

Micafungin Use in the Treatment of Neonatal and Pediatric Fungal Infections

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Invasive candidemia and *Candida* meningoen­cephalitis are significant causes of morbidity and mortality in premature neonates and critically ill or immunocompromised pediatric patients.¹ The incidence of candidemia ranges from 2 to 10 cases per 100,000 subjects in surveillance studies of both adults and children, with a mortality rate of 5-10%. The echinocandins (caspofungin, micafungin, and anidulafungin) have become important options for the treatment of these infections. Micafungin, the second drug in this class to be developed, was approved by the Food and Drug Administration in 2005 for use in adults. It offers the advantages of once daily dosing, a low degree of resistance, and a relatively mild adverse effect profile.² Shortly after approval micafungin began to be used in children with resistant fungal infections and in those who were unable to tolerate the adverse effects of other agents. On June 21, 2013, the FDA extended approval to use in children 4 months of age and older.^{3,4} While not yet approved for infants, recent studies have shown benefit in this patient population with the use of higher weight-based doses to account for a more rapid drug clearance.

Mechanism of Action

The echinocandins are semisynthetic lipopeptides produced by modification of a fermentation product of *Coleophoma empetri*. The echinocandins inhibit 1,3-beta-D-glucan synthase and, as a result, alter the integrity of fungal cell walls. Micafungin has been shown to have activity against *Candida albicans*, *C. glabrata*, *C. guilliermondii*, *C. krusei*, *C. parapsilosis*, and *C. tropicalis* in both *in vitro* and clinical testing. Cases of treatment failure resulting from micafungin resistance have been reported. Resistance has been associated with mutations of the FKS protein component of the 1,3-beta-D-glucan synthase enzyme.^{1,4}

Pharmacokinetics

After intravenous (IV) administration, micafungin exhibits a linear relationship between dose and area under the concentration-time curve (AUC). In adults, the volume of distribution of

micafungin is approximately 0.4 L/kg. It is highly protein bound (> 99%), primarily to albumin but also to alpha-1-acid-glycoprotein. Micafungin is metabolized by arylsulfatase to the catechol form (M-1). This intermediate byproduct undergoes metabolism via catechol-O-methyltransferase to form the M-2 metabolite. A second pathway, cytochrome P450-mediated hydroxylation, forms the M-5 metabolite. Less than 30% of a dose is excreted in the urine as unchanged drug. The clearance of micafungin in adults is approximately 0.21-0.36 mL/min/kg, with an elimination half-life of 13-17 hrs.⁴

The pharmacokinetic profile of micafungin has been compiled using data obtained from 229 pediatric patients (4 months-16 years of age) enrolled in manufacturer-sponsored clinical trials.⁴ In these trials, patients were divided into two groups (those \leq 30 kg and those > 30 kg). Smaller children were given a once daily dose of 1, 2, or 3 mg/kg, while larger children received doses of 1, 2, or 2.5 mg/kg. In the smaller children, maximum serum concentrations ranged from 7.1 ± 4.7 mcg/mL in the children given 1 mg/kg to 21.3 ± 14.0 mcg/mL in the 3 mg/kg group, while AUC ranged from 55 ± 16 mcg•hr/mL to 164 ± 47 mcg•hr/mL. The mean clearance of micafungin in these patients was 0.328 ± 0.091 mL/min/kg, with an elimination half-life of 12.5 ± 4.6 hrs. The children weighing more than 30 kg had maximum serum concentrations ranging from 8.7 ± 5.6 mcg/mL with the 1 mg/kg dose to 23.0 ± 14.5 mcg/mL with the 2.5 mg/kg dose, with AUC values from 67 ± 17 mcg•hr/mL to 176 ± 42 mcg•hr/mL. The mean clearance in this group, 0.241 ± 0.061 mL/min/kg, was slower than that of the smaller children, with a slightly longer elimination half-life of 13.6 ± 8.8 hrs. The values in the larger children were similar to those previously reported in adults.

