JPPT

REVIEW ARTICLE

A Review of Clinical Experience with Newer Antifungals in Children

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Fungal infections are a significant cause of morbidity and mortality in immunocompromised children. Since the beginning of the 21st century, many new antifungals including the echinocandins (i.e., caspofungin, micafungin, anidulafungin) and the newer generation triazoles (i.e., voriconazole and posaconazole) have received Food and Drug Administration approval. Unfortunately, despite making great strides in the adult arena, these agents are not currently approved in the pediatric population. However, pharmacokinetic data and clinical experiences with these agents in infants, children, and adolescents are mounting. As such, this review will discuss key concepts in pediatric pharmacology and clinical use of these newer antifungal agents.

KEYWORDS anidulafungin, antifungal, caspofungin, micafungin, pediatric, posaconazole, voriconazole

J Pediatr Pharmacol Ther 2008;13:124-140

INTRODUCTION

Invasive fungal infections are an important cause of morbidity and mortality in hospitalized children. Those at highest risk include premature newborns, patients with childhood cancers, and those with human immunodeficiency virus.[1,2] Although *Candida* species are the most common isolated fungi within immunocompromised children, serious infections due to *Aspergillus* species and other filamentous fungi, such as zygomycetes and *Fusarium* species may also occur.[3] The use of traditional antifungal agents including amphotericin B, fluconazole, and itraconazole for invasive mycoses has been limited by concerns of resistance (e.g., fluconazole) and poor tolerability (e.g., amphotericin B and itraconazole).[4-6] As such, newer agents including the echinocandins and second-generation triazoles have recently been added to the antifungal armamentarium. This article reviews pertinent pediatric pharmacology and clinical experience of these newer antifungal agents including caspofungin, micafungin, anidulafungin, voriconazole, posaconazole, and ravuconazole.

ABBREVIATIONS CYP450, cytochrome p450; FDA, Food and Drug Administration

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ECHINOCANDINS

The echinocandins are a novel class of antifungal agents that act via non-competitive, irreversible inhibition of β-1-3-D-glucan synthase in the cell walls of pathogenic fungi.[7-9] Specifically, they interrupt glucan polymer formation which is thought to cause osmotic stress, lysis, leading to fungal cell death.[7] This

unique mechanism is theorized to decrease the likelihood of cross-resistance with other classes, as well as potentially provide additive activity for combination antifungal therapy.[4,7,8] The echinocandins appear to have potent *in vitro* activity against most *Candida* species (the minimum inhibitory concentration may be higher for *C parapsilosis* and *C guilliermondii*) and *Aspergillus* species.[10-12] They have no activity against zygomycetes.

None of the echinocandins have significant oral bioavailability, making them only useful by intravenous infusion.[10-12] Echinocandins have high protein binding (> 95%) and appear to distribute well into most tissues.[10-12] As a class, echinocandins have predominantly displayed concentration-dependent activity.[8] Currently, none of these agents have a pediatric indication.

Caspofungin

Overview

In January 2001, caspofungin (Cancidas, Merck & Co., Inc., Whitehouse Station, NJ) marked the first of the 3 echinocandins currently approved by the Food and Drug Administration (FDA).[13-15] Adult indications presently include invasive aspergillosis, esophageal candidiasis, empiric antifungal therapy for febrile neutropenia, and invasive *Candida* species infections including candidemia, intra-abdominal abscesses, peritonitis, and pleural space infections.[12] Caspofungin undergoes hepatic metabolism via hydrolysis and n-acetylation. As such, caution should be exercised in using caspofungin in patients with hepatic insufficiency and dosage adjustment should be performed as appropriate.[12,16] Although caspofungin has not been shown to be an inducer or an inhibitor of cytochrome p450 (CYP450), it is a weak substrate of CYP450.[17,18] Known drug interactions include cyclosporine, tacrolimus, and selected inducers or inhibitors of the CYP450 enzyme system.[12]

Pediatric Pharmacokinetics

The pharmacokinetics of caspofungin have been profiled in 39 pediatric patients ages 2 to 17 years with febrile neutropenia.[19] Initial dosing employed a weight based dosing approach in 9 pediatric patients (7 children and 2 adolescents). At a dose of 1 mg/kg/day (up to 50 mg/day), patients had significantly lower total drug exposure when compared to historical adult data using 50 mg/day ($P < .001$). Further, the resultant concentrations in these children appeared to be both weight dependent and age-related. Therefore, dosing was switched to a body surface area approach with 10 children and 8 adolescent patients receiving 50 mg/m^2/day (up to 70 mg/day); these patients had comparable drug exposures to adults receiving 50 mg daily. Data from this evaluation suggest that a dose of 50 mg/m^2/day (up to 70 mg/day) would provide similar exposure to adult patients receiving a 50 mg/day dose.[19]

Pediatric Safety, Efficacy and Case Reports

Presently, caspofungin has the most published pediatric outcomes data of the echinocandins for use in invasive fungal infections, as shown in Table 1.[20-32] In 2003, the first study was published evaluating the safety of caspofungin in children and adolescents.[29] Twenty-five patients received caspofungin for fungal prophylaxis or treatment at a dose of 0.8–1.6 mg/kg/day (max 75 mg/day). The median age of patients was 9.8 years (range, 0.3–26.2 years) and they received caspofungin for a median of 32 days (range, 1–116 days). Of the 25 patients included, only 3 (12%) experienced an adverse effect possibly related to caspofungin (most commonly hypokalemia); however, it should also be noted that 21 patients received concomitant amphotericin B. Additionally, elevations in total bilirubin concentrations were present in 2 patients and increased alanine transferase was noted in 1 patient. Yet, no patients discontinued caspofungin therapy due to an adverse event.[29]

