialysis, no significant alteration in posaconazole pharmacokinetics was observed [216]. In elderly patients (≥ 65 years) AUC was enhanced by 29% to 42%. In liver failure of a different degree, so far no significant differences in plasma levels could be detected [217].

Like all the other triazoles, posaconazole is an inhibitor of CYP3A4. It is transformed into inactive metabolites by glucuronidation in the liver. 77% of the administered drug

are eliminated by the feces without modification, about 14% are excreted in the urine after glucuronidation by UDP-glucuronyl-transferase 1A4 and minor amounts as parent drug. Posaconazole is not a substrate for CYP1A2, CYP2C8, CYP2C9, CYP2D6, and CYP2E1. Drug interactions have been reported with tacrolimus (leading to a 2.2 fold C_{max} and a 4.5 fold AUC of tacrolimus), with cyclosporine A, glipizide and with midazolam [209, 218]¹. No interactions have been observed with caffeine (metabolized by CYP1A2), tolbutamide (metabolized by CYP2C8/9), dextrometorphan (metabolized by CYP2D6) and chloroxazone (metabolized by CYP2E1) [218]. The AUC values of etonavir and indinavir were enhanced when co-administered with posaconazole. Rifabutin, phenytoin and cimetidine lowered the AUC of posaconazole by about 50% [217].

The broad spectrum of activity, including *Zygomycetes*, is an advantage of posaconazole. Although published data on its tissue penetration are very limited, it can be assumed that its CNS penetration is superior to that of amphotericin B.

Ravuconazole

The chemical structure of ravuconazole is similar to that of fluconazole and voriconazole. The fluorinated pyrimidine ring of voriconazole is replaced by a thiazole ring bound to a cyano-phenyl group. It appears to have a broad antimycotic spectrum comprising *Candida*, *Aspergillus*, *Scedosporium*, *Cryptococcus neoformans*, *Histoplasma* and *Trichosporon* species. It is reported to be less active against *Fusarium* [219]. Published data on ravuconazole pharmacokinetics are very sparse: In a murine candidiasis model, ravuconazole had been administered p.o. at single doses of 10, 40, and 160 mg/kg. The C_{max} values were $0.36 \pm 0.01 \mu\text{g/mL}$ after 10 mg/kg and $4.37 \pm 0.64 \mu\text{g/mL}$ after 140 mg/mL, the AUCs were 3.4 and 48.0 $\mu\text{g}\cdot\text{h/mL}$ respectively and half-lives were 3.9-4.8 h. The protein binding of ravuconazole was determined at concentrations of 100 and 400 $\mu\text{g/mL}$ and amounted 95.8% [220]. Its bioavailability has been found to be 48 to 74% in animals.

In healthy volunteers, however, a half-life ranging from 80 to 157 h has been reported after doses between 50 and 800 mg. Peak levels were between 0.23 and 1.15 $\mu\text{g/mL}$. Because of the long $t_{1/2}$, a remarkable accumulation took place (e.g. 8-10 fold C_{max} after 14 days of treatment) [221]. In 24 adult patients who had undergone allogeneic hematopoietic stem cell transplantation, 3 dosages were compared: 400 mg, 600 mg and 800 mg once daily p.o. (8 patients in each group). After a single dose, the ravuconazole clearance was between 25 ± 4 L/h and 31 ± 7 L/h (about 350 mL/h/kg) and Vd was between 760 ± 84 and 816 ± 116 (about 10 L/kg). The 400 mg dose resulted in a C_{max} of $0.82 \pm 0.11 \mu\text{g/mL}$ and an $AUC_{0-\infty}$ of $18.93 \pm 3.33 \mu\text{g}\cdot\text{h/mL}$, the intake of 800 mg in a C_{max} of $1.68 \pm 0.29 \mu\text{g/mL}$ and an $AUC_{0-\infty}$ of $37.93 \pm 6.20 \mu\text{g}\cdot\text{h/mL}$. Thus, plasma levels appear to increase in linear fashion with the dose. The half life was 22-36 h after a single dose (" $t_{1/2, 0-24}$ ") and 371 h- 733 h in the wash-out phase ($t_{1/2}$ γ)

¹ Sansone A, Belle D, Statkevich P, Joseph D, Kantesaria B, Laughlin M, Courtney R. Effect of posaconazole on the pharmacokinetics of tacrolimus in healthy volunteers. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy 2003; 1603 (abstr).

in this study². A $t_{1/2}$ of 5-7 d has been reported elsewhere [222].

For i.v. administration a lysine phosphorester of ravuconazole has been developed. After i.v. injection of ravuconazole lysine phosphorester at doses of 2.5, 5 or 10 µg/kg for 6 days in rabbits, C_{max} values of 2.7 ± 0.38 , 7.96 ± 0.74 and 13.88 ± 1.37 µg/mL, respectively, were measured. The dose normalized AUC, $AUC_{0-\infty}/\text{dose}$, was dose-independent (the values were 2.86 ± 0.40 h/mL, 2.36 ± 0.20 h/mL and 2.53 ± 0.28 h/mL, respectively). The V_{ss} was 9.65 L/kg after 2.50 mg/kg, 5.02 L/kg after 5 mg/kg and 3.50 L/kg after administration of 10 mg/kg [223].

Ravuconazole tissue penetration has been investigated in rat lung and uterus: levels were 2 to 6 times higher than in the corresponding plasma samples [224]. In patients with onychomycosis ravuconazole concentrations in plasma and toenails were determined during three different twelve-week regimens i.e. 200 mg per day, 100 mg once per week and 400 mg once per week. By administration of 200 mg daily plasma levels of 2-3 mg/mL and toenail concentrations of about 1 µg/mL were achieved. In patients treated with 100 mg/week plasma levels reached only about 0.2 µg/mL and nail concentrations about 0.1 µg/mL [222].

Ravuconazole is still under investigation. Published clinical data are limited at the time and its position in the antimycotic armamentarium has yet to be determined, despite of its broad antifungal spectrum.

ECHINOCANDINS

Echinocandins are semi-synthetic derivatives of fungal fermentation products. They are cyclic lipopeptides comprising six amino acids. An N-aryl side chain which is relevant for their antifungal activity as well as for their toxicity is bound to the N-terminus of the cyclic peptide by N-acetylation. Echinocandins inhibit the fungal β -(1, 3)-D-glucan synthase. β -(1, 3)-D-glucan is an essential component of the inner layer of the fungal cell wall, which plays an important role in cell metabolism and resistance against host defense mechanisms. Echinocandins display a poor enteral absorption and are therefore only available as i.v. formulations [225].

Caspofungin

Caspofungin (Cancidas[®], Merck & Co., Inc., Whitehouse Station, N.J., USA) has a molecular weight of 1093 Da. It is active against *Candida* including several non-albicans strains e.g. *C. lusitanae* and against *Aspergilli*. *Cryptococcus neoformans*, *Fusarium species* and *Zygomycetes* are not sensitive to caspofungin.

The pharmacokinetics of caspofungin has been studied in male healthy volunteers [226, 227]. Plasma concentration-time curves declined in a polyexponential fashion, $t_{1/2\beta}$ was 8-10 h, $t_{1/2\gamma}$ 27 h. After infusion of a single dose of 70 mg ($T_{inf}=1$ h) a mean C_{max} of about 12 µg/mL and a trough level

of about 1.3 mg/mL and a mean $AUC_{0-\infty}$ of 118 µg·h/mL were obtained [226]. Mean $AUC_{0-\infty}$ values of 635 to 814 µg·h/mL have been found using ³H caspofungin by the same investigators [227]. The caspofungin clearance was about 10 mL/h/kg. After 2 weeks of treatment with the standard dosage (70 mg on day 1 followed by a maintenance dose of 50 mg/d) the mean $AUC_{0-\infty}$ was 100 µg·h/mL and the C_{max} was 10 µg/mL. Within the first hours after infusion, caspofungin is mainly eliminated by uptake into tissues where active transport may be involved. Within 27 d after infusion of 70 mg of ³H caspofungin, 41% of the radioactivity have been recovered from urine and 34% from the feces [226, 227]. About 95% of caspofungin are bound to plasma proteins [226, 227]. The apparent volume of distribution of caspofungin has been estimated to be very low at the beginning of treatment (about 0.05 L/kg) and to increase during the first 3 to 4 days until it reached a plateau of 23 to 160 L (0.3 to 2.0 L/kg) [226].

Caspofungin is metabolized in the liver independently from the CYP system. M0 is the main metabolite emerging in the plasma 24-30 h after administration. It is formed by hydrolysis. The metabolites M1, also formed by hydrolysis, and M2, an N-acetylation product of M1, are excreted in the urine, where only small amounts of unchanged parent drug can be detected [228].

Tissue concentrations of caspofungin were measured in rats 0.5, 2.0, 24 and 288 h after injection of 2.0 mg/kg of [³H] caspofungin. Half an hour after the injection, the maximum concentrations appeared in red blood cells (4.08 ± 2.57 µg Eq/mL), lung (5.12 ± 0.19 µg Eq/mL), spleen (4.37 ± 0.04 µg Eq/mL), heart (2.31 ± 0.14 µg Eq/mL), in fat, intestine, lymph nodes (1.93 ± 0.12 µg Eq/mL) and in the eye (0.52 ± 0.06 µg Eq/mL). In skeletal muscle, peak concentrations were measured after 2 h, in the kidney (11.40 ± 1.64 µg Eq/mL), liver (22.20 ± 2.43 µg Eq/mL) and in the brain (0.16 ± 0.11 µg Eq/mL) the maximum levels appeared 24 h after injection. The respective plasma concentrations were 11.00 ± 5.73 µg/mL 0.5 h after injection, 6.10 ± 0.60 µg/mL after 2 h, 1.74 ± 0.85 µg/mL and 0.07 ± 0.04 µg/mL 288 h after the caspofungin bolus. Thus, caspofungin displays a relatively high penetration into the liver and the kidneys and an intermediate penetration into spleen, lung, red blood cells, and small intestine. Caspofungin concentrations in heart, lymph nodes, muscle, eyes and brain are low [227].

Since caspofungin is not an inhibitor or a substrate of CYP enzymes or for P-glycoprotein (PGP), drug interactions can be expected to play a minor role in patients on caspofungin treatment. Nevertheless, the AUC of caspofungin was enhanced by 35%, when cyclosporine A was co-administered, and elevated serum transaminase activities (ALT, AST) were observed. A 26% decrease in C_{max} of caspofungin was found when it was combined with tacrolimus. A reduced AUC for caspofungin has been reported for simultaneous administration of caspofungin together with efavirenz, nevirapine, rifampicin, dexamethasone, phenytoin or carbamazepine [229].