Several pharmacokinetic studies have replicated the findings of a more rapid clearance and shorter elimination half-life in younger children compared to older children and adults.^{5,6} The clearance in children 2-8 years of age has been

estimated to be approximately 1.35 times that of children 9 years of age and older.⁶ The difference is even more striking in studies of neonates.⁷⁻¹³ In 2006, Heresi and colleagues published the results of a phase 1, single-dose multicenter open-label, sequential-dose trial of micafungin in 18 premature infants weighing over 1,000 g.⁷ Six patients were randomized to each of the three drug doses: 0.75, 1.5, or 3 mg/kg. The mean values for clearance and half-life were 0.65 ± 0.2 mL/min/kg and 8.3 hrs (range 5.6-11.0 hrs). Similar results were found by Kawada and colleagues in a study of 25 premature infants given a dose of 1 mg/kg within 24 hours of birth.⁸ The apparent volume of distribution in these patients was 0.76 ± 0.28 L/kg, with a clearance of 0.089 ± 0.047 L/kg/hr and a half-life of 6.7 ± 2.2 hrs.

It has been suggested that the more rapid clearance of micafungin in neonates reflects reduced serum protein binding and necessitates higher doses in this age group.⁹⁻¹³ While doses as high as 15 mg/kg/day have been shown to be well tolerated,¹⁰ a dose range of 7-10 mg/kg/day appears to produce adequate micafungin concentrations for treating invasive *Candida* infections, including those in the central nervous system (CNS), without an increase in the incidence of adverse effects. In a pharmacokinetic simulation using serum samples collected from 47 infants enrolled in three clinical trials, a dose of 10 mg/kg/day resulted in 82.6% of patients having a micafungin AUC at the level associated with near-maximal decline in fungal burden within the CNS.⁹

Benjamin and colleagues described the pharmacokinetic profile of 7 and 10 mg/kg doses in 13 infants with suspected candidemia or invasive candidiasis.¹¹ In their study, patients $\geq 1,000$ g received 7 mg/kg while those $< 1,000$ g received 10 mg/kg. All doses were administered once daily for at least 4 days. Median AUC was 258.1 mcg•hr/mL for the 7 mg/kg group and 291.2 mcg•hr/mL for the 10 mg/kg group, above the level considered necessary for the treatment of *Candida* meningoenophalitis. Mean clearance was 0.4 ± 0.2 mL/min/kg and 0.6 ± 0.2 mL/min/kg in the 7 mg/kg and 10 mg/kg groups, with elimination half-lives of 11.4 ± 3.5 hrs and 10.6 ± 3.2 hrs, respectively.

Clinical Experience

The first pediatric micafungin study was published in 2005.⁵ This phase 1 open-label dose escalation study described the safety, tolerability, and pharmacokinetics of micafungin in 77 children with febrile neutropenia associated with leukemia, lymphoma, bone marrow transplant, aplastic anemia, or a myelodysplastic syndrome. The patients were grouped by age (children 2-12 years and adolescents 13-17 years). Treatment was initiated with a micafungin dose of 0.5

mg/kg given once daily, with escalation to 1, 1.5, 2, 3, and 4 mg/kg per day if tolerated. Treatment continued until recovery from neutropenia (an absolute neutrophil count ≥ 250 cells/mm³), development of a serious adverse effect, or evidence of the need for another antifungal agent. There was no evidence of dose-limiting toxicity. Nine patients (12%) experienced an adverse reaction considered to be related to micafungin. The most common adverse reactions were diarrhea, epistaxis, abdominal pain, and headache (each in 16-20% of patients). Only one patient, a 15-year-old receiving a dose of 0.5 mg/kg/day for 2 weeks, developed an invasive fungal infection. There was no clinical evidence of the infection during treatment, and cultures obtained at the time of study completion (day 22) revealed no evidence of a fungal infection. She died on day 33 and an autopsy revealed pulmonary aspergillosis. One other patient was removed from the study for persistent fever and neutropenia and treated with amphotericin.

In 2008, Queiroz-Telles and colleagues of the Micafungin Invasive Candidiasis Study Group conducted a substudy of pediatric patients enrolled in a multinational randomized double-blind trial comparing micafungin with liposomal amphotericin B for invasive candidiasis.¹⁴ A total of 106 infants and children were included. Most patients (92.9%) had candidemia. Treatment success, based on clinical and mycologic response, was reported in 72.9% of the patients receiving micafungin and 76% of those given amphotericin. The study was not adequately powered to determine significance. Although the authors noted that both drugs were well tolerated, amphotericin was discontinued in 16.7% of patients because of adverse events, compared to only 3.8% with micafungin.