More recently, the safety and efficacy of caspofungin as either treatment (75%) or empiric (25%) antifungal therapy was evaluated in 64 patients less than 18 years old (median, 11.5 years; range, 0.4–17.9 years).[30] Half of patients had received combination antifungal therapy. Dosing was at the provider's discretion with a median daily maintenance dose of 34.3 mg/m^2 (16–57 mg/m^2) and nearly 50% of the patients receiving 50 mg. Overall positive response, defined as having complete or partial response, was seen in 70% (n = 17), 50% (n = 7), and 87% (n = 15) for proven, probable, and possible infections, respectively. In terms of safety, 34 patients had documented adverse effects, possibly related

Table 1. Summary of Caspofungin Pediatric Clinical Experience

Author (Reference)	Patient Population	Caspofungin Dosing	Concomitant Antifungal Therapy	Treatment Group	Outcomes
Manzar, et al. (22)	23 WGA, 18 days PNA female	LD 1 mg/kg/day MD 2 mg/kg/day	AmBD	*C glabrata* candidemia	Resolution within 3 days
Hesseling, et al. (23)	24 WGA, 6 wk PNA infant	LD 50 mg/m^2/day MD 35 mg/m^2/day	AmBD/ ABLC 5-FC	*C guilliermondii* candidemia and endocarditis	Lack of resolution after 7 days; Pt died 2 days after therapy DC
Yalaz, et al. (24)	27 WGA, 3 wks PNA, extremely low birth weight male	LD 5 mg/kg/day MD 2.5 mg/kg/day	NA	Multi-drug resistant *C parapsilosis* candidemia	Resolution within 7 days
Smith, et al. (32)	25 WGA, 11 wk PNA infant	LD 8 mg/kg/day MD 6 mg/kg/day	AmBD	*C albicans* candidemia	Rapid clinical improvement. Patient experienced hypercalcemia after 14 days, transitioned to VRC briefly, but after susceptibility testing was restarted on CAS 3 mg/kg/day
Odio, et al. (25)	9 preterm infants 1 term infant 33 WGA (mean), 44 days PNA (mean)	LD 1 mg/kg/day MD 2 mg/kg/day†	NA	Refractory *Candida* species infections *C albicans* (n = 4) *C parapsilosis* (n = 3) *C tropicalis* (n = 2) *C glabrata* (n = 1)	Improvement in all pts
Natarajan, et al. (26)	12 preterm infants 1 term infant 27 WGA (median), 24 days PNA (median)	1 mg/kg/day; 5 infants also received LD 1.5 mg/kg/day	AMB (n = 13) FLUC (n = 8) 5-FC (n = 1)	Refractory candidemias *C parapsilosis* (n = 6) *C albicans* (n = 5) *C tropicalis* (n = 1) Mixed *C. albicans/ C parapsilosis* (n = 1)	Resolution in 11 pts
Mrowczynski, et al. (21)	2-month-old infant	LD 5 mg/kg/day MD 3 mg/kg/day	AmBD	*C glabrata* endocarditis and sepsis	Resolution of cultures
Elanjikal, et al. (27)	2-yr-old female	LD 2 mg/kg/day MD 1.5 mg/kg/day	LAMB	Refractory aspergillosis	Improvement in size/ number of pulmonary infiltrates
Wertz, et al. (28)	3-yr-old child	MD 0.9 mg/kg/day	LAMB 5-FC	Refractory *C albicans* candidemia	Rapid resolution
Franklin, et al. (29)	25 pts 0.3 to 26 yrs old	<50 kg 0.8-1.6 mg/kg/day >50 kg 50-75 mg/day	LAMB (n = 21) ITRA (n = 3) VRC (n = 3)	Fungal prophylaxis (84%) Treatment of fungal infection (16%)	Efficacy not assessed

Table 1. Summary of Caspofungin Pediatric Clinical Experience (cont.)

Author (Reference)	Patient Population	Caspofungin Dosing	Concomitant Antifungal Therapy	Treatment Group	Outcomes
Groll, et al. (30)	64 pts 0.4 to 17 yrs old, 39 males	Dosing at provider's discretion; median daily MD 34.3 mg/m^2 or 1.07 mg/kg	32 patients received therapy with ≥ 1 of the following: AMB, an azole, 5-FC	Empirical antifungal treatment (25%) Treatment of (possible, probable, and proven) fungal infections (75%)	Overall response rate (complete/partial): 50%– 87%; End of therapy overall survival rate: 75% in those who had prior antifungal therapy 3 of 16 patients receiving empiric therapy had breakthrough infections
Castagnola, et al. (20)	3 adolescent males	LD 40 mg/m^2/day MD 30 mg/m^2/day	LAMB (n = 2) VRC (n = 1)	Refractory pulmonary aspergillosis	Improvement in 2 pts; Death due to bacterial sepsis in 1 pt
Pancham, et al. (31)	3 adolescents; 1 male	Varied dosing; MD range 0.9-1.8 mg/kg/day‡	LAMB	Refractory fungal infections including *A fumigatus* (n = 2) and *C krusei* candidemia (n = 1)	Improvement in 2 pts; Death due to pulmonary hemorrhage in 1 pt

