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Pharmacokinetics of Antifungal Agents in Children

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Abstract

Invasive fungal infections in immunocompromised children are common and often fatal. The first antifungal agents such as amphotericin B and fluconazole offered effective treatment, but their use was often limited by toxicity and resistance. Numerous new antifungal agents have since been developed and appear to be as effective. Most dosing and safety trials have been done in adults, and extrapolation of this data to children has proven inadequate. We reviewed the literature regarding the pharmacokinetics/pharmacodynamics (PK/PD) and safety of antifungal agents with an emphasis on the newer azoles and echinocandins. From a small but growing number of PK/PD trials, better dosing guidelines have been developed.

Keywords

antifungal agents; pharmacology; pharmacokinetics; neonates; infants; children

INTRODUCTION

Invasive fungal infections in immunocompromised children are common and often fatal. Amphotericin B deoxycholate has been a mainstay of therapy for over 50 years but its use has been limited by toxicity. The introduction of the azole class of antifungal agents offered fewer side effects; however, heavy use of fluconazole in adult patients has resulted in the selection of resistant organisms, though this is not yet widespread in children (1–3). Since the introduction of fluconazole, there have been a number of new azoles brought to market as well as a new class of antifungal agents, the echinocandins. Amphotericin B deoxycholate has often been the standard against which these new therapies are measured (4–9). This paper will review our current knowledge of antifungal pharmacokinetics/pharmacodynamics

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CONFLICT OF INTEREST
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(PK/PD) in children, with an emphasis on the newer azole and echinocandin systemic antifungals.

POLYENES

The polyene macrolides are the oldest class of antifungal agents and are comprised of amphotericin B deoxycholate and its associated lipid-based formulations: amphotericin B lipid complex (ABLC) and liposomal amphotericin B. The polyenes work by binding the sterol component of cell walls which results in increased membrane permeability and cell death. Amphotericin B deoxycholate is active against *Candida* spp., *Aspergillus* spp., and zygomycetes.

Amphotericin B deoxycholate

In spite of being approved for use in adults in 1958, there have been relatively few studies of amphotericin B deoxycholate PK/PD in children. Amphotericin B was initially dosed in children at 1.0 mg/kg/day based on clinical experience and a dose escalation study involving 41 children who had undergone bone marrow transplant (10). Several subsequent PK/PD studies in infants and children, including premature infants, found extreme inter-subject variability for the half-life, volume of distribution, and clearance but overall supported dosing with 1.0–1.5 mg/kg/day (11–14). A more recent population PK study of amphotericin B in 57 children ages 9 mos to 16 years with malignancy developed a model that suggested younger, lighter infants may be under-dosed at 1 mg/kg/day while older, heavier children may be overdosed at that same dose (15). Penetration into the CSF seems to be age dependent. In adults, cerebrospinal fluid (CSF) values are only 2–4% of serum concentrations (16). In contrast, in a small series of premature infants born at 27.4 (± 5) weeks gestational age (n=5), amphotericin B concentrations in CSF were 40–90% of simultaneously collected serum concentrations (11).

Lipid-based amphotericin B preparations

Lipid formulations of amphotericin B generally have a slower onset of action and are less active than amphotericin B in time-kill studies, presumably due to the required disassociation of free amphotericin B from the lipid vehicle (17). The different PK and toxicities of the lipid formulations are reflected in the dosing recommendations: amphotericin B lipid complex (ABLC) is recommended at 3–5mg/kg/day (18) and liposomal amphotericin B at 1–5 mg/kg/day (19, 20). A multicenter maximum tolerated dose study of L-amphotericin B using doses from 7.5 to 15 mg/kg/day found a non-linear plasma PK profile with a maximal concentration at 10 mg/kg/day and no demonstrable dose-limiting nephrotoxicity or infusionrelated toxicity (21).

NUCLEOSIDE ANALOGS

5-Flucytosine

5-Flucytosine (5-FC) is an antimetabolite drug with excellent activity against *Candida* spp, *Cryptococcus neoformans*and *Chromomycosis* spp (22, 23). Resistance develops rapidly to 5-FC mono-therapy, so clinicians have reserved it for combination therapy to augment other antifungals. 5-FC has been shown to enhance the antifungal activity of amphotericin B, especially in anatomical sites where amphotericin B penetration is often suboptimal such as CSF, heart valves, and the vitreal body (24). 5-FC is only available as an oral formulation in the United States, and is given 150 mg/kg/day in four divided doses.

