НОВИНИ МЕДИЦИНИ

УДК: 616-053.32-085.272.015.13

SAFETY OF MICAFUNGIN IN INFANTS: INSIGHTS INTO OPTIMAL DOSING

Simon Ascher, BS[1,2], P. Brian Smith, MD, MPH, MHS[1,2], Daniel K. Benjamin Jr., MD, PhD, MPH[1,2]

[1]Department of Pediatrics, Duke University, Durham, NC
[2] Duke Clinical Research Institute, Duke University, Durham, NC

Keywords:*adverse effects; drug toxicity; micafungin; premature infants.*

Abstract.

Introduction – *Invasive Candida infections are a leading cause of mortality and morbidity in neonatal intensive care units (NICUs). Micafungin is a promising therapeutic option for treatment of invasive fungal infections in infants given its safety profile in older children and adults.Understanding micafungin safety in infants is particularly important because antifungals are most often used in premature infants with multiple underlying medical conditions in a critical care setting.*

Areas covered – *This article reviews the literature evaluating the safety profile of micafungin in infants and offers recommendations for optimal dosing for treatment of invasive candidiasis in the NICU setting. The review was performed using a Medline search in September 2010 for related articles from 1990 to present with the Mesh related terms 'micafungin' and 'safety' in combination with the free words 'antifungal', 'candidiasis', 'drug toxicity','infant, premature', and 'infant, newborn'.*

Expert opinion – *Despite the limitations of the existing literature, we believe micafungin dosing of 10 mg/kg/day for all term and preterm infants is a viable treatment option in the NICU setting for management of invasive candidiasis. Although the number of infants for whom safety data are reported is small, higher doses of micafungin appear safe and well-tolerated in this population.*

1. Introduction

Invasive Candida infections are a leading cause of mortality and morbidity in neonatalintensive care units (NICUs)[1–4]. The cumulative incidence of candidemia among extremely low birth weight infants (<1000 g birth weight) is 7%. Invasive Candida infections result in an associated mortality rate of 20–30% in this population and frequently lead to significant morbidities including neurodevelopmental impairment, chronic lung disease, and severe retinopathy of prematurity[1–2,4].

Address for correspondence: Danny Benjamin, MD, PhD, MPH, Duke University, Pediatrics, 2400 Pratt St., Duke Clinical Research Institute, Durham, NC 27715, USA, danny.benjamin@duke.edu. Declaration of interest D Benjamin receives support from 1R01HD057956-02,1R01FD003519-01, 1U10-HD45962-06, 1K24HD058735-01, Government Contract HHSN267200700051C, and the Thrasher Research Foundation. D Benjamin reports receiving grant support from Astellas

Pharma US, AstraZeneca, Johnson & Johnson Pharmaceutical Research & Development, MedImmune, Pfizer, and The Medicines Company. D Benjamin reports consulting fees from Biosynexus, GlaxoSmithKline and Pfizer. B Smith receives support from NICHD 1K23HD060040-01 and DHHS-1R18AE000028-01. B Smith reports receiving grant support from Astellas Pharma US, Cubist Pharmaceuticals, and Pfizer. B Smith reports receiving consulting fees from Pfizer.

Treatment of invasive Candida infections in infants typically consists of amphotericin B deoxycholate or fluconazole. However, use of echinocandin antifungals in this population is increasing[5–7]. Echinocandins compromise fungal cell wall synthesis by non-competitive inhibition of the enzyme 1,3-β glucan synthase, resulting in cell lysis [8]. This mechanism offers a high degree of specificity for fungi such as Candida. Echinocandins may play an increasingly important role in the treatment of invasive Candida infections with the rising incidence of both non-albicans species and fluconazole-resistant Candida species in the NICU[9] and studies demonstrating similar efficacy and improved safety profiles when

compared to amphotericin B deoxycholate and fluconazole[10–11]. Micafungin (FK463; Astellas Pharma US, Inc, Deerfield, IL) is an echinocandin with established in vitro and in vivo concentration-dependent fungicidal activity against most Candida species[12–13], including fluconazole-resistant species and the species most commonly affecting infants (C. albicans, C. parapsilosis, C. glabrata, C. tropicalis, and C. krusei)[14]. Although the minimum inhibitory concentration (MIC) distribution for C. parapsilosis is over 100 times higher than that for other commonly isolated Candida species[15], the MIC breakpoint of 2 μg/mL for micafungin is inclusive of nearly all Candida isolates including C. parapsilosis[16]. Like other echinocandins, micafungin has a high molecular weight and is largely protein-bound in plasma, resulting in relatively low urine and cerebrospinal fluid (CSF) levels. It is metabolized by the liver, but because the cytochrome P450 system does not play a role, micafungin has few drug-drug interactions[17].