AMB, amphotericin B (formulation not specified); AmBD, amphotericin B deoxycholate; ABLC, lipid complex amphotericin B; CAS, caspofungin; DC, discontinued; FLUC, fluconazole; 5-FC, flucytosine; WGA, weeks gestational age; ITRA, itraconazole; LAMB, liposomal amphotericin B; LD, loading dose; MD, maintenance dose; NA, not available; PNA, postnatal age; pt, patient; VRC, voriconazole
†1 patient received CAS 0.5 mg/kg/day LD on days 1-3, then CAS 1 mg/kg/day MD
‡1 patient received CAS 1.2 mg/kg/day LD

to caspofungin administration. Of these, fever, nausea and/or vomiting, and diarrhea were the most commonly reported. Although increases in markers of renal and hepatic dysfunction were frequently documented, only slight elevations in liver transaminases were present at end of therapy; significant increases in end of therapy bilirubin, alkaline phosphatase, and serum creatinine were not documented.[30]

There are also several retrospective studies, case reports, and case series of the use of caspofungin for treatment of *Candida* and *Aspergillus* species infections in children ranging from preterm infants to older adolescents (Table 1).[20-32] Published reports document loading doses between 1–8 mg/kg/day or 40–50 mg/m^2/day, followed by maintenance doses of 0.9–6 mg/kg/day or 30–35 mg/m^2/day. Caspofungin therapy was most often reserved for patients with fungal infections refractory to conventional therapies and in patients receiving combination therapy with amphotericin, flucytosine, and/or an azole. Greater than 90% of the 34 cases reported clinical resolution or improvement. However, 3 patients were reported to have died: 1 after discontinuation of therapy, 1 secondary to bacterial sepsis, and 1 as a result of a pulmonary hemorrhage.[20,23,31] In pediatric reports, caspofungin was well tolerated with hypokalemia, liver transaminase elevations, hyperbilirubinemia, and injection site phlebitis being the most commonly reported side effects.[19,20,26,28] Again, many patients were also receiving concomitant amphotericin B which may have further contributed to the incidence of these side effects, especially hypokalemia. Overall, these data suggest that caspofungin may be a safe and efficacious treatment at least as part of combination therapy for refractory *Candida* and *Aspergillus* species infections in the pediatric population.

Micafungin

Overview

The second agent to enter the echinocandin class, micafungin (Mycamine, Astellas Pharma,

Deerfield, IL) was granted FDA approval in March 2005.[11] Presently, micafungin is indicated for adult patients for the treatment of esophageal candidiasis and as prophylaxis in patients undergoing hematopoietic stem cell transplantation.[11] It undergoes hepatic metabolism, but does not require dosage adjustments for mild to moderate renal dysfunction.[11,33] No data exists for severe hepatic dysfunction. Micafungin is also a poor substrate of the cytochrome P450 3A system; therefore, it is associated with few drug interactions including nifedipine and sirolimus.[11,33,34]

Pharmacokinetics

Pharmacokinetic studies have been conducted for micafungin in premature infants and children.[35,36] Micafungin displayed linear pharmacokinetics in 18 premature infants at doses from 0.75 mg/kg to 3 mg/kg.[35] Interestingly, the premature infants demonstrated increased clearance (~39 mL/kg/hr) and a shorter half-life (8 hours) than previous data from older children and adults. As such, additional studies are needed to determine optimal dosing of micafungin in these patients. In a pharmacokinetic study of older children aged 2 to 17 years doses were escalated from 0.5 mg/kg/day up to 1.5 mg/kg/day or 4 mg/kg/day.[36] Children in the 2 to 8-year-old group demonstrated significantly increased clearance when compared to those more than 9 years (0.385 ± 0.15 mL/min/kg vs. 0.285 ± 0.12 mL/min/kg, respectively), suggesting the need to utilize a higher mg/kg dosing scheme for this patient population.[36] Given the aforementioned pharmacokinetic data, micafungin appears to have age-dependent clearance up to the age of 8 years.

Pediatric Safety, Efficacy and Case Reports

The evidence to support micafungin's role as antifungal therapy in pediatrics is quickly expanding, as shown in Table 2.[37-42] A double blind, multi-center trial has been conducted comparing micafungin and fluconazole as fungal prophylaxis in neutropenic hematopoietic stem cell transplant recipients.[40] Patients were stratified based on age, study center, and transplant type, and then randomized to receive micafungin (1 mg/kg once daily, maximum dose 50 mg) or fluconazole (8 mg/kg once daily, maximum dose 400 mg). Only 10% of the study population was less than 16 years old. Overall, micafungin demonstrated non-inferiority compared to fluconazole. Further, similar data were mimicked by the pediatric subgroup with 69% (27 of 39) of the micafungin and 53.3% (24 of 45) of the fluconazole group achieving success (P = 0.03). Successes were defined as having no possible, probable, or proven infection during the treatment period and 4 weeks after commencing therapy.[40]