5-FC has a narrow therapeutic window with elevated serum concentrations resulting in hepatic injury (25, 26), bone marrow suppression (27), and gastrointestinal intolerance (28).

Because of this routine therapeutic drug monitoring is standard of care throughout the treatment course as amphotericin-related renal insufficiency may develop over time and result in decreased clearance of 5-FC. The use of 5-FC in premature neonates is discouraged. A study evaluating risk factors and mortality rates of neonatal candidiasis among extremely premature infants showed that infants with *Candida* meningitis who received amphotericin B in combination with 5-FC had significantly longer time to sterilization of the CSF compared to those receiving amphotericin B monotherapy (median of 17.5 versus 6 days, respectively) (29).

TRIAZOLES

The triazoles work by inhibiting the enzyme responsible for converting lanosterol to ergosterol, a key component of fungal cell membranes, resulting in cell lysis and death (8, 30, 31).

Fluconazole

Fluconazole is available in both intravenous (IV) and oral formulations with rapid absorption from GI tract with high oral availability (~92% bioavailability compared with the IV form). It has low protein binding and excellent penetration into the CSF with concentrations ~80% of those found in the serum. Penetration into other body tissues such as joint spaces, saliva, vaginal secretions, and vitreous humor of the eye also approximate or exceed levels found in the serum. Fluconazole is eliminated primarily through the kidneys and excreted largely unchanged resulting in urine concentrations 10–20 times higher than those found in blood (32, 33).

Scaling of the corresponding adult dosage of fluconazole on a body weight basis is inappropriate for children. A review of 5 separate fluconazole PK studies in 113 children, including 12 premature neonates (34) showed that fluconazole clearance is generally more rapid in children than adults, with a mean plasma half-life of approximately 20 hours compared to approximately 30 hours in adults. Therefore, to achieve comparable exposure in children, the daily fluconazole dose needs to be essentially doubled. Correct pediatric fluconazole doses should be proportionately higher than adult doses, generally 12 mg/kg/day.

Neonates require approximately 5 days to reach steady-state (35), and maintenance fluconazole doses of 12 mg/kg/day are necessary to achieve exposures similar to older children and adults (36). Thus, a loading dose of 25 mg/kg to achieve steady-state concentrations sooner than the traditional dosing scheme may be appropriate. Data from a phase 1 trial investigating a fluconazole loading dose in 12 critically ill children showed that the therapeutic target ($AUC_{0–24}$ = 400 ug*h/mL) was reached with the loading dose in 72% of subjects with no related adverse events (37).

Voriconazole

Voriconazole is a synthetic derivative of fluconazole and has both fungicidal and fungistatic activity against *Aspergillus* (38–40). It is extensively metabolized by the liver with less than 5% excreted unchanged in the urine. Voriconazole is 58% protein bound, has a large volume of distribution and penetrates well into the CSF.

Voriconazole serum concentrations demonstrate wide inter-patient variability. There are several factors that are thought to contribute to this variability including nonlinear PK of voriconazole and genetic polymorphisms of CYP2C19. Studies in both healthy volunteers (41–43) and critically ill adults (44, 45) have shown nonlinear PK that is thought to be due to saturable first-pass metabolism and decreased systemic clearance. Individuals with poor

metabolizing phenotypes have a roughly two-fold higher drug exposure than heterozygous extensive metabolizers and four-fold higher exposure than homozygous extensive metabolizes (46, 47).

In contrast to adults, the PK of voriconazole in children is linear at lower doses and patient weight rather than age seems to play a larger role in determining drug exposure, making extrapolation of adult data problematic. Based on PK/PD analysis in a prospective multicenter study of 39 immunocompromised children age 2–11 y, a dose of 4 mg/kg intravenously was found to be equivalent to the recommended dose of 3 mg/kg in adults (48). Similar to adults, drug elimination correlated with CYP2C19 phenotype, but children were found to have higher elimination rates than those found in adults, which at least partially explains the linear kinetics at lower doses. In a population PK analysis of 3 open label pediatric studies involving 82 children 2–11 y of age, an intravenous dose of 7 mg/kg or 200 mg orally twice daily was found to be equivalent to adult dosing (49).

Because of the nonlinear PK observed in adults and high inter-patient variability in serum concentration, voriconazole therapeutic drug monitoring is recommended. Therapeutic failures occur with voriconazole plasma levels <1 μg/ml and toxicity rises when levels exceed 5–6 μg/ml (50–54).