The recommended standard dosage of caspofungin is 70 mg as a loading dose, followed by a maintenance dose of 50 mg once per day. In patients with a body weight above 80

² Lin P, Micijene D, Roden MM, Buchanan W, Knudsen T, Sarkisova T, Geabana-cloche J, Childs R, Walsh TJ. Pharmacokinetics and safety of ravuconazole for prophylaxis in patients undergoing allogeneic hematopoietic stem cell transplantation. 45th Interscience Conference on Antimicrobial Agents and Chemotherapy 2005; 220 (abstr).

kg, 70 mg once daily should be given throughout the entire treatment. No dose adjustment is suggested in patients with impaired renal function, even in those with terminal renal failure requiring hemodialysis. In mild to moderate liver dysfunction (Child-Plough 7-9), the maintenance dose should be 35 mg once daily [229]. For treatment of children a daily dose of 50 mg/m² body surface has recently been recommended [230]. No pharmacokinetic data is available for critically ill patients, for patients on continuous renal replacement therapy and for severe liver failure.

Caspofungin is the first licensed echinocandin. It is characterized by its activity against various *Candida* and *Aspergillus* species, a low toxicity and a low potential for relevant drug interactions. Therefore it is an important antimycotic for treatment of severely compromised patients requiring a multitude of co-medications, particularly in infections with fluconazole resistant *Candida* species.

Micafungin

Micafungin (Fungard[®], Astellas, Japan) has a molecular weight of 1,292 Da. A side chain containing 3 aromatic rings was inserted instead of the aliphatic side chain of caspofungin.

Micafungin has a very high protein binding of 99.85 %³ and can be administered only i.v. because of its poor absorption from the gastrointestinal tract. In adult patients undergoing bone marrow or peripheral stem cell transplantation, pharmacokinetics of micafungin was studied on day 1 and day 7 of therapy with 12.5, 25, 50, 75, 100, 150 or 200 mg once daily. After a daily dose of 200 mg (T_{inf}=1 h), which was well tolerated, the mean C_{max} was 13.1 µg/mL on day 1 and 22.6 on day 7, the AUC_{0-∞} amounted 164 µg·h/mL on day 1 and 238 µg·h/mL on day 7. The t_{1/2} was about 13 to 20 h being longer at steady state. The micafungin clearance was about 1 L/h (about 12.5 mL/kg) and V_{ss} amounted about 25 L (0.3 L/kg) [231].

Tissue distribution of micafungin was investigated in rabbits [232] and more recently in rats [233]. In rabbits treated with micafungin for 8 d at a daily dose of 2 mg/kg (injected as a 4 min bolus), the following mean tissue concentrations were found 30 minutes after the last application: 11.76 ± 1.40 µg/g in the lung, 8.82 ± 0.72 µg/g in the liver, 9.05 ± 0.25 µg/g in the spleen, 6.12 ± 0.17 µg/g in the kidney and 0.18 ± 0.02 µg/g in the brain. On day 7, the C_{max} in plasma was 19.17 ± 0.31 µg/mL [232]. In another experiment on rats, tissue levels were measured 0.083, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h after a 1.0 mg/kg bolus injection. The peak tissue concentrations appeared 5 minutes later. The lung concentrations exceeded the respective plasma levels by 258 %. The tissue half-life was about 5h [233].

Micafungin is reported to be a weak inhibitor of CYP 3A. When 5 mg/kg of cyclosporine A were administered p.o. together with 100 mg of micafungin i.v. as a single dose or until steady state was reached, the clearance of cyclosporine A was significantly reduced by 15% [234]. However, ad-

ministration of micafungin as a single dose of 100 mg or at steady state did not exert any influence on the AUC of tacrolimus (5 mg p.o.) in healthy volunteers [235]. Co-administration of fluconazole and micafungin had no influence on the pharmacokinetics of either of the two drugs [236]. Rifampicin, an inducer of CYP3A4, and ritonavir, a strong inhibitor of CYP3A4, had no influence on the AUC_{0-∞} of micafungin. Treatment with warfarin, diazepam, salicylic acid or methotrexate had no influence on micafungin pharmacokinetics [237].

For prophylaxis in liver transplant recipients a dose of 40 mg - 50 mg per day has been suggested [238]. The standard dosage recommended for the therapy of invasive aspergillosis is 50 mg -150 mg once daily (maximum 150 mg per day), for invasive candidiasis it is 50 mg/d (maximum 150 mg per day) [239].

Micafungin pharmacokinetics was investigated in 73 pediatric patients (children aged 2-12 years and adolescents aged 13-17 years) with febrile neutropenia. Children were treated with 0.5-4.0 mg/kg/day, adolescents with 0.5-1.5 mg/kg/day. The time-concentration profiles were determined on day 1 and day 4 of treatment, T_{inf} was 1 h. After 2 mg/kg, the pharmacokinetic parameters were similar to the respective values obtained in adults after administration of 400 mg: C_{max} values were 15.3 ± 3.8 µg/mL on day 1 and 21.4 ± 9.7 µg/mL on day 4; the AUCs_{0-∞} were 113.8 ± 16.0 µg·h/mL and 132.3 ± 27.1 µg·h/mL, respectively [240]. The half-life was 12-13 h, the clearance about 20 mL/h/kg and V_{ss} was 0.3-0.4 L/kg. There was a statistically significant difference in CL, V_{ss} and t_{1/2} between the age group of 2 to 8-year-old children and the group of 9- to 17-year-old patients: the micafungin elimination appears to be faster in younger children [240]. In premature infants, who had obtained a single dose of 0.75 mg/kg, the C_{max} was 2.52 µg/mL, the AUC 20.6 µg·h/mL and t_{1/2} 7.5 h [239]. No difference in C_{max}, t_{1/2}, CL and V_{ss} was detected between healthy volunteers aged 66-78 years and subjects aged 20-24 years.³

In 8 patients with moderately impaired liver function (Child Pugh score 7 to 9), the AUC_{0-∞} was significantly reduced (97.5 ± 19 µg·h/mL vs. 125.9 ± 26.4 µg·h/mL, p=0.03) in comparison with 9 healthy volunteers. A single dose of 100 mg of micafungin had been administered to both groups. The difference in mean AUC_{0-∞} has been attributed to differences in body weight between the two groups, and thus, no dose adjustment is recommended for patients with moderately impaired liver function [239, 241]. Recently, in rats with carbon tetrachloride induced acute liver failure, V_{ss} of micafungin was found to be significantly enhanced, while the CL was unaffected [242].

Renal impairment did not influence micafungin pharmacokinetics [241].

The influence of continuous hemofiltration on micafungin pharmacokinetics was investigated in 3 liver transplant recipients, who had obtained a prophylactic dose of 40-50 mg of micafungin once daily. Pharmacokinetics was determined on the third day of treatment with micafungin. The

³ Mukai T, Ohkuma T, Nakahara K, Takaya T, Uematsu T, Azuma J. Pharmacokinetic of FK 463, anovel echinocandin analogue, in elderly and non-elderly subjects. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy 2001; 30 (abstr).

⁴ Undre NA, Stevenson P, Amakye DD. Rifampicin and ritonavir do not affect the pharmacokinetics of micafungin (FK 463), an echinocandin antifungal. 14th European Congress of Clinical Microbiology and Infectious Diseases 2004 (abstr).

half-lives were 13 h and 14 h and the total micafungin clearances were 0.65 L/h and 0.59 L/h on and off hemofiltration, respectively. The hemofilter clearance was as low as 0.054 ± 0.04 L/h (8 % of the total micafungin clearance). Therefore hemofiltration appears to have a minor impact on micafungin pharmacokinetics [243].

Micafungin, which is not licensed in several countries yet, resembles caspofungin in its antimycotic spectrum and its pharmacokinetics. A considerable amount of data is already available for special clinical conditions. Pre-clinical data suggests a satisfying lung penetration of micafungin.

Anidulafungin

The chemical structure of anidulafungin is similar to that of micafungin. Its side chain contains three phenyl groups. The antimycotic spectrum of anidulafungin comprises *Candida*, species including *C. albicans*, *C. glabrata*, *C. krusei* and *C. tropicalis*, as well as *Aspergillus flavus*, *A. fumigatus*, *A. terreus* and *A. niger*. Anidulafungin is less active against other filamentous fungi, against *Blastomyces dermatitidis* and *Histoplasma capsulatum* and it is inactive against *Fusarium* species and *Cryptococcus neoformans* [244].

The protein binding of anidulafungin is 84%, and thus, it is lower than that of caspofungin and micafungin [245]. Like caspofungin and micafungin, anidulafungin is poorly absorbed after enteral administration and therefore only available for i.v. infusion. Plasma pharmacokinetics was studied in healthy volunteers and in patients suffering from esophageal or invasive candidiasis [246]^{5,6}. Dowell and colleagues analyzed 600 plasma levels collected from 225 patients with *Candida* infection during phase II and phase III trials. An elimination half-life of 25.6 h, a V_{ss} of 32.5 L (0.54 L/kg) and an anidulafungin clearance of 0.93 L/h (15 mL/h/kg) have been calculated. Peak levels of about 7 and 3.5 $\mu\text{g/mL}$ are to be anticipated after daily doses of 100 mg and 50 mg, respectively. The respective values for the $\text{AUC}_{0-\infty}$ were 106 $\mu\text{g}\cdot\text{h/mL}$ and 53 $\mu\text{g}\cdot\text{h/mL}$ [246]. In 9 healthy volunteers, who had obtained 90 mg of ¹⁴C-labeled anidulafungin, the mean C_{max} was 4.11 $\mu\text{g/mL}$, the AUC was 102.2 $\mu\text{g}\cdot\text{h/mL}$ and the $t_{1/2}$ amounted 28 h. Anidulafungin was eliminated by the feces. Only 10% of the administered radioactivity was recovered as intact drug, 90% as degradants⁷. Anidulafungin is not metabolized but undergoes spontaneous chemical degradation [247].

Tissue distribution of anidulafungin was investigated in rabbits after 10 days of treatment with doses ranging from 0.1 to 10 mg/kg/d. In the animals, that had obtained 5 mg/kg by bolus injection, the highest concentrations were measured in the lung (17.9 ± 0.9 $\mu\text{g/g}$) and in the liver (16.8 ± 0.8 $\mu\text{g/g}$), followed by spleen (9.8 ± 0.8 $\mu\text{g/g}$), kidney (6.8 ± 0.7

$\mu\text{g/g}$) and brain (1.6 ± 0.1 $\mu\text{g/g}$). In the vitreous humor, the aqueous humor and the choroid, anidulafungin concentrations were negligible. On day 7, peak plasma concentration had amounted 14.28 ± 2.26 $\mu\text{g/mL}$ and the trough level had been 0.49 ± 0.08 $\mu\text{g/mL}$ [248].