In addition to the fungal prophylaxis study, multiple reports describe micafungin for the prophylaxis and treatment of *Candida* and *Aspergillus* species infections in children between the ages of 2 months and 18 years.[37-39,41,42] As illustrated in Table 2, such data consist of treatment of primary and refractory aspergillosis and candidemia, and as fungal prophylaxis in patients undergoing hematopoietic stem cell transplant. In pediatric micafungin studies and reports, the dose most commonly reported was 1.5 mg/kg/day for those less than 40 kg with dose escalation often permitted at the provider's discretion.[37-39,41,42] Pediatric response rates varied among the dose used and were higher for *Candida* species infections (75%) as compared to *Aspergillus* (18-45%).[39,41,42] Furthermore, response rates were mostly higher among non-*A fumigatus* species than *A fumigatus*.[38,39] Adverse effects in children were similar in nature to those reported in adult evaluations with the most common including abnormal liver transaminases (2%-5%), alkaline phosphatase elevations (2%-3%), hyperbilirubinemia (3%-4%), and nausea (4%-6%). Given the aforementioned data, micafungin may be a prudent option for *Candida* and some *Aspergillus* species infections in the pediatric population.[37-39,41,42]

Anidulafungin

Overview

Anidulafungin (Eraxis, Pfizer, New York, NY) was the third echinocandin to enter the market in February 2006. Data from *in vitro* studies suggest that anidulafungin may have potent activity against *Candida* species and *Aspergillus* species.[43-45] It is currently approved for use in the adult population as treatment for candidemia and selected forms of candidal infections (intra-abdominal abscess and peri-

Table 2. Summary of Micafungin Pediatric Clinical Experience

Author (Reference)	Patient Population	Micafungin Dosing	Concomitant Antifungal Therapy	Treatment Group	Outcomes
Flynn, et al. (39) Denning, et al. (38)	58 pediatric pts 0.2 to15 yrs old	1.5 mg/kg/day Dose escalation by 1.5 mg/kg/day permitted at provider discretion < 1 mg/kg/day (n = 5) 1-1.5 mg/kg/day (n = 14) 1.5-4 mg/kg/day (n = 35) > 4 mg/kg/day (n = 4)	All pts may have received ≥ 1 of the following: AMB, an azole, and/or 5-FC	Primary aspergillosis (7%) Refractory/toxicity failure aspergillosis (93%)	Overall response rate (complete/ partial response): 45% Varied among dosing groups/ species < 1 mg/kg/day: (60%) 1-1.5 mg/kg/day: (43%) 1.5-4 mg/kg/day (43%) >4 mg/kg/day (50%) *A flavus* (55%) *A fumigatus* (24%).
Singer, et al. (37)	4-mo-old male and 13-yr-old male	1.5 mg/kg/day Dose escalated to 4 mg/kg/day in infant over 10 days	LAMB	*A flavus* aspergillosis	Resolution after long-term therapy
van Burik, et al. (40)	882 pts (including 84 pediatric)	1 mg/kg/day (max 50 mg/dose) vs. FLUC 8 mg/kg/day (max 400 mg/dose)	None	Fungal prophylaxis	Pediatric response rates: MICA (69%) vs. FLUC (53%), P = 0.03
Ostrosky-Zeichner, et al. (41)	126 pts(including 20 pts < 16 yrs old)	<40 kg: *C albicans* species 1 mg/kg/day (max 50 mg/day) Non-*C albicans* species 2 mg/kg/day Dose escalation permitted by 1.5 mg/kg/day if necessary every 5 days (max 75 mg/day)	Refractory pts received > 1 of the following: AMB, an azole, and/or 5-FC	Primary candidemias (57%) Most common species: *C albicans, C glabrata,* and *C tropicalis* Refractory candidemias (43%) Most common species: *C glabrata, C parapsilosis,* and *C albicans*	Overall response rates: 83% Varied among species. *C glabrata* (94%) *C parapsilosis* (86%) *C albicans* (85%) *C tropicalis* (83%) Pediatric response rate: 75%
Kontoyiannis, et al. (42)	98 pts (including 27 pts < 1 yr old)	<40 kg: 1.5 mg/kg/day (max 75 mg/day) Dose escalation permitted at provider discretion	Refractory pts received AMB ± an azole	Primary aspergillosis (9%) Refractory/toxicity failure aspergillosis (91%)	Overall response rate: 25% Varied among species Non-*A fumigatus* (20%) *A fumigatus* (32%) Pediatric response rate: 18%

AMB, amphotericin B (formulation not specified); 5-FC, flucytosine; FLUC, fluconazole; LAMB, liposomal amphotericin B; MICA, micafungin

tonitis) and esophageal candidiasis.[46] Notably, anidulafungin's intravenous formulation must be reconstituted with 20% (w/w) Dehydrated Alcohol in Water for Injection.[46] As such, the relatively large amount of alcohol in each dose may appropriately be a concern in the pediatric population. Anidulafungin is chemically degraded and does not undergo hepatic or renal elimination; therefore, dosage adjustment is proposed only for weight.[47-49] To date, no clinically significant drug interactions have been demonstrated with anidulafungin and other medications studied including rifampin, cyclosporine, tacrolimus, voriconazole, and amphotericin B.[50-51]

Pharmacokinetics

Presently, the only published pediatric study is a pharmacokinetic analysis.[52] This study included 25 pediatric patients between the ages of 2 and 17 years. Patients were stratified into 2 groups based on age (2 to 11 and 12 to 17 years) and dose utilized (0.75 mg/kg/day and 1.5 mg/kg/day). The pharmacokinetics in each of the groups were similar and also appeared analogous to adult controls. The study authors concluded that only dose adjustment for weight is needed and that 0.75 mg/kg/day may provide similar exposure in pediatric patients as adult patients receiving 50 mg/day; likewise, 1.5 mg/kg/day in children may be comparable to 100 mg/day in an adult.[52]