Studies in children are more limited, but retrospective studies show that children also experience high inter-patient variability in voriconazole concentrations (55) and that mortality decreases when voriconazole serum trough concentrations >1μg/ml are achieved (56). Case studies in infants suggest that even higher voriconazole doses are needed to achieve this target trough concentration, underscoring the need for therapeutic drug monitoring (57–59). Even though the data acquired thus far supports the use of therapeutic drug monitoring, prospective studies are lacking in children and need to be conducted to answer this question.

Posaconazole

Posaconazole is a second-generation triazole antifungal agent available as a suspension for oral administration. The antimicrobial spectrum of posaconazole is similar to voriconazole, but with additional activity against zygomycetes. Experience with posaconazole in children is very limited. In adults, dose-proportional increases in plasma exposure (AUC) to posaconazole were observed following single oral doses from 50 mg to 800 mg and following multi-dose administration from 50 mg to 400 mg twice daily. Steady-state plasma concentrations are attained at 7 to 10 days following multi-dose administration (60). Posaconazole is predominantly eliminated in the feces with renal clearance playing a minor role. Therefore, no dose adjustment is necessary in mild to moderate renal insufficiency. Posaconazole is fungicidal *in vitro* with likely time-dependent killing (61).

Ravuconazole

Ravuconazole is structurally more similar to fluconazole and voriconazole, containing a thiazole instead of a second triazole. It is often fungicidal (62, 63), has 47–74% bioavailability with linear PK, and a long half-life of approximately 100 hours (64). The drug is well-absorbed following oral administration, and its absorption is enhanced by food (63). Penetration of ravuconazole into healthy rat tissue showed that concentration of drug in the lungs was 2–6 times higher than the corresponding blood concentration (65). Ravuconazole has not been approved by the FDA. Ravuconazole was well-tolerated in healthy human subjects in single (64) and multiple doses (66). To our knowledge, there are no clinical trials of ravuconazole in children.

ECHINOCANDINS

There are three drugs in this class: caspofungin, micafungin, and anidulafungin, and they all work by inhibiting 1,3 β-D-glucan synthase, an enzyme important in fungal cell wall biosynthesis (67, 68). The echinocandins are fungicidal against *Candida* spp and fungistatic against *Aspergillus* spp, though only caspofungin carries an FDA indication for *Aspergillus* (68, 69). Additionally, caspofungin is the only echinocandin approved by the FDA for use in children (age >3 mos) (70). Because the echinocandins are not hepatically metabolized they have the potential for fewer drug interactions as a class than the other antifungals (71).

Caspofungin

There have been three PK/PD studies of caspofungin in infants and children that have demonstrated significant differences in PK/PD parameters than those described in adults (68, 72, 73). Extrapolating the adult dose of 50 mg/day to a per kilo dose in children ages 2–17 y (1 mg/kg/day) resulted in significantly lower AUC_{0-24} (46%) (68). Dosing based on body surface area, however, resulted in comparable AUC_{0-24}. Infants and children ages 3 mos – 17y required 50 mg/m^2/day (68, 72), while infants <3 mos achieved therapeutic serum concentrations with 25 mg/m^2/day (73). The appropriate dosage of caspofungin in the nursery is not known.

Micafungin

Though it does not carry an FDA label for use in children, micafungin has been almost as well studied in pediatric populations as caspofungin. The first PK study of micafungin in children was a phase 1, open-label dose escalation study in 77 neutropenic children ages 2–17 y who were given doses ranging from 0.5–4 mg/kg/day (74). The authors noted linear PK with increased clearance in the 2–8 y cohort resulting in dosing recommendations of 3–4.5 mg/kg/day for 2–8 y and 2–3 mg/kg/day for those 9–17 y to achieve concentrations comparable with standard adult dosing. Importantly, the investigators found no dose-related side effects, which is in line with previous adult studies (74). In a smaller study of 19 children ages 8 mos to 15 y with confirmed invasive fungal infection, Tabata et al (75) also noted linear PK but without age-associated differences in clearance, though this may have been due to the smaller size of the study. These investigators recommended dosing of 3 mg/kg/day.