Micafungin is not approved for pediatric use in the United States. In the European Union and Japan, it is approved for children including neonates for treatment of invasive candidiasis and for prophylaxis against Candida infections in patients with anticipated neutropenia or patients undergoing allogeneic hematopoietic stem cell transplantation. While adult studies have demonstrated both efficacy and safety, there is a paucity of data demonstrating safety and optimal dosing in infants. Understanding micafungin safety in infants is particularly important because antifungals are most often used in premature infants with multiple underlying medical conditions in a critical care setting. The purpose of this article is to review the literature evaluating the safety profile of micafungin in infants and offer recommendations for optimal dosing for treatment of invasive candidiasis in the NICU setting.

2. Search strategy

This review was performed using a Medline search in September 2010 for related articles from 1990 to present with the Mesh related terms ‘micafungin’ and ‘safety’ in combination with the free words ‘antifungal’, ‘candidiasis’, ‘drug toxicity’, ‘infant, premature’, and ‘infant, newborn’. Both abstracts and manuscripts were considered. References from relevant articles were also reviewed. No language restriction was applied.

3. Safety profile in adults, children, and infants

3.1 Adults

Several trials in adult patients have demonstrated the safety of micafungin[18–21]. Two dose-escalation studies of adult cancer patients undergoing hematopoietic stem cell transplant showed micafungin to be well-tolerated in this high-risk group[19,21]. A study of 74 patients assessed micafungin safety at 12.5, 25, 50, 75, 100, 150, and 200 mg/day in combination with fluconazole 400 mg/day for up to 4 weeks[19]. The second study of 36 patients assessed the maximum tolerated dose of micafungin at 3, 4, 6, and 8 mg/kg/day for up to 4 weeks[21]. In both studies, the maximum planned dose was reached with no apparent toxicity. Changes in hepatic and renal function showed no meaningful dose trend.

Common adverse events related to micafungin use in adults included headache (7%), arthralgias (7%), hypophosphatemia (4%), insomnia (4%), and rash (4%)[19].

A dose-response trial found micafungin doses of 100 mg and 150 mg compared favorably with a fluconazole dose of 200 mg in safety and tolerability for treatment of esophageal candidiasis in 245 HIV-positive adult patients[20]. The study showed a comparable incidence of all-cause adverse events between the fluconazole group (89.2%) and the micafungin dose groups (93.3%). Micafungin was not associated with any clinically relevant laboratory changes, and there was no difference in the incidence of mild liver function test (LFT) changes between fluconazole (11.7%) and micafungin (12.9%) cohorts. Safety in adults has been demonstrated in hematopoietic stem cell transplant patients at 8 mg/kg/day and a mean area under the curve (AUC) up to 663 μg*hr/mL.[21–22]

3.2 Children

Pediatric studies have also examined the safety profile of micafungin [23–24]. A multicenter dose-escalation study of 77 febrile neutropenic pediatric patients ages 2 to 17 years assessed micafungin dosing ranging from 0.5 to 4 mg/kg/day and demonstrated excellent safety and tolerability [23]. Only two patients, ages 13 to 17 years, experienced modest LFT changes at 0.5 mg/kg that were considered possibly related to the micafungin. There were no other significant changes in LFTs, renal function, or hematology parameters. Nine patients (12%) experienced adverse events considered possibly related to micafungin; most common were diarrhea (2.6%), vomiting (2.6%), and headache (2.6%). There were no deaths or withdrawal from the study related to micafungin use, and no dose-limiting toxicity was observed.

An analysis of 296 pediatric patients that pooled adverse events data from several clinical trials found a favorable micafungin safety profile in a wide range of pediatric patients [25].

The average age was 6.5 years, and 26% were < 2 years of age and 6% were < 4 weeks of age. The patients had multiple underlying conditions, including neutropenia (40%), malignancy (38%), and hematopoietic stem cell or solid organ transplantation (34%).