Pediatric Safety, Efficacy and Case Reports

Safety was also evaluated in the pharmacokinetic study mentioned above.[52] All pediatric patients experienced at least one adverse effect with majority being mild to moderate in nature. In particular, the most common adverse effects included the following: fever (44%), graft-versus-host disease (24%), mucosal inflammation (24%), vomiting (24%), cough (20%), hypertension (20%), and hypomagnesemia (20%). In the low-dosage group, 1 patient developed infusion-related erythema and rash which resolved upon discontinuation and did not recur with subsequent infusions. Notably, the authors reported no serious adverse events thought to be related to anidulafungin administration. The 2 documented deaths during the study period were deemed to be the result of multi-system organ failure and respiratory failure, respectively.[52]

TRIAZOLES

Unlike echinocandins which act on the fungal cell wall, triazoles exert their pharmacological activity through inhibiting CYP450-dependent lanosterol 14-demethylase in the fungal cell membrane; thus, triazoles interrupt ergosterol synthesis, a critical component for fungal cell membrane integrity.[8,53] Although extensive data exists regarding fluconazole and itraconazole in children, their usage has been limited by increasing resistance and tolerability concerns, respectively.[4] The newer generation triazole derivatives including voriconazole, posaconazole, and ravuconazole have been designed to help improve tolerability and possibly expand the spectrum and activity against common fungi, although acquired azole cross-resistance among selected *Candida* species may still be a concern.[8,54-56]

Voriconazole

Overview

Voriconazole (Vfend, Pfizer, New York, NY) received FDA approval in November 2003.[56] It demonstrates potent *in vitro* activity against *Candida* and *Aspergillus* species. Currently voriconazole is indicated for use in adolescents more than 12 years old and adults for the treatment of invasive aspergillosis, esophageal candidiasis, and candidemia in non-neutropenic patients and other invasive candidal infections.[56] Importantly, in adult patients with invasive aspergillosis, initial voriconazole use was more likely to demonstrate a successful outcome compared to amphotericin B deoxycholate.[57] Voriconazole is structurally similar to fluconazole and retains some of fluconazole's properties, such as high oral bioavailability (96%) and extensive tissue distribution (including the cerebrospinal fluid).[8,56] It has the potential to have many drug interactions because it is metabolized via CYP450 2C19, 2C9 and 3A4.[56] Specifically, co-administration with terfenadine, astemizole, cisapride, pimozide, quinidine, rifampin, carbamazepine, long-acting barbiturates, rifabutin, sirolimus, ergot alkaloids, ritonavir (high-dose), and efavirenz are contraindicated.[55] Dosage adjustment is required for those with mild to moderate hepatic impairment and it should not be used

in patients with severe hepatic deficiency.[56] In addition to the potential drug interactions associated with voriconazole's metabolism via CYP450 2C19, it is also known to have inter-patient metabolism variability due to genetic polymorphisms.[56] The efficacy of voriconazole has recently been shown to be correlated with trough concentrations greater than 2.05 mg/L.[58,59] Additionally, new preliminary information suggests that troughs of more than 5.5 mg/L may be associated with neurological adverse effects.[60] Therefore, suggested trough concentrations are between 2.05 mg/L and 5.5 mg/L.[58-60]

Pharmacokinetics

The pharmacokinetics of voriconazole have been investigated in multiple studies in an effort to determine the best dosage for pediatric patients.[61,62] The first pharmacokinetic evaluation was performed in immunocompromised children ages 2 to 11 years old.[61] Thirty-nine patients received either single dose therapy (3 or 4 mg/kg single dose, n = 11) or load/maintenance dose therapy (6 mg/kg load × 2 doses, followed by 3 mg/kg every 12 hours for 5 doses, then increased to 4 mg/kg if tolerated until at least day 8 to 21, n = 28). In this study, the authors note that the dose of 4 mg/kg provided similar exposure to a dose of 3 mg/kg in adult patients, which were median concentrations of approximately 0.7 µg/mL in children 6 to 11 years and 0.3 µg/mL in children 2 to 6 years.[61] Further, the authors noted that the pharmacokinetics of 4 mg/kg of voriconazole remained linear; therefore, an estimated dose equivalent to the usual 4 mg/kg would require more extensive evaluation.[61]

Walsh and colleagues later investigated the pharmacokinetics of voriconazole in 2 cohorts of 18 patients.[62] Patients in each cohort were divided into 2 groups by age: 2 to less than 6 years (n = 9) and 6 to 12 years (n = 9). Dosing was provided in 3 phases (Cohort 1: 4 mg/kg IV every 12 hours, then 6 mg/kg IV every 12 hours, then 4 mg/kg orally every 12 hours; Cohort 2: 6 mg/kg IV every 12 hours, then 8 mg/kg IV every 12 hours, then 6 mg/kg orally every 12 hours).[62] Overall, the dose of 8 mg/kg twice daily in children 2 to 12 years old appeared to achieve similar total drug exposures as the adult dose of 4 mg/kg every 12 hours.[62]