Potential drug interactions with anidulafungin were analyzed in several studies. In healthy volunteers, who had obtained anidulafungin together with voriconazole, co-administration had no effect on pharmacokinetics on either of the two drugs [249]. Simultaneous administration of cyclosporine A (1.25 mg/kg p.o.) and anidulafungin resulted in an increase in $\text{AUC}_{0-\infty}$ of anidulafungin by 22%, in peak concentration by 8%, and in trough concentration by 22%. The anidulafungin clearance was decreased by 16%. These changes, however, were considered to be of minor clinical relevance and therefore no dose adjustment is recommended by the authors. In an *in vitro* experiment, no influence of anidulafungin on cyclosporine A metabolism was observed [250]. Tacrolimus and anidulafungin did not display any significant drug interaction in a study on 35 healthy volunteers⁶.

A loading dose of 100 mg followed by 50 mg per day is looked upon as appropriate in esophageal candidiasis. For patients with invasive candidiasis, the loading dose should be 200 mg and the maintenance dose 100 mg once daily. Children with neutropenia were treated with anidulafungin doses of 0.75 and 1.5 mg/kg/d, respectively (a 2 fold loading dose had been injected on day 1). The pharmacokinetic data was quite comparable with that obtained in adults after 100 mg and 50 mg per day, respectively⁷.

In patients with mild renal impairment (creatinine clearance between 51 and 79 mL/min/1.73 m² body surface area), moderate impairment (creatinine clearance between 31 and 50 mL/min/1.73 m²) and severe renal dysfunction (creatinine clearance below 30 mL/min/1.73 m²) as well as in patients on intermittent hemodialysis, the C_{max} and the AUC values for anidulafungin were largely unaffected [247].

Impaired liver function, however, appears to cause a decay in anidulafungin plasma levels. After administration of a 50-mg single dose to patients with mild, moderate or severe hepatic impairment and to healthy volunteers, there was a significant reduction of the C_{max} and the AUC in patients with severe liver dysfunction. In mild and moderate liver impairment, anidulafungin exposure was only slightly and insignificantly reduced. The lowered anidulafungin plasma levels have been ascribed to enhanced volume of distribution and increased degradation because of a reduced plasma protein binding [247].

Anidulafungin is not on the market yet. It merits interest, particularly, because of its unique pharmacokinetics.

SUGGESTIONS FOR THE CHOICE OF ANTIMYCOTICS IN DIFFERENT CLINICAL CONDITIONS

The choice of the most appropriate antimycotic depends on the causative agent which is suspected or has been microbiologically confirmed, on the site of infection and on the clinical condition of the patient. Infections caused by *C. albicans* will be treated with fluconazole which has a low toxicity, is comparatively inexpensive and displays a favorable

⁵ Dowell J, Pu F, Stogniew M, Krause D, Henkel T. A clinical mass balance study of Anidulafungin (ANID) showing complete fecal elimination. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy 2003; 1576 (abstr).

⁶ Dowell J, Schranz M, Buckwater M, Stogniew M, Krause D. Safety and pharmacokinetics of co-administered anidulafungin and tacrolimus 45th Interscience Conference on Antimicrobial Agents and Chemotherapy 2005; 1190 (abstr).

⁷ Benjamin DK, Driscoll T, Seibel NL, Gonzales CE, Roden MM, Doweck JA, Schranz J, Walsh TJ. Safety and Pharmacokinetics of Anidulafungin in Pediatric Patients with Neutropenia. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy 2004; 34 (abstr).

tissue distribution. For fluconazole-resistant *Candida* (non-albicans *Candida*) echinocandins, such as caspofungin are an effective option with low toxicity. Amphotericin B preparations and voriconazole are also effective.

For aspergillosis, amphotericin B and itraconazole have been the only effective drugs for years. The armamentarium has now been increased by the new broad-spectrum azoles, voriconazole and posaconazole and by the echinocandins. Thus, amphotericin B and its lipid formulations, voriconazole (eventually posaconazole, which is available only orally) and echinocandins, such as caspofungin, are treatment options for invasive aspergillosis. Caspofungin is licensed for treatment of refractory invasive aspergillosis. When *Aspergillus terreus* has been identified, amphotericin B should be avoided because of its poor activity against this species. In pulmonary aspergillosis, lung concentrations are probably crucial for the outcome. Amphotericin B lung concentrations after colloidal amphotericin B appear to exceed those measured after therapy with liposomal amphotericin B. Whether colloidal amphotericin B is superior in pulmonary mycoses, however, has not been investigated in clinical studies so far. Voriconazole penetration into alveolar epithelial lining fluid was recently found to be favorable. In CNS manifestations, voriconazole may be preferred because its CNS penetration is probably superior, as assessed in animal models.

Zygomycetes are very difficult to treat and are only sensitive to amphotericin B and to posaconazole. The latter is available only as an oral formulation with a highly variable, food dependent bioavailability. Therefore the use of posaconazole is presently confined to patients without gastrointestinal impairment.

For antimycotic prophylaxis, fluconazole or itraconazole are usually administered. Fluconazole has a lower potential for drug interactions, but a narrow antimycotic spectrum. For secondary prophylaxis in patients with previous invasive fungal infection, amphotericin B may still be the drug of choice.

The choice of the appropriate antimycotic for empiric therapy depends on the suspected fungi and thus on the regional epidemiology. If zygomycosis is a concern, amphotericin B – conventional or lipid-formulated – is the drug of choice. In febrile neutropenia refractory to antibacterial treatment, voriconazole and caspofungin are licensed beside amphotericin B.

In patients with renal impairment the dosage has to be adjusted for fluconazole and flucytosine. High fluconazole doses are required in the critically ill on continuous renal replacement therapy. Renal impairment and the requirement of nephrotoxic co-medication are contraindications for amphotericin deoxycholate. The nephrotoxicity of amphotericin B is reduced, but not abolished by lipid encapsulation.

By the use of liposomal amphotericin B or of amphotericin B colloidal dispersion, the incidence of renal toxicity can be reduced by about 50% in comparison with conventional amphotericin B treatment. For amphotericin B lipid complex a reduced nephrotoxicity is generally accepted. However, in one randomized double blind study, renal im-

pairment occurred more frequently during treatment with amphotericin B lipid complex than on therapy with liposomal amphotericin B (in 42% vs. 15% of the patients) [84]. Thus, liposomal amphotericin B and amphotericin colloidal dispersion can be administered to patients with renal impairment, if the broad spectrum of amphotericin B is required. Amphotericin B lipid complex may be the preparation of choice, if the renal function is more stable, but infusion-related toxicity is a major concern. Lipid-formulations of amphotericin B can be administered at standard dosage in renal failure and during continuous hemofiltration. For voriconazole, posaconazole and echinocandins, no dose adjustment is necessary in renal impairment and intermittent hemodialysis. Data on continuous renal replacement are almost lacking for these new drugs, but based on theoretical considerations, standard dosages are probably applicable.

In patients with impaired liver function, dose reductions are recommended for voriconazole and caspofungin. In severe liver failure published data on these new drugs are lacking, but a significant accumulation has to be anticipated.

Drug interactions are a major problem in the treatment with azoles, particularly in patients under immunosuppressive, antiepileptic or antiretroviral therapy. Several antibacterial drugs, such as macrolides and quinolones, interact also relevantly with triazoles. This can result in cardiac arrhythmias caused by a prolonged QT interval and in an increased hepatotoxicity.

Combination therapy is an option for refractory invasive fungal infections. Flucytosine has been traditionally combined with amphotericin B and fluconazole. Combination of amphotericin B and azoles is still discussed controversially for potential antagonistic effects. The use of echinocandins together with any of the other drugs appears to be attractive.

FINAL REMARKS

Despite considerable efforts in the development of new antifungal drugs during the last decades, the mortality of invasive fungal infections is still very high. The reasons for this modest progress in clinical outcome comprise host factors (patients with fungal infections are usually immunocompromised), as well as properties of the infectious agent (fungi are eukaryotes and therefore less susceptible to antimicrobial agents without significant toxicity). The improvement of our knowledge on pharmacokinetics of antimycotics may contribute to the clinical outcome, since it can help to avoid toxicity and to warrant effective drug concentrations, particularly at the site of fungal infection. Lacking clinical efficacy in spite of documented *in vitro* sensitivity of the infectious agent may in part be ascribed to insufficient drug exposure at the target site.

The first pharmacokinetics study on amphotericin B has been performed almost 20 years after its introduction into therapy. Considering the long time of its clinical use, our knowledge on pharmacokinetics of this drug is still relatively incomplete. The pharmacokinetics of amphotericin B lipid formulations is complex. Despite numerous *in vitro* approaches and clinical studies, there are still many unresolved questions e.g. concerning the liberation of the active drug from lipid-encapsulation and its disposition at the target site.

The availability of basic pharmacokinetic data is nowadays a standard requirement for marketing authorization. Therefore, plasma pharmacokinetics of the newer antimycotics, such as triazoles and echinocandins, has been investigated in healthy volunteers and under the most common clinical conditions. Therapeutic drug monitoring would be a valuable option under special clinical circumstances, such as treatment of multi-organ dysfunction at the ICU. Information about tissue penetration of antimycotics is mainly derived from homogenized tissue samples obtained in animal experiments or studies with radioactive markers. Thus, a discrimination between intra- and extra-cellular drug concentrations and between free and protein-bound substance is precluded. In contrary, target site pharmacokinetics of antibacterial agents has been assessed to a much greater extend and by more sophisticated approaches e.g. by *in vivo* microdialysis technique. The only antifungal drug investigated by the latter method is fluconazole. Methodical problems, such as high molecular weight and lipophilicity of most antimycotics, have to be solved.

Beside the development of new, more potent antifungal drugs, a more detailed knowledge of pharmacokinetics is required to improve the outcome in invasive fungal infections.

