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REVIEW ARTICLE

Clinical Pharmacokinetics and Pharmacodynamics of Micafungin

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Abstract Micafungin is a selective inhibitor of the synthesis of fungal 1,3-β-D-glucan, an essential component of the fungal cell wall. It is available as a powder for infusion only and is registered for the treatment of invasive and esophageal candidiasis in addition to prophylaxis of *Candida* infections in both adults and children. Average exposure after a single intravenous 100 mg dose in healthy adults is 133 mg h/L. Both exposure and maximum plasma concentration show linear dose proportional pharmacokinetics (PK) over a 0.15–8 mg/kg dose range. In healthy adults, the clearance (CL) is 10.4 mL/h/kg and volume of distribution is 0.2 L/kg; both are independent of the dose. Micafungin is metabolized by arylsulfatase, catechol-*O*-methyltransferase, and several cytochrome P450 (CYP) isoenzymes (3A4, 1A2, 2B6 and 2C), but no dose adjustments are necessary in patients with (severe) hepatic dysfunction. Exposure to micafungin is lower in hematology patients, and is even further lowered in critically ill patients (including burn patients) compared with healthy volunteers, which might have consequences for treatment efficacy. In children, an increased CL has been reported: 40–80 mL/h/kg in premature neonates and 20 mL/h/kg in children >4 months of age. Therefore, relatively higher doses of 4–10 mg/kg in premature neonates and 2–4 mg/kg in children with invasive candidiasis are used. However, these higher CLs may also be explained by the eightfold higher free fraction of unbound micafungin in premature neonates, meaning that an augmented dose might not be required.

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Key Points

Micafungin is a selective inhibitor of 1,3-β-D-glucan synthesis and effectively inhibits the production of the fungal cell wall.

Human cells do not have a cell wall, nor do their cells contain 1,3-β-D-glucan. This explains the good tolerability of echinocandins, even at a high dose.

Micafungin has linear dose proportional PK over a dose range of 0.15–8 mg/kg.

Exposure to micafungin is considerably lower in critically ill patients, including burn patients. These patients could benefit from an augmented dose of micafungin 150–200 mg.

The clearance of micafungin is much higher in neonates and older children and these populations receive a considerably higher weight-corrected dose than adults.

High-dose micafungin is a candidate for less frequent dosing (i.e. 200 mg every 48 h, or 300 mg every 72 h) due to its favorable toxicity profile and a possible post-antifungal effect, as well as practical reasons.

1 Introduction

Micafungin is one of three currently available echinocandins that are first-line treatment options in candidiasis and candidemia. Along with caspofungin and anidulafungin, micafungin is indicated for the treatment of both invasive and esophageal candidiasis in addition to prophylaxis of *Candida* infections that are frequently seen in immunocompromised patients [1]. In high-risk populations, such as patients treated with chemotherapy or other immunosuppressive agents, and critically ill patients in the intensive care unit, invasive *Candida* infections remain an important cause of mortality and morbidity, with reported *Candida*-associated mortality rates of between 20 and 60% [2–4]. Echinocandins outperform azole antifungal agents when it comes to treatment outcome of invasive candidiasis or candidemia and are recommended as first-line treatment for both critically and non-critically ill patients [5–8].

Micafungin (Mycamine®, FK463) is a water-soluble, semisynthetic lipopeptide that is synthesized by chemical modification of a fermentation product from *Coleophoma empetri* [9]. It selectively inhibits the synthesis of 1,3-β-D-glucan, an essential component of the fungal cell wall. Continued synthesis of 1,3-β-D-glucan is crucial in maintaining fungal cell wall integrity, and inhibition leads to osmotic instability, eventually resulting in cell lysis. Fungicidal activity is seen in the majority of *Candida* species, with low *in vitro* minimum inhibitory concentrations (MICs) for *C. albicans, C. glabrata* and *C. tropicalis*, and relatively higher MICs for *C. krusei* and *C. parapsilosis* [10]. Fungistatic activity was seen in *Aspergillus* species where echinocandins specifically show effects during active cell growth of the hyphae, leading to damage of these structures [11]. In a neutropenic rabbit model for pulmonary aspergillosis, this activity led to decreased blood vessel invasion, prevention of pulmonary injury, and improvement of survival compared with untreated controls [12]. Micafungin is not active against *Cryptococcus neoformans* despite the fact that its cell wall contains 1,3-β-D-glucan, and also shows little activity against *Fusarium* spp. and zygomycetes [13].

Micafungin was first approved in Japan in late 2002 and by the US FDA in March 2005, followed by several Asian countries between 2005 and 2007 and in the EU in April 2008 [9]. It is available as a powder for intravenous solution and recommended doses are 50–200 mg/day for patients weighing 40 kg or more and 1–4 mg/kg/day for children >4 months of age with a weight below 40 kg. For children <4 months of age, including preterm neonates, a dose of 4–10 mg/kg/day is registered for the treatment of invasive candidiasis. A loading dose is not required [1].

This review discusses the clinical pharmacology of micafungin in adult and pediatric patients, including pharmacokinetics (PK), pharmacodynamics (PD), special patient populations, and future perspectives in terms of prospective and upcoming clinical trials. The method used in this review can be found in the electronic supplementary material.

2 Pharmacokinetics (PK) in Adults Patients

Micafungin is a large molecule with a molar mass of 1270.28 g/mol. Although oral bioavailability of micafungin has not been reported, it is predicted to be poor analogous to anidulafungin, which has a similar molar mass and bioavailability of 2–7% [14]. Due to the expected poor bioavailability, micafungin is only intended for parenteral use. Linear PK have been shown over a dose ranging between 0.15 and 8 mg/kg/day, corresponding to doses of 12.5–869 mg/day [1, 15–18].

2.1 PK in Healthy Subjects

The PK in healthy subjects has been investigated in both single- and repeated-dose studies [19–24]. Table 1 shows

Table 1 Pharmacokinetic parameters of micafungin in healthy subjects

Dose (mg)	Subjects		Mean pharmacokinetic parameters (% coefficient of variation) [range]										References
	n	SD or SS	Weight (kg)	C_{max} (mg/L)	C_{max} at SS (mg/L)	C_{24h}, mg/L	C_{24h} at SS (mg/L)	AUC_{24} (mg h/L)	AUC (mg h/L)	$t_{½}$ (h)	CL (mL/h/kg)	V_d (L/kg)	
100	26	SD	73.7	NR	NR	NR	NR	NR	136.4 (19)[a]	16.4 (16)	10.4 (20)	0.215 (13)	[20]
	8	SD	84 (11)	8.8 (20) [5.1–11.3]	NR	NR	NR	NR	125.9 (21) [84.3–160.4][a]	14.6 (21) [11.7–20.4]	9.8 (18) [7.2–13.6]	0.199 (14) [0.167–0.260]	[21]
	9	SD	85 (18)	8.2 (17) [5.7–9.8]	NR	NR	NR	NR	120.9 (14) [102.6–149.4][a]	15.1 (12) [12.4–17.8]	10 (16) [8–13.4]	0.202 (18) [0.168–0.284]	[21]
	27	SD	71.7	NR	NR	NR	NR	NR	133.4 (14)[a]	14.8 (9)	10.8 (11)	NR	[19]
	8	SD	70.2 (22)	10.3 (24)	NR	2[b]	NR	96.8 (21)	142.4 (20)[a]	14.9 (10)	10.4 (20)	0.224 (25)	[24]
Weighted average			75	9.1 (20)					133 (17)	15.4 (13)	10.4 (16)	0.2 (16)	
150	23	SS	NR	NR	15.9 (13)	NR	4[b]	NR	180.9 (17)	NR	NR	NR	[22]
	16	SS	NR	12 (19)	16 (17)	2.5[b]	4[b]	116 (19)	182 (19)	NR	NR	NR	[23]
Weighted average					16 (15)		4		181 (18)				

NR not reported, C_{max} maximum plasma concentration, *SD* single dose, *SS* steady state, C_{24h} trough plasma concentration 24 h after dosing, AUC_{24} area under the plasma concentration-time curve after a single dose from zero to 24 h, *AUC* area under the plasma concentration-time curve at steady state from zero to 24 h, or, when indicated, from zero to infinity after a single dose, $t_{½}$ terminal half-life, *CL* clearance, V_d volume of distribution; average is weighted by the number of patients reported