Pediatric Safety, Efficacy and Case Reports

Voriconazole has a large body of evidence to support its role in the treatment of pediatric mycoses (Table 3).[63-75] Such data includes a large, multi-center, open-label, trial in patients more than 12 years old comparing voriconazole with amphotericin B as primary therapy for definite or probable invasive aspergillosis infections.[70] Patients were randomized to receive either voriconazole at adult doses (IV for at least 7 days) or traditional amphotericin B 1–1.5 mg/kg/day for 12 weeks. Although limited adolescent data are provided, the authors concluded that voriconazole was able to demonstrate non-inferiority to amphotericin with an overall response of 53% for voriconazole and 32% for amphotericin B in the modified intent-to-treat population at week 12. In terms of safety and tolerability, there were significantly less adverse effects observed during voriconazole therapy (343 events) as compared to amphotericin B (421 events). Renal impairment (n = 19) and transaminase elevations (n = 7) were the most frequently reported adverse effects in the amphotericin B and voriconazole groups, respectively. Additionally, there was a high dropout rate in the amphotericin B group making the median duration of therapies completely different, 10 days (range, 1–84 days) for the amphotericin B and 77 days (range, 2–84 days) for the voriconazole group.[70]

As shown in Table 3, there are also several documented cases of pediatric voriconazole use for a variety of mycoses including *Aspergillus* and *Candida* species, as well as other less common fungi such as *Trichosporon beigelii, Fusarium solani,* and *Scedosporium prolificans.*[63-75] Among these reports, the most commonly used dosing scheme was a 6 mg/kg twice-daily loading dose, followed by 4 mg/kg twice daily maintenance dose. Nine of the eleven reports associated voriconazole with improvement or resolution of infection.[60-75] Two of the reports describe unfortunate deaths: a 10-week-old infant passed away from a stroke and a 13-year-old male died as a result of respiratory distress syndrome.[63,72]

Despite consistent data demonstrating the efficacy of voriconazole for refractory fungal infections, there have also been several documented adverse effects in children. The most commonly reported adverse effects include

Table 3. Summary of Voriconazole Pediatric Clinical Experience

Author (Reference)	Patient Population	Voriconazole Dosing§	Concomitant Antifungal Therapy	Treatment Group	Outcomes
Muldrew, et al. (74)	27 WGA, 14 days PNA	6 mg/kg/dose q12 hr, may ↑ to 6 mg/kg/dose q 8 hr*	LAMB FLUC	*Candida* species infection	Resolution of cultures
Maples, et al. (63)	10-wk-old infant	6 mg/kg/dose q12 hr, may ↑ to 7.4 mg/kg/dose q 12 hr*	AmBD	*Trichosporon beigelii* foot infection	Initial improvement, but eventual death due to a stroke
Guzman-Cottrill, et al. (64)	3-mo-old female	LD 6 mg/kg x 2 doses MD 4 mg/kg/dose q 12 hr	LAMB	*Fusarium solani* endocarditis	Stable after 11 mo
Bethell, et al. (65)	2½-yr-old female	LD 9 mg/kg/day MD 6 mg/kg/day	LAMB	Orbitocerebral aspergillosis	Stable after 6 wks
Rodriguez, et al. (66)	3-yr-old female	LD 6 mg/kg × 2 doses, MD 4 mg/kg/dose q 12 hr	ABLC	*Fusarium* species infection	Improvement after 9 mo
Verweij, et al. (75)	4-yr-old male	4 mg/kg/dose q12 hr	None	Pulmonary *A fumigatus*	Improvement after 4 wks
van't Hek, et al. (67)	5-yr-old child	3-9 mg/kg/dose q 12 hr*	None	Pulmonary aspergillosis and cutaneous *A nidulans*	Improvement after 4 wks
Whyte, et al. (68)	8-yr-old female	LD 6 mg/kg q 12 hr x 2 doses MD 4 mg/kg/dose q 12 hr IV	Terbinafine	*Scedosporium prolificans* infection	Improvement after prolonged course and repeated debridements
Studahl, et al. (69)	9-yr-old male	100 mg PO q 12 hr (weight reported < 40 kg)	None	*Scedosporium prolificans* osteomyelitis and arthritis	Resolution of knee biopsies after 3 mo
Herbrecht, et al. (70)	277 pts (including pts > 12 years old)	LD 6 mg/kg x 2 doses MD 4 mg/kg/dose q 12 hr† *vs.* AMB 1-1.5 mg/kg/day	None	Primary treatment for definite or probable aspergillosis	Overall response rates (week 12): VRC (53%) vs. AMB (32%), 95% CI for absolute difference 10%-33% Pediatric response rates: Not provided
Shouldice, et al. (71)	13-yr-old female	LD 6 mg/kg q 12 hr x 2 doses MD 4 mg/kg/dose q 12 hr	ABLC	*Aspergillus* species infection	Stable after 1 yr
Rosen-wolf, et al. (72)	13-yr-old male	LD 6 mg/kg x 2 doses MD 4 mg/kg q 12 h	None	Pulmonary A. *nidulans*	Improvement after 9 mo Eventual death due to complications from transplant
Walsh, et al. (73)	58 pediatric pts 0.75 to 15 yrs old	LD 6 mg/kg q 12 hr x 2 doses MD 4 mg/kg/dose q 12 hr‡	None	Primary (17%) Refractory fungal infections (93%)	Overall response rate (complete/partial): 45% Varied among species Aspergillosis (43%), Scedosporiosis (63%) Candidiasis (24%)

ABLC, lipid complex amphotericin B; AmBD, conventional amphotericin B; FLUC, fluconazole; WGA, weeks gestational age; LAMB, liposomal amphotericin B; PNA, postnatal age; LD, loading dose; MD, maintenance dose; PO, by mouth; pts, patients intravenous dosing unless specified otherwise

** Dosage adjustment based on serum concentrations*

† May be transitioned to oral voriconazole after ≥ 7days; oral dosing 200 mg q 12 hr

‡ May be transitioned to oral voriconazole when feasible; oral dosing < 40 kg: 100 mg q 12 hr, ≥ 40 kg: 200 mg q 12 hr

§ Intavenous dosing unless otherwise specified

reversible dose-dependent visual disturbances, dose-dependent liver transaminases and bilirubin elevations, and photosensitivity reactions.[65,69-72] Although less frequent, severe adverse effects including significant phototoxicity and liver failure (resulting in death) have been also documented in adolescent patients.[76,77] From the reviewed data, voriconazole appears to be a strong option, especially against *Aspergillus* species infections in the pediatric population with therapeutic drug monitoring to assure reasonable trough concentrations.