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REFERENCES

- [1] Kullberg BJ, Oude Lashof AML. Epidemiology of opportunistic invasive mycoses. *Eur J Med Res* 2002; 7: 183-91.
- [2] Pea F, Furlanut M. Pharmacokinetic aspects of treating infections in the intensive care unit: focus on drug interactions. *Clin Pharmacokinet* 2001; 40: 833-68.
- [3] Harbarth S, Burke JP, Lloyd JF, Evans RS, Pestotnik SL, Samore MH. Clinical and economic outcomes of conventional amphotericin B-associated nephrotoxicity. *Clin Infect Dis* 2002; 35: 120-7.
- [4] Oura M, Sternberg TH, Wright ET. A new antifungal antibiotic, amphotericin B. *Antibiot Annu 1955-1956*; 3: 566-73.
- [5] Louria DB, Feder N, Emmons CW. Amphotericin B in experimental histoplasmosis and Cryptococcosis. *Antibiot Annu 1956-1957*; 870-7.
- [6] Kozinn PJ, Taschdjian CL, Dragutsky D, Minsky A. Treatment of cutaneous candidiasis in infancy and childhood with nystatin and amphotericin B. *Antibiot Annu 1956-1957*: 128-34.
- [7] Halde C, Wright ET, Pollard WH, Newcomer VD, Sternberg THH. The effect of amphotericin B upon the yeast flora of the gastrointestinal tract of man. *Antibiot Annu 1956-1957*: 123-7.
- [8] Utz JP, Treger A, McCulloch NB, Emmons CW. Amphotericin B: intravenous use in 21 patients with systemic fungal diseases. *Antibiot Annu 1958-1959*; 6: 628-34.
- [9] De Kruijff B, Demel RA. Polyene antibiotic-sterol interactions in membranes of *Acholeplasma laidlawii* cells and lecithin liposomes. 3. Molecular structure of the polyene antibiotic-cholesterol complexes. *Biochim Biophys Acta* 1974; 339: 57-70.
- [10] Baginski M, Resat H, McCammon JA. Molecular properties of amphotericin B membrane channel: a molecular dynamics simulation. *Mol Pharmacol* 1997; 52: 560-70.
- [11] Lemke A, Kiderlen AF, Kayser O. Amphotericin B. *Appl Microbiol Biotechnol* 2005; 68: 151-62.
- [12] Ellis D. Amphotericin B: spectrum and resistance. *J Antimicrob Chemother* 2002; 49 Suppl 1: 7-10.
- [13] Hughes WT, Armstrong D, Bodey GP, *et al.* 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002; 34: 730-51.
- [14] Bowden R, Chandrasekar P, White MH, *et al.* A double-blind, randomized, controlled trial of amphotericin B colloidal dispersion versus amphotericin B for treatment of invasive aspergillosis in immunocompromised patients. *Clin Infect Dis* 2002; 35: 359-66.
- [15] Walsh TJ, Finberg RW, Arndt C, *et al.* Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *N Engl J Med* 1999; 340: 764-71.
- [16] Wingard JR, Kubilis P, Lee L, *et al.* Clinical significance of nephrotoxicity in patients treated with amphotericin B for suspected or proven aspergillosis. *Clin Infect Dis* 1999; 29: 1402-7.
- [17] Fanos V, Cataldi L. Amphotericin B-induced nephrotoxicity: a review. *J Chemotherapy* 2000; 12: 463-70.
- [18] Eriksson U, Seifert B, Schaffner A. Comparison of effects of amphotericin B deoxycholate infused over 4 or 24 hours: randomised controlled trial. *Brit Med J* 2001; 322: 579-82.
- [19] Girois SB, Chapuis F, Decullier E, Revol BG. Adverse effects of antifungal therapies in invasive fungal infections: review and meta-analysis. *Eur J Clin Microbiol Infect Dis* 2005; 24: 119-30.
- [20] Bates DW, Su L, Yu DT, *et al.* Correlates of acute renal failure in patients receiving parenteral amphotericin B. *Kidney Int* 2001; 60: 1452-9.
- [21] Bates DW, Su L, Yu DT, *et al.* Mortality and costs of acute renal failure associated with amphotericin B therapy. *Clin Infect Dis* 2001; 32: 686-93.
- [22] Deray G. Amphotericin B nephrotoxicity. *J Antimicrob Chemother* 2002; 49 Suppl 1: 37-41.
- [23] Bekersky I, Fielding RM, Dressler DE, Lee JW, Buell DN, Walsh TJ. Plasma protein binding of amphotericin B and pharmacokinetics of bound versus unbound amphotericin B after administration of intravenous liposomal amphotericin B (AmBisome) and amphotericin B deoxycholate. *Antimicrob Agents Chemother* 2002; 46: 834-40.
- [24] Ridente Y, Aubard J, Bolard J. Absence in amphotericin B-spiked human plasma of the free monomeric drug, as detected by SERS. *FEBS Lett* 1999; 446: 283-6.
- [25] Atkinson AJ Jr, Bennett JE. Amphotericin B pharmacokinetics in humans. *Antimicrob Agents Chemother* 1978; 13: 271-6.
- [26] Hoeprich PD. Elimination half-life of amphotericin B. *J Infect* 1990; 20: 173-75.
- [27] Kan VL, Bennett JE, Amantea MA, *et al.* Comparative safety, tolerance, and pharmacokinetics of amphotericin B lipid complex and amphotericin B desoxycholate in healthy male volunteers. *J Infect Dis* 1991; 164: 418-21.
- [28] Ayestaran A, Lopez RM, Montoro JB, *et al.* Pharmacokinetics of conventional formulation versus fat emulsion formulation of amphotericin B in a group of patients with neutropenia. *Antimicrob Agents Chemother* 1996; 40: 609-12.
- [29] Heinemann V, Bosse D, Jehn, *et al.* Pharmacokinetics of liposomal amphotericin B (AmBisome) in critically ill patients. *Antimicrob Agents Chemother* 1997; 41: 1275-80.
- [30] Bekersky I, Fielding RM, Dressler DE, Lee JW, Buell DN, Walsh TJ. Pharmacokinetics, excretion, and mass balance of liposomal amphotericin B (AmBisome) and amphotericin B desoxycholate in humans. *Antimicrob Agents Chemother* 2002; 46: 828-33.
- [31] Benson JM, Nahata MC. Pharmacokinetics of amphotericin B in children. *Antimicrob Agents Chemother* 1989; 33: 1989-93.
- [32] Koren G, Lau A, Klein J, *et al.* Pharmacokinetics and adverse effects of amphotericin B in infants and children. *J Pediatr* 1988; 113: 559-63.
- [33] Starke JR, Mason EO Jr, Kramer WG, Kaplan SL. Pharmacokinetics of amphotericin B in infants and children. *J Infect Dis* 1987; 155: 766-74.
- [34] Block ER, Bennett JE, Livoti LG, Klein WJ Jr, MacGregor RR, Henderson L. Flucytosine and amphotericin B: hemodialysis effects on the plasma concentration and clearance. *Studies in man. Ann Intern Med* 1974; 80: 613-7.
- [35] Gussak HM, Rahman S, Bastani B. Administration and clearance of amphotericin B during high-efficiency or high-efficiency/high-flux dialysis. *Am J Kidney Dis* 2001; 37: E45.
- [36] Wood JE, Mahnensmith MP, Mahnensmith RL, Perazella MA. Intradialytic administration of amphotericin B: clinical observations on efficacy and safety. *Am J Med Sci* 2004; 327: 5-8.
- [37] Bellmann R, Egger P, Gritsch W, *et al.* Amphotericin B lipid formulations in critically ill patients on continuous veno-venous haemofiltration. *J Antimicrob Chemother* 2003; 51: 671-81.