[a] AUC_{∞} after a single dose

[b] Values not reported but extracted from figures with time versus concentration curves

the PK parameters and weighted averages. After a 100 mg single dose infused in 60 min, typical values for maximum plasma concentration (C_{max}) of 9.1 mg/L, trough plasma concentration 24 h after dosing (C_{24h}) of approximately 2 mg/L, area under the concentration–time curve (AUC) from zero to infinity (AUC_{∞}) of 133 mg h/L, clearance (CL) of 10.4 mL/h/kg, apparent volume of distribution (V_d) of 0.2 L/kg, and terminal half-life ($t_{½}$) of 15.4 h were found. Additionally, after a daily 150 mg dose infused in 60 min, C_{max} values after a single dose and at steady state of 12 and 16 mg/L were achieved, respectively; C_{24h} after a single dose and at steady state was approximately 2.5 and 4.5 mg/L, respectively; and AUC from zero to 24 h (AUC_{24}) after a single dose and at steady state of 116 and 181.5 mg h/L, respectively, were reported.

In a repeated-dose study in healthy volunteers, HIV patients and hematology patients receiving micafungin 50–150 mg daily, the drug was found to show accumulation in the body over time, with a ratio of approximately 1.5 [23, 25, 26]. This accumulation factor describes the elimination of micafungin from the body in relation to the dose interval, meaning that for micafungin administered daily, the AUC_{24} at steady state was approximately 1.5-fold greater than the AUC_{24} after a single dose.

2.2 Distribution

In HIV patients with esophageal candidiasis treated with an intravenous dose of micafungin ranging from 50 to 150 mg/day, the V_d was approximately 0.4 L/kg, with the V_d after a single dose being similar to the V_d at steady state, indicating that equilibrium between plasma and tissue is rapidly reached [15]. Steady state is reached after approximately 4–5 days. Micafungin is highly protein bound in plasma (99.8%), mainly to albumin and α-1-acid glycoprotein, which is concentration-independent over a range of 10–100 mg/L [9]. At clinically relevant concentrations, binding to albumin was shown to be non-competitive, did not displace albumin-bound bilirubin, and showed no interaction with other protein-bound medication [9]. Micafungin is not significantly taken up by red blood cells, with a cell/plasma ratio of 0.7. Intracellular concentrations of micafungin in peripheral blood mononuclear cells and polymorphonuclear leukocytes were approximately tenfold higher compared with corresponding plasma concentrations [27].

2.3 Tissue Penetration

Distribution into tissues throughout the body has not been extensively investigated and data mainly come from a limited number of case reports [28–38]. Furthermore, these data are often difficult to interpret because homogenate samples may show incorrect concentrations due to differences between intra- and extracellular concentrations. Also, an unusually high number of mononuclear cells due to a local infection could lead to an overestimation of extracellular micafungin concentration [39]. However, some more easily accessible compartments can give a good estimation of tissue penetration, such as measurements in cerebrospinal fluid (CSF) and epithelial lining fluid (ELF). Tissue penetration of micafungin in relation to other antifungal agents has been thoroughly reviewed previously [39]. Penetration differs per organ system and a detailed description of available data is provided below.

The penetration of micafungin in burn eschar tissue has been reported in several publications [40–43]. Asensio et al. reported an average tissue (T)/C_{max} ratio of 0.08, 1–3 h after administration of 100 mg on day 5 of therapy [40], while two investigations by Sasaki et al. examined tissue 24 h after a 200–300 mg dose and reported tissue/plasma (T/P) ratios ranging from 2.2 to 6.5 in one patient and from 0.76 to 2.32 in three other patients [42, 43].

Penetration in the lung, specifically the ELF and alveolar cells (AC) was investigated in two prospective studies, with a total of 35 volunteers receiving micafungin 150 mg [44, 45]. The T/P ratios changed over time and ranged from 0.01 to 1.1 for ELF/P and 0.61 to 7.62 for AC/P. By modeling and simulation, the authors predicted a mean AUC ratio from days 1 to 14 of 1.3 for ELF/P and 3.5 for AC/P [44, 45]. In two other patients, micafungin reached lower concentrations in pleural fluid, with an average T/P of 0.14 at steady state 2–4 h after dosing [46]. In another patient, T/P ratios of 0.57 (day 29) and 0.67 (day 43) were seen 22 h after the last dose [32].

Peritoneal fluid concentrations were assessed in 10 postsurgical patients receiving micafungin 100 mg daily. Samples were taken at seven time points on days 1 and 3. On both days, the AUC T/P ratio was between 0.3 and 0.4 [47] and the penetration was shown to be twice as high as previously reported in a patient, with an ascites/plasma ratio of 0.15 [46].

Similar to the other echinocandins, micafungin penetrates poorly into brain and CSF. The CSF/P ratio found in three patients 2–5 h after administration varied widely, with values ranging between 0.002 and 0.73 [36, 46]. In another patient, brain tissue was obtained which contained a T/P ratio for micafungin of 0.18 [30]. The most recent study measured micafungin concentrations in nine samples of three premature neonates after a 10 mg/kg dose and measured between 1 and 1.5 mg/L, corresponding with a CSF/C_{24h} ratio of 0.16, and CSF/C_{max} ratio of 0.04 [38, 48]. Although highly variable, these data might indicate that there is sufficient penetration of micafungin in these compartments for an antifungal effect, specifically in

neonates with *Candida* meningoencephalitis treated with a high dose.

Low penetration of micafungin was seen intraocularly after intravenous infusion. Eight patients with *Candida* endophthalmitis were described, with mean aqueous and vitreous humor-to-plasma ratios of 0.0043 and 0.0046, respectively [33–35]. In one patient, the tissue concentration of other structures in the eye were also measured and penetration was much better compared with intraocular penetration, with *T*/*P* ratios of 0.094 in the cornea, 0.86 in irises, 0.071 in retinas, and 0.34 in choroids [34].

Distribution of micafungin to the bladder is known to be poor, with <1% unchanged micafungin excreted in urine. Despite this finding, some cases are reported where micafungin was successfully used for the treatment of candiduria [28, 29, 37, 49]. This might be due to the excellent penetration of micafungin in the kidney. Investigations in rabbits showed that the concentration of micafungin in the kidney was similar to the concentration found in plasma [50]. On the other hand, the lack of reports describing therapy failure when using micafungin for candiduria could be the result of publication bias. High-quality evidence is still poor, and guidelines, such as the recent Infectious Diseases Society of America (IDSA) guideline, do not recommend the use of echinocandins for the treatment of urinary tract infections due to *Candida* species [6].

Other compartments where micafungin concentrations have been measured are wound tissue (*T*/*P* ratio of 0.46) [46], bile fluid (*T*/*P* ratio of 1.25) [31], and pancreatic pseudocyst fluid [30]. In the latter, only one sample was measured 24 h after a dose that contained 0.38 μg/mL, but no dose or plasma concentration was reported [30].

2.4 Metabolism

Micafungin undergoes metabolism to at least 11 compounds (M1–M11). It is the main circulating compound, but also M1 (catechol form), M2 (methoxy form of M1) and M5 (hydroxylation at the side chain) have been detected in plasma. Both M1 and M2 are pharmacologically active metabolites, with an exposure of up to 11 and 2%, relative to the parent compound [26]. The M1 metabolite is produced by arylsulfatase and is further metabolized to M2 by catechol-*O*-methyltransferase [51]. All other metabolites are thought to be inactive. The main inactive metabolite is M5, with an exposure of 9–14% relative to the parent compound; this metabolite is formed mainly by cytochrome P450 (CYP) 3A4 but also by several other CYP isoenzymes (CYP1A2, 2B6, and 2C). Like the parent drug, all metabolites show linear PK [26].