Posaconazole

Overview

Posaconazole (Noxafil, Schering Plough, Kenilworth, NJ) is a novel, broad spectrum, orally administered, second-generation triazole antifungal. As the most recently approved antifungal in September 2006, it has activity against *Candida* species (including triazole-resistant isolates), *Aspergillus* species, and zygomycetes including *Mucor* and *Rhizopus*.[15,78] Current indications include prophylaxis of invasive *Aspergillus* and *Candida* species infections and treatment of oropharyngeal candidiasis including triazole-refractory cases in patients more than 13 years old.[78] Posaconazole is currently only available as an oral suspension; however, an intravenous formulation is under development.[78,79] Like itraconazole, it should also be administered with food (specifically, a high fat containing meal) to optimize absorption; however, posaconazole absorption is not affected by antacid or proton-pump inhibitor administration. Although highly protein bound (greater than 96%), posaconazole has a large volume of distribution and is extensively distributed throughout peripheral tissues.[78] Posaconazole is a CYP450 3A4 inhibitor and may interact with medications metabolized via this pathway.[80] Specifically, it should be avoided in patients receiving rifabutin and its use should be closely monitored with immunosuppressants, phenytoin, tacrolimus and cyclosporine.[78,81]

Pediatric Safety, Efficacy and Case Reports

Although there is presently limited pediatric dosing information, preliminary data are available from 2 compassionate use trials and a case series (Table 4).[82-84] In these evaluations, a total of 20 pediatric patients (1 to 18 years old) received posaconazole 800 mg daily (divided every 6-12 hours) as salvage therapy (as either monotherapy or in combination with an amphotericin B product) for a variety of species including zygomycosis such as *Mucor* species and *Rhizopus stolonifer*. Overall response rates (including partial and complete responders) ranged from 60%–87.5%. However, pediatric specific response rates appeared higher, at 85.7%–100%. As such, there are promising data to suggest that posaconazole may be a suitable addition or alternative for salvage treatment of zygomycosis in children.[82-84]

Although the data for posaconazole use are very limited, it appeared to be well tolerated in children. Adverse effects include nausea and gastrointestinal symptoms.[82] In one report, a patient with a brain lesion reported loss of visual acuity 1 month after starting posaconazole thought to be unrelated to posaconazole and another patient reported a purpuric rash that resolved upon discontinuation of study medication.[83] Hospitalizations and deaths during compassionate use trials were thought to be likely the result of the nature of the infection versus a result of posaconazole administration.[83,84]

Ravuconazole

Overview

A second-generation triazole antifungal, ravuconazole (BMS-207147, Bristol-Myers Squibb, New York, NY) is in development for oral use.[16] It possesses broad-spectrum activity against many fungi including *Candida* species, *Cryptococcous neoformans,* and other yeast species. In adults, ravuconazole had displayed a much longer half-life than the other triazoles of approximately of 100 hours, lending to a potential role as a prophylactic agent or a prolonged dosing interval.[16] Presently, there are no pediatric data.

COMBINATION THERAPY

Data using combination antifungal therapy exclusively with the newer agents in children are increasing. There is a retrospective review and 4 published reports involving all ages of the pediatric population (Table 5).[85-89] In the retrospective evaluation, the safety and efficacy of caspofungin-based combination therapy for the treatment of aspergillosis was assessed in 40

Table 4. Summary of Posaconazole Pediatric Clinical Experience

Author (Reference)	Patient Population	Posaconazole Dosing*	Additional Concomitant Antifungal Therapy	Treatment Group	Outcomes
Segal, et al. (82)	8 pts (including 7 pediatric 9 to 18 yrs old) 7 males	400 mg PO q 12 hr†	None	Primary refractory/ toxicity failure (75%) Invasive filamentous disease (25%)	Complete response in 7 pts Treatment failure for a P. variotti pneumonia in 1 pt
Greenberg, et al. (83)	24 pts (including 3 pediatric 7 to 17 yrs old) 2 males	800 mg PO daily (either 400 mg q 12 hr or 200 mg q 6 hr)	ABLC (n = 1)	Refractory/toxicity failure zygomycosis	Pediatric complete response (n = 1) Pediatric partial response (n = 2)
van Burik, et al. (84)	91 pts (including 11 pts < 18 yrs old)	800 mg PO daily (either 400 mg q 12 hr or 200 mg q 6 hr)	LAMB/ ABLC (n = 13)	Refractory/toxicity failure zygomycosis	Overall response rate (complete/ partial): 81% Pediatric response rate: Not provided