- [38] Craven PC, Ludden TM, Drutz DJ, Rogers W, Haegele KA, Skrdlant HB. Excretion pathways of amphotericin B. *J Infect Dis* 1979; 140: 329-41.
- [39] Amphotericin B BMS[®], package insert, Bristol-Myers Squibb, Vienna, Austria.
- [40] Hong Y, Ramzan I, McLachlan AJ. Disposition of amphotericin B in the isolated perfused rat liver. *J Pharm Pharmacol* 2004; 56: 35-41.
- [41] Inselmann G, Inselmann U, Heidemann HT. Amphotericin B and liver function. *Eur J Intern Med* 2002; 13: 288-292.
- [42] Fischer MA, Winkelmayer WC, Rubin RH, Avorn J. The hepatotoxicity of antifungal medications in bone marrow transplant recipients. *Clin Infect Dis* 2005; 41: 301-7.
- [43] Brockmeyer NH, Gambichler T, Bader A, *et al.* Impact of amphotericin B on the cytochrome P450 system in HIV-infected patients. *Eur J Med Res* 2004; 9: 51-4.
- [44] Souza LC, Campa A. Pharmacological parameters of intravenously administered amphotericin B in rats: comparison of the conventional formulation with amphotericin B associated with a triglyceride-rich emulsion. *J Antimicrob Chemother* 1999; 44: 77-84.
- [45] van Etten EW, Otte-Lambillion M, vanVianen W, ten Kate MT, Bakker-Woudenberg AJ. Biodistribution of liposomal amphotericin B (AmBisome) and amphotericin B-desoxycholate (Fungizone) in uninfected immunocompetent mice and leucopenic mice infected with *Candida albicans*. *J Antimicrob Chemother* 1995; 3: 509-19.
- [46] Matot I, Pizov R. Pulmonary extraction and accumulation of lipid formulations of amphotericin B. *Crit Care Med* 2000; 28: 2528-32.
- [47] Ramaswamy M, Peteherych KD, Kennedy AL, Wasan KM. Amphotericin B Lipid Complex or Amphotericin B Multiple-Dose Administration to Rabbits with Elevated Plasma Cholesterol Levels: Pharmacokinetics in Plasma and Blood, Plasma Lipoprotein Levels, Distribution in Tissues, and Renal Toxicities. *Antimicrob Agents Chemother* 2001; 45: 1184-91.
- [48] Fielding RM, Smith PC, Wang LH, Porter J, Guo LS. Comparative pharmacokinetics of amphotericin B after administration of a novel colloidal delivery system, ABCD, and a conventional formulation to rats. *Antimicrob Agents Chemother* 1991; 35: 1208-13.
- [49] Fielding RM, Singer AW, Wang LH, Babbar S, Guo LS. Relationship of pharmacokinetics and drug distribution in tissue to increased safety of amphotericin B colloidal dispersion in dogs. *Antimicrob Agents Chemother* 1992; 36: 299-307.
- [50] Wasan KM, Grossie VB Jr, Lopez-Berestein G. Concentrations in serum and distribution in tissue of free and liposomal amphotericin B in rats during continuous intralipid infusion. *Antimicrob Agents Chemother* 1994; 38: 2224-6.
- [51] Echevarria I, Barturen C, Renedo MJ, Troconiz IF, Dios-Vieitez MC. Comparative pharmacokinetics, tissue distributions, and effects on renal function of novel polymeric formulations of amphotericin B and amphotericin B-desoxycholate in rats. *Antimicrob Agents Chemother* 2000; 44: 898-904.
- [52] Risovic V, Boyd M, Choo E, Wasan KM. Effects of lipid-based oral formulations on plasma and tissue amphotericin B concentrations and renal toxicity in male rats. *Antimicrob Agents Chemother* 2003; 47: 3339-42.
- [53] Wang LH, Fielding RM, Smith PC, Guo LS. Comparative tissue distribution and elimination of amphotericin B colloidal dispersion (Amphocil) and Fungizone after repeated dosing in rats. *Pharm Res* 1995; 12: 275-83.
- [54] Christiansen KJ, Bernard EM, Gold JW, *et al.* Distribution and activity of amphotericin B in humans. *J Infect Dis* 1985; 152: 1037-43.
- [55] Collette N, van der Auwera P, Lopez AP, *et al.* Tissue concentrations and bioactivity of amphotericin B in cancer patients treated with amphotericin B desoxycholate. *Antimicrob Agents Chemother* 1989; 33: 362-8.
- [56] Adler-Moore JP, Proffitt RT. Development, characterization, efficacy and mode of action of AmBisome, a unilamellar liposomal formulation of amphotericin B. *J Liposome Res* 1993; 3: 429-50.
- [57] Guo LS. Amphotericin B colloidal dispersion: an improved antifungal therapy. *Adv Drug Deliv Rev* 2001; 47: 149-63.
- [58] Janoff AS, Perkins WR, Saletan SL, *et al.* Amphotericin B lipid complex (ABLCTM): a molecular rationale for the attenuation of amphotericin B related toxicities. *J Liposome Res* 1993; 3: 451-71.
- [59] Boswell GW, Buell D, Bekersky I. AmBisome (liposomal amphotericin B): a comparative review. *J Clin Pharmacol* 1998; 38: 583-92.
- [60] Heinemann V, Kahny B, Debus A, Wachholz K, Jehn U. Pharmacokinetics of liposomal amphotericin B (AmBisome) versus other lipid-based formulations. *Bone Marrow Transplant* 1994; 14 Suppl 5: S8-9.
- [61] Walsh TJ, Yeldandi V, McEvoy M, *et al.* Safety, tolerance, and pharmacokinetics of a small unilamellar liposomal formulation of amphotericin B (AmBisome) in neutropenic patients. *Antimicrob Agents Chemother* 1998; 42: 2391-8.
- [62] Gokhale PC, Barapatre RJ, Advani SH, Kshirsagar NA, Pandya SK. Pharmacokinetics and tolerance of liposomal amphotericin B in patients. *J Antimicrob Chemother* 1993; 32: 133-9.
- [63] Walsh TJ, Goodman JL, Pappas P, *et al.* Safety, tolerance, and pharmacokinetics of high-dose liposomal amphotericin B (AmBisome) in patients infected with *Aspergillus* species and other filamentous fungi: maximum tolerated dose study. *Antimicrob Agents Chemother* 2001; 45: 3487-96.
- [64] Humphreys H, Oliver D, Winter R, Warnock DW. Liposomal amphotericin B and continuous veno-venous hemofiltration. *J Antimicrob Chemother* 1994; 33: 1070-1.
- [65] Tomlin M, Priestley GS. Elimination of liposomal amphotericin by hemodiafiltration. *Intensive Care Med* 1995; 21: 699-700.
- [66] Heinemann V, Bosse D, Jehn U, *et al.* Pharmacokinetics of liposomal amphotericin B (AmBisome) in critically ill patients. *Antimicrob Agents and Chemother* 1997; 41: 1275-80.
- [67] Vogelsinger H, Joannidis M, Kountchev J, Bellmann-Weiler R, Wiedermann CJ, Bellmann R. Pharmacokinetics of Liposomal Amphotericin B during Extracorporeal Albumin Dialysis. *Artif Organs* 2006; 30: 118-20.
- [68] Sanders SW, Buchi KN, Goddard MS, Lang JK, Tolman KG. Single-dose pharmacokinetics and tolerance of a cholesteryl sulfate complex of amphotericin B administered to healthy volunteers. *Antimicrob Agents Chemother* 1991; 35: 1029-34.
- [69] Amantea MA, Bowden RA, Forrest A, Working PK, Newman MS, Mamelok RD. Population pharmacokinetics and renal function-sparing effects of amphotericin B colloidal dispersion in patients receiving bone marrow transplants. *Antimicrob Agents Chemother* 1995; 39: 2042-7.
- [70] Adedoyin A, Bernardo JF, Swenson CE, *et al.* Pharmacokinetic profile of ABELCET (amphotericin B lipid complex injection): combined experience from phase I and phase II studies. *Antimicrob Agents Chemother* 1997; 41: 2201-8.
- [71] Adedoyin A, Swenson CE, Bolcsak LE, *et al.* A pharmacokinetic study of amphotericin B lipid complex injection (Abelcet) in patients with definite or probable systemic fungal infections. *Antimicrob Agents Chemother* 2000; 44: 2900-2.
- [72] Walsh TJ, Whitcomb P, Piscitelli S, *et al.* Safety, tolerance, and pharmacokinetics of amphotericin B lipid complex in children with hepatosplenic candidiasis. *Antimicrob Agents Chemother* 1997; 4: 1944-8.
- [73] Bellmann R, Egger P, Djanani A, Wiedermann CJ. Pharmacokinetics of amphotericin B lipid complex in critically ill patients on continuous veno-venous haemofiltration. *Int J Antimicrob Agents* 2004; 23: 80-3.
- [74] Heinemann V, Bosse D, Jehn U, *et al.* Enhanced pulmonary accumulation of liposomal amphotericin B (AmBisome) in acute liver transplant failure. *J Antimicrob Chemother* 1997; 40: 295-7.
- [75] Proffitt RT, Satorius A, Chiang SM, Sullivan L, Adler-Moore JP. Pharmacology and toxicology of a liposomal formulation of amphotericin B (AmBisome) in rodents. *J Antimicrob Chemother* 1991; 28 Suppl B: 49-61.
- [76] Ringden O, Meunier F, Tollemer J, *et al.* Efficacy of amphotericin B encapsulated in liposomes (AmBisome) in the treatment of invasive fungal infections in immunocompromised patients. *J Antimicrob Chemother* 1991; 28 Suppl B: 73-82.
- [77] Williams P. Amphotericin B concentrations attained in tissues obtained at autopsy from patients administered amphotericin B lipid complex injection (Abelcet[®]). *Transpl* 1999; 67: 93. (Abstract)
- [78] Vogelsinger H, Weiler S, Djanani A, Kountchev J, Bellmann-Weiler R, Wiedermann CJ, Bellmann R. Amphotericin B Tissue Distribution in Autopsy Material after Treatment with Liposomal