2.5 Elimination

Systemic CL after infusion is approximately 12 mL/h/kg, which is 840 mL/h for a 70 kg adult individual. $t_{½}$ is 14–15 h and is independent of the dose. The main metabolite, M5, has a half-life of 32 h. Excretion of micafungin and its metabolites was investigated in two mass balance studies, each with six subjects, with a collection period of 169 h and 28 days, respectively. After 28 days, a total of 83% of the administered dose was collected, 71% in the feces and 12% in urine. The distribution of metabolites in these excretion fluids was not reported. The mean $t_{½}$ for all metabolites was estimated on 340 h [15].

2.6 Variability Between Patients

The effects of intrinsic factors on the PK of micafungin have been investigated in several large studies. No significant differences were found between sex, race, and age, with, for the latter covariate, a group of 66- to 78-year-olds being compared with a group of 20- to 24-year-olds. No differences were found in C_{max}, AUC, $t_{½}$, V_d, CL, and percentage protein binding between these groups [1, 15, 17, 26, 52]. Weight was found to explain a large proportion of variability in CL in a group of 64 hematology patients receiving a dose ranging from 12.5 to 200 mg/day. Patients weighing less than 66.3 kg were found to have a higher average AUC_{24} of 121 mg h/L, compared with 81 mg h/L in patients weighing more than 66.3 kg [53]. Furthermore, micafungin plasma concentrations in a 230 kg patient were approximately 50% lower compared with a group of hematology patients with a mean weight of 82.6 kg [18, 54].

In a study of three groups of healthy volunteers with body mass indexes (BMIs) of <25, 25–40, and >40 kg/m^2, the effect of weight on the CL of subjects >66 kg was described by the function CL (L/h) = 1.04 × (weight/66)$^{0.75}$ [55, 56]. This relation seems to conflict with the CL found in healthy subjects in other reports (see Table 1). For example, Hebert et al. reported a mean CL of 10 mL/h/kg in subjects with a mean weight of 71.7 kg, thus having a CL of 0.717 L/h [21]. According to the formula, these subjects should have had a mean CL of 1.10 L/h, which is an overestimation by more than 50%. This questions the validity of a general formula using weight above a certain cut-off, without taking into account physiological changes that are associated with obesity [57].

2.7 Population PK Models

The plasma concentrations of micafungin and covariates influencing the concentration have been investigated in 15

population PK models (see Table 2 for details) [38, 41, 45, 47, 52, 53, 55, 58–65]. In all cases, the plasma concentration was best described using a two-compartment model; additional compartments were used to explain tissue concentrations in two studies [41, 47]. In the majority of the models, weight was incorporated to explain variability in systemic CL, and, in approximately half of the models, weight was also able to explain variability in V_d of the central compartment. Interestingly enough, with the exception of BMI, no other weight-derived covariates such as fat-free mass, normalized fat mass, or lean body weight have been investigated to explain variability in CL or volume. Other covariates explaining variability in systemic CL were platelet count in Japanese adults and pediatric patients [52], alanine transferase and total bilirubin in pediatric patients [58], the ratio of aspartate transaminase and alanine transaminase in preterm neonates [38], and, finally, albumin and Sequential Organ Failure Assessment (SOFA) score in critically ill patients [61]. Variability in volume in distribution was explained by albumin concentrations in both postsurgical patients with peritonitis and critically ill patients [47, 61].

2.8 Interactions

Micafungin is metabolized partly by the liver through various enzymatic systems, as described above [1]. Micafungin is not a substrate for P-glycoprotein [9]. It has been demonstrated in vitro that micafungin is a strong inhibitor of a wide variety of efflux pumps [66]. As a perpetrator drug, it has been demonstrated that micafungin influences the CL of the following drugs: sirolimus, nifedipine and itraconazole. A mechanistic basis for these interactions is not provided in the Summary of Product Characteristics (SmPC) but possibly due to inhibition of CYP3A4. As increases in AUCs of sirolimus, nifedipine, and itraconazole have been found to not be clinically relevant (increases of 21, 18, and 22%, respectively), they do not warrant dose adaptations of the victim drug [1, 18–20, 22, 23, 67–69]. Coadministration of micafungin with amphotericin B deoxycholate leads to an increase in amphotericin B exposure of 30%, accompanied by the occurrence of more side effects [70], while micafungin remains unaffected. Patients receiving this combination should be monitored closely for (renal) side effects.

2.9 Safety

Micafungin acts by selective inhibition of the fungal enzyme that produces the cell wall polymer 1,3-β-D-glucan synthase. As human cells do not contain this polymer, a favorable toxicity profile can be expected through the absence of a direct pharmacological effect. Indeed, no dose-limiting toxicity has been reported up to a daily dose of 8 mg/kg (896 mg) for 1–4 weeks in adults [71]. Furthermore, one patient was described as receiving 1400 mg every other week for 12 weeks without any side effects associated with micafungin [72]. In addition, a newborn was accidently treated with a single 16 mg/kg dose of micafungin without any adverse reactions [1]. The most common side effects associated with micafungin are diarrhea, nausea, vomiting, pyrexia, thrombocytopenia, and headache [15]. The European Medicines Agency, but not the US FDA, issued a black-box warning for possible development of foci of altered hepatocytes (FAHs) and hepatocellular tumors as preclinical data indicated these tumors developed in rats treated with high-dose micafungin for 13 weeks [1]. After treatment discontinuation, the rats recovered for 13 weeks but the FAHs were still present. At least a part of these foci was not reversible [9]. The relevance of the hepatocarcinogenic potential for use in humans is unknown. As of today, no cases have been published reporting this effect in humans.

3 Special Populations

The PK parameters of the below-described populations are summarized in Table 3.

3.1 Hepatic Impairment

The effect of hepatic impairment was investigated as part of the registration studies in eight volunteers with moderate hepatic impairment due to hepatitis C, primary biliary cirrhosis, or alcohol abuse, with Child–Pugh scores ranging between 7 and 9. Exposure after a single 100 mg dose was decreased to a mean of 98 mg h/L, versus 126 mg h/L in matched healthy volunteers [21]. Similar results were found in a study of eight subjects with severe hepatic impairment who had an exposure of 100 versus 142 mg h/L in eight matched healthy controls [24]. A possible explanation can be found in decreased levels of albumin, resulting in an increased free fraction of micafungin [21, 24]. This results in a lower total plasma concentration and explains the decrease in AUC. Nevertheless, this decreased AUC is not considered to be clinically relevant and no dose adjustments are recommended for patients with moderate or severe hepatic dysfunction. Similar results were observed in 34 liver transplant recipients reported in three studies, with one patient being a remarkable exception [73–75]. This patient had a small-for-size graft liver with a volume of only 26% of a standard liver, and showed a normal half-life of 16 h after a 50 mg dose. However, after administration of a 100 mg dose, the half-life increased to 76 h and the AUC_{12} of this patient

Table 2 Population pharmacokinetic models for micafungin

Year	Population	Subjects, *n*	Samples, *n*	Covariates tested	Compartments, *n*	Covariates in final model				References
						CL	$V_{central}$	*Q*	$V_{peripheral}$	
2009	Preterm neonates	30	NR	NR	2	None	None	None	None	[64]
2016	Preterm neonates	18	72	NR	2	Weight, AST/ALT ratio	Weight	Weight	None	[38]
2010	Preterm neonates and young infants	47	NR	Weight	2	Weight	Weight	None	None	[60]
2015	Pediatric patients (4 months–17 years)	229	1919	Weight, age, age group, sex, albumin, serum creatinine, ALT, AST, total bilirubin, red blood cell count, platelet count	2	Weight, AST, total bilirubin	None	None	None	[58]
2007	Pediatric patients (2–17 years)	72	NR	Weight	2	Weight	Weight	None	None	[59]
2006	Japanese adult and pediatric patients	198	1825	Age, weight, BMI, total protein, albumin, urea nitrogen, total bilirubin, AST, ALT, GGT, LDH, AP, creatinine clearance, red blood cell count, hematocrit, platelet count	2	Weight, platelet count	None	None	None	[52]
2008	Adult patients	62	1128	Weight, height, age, sex, race, dose	2	Weight	None	None	None	[53]
2009	Hematology patients	10	48	NR	2	None	None	None	None	[65]
2010	Lung transplant patients	20	NR	Weight, age, sex, race, height, BAL location, BAL duration	4[a]	None	None	None	None	[45]
2011	Overweight and obese adults	36	252	Weight, sex, age, comorbidities, medication	2	Weight	None	None	None	[55]
2015	Postsurgical patients with peritonitis	10	NR	Weight, serum creatinine, albumin, total bilirubin, medication (vasopressors or diuretics)	3[a]	Weight	Albumin	None	None	[47]
2016	ICU patients with burns and patients with intra-abdominal infections	25	NR	Weight, sex, dose, percentage burned, others unspecified	3[a]	None	None	None	None	[41]
2014	ICU patients receiving CVVH	10	NR	Weight, age, sex, total bilirubin, serum creatinine, urea nitrogen, albumin, presence of vasopressor	2	Weight	None	None	None	[63]
2016	ICU patients	99	436	Weight, age, sex, total protein, AST, ALT, AP, total bilirubin, prothrombin time, albumin, SOFA score, ECMO, hemodialysis	2	Weight, albumin, SOFA score	Weight, albumin	None	Weight, albumin	[61]
2017	ICU patients	20	356	Weight, albumin, CVVH, SOFA score	2	Weight	Weight	Weight	Weight	[62]

