Echinocandins in Children

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Key Words: echinocandins, antifungal, candida, aspergillus

(Pediatr Infect Dis J 2011;30: 508–509)

The echinocandins (ECs), caspofungin (CA), micafungin (MI), anidulafungin (AD), and aminocandin (AM) are the newest class of parenterally administered antifungal agents. This review will discuss their general properties, current indications, and available pediatric data.

ECs are semisynthetic cyclic lipopeptides which inhibit cell wall biosynthesis through noncompetitive inhibition of the (1→3)-β-D-glucan synthase complex. This target is unique to fungi, thus contributing to favorable toxicity profile of ECs. The spectrum of activity is related to the content of (1→3)-β-D-glucan in cell walls. Candida and Aspergillus contain substantial amounts, leading to excellent activity against these fungi. In Candida spp., decreased synthesis of (1→3)-β-D-glucan, composing up to 60% of the cell wall and responsible for cell wall integrity, leads to fungicidal instability of the cell. ECs exhibit concentration-dependent killing of Candida related to AUC/MIC or Cmax/MIC. The interpretive breakpoint for EC susceptible Candida spp. is ≥2.0 μg/mL, which also is achieved for triazole-resistant Candida albicans, Candida Krusei, and Candida glabrata. Concern exists about higher MICs for Candida parapsilosis (50–100 fold more than those of C. albicans). A naturally occurring proline-to-alanine amino acid change in Fks1p in C. parapsilosis accounts for this reduced susceptibility. Although clinical failures in treatment of C. parapsilosis with ECs have been reported, organisms with MICs ≥2.0 μg/mL are usually responsive. The finding that ECs exert activity against Candida biofilms may have important therapeutic implications for the treatment of foreign body/catheter infections.

ECs have a unique form of activity against Aspergillus spp., causing destruction of the hyphal tips and branch points of growing cells, thus decreasing invasion. The potency of ECs may be further augmented by immunomodulatory activity resulting from release or unmasking of cell wall glucans leading to dectin-1 dependent, proinflammatory enhancement of macrophage and neutrophil killing activity.

In vitro, high concentrations of ECs can lead to attenuated activity against Candida and Aspergillus. A compensatory cell wall stress response upregulates cell wall chitin biosynthesis permitting paradoxical growth despite decreased glucan. In vivo, increased biomarkers and fungal burden may be observed, although the clinical relevance of paradoxical growth is not well understood.

ECs are not active as single agents against zygomycetes (Mucorales), Fusarium spp., or Scedosporium spp. (due to diminished (1→3)-β-D-glucan synthase activity) or against Trichosporon spp. and Cryptococcus neoformans (due to predominantly (1→6)-β-D glucan linkages). ECs have high MICs against the yeast phase of dimorphic fungi, and are not recommended for treatment of endemic fungi.

ECs are highly protein bound, distribute well into most tissues, but achieve low cerebrospinal fluid and urine concentrations. Long half lives allow for once daily dosing. They are well tolerated; the most notable toxicity is transaminase elevation and gastrointestinal symptoms, rarely necessitating discontinuation. Severe liver toxicity has been infrequently reported in patients with other contributing factors. Infusion-related hypersensitivity reactions are rare. Dose adjustment is not necessary for renal dysfunction, but may be warranted in patients with severe hepatic dysfunction for CA and MI, which are hepatically transported and metabolized.

Table 1 outlines current recommendations and licensure status for CA, MI, and AD. There do not appear to be clinically significant differences among the current ECs in spectrum, efficacy, or toxicity. Further details on the therapeutic and prophylactic roles of ECs, in the context of other antifungal agents, are discussed in Practice Guidelines of the Infectious Diseases Society of America, aspergillosis and candidiasis (available at: http://www.idsociety.org/).

The recommended dose for children aged 3 months to 17 years is 50 mg/m²/d (maximum, 70 mg), following a loading dose of 70 mg/m²/d in comparison to that of adults at 50 mg/d. Clearance is lower in neonates and adults, and increased during childhood. These differences may be determined by the differential rate of distribution from plasma into hepatic tissue. Data based on 18 infants <3 months of age suggest a dose of 25 mg/m²/d providing comparable plasma exposure to that in children and adults.

The first pediatric double-blind, randomized controlled trial of empiric antifungal therapy (EAFT) compared liposomal amphotericin B with CA. Although not powered to test specific hypotheses (n = 82), this study found comparable tolerability, safety, and efficacy between the 2 groups, and similar to that observed in adults. Although nephrotoxicity was similar in both groups (8.0% vs. 5.6%), 11.5% of patients receiving amphotericin B discontinued due to adverse events, compared with 3.6% receiving CA. A prospective multicenter trial for primary or salvage treatment of Candida and Aspergillus infections in 48 children, documented complete or partial response in 81% and 50% of patients, respectively, suggesting similar safety and efficacy as observed in adults. CA was used successfully in treatment of candidemia, renal candidiasis, and endocardial infection in 9 premature and 1 term infant.