Based on papers such as these, micafungin has become an accepted option for the prevention and treatment of invasive *Candida* infections in infants and children. The 2012 guidelines from the European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group included micafungin in their recommendations for the management of *Candida* diseases.¹⁵ In scoring the available studies, the authors rated each drug based on the strength of the recommendation (A-D as highest to lowest) and the level of evidence (I-III). Micafungin was rated as a level B-II recommendation for the treatment of invasive candidiasis in neonates and a level A-I recommendation for prevention or treatment of invasive *Candida* infections in children.

In 2013, Kobayashi and colleagues conducted a prospective multicenter trial of micafungin for febrile neutropenia in children receiving chemotherapy or who had undergone stem cell transplantation.¹⁶ Thirty treatment episodes were evaluated. The median daily dose and duration

were 3 mg/kg and 13.5 days. Using a composite score response (resolution of fever during neutropenia, successful treatment of infection, absence of breakthrough infection, survival for > 7 days post-study, and no cases of discontinuation for toxicity or lack of efficacy), micafungin was effective in 56.7% of episodes. Body temperature and C-reactive protein were significantly lower after treatment, compared to baseline values. Two children experienced transient elevated serum transaminases. The authors concluded that micafungin was a safe and effective antifungal for empiric therapy in this patient population.

Three additional pediatric micafungin trials are listed on www.ClinicalTrials.gov as currently enrolling patients. Duke University is conducting a pharmacokinetic study of micafungin in children undergoing extracorporeal membrane oxygenation. This open-label interventional study is designed to provide pharmacokinetic parameters as well as information on adverse reactions. Seoul National University Hospital is conducting an open-label study of the efficacy of micafungin in preventing invasive fungal disease in pediatric and adolescent patients undergoing autologous hematopoietic stem cell transplantation. Astellas, the manufacturer of micafungin, is enrolling patients in the MAGIC-2 trial, a phase 3 randomized, double-blind international multicenter study comparing micafungin to amphotericin B deoxycholate for treatment of neonatal candidiasis.

Contraindications and Warnings

Use of micafungin is contraindicated in patients with a previous history of a hypersensitivity reaction to it or any other echinocandin. Rare, but serious hypersensitivity reactions, including anaphylaxis and anaphylactoid reactions, have been reported with micafungin administration.⁴ Isolated cases of acute intravascular hemolysis and hemolytic anemia have been reported in patients receiving micafungin. Approximately 4-10% of children in clinical trials have developed decreased urine output or elevated serum transaminases and hyperbilirubinemia during micafungin administration. In these cases, continued use of micafungin should be evaluated based on the relative benefit of treatment. If therapy is continued, appropriate monitoring tests should be continued throughout treatment.⁴

Adverse Effects

The safety profile of micafungin has been evaluated by the manufacturer in 479 pediatric patients (3 days-16 years of age) enrolled in one of 11 clinical trials. Adverse effects resulted in the discontinuation of micafungin in 4-7% of children in randomized, double-blind trials. The most common adverse reactions reported included vomiting (in 31% of patients), diarrhea (22%), nausea (19%), or abdominal pain and distension (9-16%), pyrexia (22%), rash,

urticaria or pruritus (5-12%), thrombocytopenia, neutropenia, anemia (13-15%), tachycardia (10%), epistaxis (9%), anxiety (7%), decreased urine output or hematuria (4%). Infusion-related reactions were reported in 5%. Similar results have been reported by other investigators.^{1,2,4,5,17}

Preliminary safety data with micafungin doses up to 15 mg/kg in premature infants have found no greater incidence of adverse effects than in previous reports in older children and adults.¹⁰ In the 2011 study by Benjamin and colleagues, only three of the 13 patients treated with a daily micafungin dose of 7 or 10 mg/kg had an adverse reaction considered to be potentially drug-related.¹¹ These reactions included increased alkaline phosphatase, hypokalemia, fever, and infusion site phlebitis. There were no reports of renal toxicity or hematologic changes.