- Amphotericin B and Amphotericin B Colloidal Dispersion; J Antimicrob Chemother 2006; 57:1153-60.
- [79] Demartini G, Lequaglie C, Brega Massone PP, Scaglione F, Frascini F. Penetration of amphotericin B in human lung tissue after single liposomal amphotericin B (AmBisome) infusion. J Chemother 2005; 17: 82-5.
- [80] Hiemenz JW, Walsh T J. Lipid formulations of amphotericin B: recent progress and future directions. Clin Infect Dis 1996; 22 Suppl 2: S133-144.
- [81] Janknegt R, de Marie S, Bakker-Woudenberg IA, Crommelin DJ. Liposomal and lipid formulations of amphotericin B. Clin Pharmacokinet 1992; 23: 279-91.
- [82] Frothingham R. Lipid formulations of amphotericin B for empirical treatment of fever and neutropenia. Clin Infect Dis 2002; 35: 896-7.
- [83] Wingard JR. Lipid formulations of amphotericins: Are you a lump or a splitter? Clin Infect Dis 2002; 35: 891-5.
- [84] Wingard JR, White MH, Anaissie E, Raffalli J, Goodman J, Arrieta A. L Amph/ABLC Collaborative Study Group. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. L Amph/ABLC Collaborative Study Group. Clin Infect Dis 2000; 31: 1155-63.
- [85] Fleming RV, Kantarjian HM, Husni R, *et al.* Comparison of amphotericin B lipid complex (ABLC) vs. AmBisome in the treatment of suspected or documented fungal infections in patients with leukemia. Leuk Lymphoma 2001; 40: 511-20.
- [86] Pahls S, Schaffner A. Comparison of the activity of free and liposomal amphotericin B *in vitro* and in a model of systemic and localized murine candidiasis. J Infect Dis 1994; 169: 1057-61.
- [87] Leenders AC, Daenen S, Jansen RL, *et al.* Liposomal amphotericin B compared with amphotericin B deoxycholate in the treatment of documented and suspected neutropenia-associated invasive fungal infections. Brit J Haematol 1998; 103: 205-12.
- [88] Leenders AC, Reiss P, Portegies P, *et al.* Liposomal amphotericin B (AmBisome) compared with amphotericin B both followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meningitis. AIDS 1997; 11: 1463-71.
- [89] Working PK. Amphotericin B colloidal dispersion. Pre-clinical review. Chemotherapy 1999; 45 Suppl 1: 15-26.
- [90] White MH, Bowden RA, Sandler ES, *et al.* Randomized, double-blind clinical trial of amphotericin B colloidal dispersion vs. amphotericin B in the empirical treatment of fever and neutropenia. Clin Infect Dis 1998; 27: 296-302.
- [91] Wasan KM, Lopez-Berestein G. Characteristics of lipid-based formulations that influence their biological behavior in the plasma of patients. Clin Infect Dis 1996; 23: 1126-38.
- [92] Wong-Beringer A, Jacobs RA, Guglielmo BJ. Lipid formulations of amphotericin B: clinical efficacy and toxicities. Clin Infect Dis 1998; 27: 603-18.
- [93] Bellmann R, Egger P, Wiedermann CJ. Differences in pharmacokinetics of amphotericin B lipid formulations despite clinical equivalence. Clin Infect Dis 2003; 36: 1500-1.
- [94] Bekersky I, Fielding RM, Dressler DE, Kline S, Buell DN, Walsh TJ. Pharmacokinetics, excretion, and mass balance of ¹⁴C after administration of ¹⁴C-cholesterol-labeled AmBisome to healthy volunteers. J Clin Pharmacol 2001; 41: 963-71.
- [95] Swenson CE, Perkins WR, Roberts P, *et al.* *In vitro* and *in vivo* antifungal activity of amphotericin B lipid complex: are phospholipases important? Antimicrob Agents Chemother 1998; 42: 767-71.
- [96] Gottfredsson M, Jessup CJ, Cox GM, Perfect JR, Ghannoum MA. Fungal phospholipase activity and susceptibility to lipid preparations of amphotericin B. Antimicrob Agents Chemother 2001; 45: 3231-3.
- [97] Kennedy AL, Wasan KM. Preferential distribution of amphotericin B lipid complex into human HDL3 is a consequence of high density lipoprotein coat lipid content. J Pharm Sci 1999; 88: 1149-55.
- [98] Tassel D, Madoff MA. Treatment of Candida sepsis and Cryptococcus meningitis with 5-fluorocytosine. A new antifungal agent. JAMA 1968; 206: 830-2.
- [99] Vermes A, Guchelaar HJ, Dankert J. Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions. J Antimicrob Chemother 2000; 46: 171-9.
- [100] Richardson MD, Warnock DW In: Fungal infection: diagnosis and management, 3rd eds. Malden, Blackwell Publishing 2003: 66
- [101] Cutler RE, Blair AD, Kelly MR. Flucytosine kinetics in subjects with normal and impaired renal function. Clin Pharmacol Ther 1978; 24: 333-42.
- [102] Block ER, Bennett JE, Livoti LG, Klein WJ Jr, MacGregor RR, Henderson L. Flucytosine and amphotericin B: hemodialysis effects on the plasma concentration and clearance. Studies in man. Ann Intern Med 1974; 80: 613-7.
- [103] Koechlin BA, Rubio F, Palmer S, Gabriel T, 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. Biochem Pharmacol 1966; 15: 435-46.
- [104] Block ER, Bennett JE. Pharmacological studies with 5-fluorocytosine. Antimicrob Agents Chemother 1972; 1: 476-82.
- [105] Ancotil[®], package insert, ICN Pharmaceuticals Austria, Salzburg, Austria, Europe.
- [106] Daneshmend TK, Warnock DW. Clinical pharmacokinetics of systemic antifungal drugs. Clin Pharmacokinet 1983; 8: 17-42.
- [107] Polak A. Pharmacokinetics of amphotericin B and flucytosine. Postgrad Med J 1979; 55: 667-70.
- [108] Polak A. In: Ancotil[®] Flucytosin Status Quo & Perspektiven 1999: 11-16. Herbert Utz Verlag, Munich Germany.
- [109] Pennington JE, Block ER, Reynolds HY. 5-fluorocytosine and amphotericin B in bronchial secretions. Antimicrob Agents Chemother 1974; 6: 324-6.
- [110] Drouhet E, Babinet P, Chapusot JP, Kleinknecht D. 5-Fluorocytosine in the treatment of candidiasis with acute renal insufficiency: its kinetics during haemodialysis and peritoneal dialysis. Biomedicine 1973; 19: 408-14.
- [111] Schönebeck J, Polak A, Fernex M, Scholer HJ. Pharmacokinetic studies on the oral antimycotic 5-fluorocytosine in individuals with normal and impaired kidney function. Chemotherapy 1973; 18: 321-36.
- [112] Ittel TH, Legler UF, Polak A, Glockner WM, Sieberth HG. 5-Fluorocytosine kinetics in patients with acute renal failure undergoing continuous hemofiltration. Chemotherapy 1987; 33: 77-84.
- [113] Thomson AH, Shankland G, Clareburt C, Binning S. Flucytosine dose requirements in a patient receiving continuous veno-venous haemofiltration. Intensive Care Med 2002; 28: 999.
- [114] Block ER. Effect of hepatic insufficiency on 5-fluorocytosine concentrations in serum. Antimicrob Agents Chemother 1973; 3: 141-2.
- [115] Van Tyle JH. Ketoconazole. Mechanism of action, spectrum of activity, pharmacokinetics, drug interactions, adverse reactions and therapeutic use. Pharmacotherapy 1984; 4: 343-73.
- [116] Figg WD, Liu Y, Arlen P, *et al.* A randomized, phase II trial of ketoconazole plus alendronate versus ketoconazole alone in patients with androgen independent prostate cancer and bone metastases. J Urol 2005; 173: 790-6.
- [117] Daneshmend TK, Warnock DW. Clinical pharmacokinetics of ketoconazole. Clin Pharmacokinet 1988; 14: 13-34.
- [118] Dutreix C, Peng B, Mehring G, *et al.* Pharmacokinetic interaction between ketoconazole and imatinib mesylate (Glivec) in healthy subjects. Cancer Chemother Pharmacol 2004; 54: 290-4.
- [119] Kovarik JM, Beyer D, Bizot MN, Jiang Q, Shenouda M, Schmoeder RL. Blood concentrations of everolimus are markedly increased by ketoconazole. J Clin Pharmacol 2005; 45: 514-8.
- [120] US Food and Drug Administration. Guidance for Industry: *In vivo* drug metabolism/drug interaction studies-study design. Data analysis and recommendations for dosing and labeling. Rockville MD: Food and Drug Administration 1999.
- [121] Lomaestro BM, Piatek MA. Update on drug interactions with azole antifungal agents. Ann Pharmacother 1998; 32: 915-28.
- [122] Albengres E, Tillement JP. Cyclosporin and ketoconazole, drug interaction or therapeutic association? Int J Clin Pharmacol Ther Toxicol 1992; 30: 555-70.
- [123] Shi J, Chapel S, Montay G, *et al.* Effect of ketoconazole on the pharmacokinetics and safety of telithromycin and clarithromycin in older subjects with renal impairment. Int J Clin Pharmacol Ther 2005; 43: 123-33.
- [124] Chaikin P, Gillen MS, Malik M, Pentikis H, Rhodes GR, Roberts DJ. Co-administration of ketoconazole with H1-antagonists ebastine and loratadine in healthy subjects: pharmacokinetic and pharmacodynamic effects. Br J Clin Pharmacol 2005; 59: 346-54.