Candida is an important pathogen in premature neonates, and there is evidence in neonates, especially those with *Candida* meningoencephalitis, that higher doses of micafungin may be required (76). Heresi et al (77) conducted a phase 1 multi-center sequential dose study (0.75 mg/kg, 1.5 mg/kg, 3.0 mg/kg) of micafungin PK in 18 premature neonates (mean gestational age 26.4 weeks; mean birth weight 1497g) with suspected or confirmed invasive fungal infection. These investigators noted a larger volume of distribution, as might be expected in neonates with larger extracellular fluid compartments, as well as an unexpected increase in clearance compared with children (1.7 fold for ages 2–8 y) and adolescents (2.6 fold for ages 9–17 y). All doses were well tolerated. More recently, Smith et al (78), investigated higher dose micafungin (15 mg/kg/day for 5 days) in 12 preterm neonates (mean gestational age 27 weeks, mean birth weight 775g) with suspected systemic infection. This higher dose was well tolerated in all subjects. The resultant PK parameters were comparable to those in adults in a maximum tolerated dose study who were dosed at 5 mg/kg (79). Benjamin et al studied doses of 7 and 10 mg/kg/day and observed exposures similar to those required to clear meningoencephalitis in animal models. Based on these results, we recommend dosing in neonates of 10 mg/kg/day.

Anidulafungin

Anidulafungin was approved by the FDA for use in adults in 2006. Like caspofungin, anidulafungin seems to concentrate in the liver, lung, and kidney with poor CSF penetration (80). PK studies in both healthy adults and adults with invasive fungal infections showed that subjects achieved therapeutic concentrations using a 200 mg loading dose on day 1 followed by a daily dose of 100 mg/day starting on day 2 (81, 82). Benjamin et al (83) enrolled 24 neutropenic children ages 2–16 y in a multi-center dose escalation PK study. Children in the low-dose group (n=12) were loaded with 1.5 mg/kg and started on maintenance of 0.75 mg/kg/day and those in the high dose group (n=12) were loaded with 3 mg/kg followed by a maintenance dose of 1.5 mg/kg/day. Based on measured PK parameters, the low- and high-dose regimens corresponded to 50 mg/day and 100 mg/day dosing in adults respectively. Preliminary data from a phase 1 PK study of anidulafungin in neonates and infants (n=14) showed that anidulafungin maintenance doses of 1.5 mg/kg/day resulted in exposures similar to older children and adults receiving comparable weight-based dosing (84). The optimal dose in neonates, who are at greatest risk of *Candida* meningoencephalitis, remains to be determined.

Conclusion

With the rapid development of new antifungal agents, clinicians have more options in the treatment of invasive fungal infections. Most of the PK/PD studies performed are in adults, but as demonstrated above, extrapolation of adult data to children has proved inadequate for many of these agents. This highlights the need to undertake dedicated PK/PD studies of antifungal agents in children.

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Table 1

Pediatric Dosing of Antifungal Agents

	Neonates (0–30 d)	Infants (31 d-2 y)	Children (2 y-17 y)
Polyenes			
Amphotericin B	0.5–1 mg/kg/day	0.5–1 mg/kg/day	0.5–1 mg/kg/day
ABLC	Unk	Unk	3–5 mg/kg/day
L-Amphotericin B	Unk	Unk	1–5 mg/kg/day
Nucleoside analogs			
5-Flucytosine	25–100 mg/kg/day div every 12–24h	50–150 mg/kg/day div every 6h	50–150 mg/kg/day div every 6h
Triazoles			
Fluconazole	6–12 mg/kg every 72h[a] 6–12 mg/kg every 48h[b] 6–12 mg/kg/day[c]	12 mg/kg/day	6–12 mg/kg/day
Voriconazole	NR	Unk	14 mg/kg/day div every 12h
Posaconazole	Unk	Unk	800 mg/day div every 6–12h[d]
Ravuconazole	Unk	Unk	Unk
Echinocandins			
Caspofungin	25 mg/m^2/day	50 mg/m^2/day	70 mg/m^2 load 50 mg/m^2/day
Micafungin	10 mg/kg/day	1–4 mg/kg/day	1–4 mg/kg/day
Anidulafungin	1.5 mg/kg/day	1.5 mg/kg/day	1.5 mg/kg/day

[a] ≤ 29wks gestation, post-natal age 0–14 d

[b] ≤29wks gestation, post-natal age >14 d *or* 30–36 wks gestation, post-natal age 0–14 d

[c] ≥30wks gestation, post-natal age >14 d *or* >36 wks gestation

[d] Dosing unknown for children <13 years of age

NR – not recommended

Unk – appropriate dosing unknown