Drug Interactions

Studies of the concomitant administration of micafungin and sirolimus in adults have shown an increase in sirolimus AUC of 21% without a change in the maximum sirolimus serum concentration. Administration of micafungin with nifedipine resulted in an increase in AUC of 18% as well as a 42% increase in maximum nifedipine serum concentration. Micafungin administration with itraconazole resulted in a 22% increase in AUC and an 11% increase in the maximum itraconazole concentration. Patients requiring concomitant use of micafungin with sirolimus, nifedipine, or itraconazole should be closely monitored for adverse effects and the dosage of the drug reduced if necessary.⁴

Availability and Dosing Recommendations

The recommended dose of micafungin varies by indication. In adults requiring treatment of candidemia, acute disseminated candidiasis, or *Candida* peritonitis and abscesses, micafungin 100 mg should be administered once daily. Patients with esophageal candidiasis should receive a dose of 150 mg. The duration of treatment in adults typically ranges from 10-30 days. A dose of 50 mg once daily is recommended for prophylaxis of *Candida* infection in adults after hematopoietic stem cell transplant. Prophylaxis has been administered for up to 6 weeks in clinical studies.⁴

Pediatric patients 4 months of age and older with candidemia, acute disseminated candidiasis, or *Candida* peritonitis and abscesses should be treated with a micafungin dose of 2 mg/kg given once daily. For the treatment of esophageal candidiasis, children ≤ 30 kg should receive a dose of 3 mg/kg and those > 30 kg should receive a dose of 2.5 mg/kg daily. Children receiving micafungin for prophylaxis after hematopoietic stem cell transplant should be given a daily dose of 1 mg/kg. The maximum pediatric dose for all indications is the recommended adult dose.⁴ Neonatal dosing

recommendations are currently based on the available pharmacokinetic and safety studies.⁵⁻⁹ In order to achieve adequate concentrations in the central nervous system to treat *Candida* meningoencephalitis, a micafungin dose of 7 to 10 mg/kg should be given once daily, based on patient weight.¹¹

A loading dose is not necessary for micafungin. Dosage adjustment is not required for patients with renal or hepatic impairment. Micafungin (Mycamine[®]) is available in 50 mg and 100 mg single-use preservative-free vials. The drug should be diluted with 5% dextrose solution or 0.9% sodium chloride to a concentration of 0.5-4 mg/mL and infused over 1 hour. To minimize the risk for infusion reactions, micafungin concentrations greater than 1.5 mg/mL should be administered through central IV access.⁴

Summary

Micafungin has been shown to be an effective treatment for *Candida* species infections in children as well as adults. It provides an alternative to amphotericin, azole antifungals, and caspofungin in patients with renal and/or hepatic impairment, and has the additional advantage of a limited number of drug interactions. Although recently approved by the FDA for pediatric use, micafungin has not yet been approved for use in neonates. Recent studies suggest that it may also be appropriate for this population, but age-related pharmacokinetic differences may necessitate a higher dosing range.

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Formulary Update

The following actions by the Pharmacy and Therapeutics Committee at their December meeting:

1. Clobazam (Onfi[®]) oral suspension was added to the Formulary.
2. Dolutegravir (Tivicay[®]) and elvitegravir, cobicistat, emtricitabine, and tenofovir (Stribild[®]) were added to the Formulary with restriction to AST approval.
3. Ibrutinib (Imbruvica[™]) was added with restriction to FDA-approved indications.
4. Celecoxib (Celebrex[®]) restrictions were amended to include use in ERAS protocols.
5. Epoprostenol (Veletri[®]) restriction was amended to use in adult patients for IV use only.
6. Epoprostenol (Flolan[®]) restriction was amended to use in pediatric patients for IV and inhalation and in adult patients for inhalation.
7. Tranexamic acid restriction was amended to include use in pediatric and neonatal ECMO.
8. Restrictions on acyclovir IV, amikacin, IV, and trimethoprim/sulfamethoxazole IV were removed due to resolution of shortages.
9. Zoledronic acid (Zometa[®]) restriction to outpatient use was removed.
10. Morphine suppositories were removed from the Formulary due to lack of use.

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