NR not reported, *CL* clearance, $V_{central}$ volume of distribution of the central compartment, *Q* intercompartmental clearance, $V_{peripheral}$ volume of distribution of the peripheral compartment, *BMI* body mass index, *AST* aspartate transaminase, *ALT* alanine transaminase, *GGT* γ-glutamyltransferase, *LDH* lactate dehydrogenase, *AP* alkaline phosphatase, *ECMO* extracorporeal membrane oxygenation, *SOFA* Sequential Organ Failure Assessment Score, *CVVH* continuous venovenous hemofiltration, *ICU* intensive care unit

[a] A two-compartment model to describe the plasma concentration, and additional compartments to describe transport to tissue

Table 3 Adult populations

Population	Dose (mg)	No. of subjects, SD or SS	Mean pharmacokinetic parameters (% coefficient of variation) [range]					
			Weight (kg)	C_{max} (mg/L)	C_{max} at SS (mg/L)	C_{24h} (mg/L)	C_{24h} at SS (mg/L)	AUC_{24} (mg h/L)
Moderate hepatic dysfunction	100	8 SD	98 (19)	7.0 (27) [4.5–9.6]	NR	NR	NR	NR
Severe hepatic dysfunction	100	8 SD	73.2 (28)	7.3 (33)	NR	1.5[e]	NR	71.6 (34)
Renal dysfunction <30 mL/min	100	9 SD	84 (29)	8.7 (33) [4.9–13.4]	NR	NR	NR	NR
CVVH	100	10 SS[a]	69.6 (9)	7.3 (13)	9.15 (21)[a]	2.2 (42)	2.46 (30)[a]	71.31 (22) [49.3–92.2]
HIV	50	20 SS	55.3 (21)[b]	4.1 (34)	5.1 (22)	1[e]	1.5[e]	35.7 (25)
	100	20 SS	55.3 (21)[b]	8.0 (30)	10.1 (26)	1.6[e]	3[e]	74.5 (25)
	150	14 SS	55.3 (21)[b]	11.6 (27)	16.4 (40)	2.2[e]	4[e]	104.3 (25)
Hematology	12.5	8 SS	82.6 (23)[b]	0.9	1.1	0.2[e]	0.2[e]	9.0
	25	8 SS	82.6 (23)[b]	1.6 [g]	4.1	0.5[e,g]	0.5[e]	16.6[g]
	50	9 SS	82.6 (23)[b]	3.6	4.4	0.7[e]	1.5[e]	33.9
	50	5 SS	NR	NR	NR	NR	2 (42) [1.2–3.5]	NR
	75	7 SS	NR	NR	NR	NR	4.2 (54) [2.2–9.0]	NR
	75	8 SS	82.6 (23)[b]	5.4 [g]	8.3	1[e,g]	1.5[e]	47.0[g]
	100	14 SS	NR	NR	NR	NR	4.5 (51) [2.5–11.3]	NR
	100	8 SS	82.6 (23)[b]	7.1 [g]	22	1.5[e,g]	2[e]	59.9[g]
	100	20 SS	67.1 (21)	5.69 (38)	10.05 (43)	1.2[e]	2[e]	56.6 (53)
	150	8 SS	82.6 (23)[b]	11.7 [h]	17.6	1.9[e,h]	3.6[e]	103.6[h]
	150	10 SS	[41–67]	NR	21.91 (39)	NR	5.62 (60)	NR
	150	6 SS	60.2 (20) [47.6–82.2]	NR	27.3	NR	9.4	NR
	150	10 SS	NR	NR	NR	NR	4.9 (40) [2.8–10.1]	NR
	200	8 SS	82.6 (23)[b]	13.1	22.6	2.5[e]	5[e]	118.1
	225	8 SS	NR	NR	21.1 (13)	NR	NR	NR
	300	2 SS	NR	NR	NR	NR	14.5 (6) [13.9–15.1]	NR
	300	10 SS	NR	NR	29.2 (21)	NR	NR	NR
	450	8 SS	NR	NR	38.4 (18)	NR	NR	NR
	600	8 SS	NR	NR	60.8 (44)	NR	NR	NR
ICU	100	20 SS	76.5 [50–134][c]	NR	6.2 [5.1–9.2][c]	NR	1.6 [1.3–2.4][c]	NR

Table 3 continued

Population	Dose (mg)	No. of subjects, SD or SS	Mean pharmacokinetic parameters (% coefficient of variation) [range]					
			Weight (kg)	C_{max} (mg/L)	C_{max} at SS (mg/L)	C_{24h} (mg/L)	C_{24h} at SS (mg/L)	AUC_{24} (mg h/L)
	100	99 SD	84.5 [48–141]	NR	NR	NR	NR	NR
Burn	100	10 SS	NR	4.6 [3.9–7.5][c]	6.4 [4.5–9.1][c]	0.7 [0.5–1.1][c]	1.0 [0.9–1.4][c]	NR
	100–150	15 SS	80 [75–87.5][c]	NR	NR	NR	NR	48.3 [37.7–55.8][c]
	200	3 SS	46.9 (19) [40–56.7]	8.81 (32) [5.55–10.79]	12.9 (11) [11.3–13.7]	2.59 (26) [1.81–3.07]	5.8 (57) [2.34–8.91]	NR
	300	5 SS	77.5 (9) [66.8–87]	18.82 (27) [13.6–24.2]	22.8 (18) [18.10–27.9]	4.65 (28) [3.5–6.1]	5.78 (31) [3–7.9]	NR
Intra-abdominal infection	100–150	10 SS	65 [60.3–73.8][c]	NR	NR	NR	NR	51.4 [44.6–56.4][c]
Healthy adult subjects (Table 1)			100 mg	9.1				
			150 mg		16		~4.5	

Population	Dose (mg)	No. of subjects, SD or SS	Mean pharmacokinetic parameters (% coefficient of variation) [range]				References
			AUC (mg h/L)	$t_{½}$ (h)	CL (mL/h/kg)	V_d (L/kg)	
Moderate hepatic dysfunction	100	8 SD	97.5 (19) [74.8–130.1][d]	14.3 (10) [12.2–16.1]	10.9 (16)	0.212 (18) [0.17–0.28]	[21]
Severe hepatic dysfunction	100	8 SD	100.1 (34)[d]	13.7 (15)	15 (32)	0.291 (27)	[24]
Renal dysfunction <30 mL/min	100	9 SD	116.2 (28) [72.9–169.2][d]	14.8 (11) [11.6–16.5]	11.1 (17)	0.215 (14) [0.16–0.26]	[21]
CVVH	100	10 SS[a]	104.54 (21) [62–136.7][a]	NR	12.69 (27) [7.47–18.25]	0.31 (16) [0.23–0.39]	[63]
HIV	50	20 SS	54.3 (24)	14.9 (29)	19.3 (31)	0.401 (31)	[26]
	100	20 SS	115.3 (22)[d]	13.8 (22)	19.8 (27)	0.388 (29)	[26]
	150	14 SS	166.5 (24)[d]	14.1 (18)	20.4 (27)	0.407 (25)	[26]
Hematology	12.5	8 SS	11.9	11.5	13.4	0.199	[18]
	25	8 SS	23.8	12.4	12.7	0.199	[18]
	50	9 SS	44.3	12.2	12.8	0.218	[18]
	50	5 SS	NR	NR	NR	NR	[68]
	75	7 SS	NR	NR	NR	NR	[68]
	75	8 SS	63	13.4	17.8	0.290	[18]
	100	14 SS	NR	NR	NR	NR	[68]
	100	8 SS	101.6	12.0	13.1	0.209	[18]
	100	20 SS	97.11 (30)	13.4 (15)	16.9 (48)	NR	[25]
	150	8 SS	166.7	12.9	11.9	0.202	[18]
	150	10 SS	NR	NR	NR	NR	[95]
	150	6 SS	367.2 (42) [217.3–617.1]	17.7 (12) [14.5–20.0]	8 (50) [4–12]	0.209 (48) [0.09–0.31]	[67]
	150	10 SS	NR	NR	NR	NR	[68]
	200	8 SS	210.6	20.1	11.6	0.283	[18]