- [125] Park JY, Kim KA, Shin JG, Lee KY. Effect of ketoconazole on the pharmacokinetics of rosiglitazone in healthy subjects. *Br J Clin Pharmacol* 2004; 58: 397-402.
- [126] Gupta AK, Kohli Y, Batra R. *In vitro* activities of posaconazole, ravuconazole, terbinafine, itraconazole and fluconazole against dermatophyte, yeast and non-dermatophyte species. *Med Mycol* 2005; 43: 179-85.
- [127] Cordonnier C. Fungal infections: current diagnosis and treatment. *Hematol J* 2004; 5 Suppl 3: S59-62.
- [128] Humphrey MJ, Jevons S, Tarbit MH. Pharmacokinetic evaluation of UK-49,858, a metabolically stable triazole antifungal drug, in animals and humans. *Antimicrob Agents Chemother* 1985; 28: 648-53.
- [129] Debruyne D, Ryckelynck JP. Clinical pharmacokinetics of fluconazole. *Clin Pharmacokinet* 1993; 24: 10-27.
- [130] Buijk SL, Gyssens IC, Mouton JW, Verbrugh HA, Touw DJ, Bruining HA. Pharmacokinetics of sequential intravenous and enteral fluconazole in critically ill surgical patients with invasive mycoses and compromised gastro-intestinal function. *Intensive Care Med* 2001; 27: 115-21.
- [131] Toon S, Ross CE, Gokal R, Rowland M. An assessment of the effects of impaired renal function and haemodialysis on the pharmacokinetics of fluconazole. *Br J Clin Pharmacol* 1990; 29: 221-6.
- [132] Albengres E, Le Louet H, Tillement JP. Systemic antifungal agents. Drug interactions of clinical significance. *Drug Saf* 1998; 18: 83-97.
- [133] Ripa S, Ferrante L, Prenna M. Pharmacokinetics of fluconazole in normal volunteers. *Chemotherapy* 1993; 39: 6-12.
- [134] Wysowski DK, Bacanyi J. Cisapride and fatal arrhythmia. *N Engl J Med* 1996; 335: 290-1.
- [135] Honig PK, Worham DC, Zamani K, Mullin JC, Conner DP, Cantilena LR. The effect of fluconazole on the steady-state pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine in humans. *Clin Pharmacol Ther* 1993; 53: 630-6.
- [136] Schotker B, Dosch A, Kraemer DM. Severe hepatotoxicity after application of desloratadine and fluconazole. *Acta Haematol* 2003; 110: 43-4.
- [137] Kerr HD. Case report: potentiation of warfarin by fluconazole. *Am J Med Sci* 1993; 305: 164-5.
- [138] Crussell-Porter LL, Rindone JP, Ford MA, Jaskar DW. Low-dose fluconazole therapy potentiates the hypoprothrombinemic response of warfarin sodium. *Arch Intern Med* 1993; 153: 102-4.
- [139] Cadle RM, Zenon GJ 3rd, Rodriguez-Barradas MC, Hamill RJ. Fluconazole-induced symptomatic phenytoin toxicity. *Ann Pharmacother* 1994; 28: 191-5.
- [140] Howitt KM, Oziemski MA. Phenytoin toxicity induced by fluconazole. *Med J Aust* 1989; 151: 603-4.
- [141] Mitchell AS, Holland JT. Fluconazole and phenytoin: a predictable interaction. *BMJ* 1989; 298: 1315.
- [142] Kramer MR, Marshall SE, Denning DW, *et al.* Cyclosporine and itraconazole interaction in heart and lung transplant recipients. *Ann Intern Med* 1990; 113: 327-9.
- [143] Olkkola KT, Ahonen J, Neuvonen PJ. The effects of the systemic antimycotics, itraconazole and fluconazole, on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. *Anesth Analg* 1996; 82: 511-6.
- [144] Diflucan[®], package insert, Pfizer Corporation Austria Ges. m. b. H, Vienna, Austria.
- [145] Konishi H, Morita K, Yamaji A. Effect of fluconazole on theophylline disposition in humans. *Eur J Clin Pharmacol* 1994; 46: 309-12.
- [146] Sahai J, Gallicano K, Ormsby E, Garber G, Cameron DW. Relationship between body weight, body surface area and serum zidovudine pharmacokinetic parameters in adult, male HIV-infected patients. *AIDS* 1994; 8: 793-6.
- [147] Apseloff G, Hilligoss DM, Gardner MJ, *et al.* Induction of fluconazole metabolism by rifampin: *in vivo* study in humans. *J Clin Pharmacol* 1991; 31: 358-61.
- [148] Nicolau DP, Crowe HM, Nightingale CH, Quintiliani R. Rifampin-fluconazole interaction in critically ill patients. *Ann Pharmacother* 1995; 29: 994-6.
- [149] Iatsimirskaja E, Tulebaev S, Storozhuk E, *et al.* Metabolism of rifabutin in human enterocyte and liver microsomes: kinetic parameters, identification of enzyme systems, and drug interactions with macrolides and antifungal agents. *Clin Pharmacol Ther* 1997; 61: 554-62.
- [150] Lazar JD, Wilner KD. Drug interactions with fluconazole. *Rev Infect Dis* 1990; 12 Suppl 3: S327-33.
- [151] Ehninger G, Jaschonek K, Schuler U, Kruger HU. Interaction of fluconazole with cyclosporin. *Lancet* 1989; 2: 104-5.
- [152] Kruger HU, Schuler U, Zimmermann R, Ehninger G. Absence of significant interaction of fluconazole with cyclosporin. *J Antimicrob Chemother* 1989; 24: 781-6.
- [153] Lopez-Gil JA. Fluconazole-cyclosporine interaction: a dose-dependent effect? *Ann Pharmacother* 1993; 27: 427-30.
- [154] Canafax DM, Graves NM, Hilligoss DM, Carleton BC, Gardner MJ, Matas AJ. Interaction between cyclosporine and fluconazole in renal allograft recipients. *Transplantation* 1991; 51: 1014-8.
- [155] Torregrosa V, De la Torre M, Campistol JM, *et al.* Interaction of fluconazole with cyclosporin A. *Nephron* 1992; 60: 125-6.
- [156] Manez R, Martin M, Raman D, *et al.* Fluconazole therapy in transplant recipients receiving FK506. *Transplantation* 1994; 57: 1521-3.
- [157] Osowski CL, Dix SP, Lin LS, Mullins RE, Geller RB, Wingard JR. Evaluation of the drug interaction between intravenous high-dose fluconazole and cyclosporine or tacrolimus in bone marrow transplant patients. *Transplantation* 1996; 61: 1268-72.
- [158] Sadaba B, Campanero MA, Quetglas EG, Azanza JR. Clinical relevance of sirolimus drug interactions in transplant patients. *Transplant Proc* 2004; 36: 3226-8.
- [159] Walsh TJ, Foulds G, Pizzo PA. Pharmacokinetics and tissue penetration of fluconazole in rabbits. *Antimicrob Agents Chemother* 1989; 33: 467-9.
- [160] Brammer KW, Farrow PR, Faulkner JK. Pharmacokinetics and tissue penetration of fluconazole in humans. *Rev Infect Dis* 1990; 12 Suppl 3: S318-26.
- [161] Foulds G, Brennan DR, Wajszczuk C, *et al.* Fluconazole penetration into cerebrospinal fluid in humans. *J Clin Pharmacol* 1988; 28: 363-6.
- [162] Ebdon P, Neill P, Farrow PR. Sputum levels of fluconazole in humans. *Antimicrob Agents Chemother* 1989; 33: 963-4.
- [163] Thaler F, Bernard B, Tod M, *et al.* Fluconazole penetration in cerebral parenchyma in humans at steady state. *Antimicrob Agents Chemother* 1995; 39: 1154-6.
- [164] Yang H, Wang Q, Elmquist WF. Fluconazole distribution to the brain: a crossover study in freely-moving rats using *in vivo* microdialysis. *Pharm Res* 1996; 13: 1570-5.
- [165] De Bellis P, Bonfiglio M, Gerbi G, *et al.* High-dose fluconazole therapy in Intensive Care Unit. *Minerva Anestesiol* 2003; 69: 145-52.
- [166] Silling G. Fluconazole: optimized antifungal therapy based on pharmacokinetics. *Mycoses* 2002; 45 Suppl 3: 39-41.
- [167] Oono S, Tabei K, Tetsuka T, Asano Y. The pharmacokinetics of fluconazole during haemodialysis in uraemic patients. *Eur J Clin Pharmacol* 1992; 42: 667-9.
- [168] Debruyne D, Ryckelynck JP, Moulin M, Hurault de Ligny B, Levaltier B, Bigot MC. Pharmacokinetics of fluconazole in patients undergoing continuous ambulatory peritoneal dialysis. *Clin Pharmacokinet* 1990; 18: 491-8.
- [169] Debruyne D, Ryckelynck JP. Fluconazole serum, urine, and dialysate levels in CAPD patients. *Perit Dial Int* 1992; 12: 328-9.
- [170] Yagasaki K, Gando S, Matsuda N, *et al.* Pharmacokinetics and the most suitable dosing regimen of fluconazole in critically ill patients receiving continuous hemodiafiltration. *Intensive Care Med* 2003; 29: 1844-8.
- [171] Muhl E, Martens T, Iven H, Rob P, Bruch HP. Influence of continuous veno-venous haemodiafiltration and continuous venovenous haemofiltration on the pharmacokinetics of fluconazole. *Eur J Clin Pharmacol* 2000; 56: 671-8.
- [172] Kishino S, Koshinami Y, Hosoi T, *et al.* Effective fluconazole therapy for liver transplant recipients during continuous hemodiafiltration. *Ther Drug Monit* 2001; 23: 4-8.
- [173] Sporanox[®], package insert, Janssen-Cilag Pharma, Vienna, Austria.
- [174] Caputo R. Itraconazole (Sporanox) in superficial and systemic fungal infections. *Expert Rev Anti Infect Ther* 2003; 1: 531-42.
- [175] Ahmad SR, Singer SJ, Leissa BG. Congestive heart failure associated with itraconazole. *Lancet* 2001; 357: 1766-7.
- [176] Heykants J, Van Peer A, Van de Velde V, *et al.* The clinical pharmacokinetics of itraconazole: an overview. *Mycoses* 1989; 32 Suppl 1: 67-87.

- [177] De Beule K, Van Gestel J. Pharmacology of itraconazole. *Drugs* 2001; 61 Suppl 1: 27-37.
- [178] Grant SM, Clissold SP. Itraconazole. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in superficial and systemic mycoses. *Drugs* 1989; 37: 310-44.
- [179] Lim SG, Sawyerr AM, Hudson M, Sercombe J, Pounder RE. Short report: the absorption of fluconazole and itraconazole under conditions of low intragastric acidity. *Aliment Pharmacol Ther* 1993; 7: 317-21.
- [180] Graybill JR, Vazquez J, Darouiche RO, *et al*. Randomized trial of itraconazole oral solution for oropharyngeal candidiasis in HIV/AIDS patients. *Am J Med* 1998; 104: 33-9.
- [181] Prentice AG, Warnock DW, Johnson SA, Phillips MJ, Oliver DA. Multiple dose pharmacokinetics of an oral solution of itraconazole in autologous bone marrow transplant recipients. *J Antimicrob Chemother* 1994; 34: 247-52.
- [182] Barone JA, Moskovitz BL, Guarnieri J, *et al*. Enhanced bioavailability of itraconazole in hydroxypropyl-beta-cyclodextrin solution versus capsules in healthy volunteers. *Antimicrob Agents Chemother* 1998; 42: 1862-5.
- [183] Willems L, van der Geest R, de Beule K. Itraconazole oral solution and intravenous formulations: a review of pharmacokinetics and pharmacodynamics. *J Clin Pharm Ther* 2001; 26: 159-69.
- [184] Poirier JM, Cheymol G. Optimisation of itraconazole therapy using target drug concentrations. *Clin Pharmacokinet* 1998; 35: 461-73.
- [185] Heykants J, Van Peer A, Van de Velde V, *et al*. The clinical pharmacokinetics of itraconazole: an overview. *Mycoses* 1989; 32 Suppl 1: 67-87.
- [186] Haria M, Bryson HM, Goa KL. Itraconazole. A reappraisal of its pharmacological properties and therapeutic use in the management of superficial fungal infections. *Drugs* 1996; 51: 585-620.
- [187] Perfect JR, Savani DV, Durack DT. Uptake of itraconazole by alveolar macrophages. *Antimicrob Agents Chemother* 1993; 37: 903-4.
- [188] Vandewoude K, Vogelaers D, Decruyenaere J, *et al*. Concentrations in plasma and safety of 7 days of intravenous itraconazole followed by 2 weeks of oral itraconazole solution in patients in intensive care units. *Antimicrob Agents Chemother* 1997; 41: 2714-8.
- [189] Coronel B, Persat F, Dorez D, Moskovtchenko JF, Peins MA, Mercatello A. Itraconazole concentrations during continuous haemodiafiltration. *J Antimicrob Chemother* 1994; 34: 448-9.
- [190] Kovarik JM, Hsu CH, McMahon L, Berthier S, Rordorf C. Population pharmacokinetics of everolimus in de novo renal transplant patients: impact of ethnicity and comedication. *Clin Pharmacol Ther* 2001; 70: 247-54.
- [191] Ahmad SR, Singer SJ, Leissa BG. Congestive heart failure associated with itraconazole. *Lancet* 2001; 357: 1766-7.
- [192] Jalava KM, Olkkola KT, Neuvonen PJ. Itraconazole greatly increases plasma concentrations and effects of felodipine. *Clin Pharmacol Ther* 1997; 61: 410-5.
- [193] Neuvonen PJ, Suhonen R. Itraconazole interacts with felodipine. *J Am Acad Dermatol* 1995; 33: 134-5.
- [194] Taylor SA, Gupta AK, Walker SE, Shear NH. Peripheral edema due to nifedipine-itraconazole interaction: a case report. *Arch Dermatol* 1996; 132: 350-2.
- [195] Jeu L, Piacenti FJ, Lyakhovetskiy AG, Fung HB. Voriconazole. *Clin Ther* 2003; 25: 1321-81.
- [196] Roffey SJ, Cole S, Comby P, *et al*. The disposition of voriconazole in mouse, rat, rabbit, guinea pig, dog, and human. *Drug Metab Dispos* 2003; 31: 731-41.
- [197] Purkins L, Wood N, Ghahramani P, Greenhalgh K, Allen MJ, Kleinerma D. Pharmacokinetics and safety of voriconazole following intravenous- to oral-dose escalation regimens. *Antimicrob Agents Chemother* 2002; 46: 2546-53.
- [198] Donnelly JP, De Pauw BE. Voriconazole-a new therapeutic agent with an extended spectrum of antifungal activity. *Clin Microbiol Infect* 2004; 10 Suppl 1: 107-17.
- [199] Wood N, Tan K, Purkins L, *et al*. Effect of omeprazole on the steady-state pharmacokinetics of voriconazole. *Br J Clin Pharmacol* 2003; 56 Suppl 1: 56-61.
- [200] Ullmann AJ. Review of the safety, tolerability, and drug interactions of the new antifungal agents caspofungin and voriconazole. *Curr Med Res Opin* 2003; 19: 263-71.
- [201] Rengelshausen J, Banfield M, Riedel KD, *et al*. Opposite effects of short-term and long-term St John's wort intake on voriconazole pharmacokinetics. *Clin Pharmacol Ther* 2005; 78: 25-33.
- [202] Dowell JA, Schranz J, Baruch A, Foster G. Safety and pharmacokinetics of coadministered voriconazole and anidulafungin. *J Clin Pharmacol* 2005; 45: 1373-82.
- [203] Lutsar I, Roffey S, Troke P. Voriconazole concentrations in the cerebrospinal fluid and brain tissue of guinea pigs and immunocompromised patients. *Clin Infect Dis* 2003; 37: 728-32.
- [204] Denes E, Pichon N, Debette-Gratien M, Bouteille B, Gaulier JM. Pharmacokinetics of voriconazole in the cerebrospinal fluid of an immunocompromised patient with a brain abscess due to *Aspergillus fumigatus*. *Clin Infect Dis* 2004; 39: 603-4.
- [205] Capitano B, Potoski BA, Husain S, *et al*. Intrapulmonary penetration of voriconazole in patients receiving an oral prophylactic regimen. *Antimicrob Agents Chemother* 2006; 50:1878-80.
- [206] Stern JB, Girard P, Caliendo R. Pleural diffusion of voriconazole in a patient with *Aspergillus fumigatus* empyema thoracis. *Antimicrob Agents Chemother* 2004; 48: 1065.
- [207] Vfend[®], package insert, Pfizer Limited, Sandwich, Kent, UK.
- [208] Robatel C, Rusca M, Padoin C, Marchetti O, Liaudet L, Buclin T. Disposition of voriconazole during continuous veno-venous haemodiafiltration (CVVHDF) in a single patient. *J Antimicrob Chemother* 2004; 54: 269-70.
- [209] Herbrecht R. Posaconazole: a potent, extended-spectrum triazole antifungal for the treatment of serious fungal infections. *Int J Clin Pract* 2004; 58: 612-24.
- [210] Courtney R, Radwanski E, Lim J, Laughlin M. Pharmacokinetics of posaconazole coadministered with antacid in fasting or nonfasting healthy men. *Antimicrob Agents Chemother* 2004; 48: 804-8.
- [211] Courtney R, Wexler D, Radwanski E, Lim J, Laughlin M. Effect of food on the relative bioavailability of two oral formulations of posaconazole in healthy adults. *Br J Clin Pharmacol* 2004; 57: 218-22.
- [212] Nomeir AA, Kumari P, Hilbert MJ, *et al*. Pharmacokinetics of SCH 56592, a new azole broad-spectrum antifungal agent, in mice, rats, rabbits, dogs, and cynomolgus monkeys. *Antimicrob Agents Chemother* 2000; 44: 727-31.
- [213] Courtney R, Pai S, Laughlin M, Lim J, Batra V. Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. *Antimicrob Agents Chemother* 2003; 47: 2788-95.
- [214] Krieter P, Flannery B, Musick T, Gohdes M, Martinho M, Courtney R. Disposition of posaconazole following single-dose oral administration in healthy subjects. *Antimicrob Agents Chemother* 2004; 48: 3543-51.
- [215] Ezzet F, Wexler D, Courtney R, Krishna G, Lim J, Laughlin M. Oral bioavailability of posaconazole in fasted healthy subjects: comparison between three regimens and basis for clinical dosage recommendations. *Clin Pharmacokinet* 2005; 44: 211-20.
- [216] Courtney R, Sansone A, Smith W, *et al*. Posaconazole pharmacokinetics, safety, and tolerability in subjects with varying degrees of chronic renal disease. *J Clin Pharmacol* 2005; 45: 185-92.
- [217] Groll AH, Walsh TJ. Posaconazole: clinical pharmacology and potential for management of fungal infections. *Expert Rev Anti Infect Ther* 2005; 3: 467-87.
- [218] Wexler D, Courtney R, Richards W, Banfield C, Lim J, Laughlin M. Effect of posaconazole on cytochrome P450 enzymes: a randomized, open-label, two-way crossover study. *Eur J Pharm Sci* 2004; 21: 645-53.
- [219] Paphitou NI, Ostrosky-Zeichner L, Paetznick VL, Rodriguez JR, Chen E, Rex JH. *In vitro* antifungal susceptibilities of *Trichosporon* species. *Antimicrob Agents Chemother* 2002; 46: 1144-6.
- [220] Andes D, Marchillo K, Stamstad T, Conklin R. *In vivo* pharmacodynamics of a new triazole, ravuconazole, in a murine candidiasis model. *Antimicrob Agents Chemother* 2003; 47: 1193-9.
- [221] Kale P, Johnson LB. Second-generation azole antifungal agents. *Drugs Today (Barc)* 2005; 41: 91-105.
- [222] Gupta AK, Leonardi C, Stoltz RR, Pierce PF, Conetta B. Ravuconazole onychomycosis group. A phase I/II randomized, double-blind, placebo-controlled, dose-ranging study evaluating the efficacy, safety and pharmacokinetics of ravuconazole in the treatment of onychomycosis. *J Eur Acad Dermatol Venereol* 2005; 19: 437-43.