A Food and Drug Administration postmarketing adverse event report states “CA is generally well tolerated by patients of all ages” and did not “identify adverse events that would suggest the safety profile differs significantly between adults and pediatrics.” Drug interactions may include rifampin, efavirenz, nevirapine, phenytoin, dexamethasone, carbamazepine, in which simultaneous use may lower CA levels. Coadministration with cyclosporine may increase CA levels and hepatobiliary events, whereas tacrolimus levels may be decreased with concomitant use.

Mycafungin

Dosing has not been firmly established for children; data suggest linear pharmacokinetics (PK) with an inverse relationship between age and clearance, such that dosages of 3 to 4 mg/kg q d for 2 to 8 years and 2 to 3 mg/kg q d for 9 to 17 years of age...
TABLE 1. Recommendations for Use of ECs in Pediatric Patients

1. Primary treatment of Candida infections: candidemia, intra-abdominal abscess, peritonitis, pleural space, esophagitis (CA, MI, AD)*
2. Prophylaxis of Candida in hematopoietic stem cell recipients (MF)
3. Empiric antifungal therapy in febrile neutropenia (CA*)
4. Salvage therapy for Aspergillus infections (refractory/intolerant to voriconazole, polyenes) (CA*)
5. Combination therapy (withazole or polyene) for Aspergillus infections: consider in selected patients based on immune and clinical status

*FDA indication for pediatrics for <3 months of age.
CA indicates caspofungin; MI, micafungin; AD, anidulafungin.

yield similar exposure of drug observed in adults. These doses were well tolerated by children without dose-limiting toxicity. The most common related adverse events in neutropenic children were diarrhea, vomiting, and headache (12%), as observed in adults (15%) and similar to fluconazole. Studies in infants <15 kg, suggest larger volumes of distribution and higher clearance than in children and adults, such that neonatal doses of at least 5 to 7 mg/kg/d may be necessary. For preterm infants, a dosage of 15 mg/kg was well tolerated and the use of this dose is supported by population pharma- and/or Japan for treatment of pediatric esokinetics models. Although not indicated for experimental hematogenous infections, dosages of 8 to 15 mg/kg of MI were effective in experi-mental hematogenous Candida meningoencephalitis, which causes serious comp iations in the neonatal population. MI has activity against experimental pulmonary aspergillosis; however, studies ad-dressing MI for aspergillosis in children are sparse. Noncomparative studies of single or combination primary or salvage therapy, and prophylaxis for hematopoietic stem cell transplantation and cancer patients and is as well tolerated as CA. The clinical significance of the recent boxed warning from the European Medicines Agency (EMEA) of MI inducing neoplastic events in laboratory animals is not clear but may be a species-dependent class effect. MI is a substrate and weak inhibitor of CYP3A in vitro with minimal clinical signif- icance. Patients receiving sirolimus, nifedi-pine, and itraconazole should be monitored and doses reduced as necessary.

ANIDULAFUNGIN
AD uniquely undergoes slow degradation or biotransformation that is independent of hepatic metabolism or renal excretion; this results in few drug interactions and no dose adjustment for renal or hepatic dysfunction. Unlike CA and MI, differences in clearance based on age have not been found for AD. A single study of safety and PK of 25 neutropenic children demonstrated that dosages of 0.75 mg/kg and 1.5 mg/kg for 2 to 17 years of age have similar pharmacokinetics as doses of 50 mg or 100 mg/d in adults for esophageal candidiasis or invasive candidiasis/candidemia, re- spectively. Both dosages were well tolerated with no treatment emergent documented fun-gal infections. AD has in vitro and in vivo activity against Aspergillus sp.; however, clinical data for aspergillosis are lacking.

AMINOCANDIN
AM has an extended half life compared with that of other ECs, with potential for 1 to 2 times/wk dosing. It has in vitro activity against Candida sp., including some triazole and polyn eye-resistant isolates, and activity against Aspergillus sp. Animal model data support efficacy in treating candidiasis and aspergillosis. Phase 1–2 data in adults demonstrate linear PK for single intravenous dose of 75 to 300 mg. AM is well tolerated, even at 7 times the anticipated clinical dose. No human efficacy or pediatric data are available.

EC AND COMBINATION THERAPY
Voriconazole remains the drug of choice for primary monotherapy of most cases of invasive aspergillosis in immuno-compromised patients; however, therapeutic response can be poor in patients who are profusely immunocompromised. Simulta-neous targeting of the fungal cell wall with an EC and the cell membrane with a triazole improves in vitro activity against Aspergillus fumigatus and in vivo efficacy in experimental invasive pulmonary aspergillosis. Retrospective or noncomparative observational studies are also consistent with these laboratory findings. Nonetheless, further clinical evidence is required before recommending the routine use of combination triazole-EC antifungal therapy for primary treatment of invasive aspergillosis.

REFERENCES