Table 3 continued

Population	Dose (mg)	No. of subjects, SD or SS	Mean pharmacokinetic parameters (% coefficient of variation) [range]				References
			AUC (mg h/L)	$t_{½}$ (h)	CL (mL/h/kg)	V_d (L/kg)	
	225	8 SS	234 (15)	14.0 (10)	12.8 (14)	0.243 (8)	[15]
	300	2 SS	NR	NR	NR	NR	[68]
	300	10 SS	339 (21)	14.2 (23)	12.2 (18)	0.240 (20)	[15]
	450	8 SS	479 (33)	14.9 (17)	13.4 (29)	0.278 (22)	[15]
	600	8 SS	663 (32)	17.2 (13)	13.4 (36)	0.307 (37)	[15]
ICU	100	20 SS	65.7 [55.9–88.7][c]	14.4 [12.8–16.3][c]	19.6 [15.7–23.5][c]	0.375 [0.22–0.42][c]	[77]
	100	99 SD	[65.5–99.5][d,f]	NR	NR	0.231 (9)	[61]
Burn	100	10 SS	NR	NR	NR	NR	[40]
	100–150	15 SS	NR	NR	NR	NR	[41]
	200	3 SS	NR	NR	NR	NR	[43]
	300	5 SS	NR	NR	NR	NR	[42]
Intra-abdominal infection	100–150	10 SS	NR	NR	NR	NR	[41]
Healthy adult subjects (Table 1)			133	15.4	10.4	0.2	
			181.4				

NR not reported, C_{max} maximum plasma concentration, *SD* single dose, *SS* steady state, C_{24h} trough plasma concentration 24 h after dosing, AUC_{24}, area under the plasma concentration-time curve after a single dose from zero to 24 h, *AUC* area under the plasma concentration-time curve at steady state from zero to 24 h, or, when indicated, from zero to infinity after a single dose, $t_{½}$ terminal half-life, *CL* clearance, V_d volume of distribution; average is weighted by the number of patients reported, *ICU* intensive care unit, *CVVH* continuous venovenous hemofiltration, *SOFA* Sequential Organ Failure Assessment Score

[a] Values on day 2 of treatment

[b] Mean group weight of all groups

[c] Median value [interquartile range]

[d] AUC_{∞} after a single dose

[e] Values not reported but extracted from figures with concentration versus time curves

[f] AUC dependent on SOFA score and albumin concentration. SOFA <10: albumin $\leq 25 = 87.3$ and albumin $>25 = 99.5$ mg*h/L; SOFA ≥ 10: albumin $\leq 25 = 65.5$ and albumin $>25 = 74.6$ mg*h/L

[g] $n = 9$

[h] $n = 10$

increased from 79 to 601 mg h/L, corresponding to an AUC after a 1000 mg dose in a healthy subject [75].

3.2 Renal Impairment

Although micafungin is not cleared renally, patients who suffer from renal impairment might have altered PK due to alterations in albumin concentrations available for protein binding. The effect of renal impairment on the PK of micafungin was investigated in nine patients with a creatinine CL below 30 mL/min after a single dose of 100 mg, and compared with nine matched healthy subjects. No differences in AUC_{∞}, CL, V_d, half-life, C_{max}, and protein binding were observed between groups [15, 21]; therefore, no adjustments are necessary for patients with renal dysfunction.

3.3 Extracorporeal Elimination Techniques

The use of extracorporeal elimination techniques can influence the PK of drugs by increasing the V_d, direct elimination and adsorption to membranes and tubing material. Micafungin is a large molecule that is highly protein bound and not renally cleared. Indeed, no changes in PK were observed in ten critically ill patients treated with micafungin 100 mg daily during continuous venovenous hemofiltration (CVVH) using polyethersulfone or polysulfone hemofilters. Samples at seven timepoints pre- and postfilter were taken, and removal of micafungin was not observed. In addition, in samples taken from the ultrafiltrate, micafungin levels were below the limit of quantification [63]. In a study of four patients receiving CVVH using cellulose triacetate hollow fiber, the same results were observed [73]. Furthermore, a similar study observed no changes in pre- versus postfilter micafungin concentrations in four critically ill patients treated daily with 150–300 mg during continuous venovenous hemodiafiltration (CVVHDF) using a hollow-fiber membrane composed of polymethyl methacrylate. In addition, these patients were compared with nine critically ill patients not receiving CVVHDF. Although interindividual variability in CL was large throughout both groups, no indication of a difference in CL or V_d was observed [76]. Dose adjustments of micafungin are not indicated in these patients.

3.4 Critically Ill Patients

Changes in micafungin PK in critically ill patients in the intensive care unit (ICU) have been investigated in two prospective studies totaling 119 ICU patients. The first study investigated micafungin concentrations over a 14-day period, with daily trough samples and intensive sampling at day 3 and limited sampling on day 7 in 20 ICU patients receiving micafungin 100 mg daily. At days 3 and 7, the AUC_{24} was 79 versus 66 mg h/L (no significant difference) [77]. These exposures are much lower than the exposure found in healthy volunteers (Table 1; mean value = 133 mg h/L). Investigations in another study of 99 ICU patients confirmed this and found an AUC_{∞} ranging between 65.5 and 99.5 mg h/L, depending on SOFA score, albumin concentration, and bodyweight as relevant covariates [61]. The lowest exposure of 65.5 mg h/L was found in patients with a SOFA score of <10 and an albumin of ≤ 25 g/L. This study also showed that micafungin PK were not influenced by using extracorporeal membrane oxygenation (ECMO), confirming a report in a previously described patient [78]. One of the reasons for lower exposure might be the availability of albumin for protein binding. A second reason is the influence of the SOFA score on micafungin PK, which may impact the metabolic routes of a drug. In the case of micafungin, an induction of arylsulfatase, catechol-O-methyltransferase or CYP isoenzymes, or a change in biliary excretion, may be anticipated [61, 77]. The lower AUC decreases the probability of target attainment (PTA) when the licensed micafungin 100 mg is used in ICU patients. Simulations show that only 62% of patients reach the MIC/AUC target for non-*C. parapsilosis* spp.; therefore, these patients could benefit from a dose escalation to micafungin 200 mg, as indicated in the manufacturer's label information [62].

3.5 Burn Patients

Critically ill patients with thermal injuries showed a lowered plasma concentration of micafungin after a daily 100 mg dose, with a mean C_{24h} of 0.9 mg/L compared with approximately 2 mg/L in healthy volunteers [40]. Two case series report that patients treated with micafungin 200–300 mg had comparable plasma concentrations compared with healthy volunteers receiving 75 mg [42, 43]. Factors causing lower exposure in this patient population are similar to those in general ICU patients. An additional factor for the lower exposure might be the hypermetabolic state, a phase occurring beyond 48 h after the injury period for up to another 48 h, and also seen with other antifungals in severely burned patients [79]. PK in burn patients were compared with PK in patients with complicated intra-abdominal infections, and data from both populations were used to build a population PK model. No differences in PK between these groups were observed, except for the rate constant describing the distribution of micafungin between blood plasma and tissue fluid. The authors concluded that these populations should not be dosed differently from each other. Simulations showed that a micafungin dose of 100–150 mg should be sufficient to achieve a PK/PD target in plasma for non-*C. parapsilosis* spp. and *C. parapsilosis*

species, with MIC values up to 0.008 and 0.064 mg/L, respectively. A licensed dose of 200 mg was found to be sufficient to achieve the European Committee on Antimicrobial Susceptibility Testing (EUCAST) susceptibility target for *C. albicans* (0.016 mg/L), but not for *C. glabrata* (0.03 mg/L) [41].