- [223] Petraitiene R, Petraitis V, Lyman CA, *et al.* Efficacy, safety, and plasma pharmacokinetics of escalating dosages of intravenously administered ravuconazole lysine phosphoester for treatment of experimental pulmonary aspergillosis in persistently neutropenic rabbits. *Antimicrob Agents Chemother* 2004; 48: 1188-96.
- [224] Mikamo H, Yin XH, Hayasaki Y, *et al.* Penetration of ravuconazole, a new triazole antifungal, into rat tissues. *Chemotherapy* 2002; 48: 7-9.
- [225] Wiederhold NP, Lewis RE. The echinocandin antifungals: an overview of the pharmacology, spectrum and clinical efficacy. *Expert Opin Investig Drugs* 2003; 12: 1313-33.
- [226] Stone JA, Xu X, Winchell GA, *et al.* Disposition of caspofungin: role of distribution in determining pharmacokinetics in plasma. *Antimicrob Agents Chemother* 2004; 48: 815-23.
- [227] Stone JA, Holland SD, Wickersham PJ, *et al.* Single- and multiple-dose pharmacokinetics of caspofungin in healthy men. *Antimicrob Agents Chemother* 2002; 46: 739-45.
- [228] Balani SK, Xu X, Arison BH, *et al.* Metabolites of caspofungin acetate, a potent antifungal agent, in human plasma and urine. *Drug Metab Dispos* 2000; 28: 1274-8.
- [229] Johnson MD, Perfect JR. Caspofungin: first approved agent in a new class of antifungals. *Expert Opin Pharmacother* 2003; 4: 807-23.
- [230] Walsh TJ, Adamson PC, Seibel NL, *et al.* Pharmacokinetics, safety, and tolerability of caspofungin in children and adolescents. *Antimicrob Agents Chemother* 2005; 49: 4536-45.
- [231] Hiemenz J, Cagnoni P, Simpson D, *et al.* Pharmacokinetic and maximum tolerated dose study of micafungin in combination with fluconazole versus fluconazole alone for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant. *Antimicrob Agents Chemother* 2005; 49: 1331-6.
- [232] Groll AH, Mickiene D, Petraitis V, *et al.* Compartmental pharmacokinetics and tissue distribution of the antifungal echinocandin lipopeptide micafungin (FK463) in rabbits. *Antimicrob Agents Chemother* 2001; 45: 3322-7.
- [233] Niwa T, Yokota Y, Tokunaga A, *et al.* Tissue distribution after intravenous dosing of micafungin, an antifungal drug, to rats. *Biol Pharm Bull* 2004; 27: 1154-6.
- [234] Hebert MF, Townsend RW, Austin S, *et al.* Concomitant cyclosporine and micafungin pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 2005; 45: 954-60.
- [235] Hebert MF, Blough DK, Townsend RW, *et al.* Concomitant tacrolimus and micafungin pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 2005; 45: 1018-24.
- [236] Jarvis B, Figgitt DP, Scott LJ. Micafungin. *Drugs* 2004; 64: 969-82.
- [237] Higashiyama Y, Kohno S. Micafungin: a therapeutic review. *Expert Rev Anti Infect Ther* 2004; 2: 345-55.
- [238] Kishino S, Ohno K, Shimamura T, Furukawatodo H. Optimal prophylactic dosage and disposition of micafungin in living donor liver recipients. *Clin Transplant* 2004; 18: 676-80.
- [239] Jarvis B, Figgitt DP, Scott LJ. Micafungin. *Drugs* 2004; 64: 969-82.
- [240] Seibel NL, Schwartz C, Arrieta A, *et al.* Safety, tolerability, and pharmacokinetics of Micafungin (FK463) in febrile neutropenic pediatric patients. *Antimicrob Agents Chemother* 2005; 49: 3317-24.
- [241] Hebert MF, Smith HE, Marbury TC, *et al.* Pharmacokinetics of micafungin in healthy volunteers, volunteers with moderate liver disease, and volunteers with renal dysfunction. *J Clin Pharmacol* 2005; 45: 1145-52.
- [242] Konishi H, Sudo M, Sumi M, *et al.* Pharmacokinetic behavior of micafungin in rats with carbon tetrachloride-induced acute hepatic failure. *Biol Pharm Bull* 2005; 28: 556-9.
- [243] Kishino S, Ohno K, Shimamura T, Furukawatodo H. Optimal prophylactic dosage and disposition of micafungin in living donor liver recipients. *Clin Transplant* 2004; 18: 676-80.
- [244] Murdoch D, Plosker GL. Anidulafungin. *Drugs* 2004; 64: 2249-58.
- [245] Theuretzbacher U. Pharmacokinetics/pharmacodynamics of echinocandins. *Eur J Clin Microbiol Infect Dis* 2004; 23: 805-12.
- [246] Dowell JA, Knebel W, Ludden T, Stogniew M, Krause D, Henkel T. Population pharmacokinetic analysis of anidulafungin, an echinocandin antifungal. *J Clin Pharmacol* 2004; 44: 590-8.
- [247] Raasch RH. Anidulafungin: review of a new echinocandin antifungal agent. *Expert Rev Anti Infect Ther* 2004; 2: 499-508.
- [248] Groll AH, Mickiene D, Petraitiene R, *et al.* Pharmacokinetic and pharmacodynamic modeling of anidulafungin (LY303366): reappraisal of its efficacy in neutropenic animal models of opportunistic mycoses using optimal plasma sampling. *Antimicrob Agents Chemother* 2001; 45: 2845-55.
- [249] Dowell JA, Schranz J, Baruch A, Foster G. Safety and pharmacokinetics of coadministered voriconazole and anidulafungin. *J Clin Pharmacol* 2005; 45: 1373-82.
- [250] Dowell JA, Stogniew M, Krause D, Henkel T, Weston IE. Assessment of the safety and pharmacokinetics of anidulafungin when administered with cyclosporine. *J Clin Pharmacol* 2005; 45: 227-33.