ABLC, lipid complex amphotericin B; LAMB, liposomal amphotericin B; PO, by mouth; pts, patients
**Oral dosing for all patients receiving posaconazole*
†1 younger patient received posaconazole 200 mg po q 8 hr

pediatric hematology/oncology patients ages 1 to 17 years old.[86] The majority (90%) of patients received either caspofungin and voriconazole (n = 9), caspofungin and liposomal amphotericin B (n = 18), or a sequence of both combinations (n = 9). Overall response (including complete and partial response) was demonstrated in 52.5% of patients. A multivariate analysis was conducted to help determine if specific factors significantly influenced the likelihood of favorable antifungal response; no specific factors were found to be associated with favorable response in this analysis.[86]

Three reports of combination therapy for the treatment of *Aspergillus* species infections have been recently reported (Table 5).[85,86,88] In the first report, a 12-year-old female received amphotericin B lipid complex, caspofungin and voriconazole for treatment of a pulmonary aspergillosis infection.[88] Overall, she improved after a total of 34, 33, and 14 days of amphotericin B lipid complex, caspofungin, and voriconazole therapy, respectively.[88] The second case reports the successful combination of voriconazole and caspofungin therapy in a 12-year-old with a bone marrow transplant for the treatment of a pulmonary *A flavus* infection.[89] The patient stabilized after 2 weeks of combination therapy and continued treatment with voriconazole for 47 days and caspofungin for 10 weeks without any signs of recurrence.[89] Most recently, a report was published documenting the use of liposomal amphotericin B, voriconazole, and an echinocandin for cutaneous aspergillosis in a premature neonate.[85] The patient was initially started on caspofungin, voriconazole, and liposomal amphotericin B for treatment of his refractory infection. However, caspofungin was switched after 1 week as authors felt micafungin had relatively more safety and pharmacokinetic data in this patient population. Due to the severity of the patient's condition, micafungin and voriconazole dosing was adjusted according to serum concentrations. Overall, the patient demonstrated slow clinical improvement on liposomal amphotericin B, voriconazole, and micafungin over a total of 3, 7, and 6 weeks, respectively.[85]

A report has also been published of combination antifungal therapy in an 8-year-old male for a disseminated *Cladophialophora bantiana* infection.[87] After extensive treatment with amphotericin B lipid complex and itraconazole, he was switched to a regimen containing flucyto-

Table 5. Summary of Combination Newer Antifungal Pediatric Clinical Experience

Author (Reference)	Study Population	Combination Antifungals*	Treatment Group	Outcomes
Santos, et al. (85)	24 WGA, 13 days PNA male	LAMB 5 mg/kg/day CAS 2 mg/kg/day; changed to MICA 8 mg/kg/day after 7 days VRC 4 mg/kg/dose q 12 hr	Cutaneous aspergillosis	Slow improvement on a total of 1, 3, 7, and 6 weeks of CAS, LAMB, VRC, and MICA, respectively
Cesaro, et al. (86)	40 pediatric pts 1.2 to 17.9 yrs old	CAS LD 70 mg/m^2, MD 50 mg/m^2/day AND either: VRC LD 6 mg/kg q 12 hr x doses, MD 4 mg/kg/dose q 12 hr, or LAMB 3-5 mg/kg/day	Aspergillosis	*Overall response rate (complete/partial):* 53% Multivariate analysis did not find a factor predictive of favorable response
Trinh, et al. (87)	8-yr-old male	CAS 0.7 mg/kg/day VRC 4 mg/kg/day 5-FC 150 mg/kg/day PO, (serum concentrations ranged from 32-50 mg/L)	*Cladophialophora bantiana* infection	Death secondary to brain herniation after 4 weeks
Sims-McCallum, et al. (88)	12-yr-old female	ABLC 5 mg/kg/day CAS LD 70 mg, MD 50 mg daily VRC LD 300 mg q 12 hr x 2 doses, MD 200 mg q 12 hr PO	Pulmonary aspergillosis	Improvement on a total of 34, 33, and 14 days of ABLC, CAS, and VRC, respectively
Schuster, et al. (89)	12-yr-old adolescent	CAS 1 mg/kg/day VRC dose uncertain	Pulmonary *A flavus*	Resolution after 2 weeks

ABLC, lipid complex amphotericin B; CAS, caspofungin; 5-FC, flucytosine; LAMB, liposomal amphotericin B; LD, loading dose; MD, maintenance dose; MICA, micafungin; PNA, postnatal age; VRC, voriconazole; WGA, weeks gestational age
**intravenous dosing unless specified otherwise*

sine, caspofungin, voriconazole and granulocyte colony stimulating factor-mobilized granulocyte transfusions. Unfortunately, the patient passed away likely due to brain herniation thought to be a result of rapid disease progression after 4 weeks of combination antifungal therapy.[87]

CONCLUSION

The addition of newer agents to the antifungal armamentarium has greatly improved the options available for the treatment of fungal infections in children, addressing many of the previous concerns of rising resistance and tolerability. With their unique mechanism of action on β-1-3-D-glucan synthase, the echinocandins have a likely role for the treatment of many *Candida* species infections in children; however, uncertainty regarding potency against *C parapsilosis* still remains. In terms of the triazoles, the dose of voriconazole needs to be solidified, but it will likely have a role in the treatment of invasive aspergillosis infections. Further, although limited pediatric dosing information is available, preliminary data from compassionate use programs suggest that posaconazole may be considered as salvage therapy for patients with zygomycosis. Data describing the use of newer antifungals in children is growing. However, larger-scale, prospective pediatric studies are needed before the true role of these newer antifungal therapies in children can be clearly defined.

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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