3.6 Hematology Patients

Hematology patients show different PK of micafungin compared with healthy subjects. PK in hematology patients has been investigated in a dose-escalation study of 62 patients treated with micafungin 12.5–200 mg/day (see Table 3 for a summary of the PK parameters). AUC_{∞} was 81.1 mg h/L after the first 100 mg dose, and seems lower compared with healthy subjects (Table 2; 133 mg h/L). CL was higher being 13.6 mL/h/kg versus 10.4 mL/h/kg in healthy subjects, but V_d seems to be in the same range as healthy subjects, both approximately 0.2 L/kg. The half-life of micafungin in hematology patients is short, 13 h versus 15.4 h in healthy subjects [18].

4 PK in Pediatric Patients

The PK parameters found in neonates, children, and adolescents are summarized in Table 4.

4.1 Neonates

PK of micafungin in premature neonates with a weight above and below 1 kg has been investigated in four small studies, with doses ranging from 0.75 to 15 mg/kg [64, 80–82]. Initial investigations started with single doses of 0.75 and 1 mg/kg, and showed that the average CL was up to tenfold higher in neonates <1 kg compared with healthy adults, i.e. 79.3–98 versus 10.4 mL/h/kg [80, 81]. The reported average half-life was 5.5 and 6.3 versus 15.4 h in healthy adults [80, 81]. Subsequently, higher doses were investigated at steady state in the <1 kg population, with a dose of 10 and 15 mg/kg. CL was approximately 36 mL/h/kg, still almost fourfold higher than CL in healthy adults [64, 82]. AUC_{24} at steady state after a daily 10 mg/kg dose was 308 mg h/L, and proportionally higher after a daily 15 mg/kg dose, with an AUC_{24} of 472 mg h/L; both doses were well-tolerated [64, 82]. The reported volumes of distribution in this select population have a wide range, with averages ranging between 0.51 and 0.81 L/kg, which is at least 2.5-fold higher than the 0.2 L/kg found in healthy adults [64, 80–82]. The high variability in both V_d and CL between the reported populations investigating PK at a very low dose of 0.75–1 mg/kg might be due to non-linear kinetics in this patient population; however, data are very sparse and this could also be an artifact due to small sample sizes.

In premature neonates with a weight above 1 kg, a dose range of 0.75–15 mg/kg has been investigated and seems to show dose proportionality of AUC [64, 80–82]. The CL of approximately 39 mL/h/kg found in this group was similar to neonates with a weight below 1 kg [64, 80, 82]. The V_d seems a bit lower in the >1 kg group, at 0.4 L/kg [64, 80, 82]. In the study by Kawada et al., the PK parameters reported in neonates >1 kg are conflicting with the above-stated parameters . Here, an augmented CL of 81 (versus 39 mL/h/kg) and a V_d of 0.72 L/kg (versus approximately 0.4 L/kg) was found; however, these differences between data were explained by the study design. Kawada et al. performed their investigations in a neonatal population with a gestational age of 24–34 weeks within 12–24 h after birth, while Heresi et al. studied the same population, but 3–8 weeks after birth [81].

Overall, neonates have a higher CL than healthy adults, which can be explained by the fraction of unbound micafungin. Yanni et al. found that the fraction of unbound micafungin can be eightfold higher in neonates compared with adults, suggesting an age-dependent serum protein binding [83]. This explanation would discourage a dose increase because it would mean that although the total exposure decreases, the concentration of unbound micafungin is not necessarily lowered. Lower total exposure can additionally be caused by increases in intrinsic CL due to, for example, maturation. Nevertheless, a dose of 10–15 mg/kg/day was well-tolerated, and reported hepatic toxicity was reversible and manageable by monitoring hepatic markers [38].

4.2 Children and Adolescents

PK of micafungin in children and adolescents has been extensively investigated, with reports of a variety of age and dose ranges, both after a single dose and in steady-state conditions [51, 84–88]. This heterogeneity in study designs complicates the comparison between studies. Table 4 summarizes the main PK parameters.

Both single dose and steady-state parameters show dose proportionality and linearity for C_{24h}, C_{max}, and AUC throughout a dose ranging 0.5–4.5 mg/kg [51, 86]. The main PK parameters, i.e. half-life (approximately 13 h), CL (approximately 19 mL/h/kg), and V_d (0.3 L/kg), did not change throughout dose cohorts or time. Compared with healthy adults, CL is almost twofold higher in children and adolescents compared with adults (19.2 versus 10.4 mL/h/kg), and the remarkably high CL seen in neonates seems to decrease with age. This has been confirmed with a pairwise comparison in a population ranging between 2 and 17 years of age, in children below and above 8 years of

Table 4 Pharmacokinetic parameters of micafungin in adolescents, children, and neonates

Population	Dose (mg/kg)	No. of subjects, SD or SS	Mean pharmacokinetic parameters (% coefficient of variation) [range]					
			Weight (kg)	C_{max} (mg/L)	C_{max} at SS (mg/L)	C_{24h} (mg/L)	C_{24h} at SS (mg/L)	AUC_{24} (mg h/L)
Neonates <1 kg	0.75	4 SD	0.8 (21)	NR	NR	NR	NR	NR
	1	12 SD	0.9 (14) [0.62–0.99]	NR	NR	NR	NR	NR
	10	6 SS	0.7 (16) [0.54–0.85]	NR	28.1 (33) [19.2–40]	NR	NR	NR
	15	7 SS	NR	NR	38.6 (30)	NR	NR	NR
Neonates >1 kg	0.75	6 SD	1.4 (12) [1.17–1.56]	2.5 (36) [1.6–3.6]	NR	0.1[b]	NR	19 (38) [10.3–28.3]
	1	13 SD	1.2 (12) [1.03–1.48]	NR	NR	NR	NR	NR
	1.5	6 SD	1.7 (17) [1.26–2.01]	4.2 (26) [2.6–5.6]	NR	0.4[b]	NR	34.5 (16) [29.7–42.1]
	3	6 SD	1.5 (26) [1.08–1.95]	9.3 (57) [2.1–15.4]	NR	0.6[b]	NR	69.0 (28) [48.9–93.1]
	7	6 SS	2.1 (65) [1.2–4.5]	NR	26.6 (41) [17.4–48.1]	NR	NR	NR
	15	5 SS	NR	NR	38.2 (9)	NR	NR	NR
Neonates <1.5 kg[d]	1	25 SD	1.1 (20) [0.62–1.48]	1.3 (67) [0.39–3.1][h]	NR	0.2 (75) [0.076–0.62][i]	0.26 (62) [0.1–0.73][g]	16.4 (56) [4.2–40.2][f]
Neonates <2 kg[d]	15	12 SS	1.0 (33) [0.54–1.62]	NR	38.4 (23)	NR	NR	NR
4–24 months	1.5	11 SS	8.1 (21) [5.2–9.8]	NR	8.1 (35) [5.6–15.3]	NR	NR	NR
3 months–4 years	2	5 SS	5.17 [1.67–9.63]	6.71 (71)	4.66 (47)	1[b]	1[b]	52.84 (42)
4–24 months	4.5	8 SS	7 (29) [4–9]	NR	32.8 (69) [18.2–84.8]	NR	5[b]	NR
2–5 years	1.5	11 SS	14.8 (30) [9.3–22.6]	NR	8.6 (57) [6.0–23.1]	NR	NR	NR
	4.5	8 SS	14 (14) [9–19]	NR	21.1 (29) [8.4–28.7]	NR	6[b]	NR
6–11 years	1	6 SS	34.2 (11) [30.8–42.0]	NR	6.7 (14) [5.5–7.7]	NR	NR	NR
	1.5	3 SS	23.4 (7) [22.2–25.2]	NR	8.7 (15) [7.2–9.7]	NR	NR	NR
	3	4 SS	32 (19) [25–44]	NR	20.8 (20) [16.8–24.8]	NR	6[b]	NR
	4.5	3 SS	19 (21) [12–24]	NR	20.7 (15) [17.9–24]	NR	5[b]	NR
11–15 years	>40 kg, 100 mg; < 40 kg, 2 mg/kg	5 SS	39.1 [25.2–46.7]	8.08 (53)	11.01 (68)	1[b]	1.5[b]	73.7 (22)
12–16 years	1	9 SS	59.8 (22) [37–75.1]	NR	5.6 (21) [4.3–8.1]	NR	NR	NR

Table 4 continued

Population	Dose (mg/kg)	No. of subjects, SD or SS	Mean pharmacokinetic parameters (% coefficient of variation) [range]					
			Weight (kg)	C_{max} (mg/L)	C_{max} at SS (mg/L)	C_{24h} (mg/L)	C_{24h} at SS (mg/L)	AUC_{24} (mg h/L)
	3	8 SS	54 (28) [26–74]	NR	20.5 (50) [12.2–44.5]	NR	4[b]	NR
	4.5	1 SS	23	NR	24.9	NR	10[b]	NR
1–13 years	2	10 SS	21 (57)	NR	9.63 (38)	NR	3.04 (40)[j]	NR
7 months – 10 years	3	15 SD	NR	12.5 (22) [8.3–18.7]	NR	2.5[b]	NR	128.5 (28) [79.3–229.2]
8 months–15 years	1	7 SS	23.5 (56) [7.0–45.6]	NR	5.0 (46) [3.4–10.2]	NR	1.3 (31) [1.0–2.0]	NR
	2	9 SS	24.5 [9.2–48.0]	NR	10.2 (43) [3.2–16.3]	NR	2.8 (36) [1.7–4.7]	NR
	3	9 SS	25.3 (62) [7.0–48.0]	NR	14.8 (37) [7.6–24.8]	NR	5.1 (37) [2.3–7.4]	NR
	6	1 SS	25	NR	21.1	5.3	NR	NR
2–17 years	0.5	15 SS	38.6	3.7 (27)	6.4 (22)[f]	NR	0.5[b,f]	19.0 (10)
	1	11 SS	45.9	10.8 (18)[f]	16.2 (23)	NR	1[b]	40.3 (9)[f]
	1.5	10 SS	36.7	13.2 (23)	16.3 (15)	NR	1.5[b]	79.4 (16)
	2	11 SS	29.5	15.3 (25)	21.4 (45)[k]	NR	2[b,k]	83.0 (9)
	3	9 SS	30.9	35.8 (20)	30.4 (29)[l]	NR	3[b,l]	162.9 (12)
	4	7 SS	28	30.3 (23)	43.5 (21)	NR	5[b]	191.4 (11)
Healthy adult subjects (Table 1)			100 mg	9.1				
			150 mg		16		~4.5	

Population	Dose (mg/kg)	No. of subjects, SD or SS	Mean pharmacokinetic parameters (% coefficient of variation) [range]				References
			AUC (mg h/L)	$T_{½}$ (h)	CL (mL/h/kg)	V_d (L/kg)	
Neonates <1 kg	0.75	4 SD	NR	5.5	79.3 (16)	NR	[80]
	1	12 SD	NR	6.3 (33) [2.9–11]	98 (41) [45–160]	0.81 (28) [0.42–1.1]	[81]
	10	6 SS	308 (33) [185.3–460.5]	10.6 (30) [7.7–16.4]	36 (33) [24–48]	0.51 (15) [0.36–0.56]	[82]
	15	7 SS	412.7 (29)	NR	37.3 (40)	0.64 (58)[a]	[64]
Neonates >1 kg	0.75	6 SD	NR	8.0[c] [5.6–10.3]	39 (46) [22.4–69.1]	0.40 (30) [0.28–0.57]	[80]
	1	13 SD	NR	7.1 (31) [4–11]	81 (65) [21–190]	0.72 (43) [0.3–1.1]	[81]
	1.5	6 SD	NR	7.8[c] [6–11]	38.6 (23) [27.7–46.7]	0.44 (14) [0.39–0.53]	[80]
	3	6 SD	NR	8.2[c] [6.2–10.5]	39.1 (27) [26.2–51.8]	0.47 (32) [0.29–0.66	[80]
	7	6 SS	307.6 (56) [162.6–643.2]	11.4 (31) [6.9–15.4]	24 (50) [12–36]	0.39 (33) [0.24–0.59]	[82]
	15	5 SS	472.2 (11)	NR	30.6 (11)	0.58 (18)[a]	[64]
Neonates <1.5 kg[d]	1	25 SD	18.8 (62) [9.4–49.1][e,f]	6.7 (33) [2.9–11]	89 (53) [21–190]	0.76 (37) [0.3–1.1]	[81]
Neonates <2 kg[d]	15	12 SS	437.5 (23)	NR	34.5 (34)	0.61 (46)[a]	[64]
4–24 months	1.5	11 SS	77.3 (15) [59.6–99.3]	11.5 (19) [7.9–16.0]	19.7 (14) [14.6–24.1]	0.32 (19) [0.24–0.45]	[84]
3 months–4 years	2	5 SS	53.82 (43)[e]	10.13 (17)	42.72 (44)	NR	[87]
4–24 months	4.5	8 SS	299.4 (47) [188–622.2]	NR	16.7 (32) [7.3–24.2]	NR	[85]

Table 4 continued

Population	Dose (mg/kg)	No. of subjects, SD or SS	Mean pharmacokinetic parameters (% coefficient of variation) [range]				References
			AUC (mg h/L)	$T_{½}$ (h)	CL (mL/h/kg)	V_d (L/kg)	
2–5 years	1.5	11 SS	76.0 (20) [62.8–106.7]	11.1 (12) [8.9–13.8]	20.4 (17) [14.2–24.0]	0.32 (24) [0.15–0.42]	[84]
	4.5	8 SS	248.9 (27) [110–335.4]	NR	20.0 (45) [13.4–40.9]	NR	[85]
6–11 years	1	6 SS	77.9 (21) [60.8–107.6]	14.7 (47) [9.8–28.4]	13.2 (18) [9.31–16.0]	0.26 (29) [0.21–0.41]	[84]
	1.5	3 SS	113.6 (11) [101.1–127.1]	15.2 (20) [12.6–18.5]	13.3 (13) [11.6–14.9]	0.29 (6) [0.27–0.30]	[84]
	3	4 SS	247.5 (19) [191.8–300.1]	NR	12.3 (20) [10.0–15.4]	NR	[85]
	4.5	3 SS	278.4 (15) [245.7–325.2]	NR	16.4 (14) [13.8–18.3]	NR	[85]
11–15 years	>40 kg, 100 mg; < 40 kg, 2 mg/kg	5 SS	81.70 (30)[e]	13.81 (32)	28.52 (28)	NR	[87]
12–16 years	1	9 SS	65.4 (17) [51.4–84.4]	13.1 (13) [10.5–16.2]	13.0 (17) [10.2–16.7]	0.24 (19) [0.20–0.34]	[84]
	3	8 SS	193.3 (16) [158.9–240.1]	NR	13.5 (23) [9.5–19.0]	NR	[85]
	4.5	1 SS	339	NR	13.3	NR	[85]
1–13 years	2	10 SS	NR	NR	NR	NR	[88]
7 months –10 years	3	15 SD	180.8 (34) [104.2–352.9][e]	13 (16) [9.5–16.8]	17.7 (33) [7.9–29.6]	0.3 (33) [0.2–0.5]	[96]
8 months–15 years	1	7 SS	NR	13.0 (14) [10.9–15.4]	NR	NR	[51]
	2	9 SS	NR	12.3 (15) [9.9–15.5]	NR	NR	[51]
	3	9 SS	NR	14.4 (22) [11.2–20.1]	NR	NR	[51]
	6	1 SS	NR	11.3	NR	NR	[51]
2–17 years	0.5	15 SS	27.9 (8)[f]	12.3 (8)[f]	19.4 (10)[f]	0.32 (10)[f]	[86]
	1	11 SS	52.4 (9)	17.3 (9)	20.6 (10)	0.39 (17)	[86]
	1.5	10 SS	100.6 (10)	12.9 (13)	16.5 (15)	0.28 (16)	[86]
	2	11 SS	94.3 (17)[k]	12.2 (6)[k]	24.3 (14)[k]	0.31 (18)[k]	[86]
	3	9 SS	190.5 (13)[l]	13.2 (9)[l]	17.0 (15)[l]	0.29 (12)[l]	[86]
	4	7 SS	301.9 (14)	13.5 (11)	14.2 (16)	0.26 (17)	[86]
Healthy adult subjects (Table 1)			133 181.4	15.4	10.4	0.2	

C_{max} maximum plasma concentration, *SD* single dose, *SS* steady state, C_{24h} trough plasma concentration 24 h after dosing, AUC_{24} area under the plasma concentration-time curve after a single dose from zero to 24 h, *AUC* area under the plasma concentration-time curve at steady state from zero to 24 h, $t_{½}$ terminal half-life, *CL* clearance, V_d volume of distribution; average is weighted by the number of patients reported, *NR* not reported

[a] V_d in the elimination phase (V_β). Steady-state volume of distributions are 1.64, 1.34 and 1.52 L for neonates <1, >1 and <2 kg, respectively

[b] Values not reported but extracted from figures with concentration versus time curves

[c] Median value

[d] The authors compiled the data of the groups above and below 1 kg into a single group

[e] AUC_∞ after a single dose

[f] $n = 16$

[g] $n = 17$

[h] $n = 19$

[i] $n = 21$

[j] $n = 13$

[k] $n = 8$

[l] $n = 5$

age. The group aged <8 years had a higher CL and V_d, i.e. 23.1 versus 17.1 mL/h/kg, and 0.35 versus 0.28 L/kg [86]. Albano et al. investigated these differences in more detail and found that children aged from 4 months to 5 years have a much higher CL at steady state of approximately 20 mL/h/kg, versus approximately 13 mL/h/kg in children aged 6–16 years [84]. V_d in this group was also higher (0.32 L/kg versus 0.26 L/kg) [84]. These changes in PK throughout the processes of maturation and growth urge the need for a higher weight-corrected dose compared with adults, especially in children less than 8 years of age. The role of protein binding remains unresolved as an explanation of this variability. Furthermore, critically ill children were shown to have an additionally increased CL of 41 mL/h/kg and an increased V_d of 0.64 L/kg, and should receive an even higher dose than the registered 1–4 mg/kg dose. After a 4 mg/kg dose, these children had an AUC of 117 mg h/L, which approximately corresponds to the AUC in a child after a 2.5 mg/kg dose. A dose increase of 2.5–5 mg/kg should be considered in critically ill children [89].

5 Pharmacodynamics

A limited number of studies investigating the relationship between PK and efficacy or toxicity have been performed in humans. The index best describing the PK/PD relation for *Candida* infections is the (free) AUC/MIC ratio [90–92]. For *Aspergillus* infections, no such relationship has yet been identified.

To our knowledge, only one study has been performed linking AUC/MIC ratios with clinical outcome. Andes et al. evaluated a large cohort of patients with invasive candidiasis or candidemia from phase II and III trials ($n = 493$) on PK, MIC of the pathogen, and clinical outcome (mycological and clinical success rate) [90]. They found a significant relationship between mycological success and AUC/MIC ratio for all *Candida* species; patients with AUC/MIC ratios >3000 to ≤12,000 had a higher percentage of mycological success than patients with AUC/MIC ratios ≤3000 and >12,000 (98.0, 85.1, and 88.1%, respectively). For *C. parapsilosis*, an AUC/MIC ratio breakpoint above 285 was suggested for mycological success [90]. Based on the abovementioned targets, a recent simulation in critically ill patients receiving a standard dose of 100 mg intravenously demonstrated that the PTA was high for organisms with an MIC up to 0.016 mg/L, but significantly decreased for attenuated MICs of 0.032 and above [62]. Since microbiology results usually take several days, these data support an empirical dose increase to 150 or 200 mg to cover the complete spectrum of susceptible species (including those with attenuated MICs). An argument to use the recommended 100 mg dose follows the findings of Pappas et al. who demonstrated non-inferiority of micafungin 100 mg compared with 150 mg [93].

6 Conclusions and Future Perspective

Micafungin has been shown to be an effective drug for the treatment and prophylaxis of candidiasis and candidemia. It shows predictable linear PK over a wide dose range of 0.15–8 mg/kg in both adults and children. The studies discussed in this review show the importance of PK investigations in special populations as patient-specific factors influence micafungin PK, showing that most critically ill patients are reported to have decreased exposure to micafungin, which might have consequences for efficacy. The importance of low exposure might not be relevant for infections with species with an MIC below 0.016 mg/L, but might become more important in the setting were the MIC of the offending organism is above 0.016 mg/L.

It is clear that the PK of micafungin have been extensively investigated, especially in adult hematology patients, children, and also, recently, ICU patients. As with many drugs, the PK are poorly characterized in (preterm) neonates, mainly due to difficulties in performing clinical trials in this population. Although micafungin is the most extensively investigated of the three echinocandins, there is still much knowledge to gain. Specifically, the rapid change in (apparent) CL in the first few months after birth and the relation to changes in the fraction of protein-bound micafungin needs further investigation. In addition, knowledge in this area can be used to develop tailor-made dosing regimens. Currently, one trial is comparing the efficacy of micafungin versus fluconazole in premature neonates with candidiasis (ClinicalTrials.gov identifier: NCT02145832).

There is an increasing interest in extending dose intervals from once daily to every other day, and even once every 2 weeks has been reported [72], mainly because of micafungin's favorable toxicity profile and the possible post-antifungal effect. Extending the dose interval will also allow patients to be ambulatory, improve quality of life, reduce hospital costs, and lower the need and frequency of accessing the central venous catheter [72]. In neutropenic mice with invasive candidiasis, a single high dose of micafungin was able to identically lower the fungal burden as the same cumulative dose administered twice weekly [72]. In children, this was investigated in a prophylactic setting with 21 children, who had a mean age of 9 years, receiving a 3–4 mg/kg dose twice weekly [94]. This therapy was well-tolerated with no reported breakthrough infection. An intermittent dosing strategy in adults with a

high risk of fungal infection using a twice-weekly dose of 300 mg is ongoing (ClinicalTrials.gov identifier: NCT02172768). However, as yet, no prospective trials could be found comparing these strategies in humans with invasive candidiasis.

We recommend that future research should focus on three aspects:

First, we see a knowledge gap in the effect of protein binding of micafungin in subpopulations with a reported lower exposure to micafungin, such as neonates, children, burn patients, ICU patients, and obese patients. The effect of changes in the free fraction of any drug are well known: a lower total concentration, a higher apparent CL, and an unchanged concentration of unbound, active drug. An increased awareness of the effect of albumin concentrations would eventually result in a better interpretation of PK and PD changes.

Second, we recommend using an MIC-based dosing approach. We propose using a stratified approach were the MIC of the offending pathogen drives the dose selection. In the setting of a pathogen with an attenuated MIC, higher exposure than achieved with regular dosing regimens is needed, and an adaptive, individualized approach might be of value.

Third, for determination of markers that can be used to monitor therapy, the most obvious candidate is 1,3-β-D-glucan. A PD marker might accelerate the investigation into pharmacokinetic-pharmacodynamic (PK-PD) targets, which are mostly lacking, although micafungin is the only echinocandin where a PK–PD target has been identified to predict therapy success in humans. PK–PD targets for both prophylactic and treatment purposes would be most welcome. These targets can then be used to improve treatment in children and adults, and specifically investigate alternate dosing strategies that are not only more patient friendly but might also have a higher rate of therapy success.

Compliance with Ethical standards

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