Adverse events considered at least possibly related to micafungin administration included: hypokalemia (3.0%), alanine transaminase (ALT) increase (3.0%), aspartate transaminase (AST) increase (2.0%), alkaline phosphatase increase (2.0%), hyperbilirubinemia

(2.0%), and hypertension (2.0%). Seven patients (2.4%) with related adverse events required treatment cessation. The adverse events included neutropenia, jaw and joint pain, rash, increased AST and ALT, abnormal LFTs, and two serious adverse events: hyperbilirubinemia and increased serum creatinine. No follow-up data was available for the patient with hyperbilirubinemia. The patient with increased serum creatinine had levels elevated from a baseline of 57 μmol/L to 73 μmol/L. After treatment cessation, serum creatinine returned to 28 μmol/L.

3.3 Infants

Four recent trials have assessed the pharmacokinetics and safety of micafungin in infants (Table 1). A multi-center, single-dose, sequential-dose study assessed micafungin dosing of 0.75, 1.5, and 3 mg/kg in 18 premature infants > 1000 g and 0.75 mg/kg in 5 infants < 1000 g[26]. The study demonstrated favorable safety and tolerability across all dose levels in the premature infants. One subject > 1000 g experienced an adverse event possibly related to micafungin (moderate hypokalemia) in the 3.0 mg/kg cohort. Two subjects > 1000 g experienced serious adverse events unrelated to micafungin use: one subject developed necrotizing enterocolitis and another subject developed bronchopulmonary dysplasia. A subsequent single-center, multiple-dose study assessed micafungin dosing at 15 mg/kg (a dose extrapolated from the initial infant pharmacokinetic study above[26] and a hematogenous Candida meningoencephalitis (HCME) model developed in rabbits[27]) in 5 premature infants > 1000 g and 7 premature infants < 1000 g[28]. No adverse events were considered related to micafungin use, though all patients had at least one adverse event. This was consistent with the underlying conditions of the critically ill patient population. Mean serum potassium was higher at the end of therapy (4.6 versus 4.0 mmol/L at baseline), but there was no other hematologic or serum chemistry laboratory changes.

Another study assessed the safety of micafungin prophylaxis at a dose of 1 mg/kg in 25 infants <1500 g birth weight[29]. Infants were given micafungin once daily for 6 weeks.

Micafungin was well tolerated in all cases, and there were no adverse events leading to treatment cessation. Additionally, there were no abnormal LFTs or renal function tests considered related to micafungin use.

Finally, a multi-center, multiple-dose study assessed micafungin dosing at 7 mg/kg in 7 premature infants > 1000 g and 10 mg/kg in 6 premature infants < 1000 g [30]. The majority, 12/13 (92.3%), of the infants in this critically ill population experienced an adverse event. Three subjects experienced adverse events considered possibly or probably related to micafungin (increased alkaline phosphatase, infusion site phlebitis, hypokalemia, and elevated temperature). The increase in alkaline phosphatase was considered a serious adverse event. No deaths occurred in the study, and no patients withdrew because of an adverse event. There was minimal or no evidence of laboratory changes in LFTs, renal function, or hematologic parameters.

4. Invasive candidasis considerations in infants

In contrast to invasive candidiasis in adults and older children, invasive candidiasis commonly manifests as HCME in premature infants [31]. Neonatal HCME, a complication of Candida spreading to the central nervous system (CNS), warrants attention given its associated high mortality rates, neurodevelopmental sequelae, and difficulty in dignosis using blood and CSF cultures [1,4,32–33].

An in vivo-to-clinical bridging study of HCME in a rabbit model provided a proof-of- principle that micafungin can treat neonatal HCME at high doses [27]. Specifically, the study administered micafungin doses up to 16 mg/kg to rabbits with HCME and demonstrated a dose-proportional exposure-response relationship where 8 mg/kg achieved near-maximal effect in this model. These results were replicated using Monte Carlo simulations in neonatal pharmacokinetic data described elsewhere [26], suggesting that doses of micafungin in the range of 9 to 15 mg/kg are required to achieve fungicidal concentrations in the CNS for treatment of neonatal HCME.

5. Pharmacokinetic considerations in infants

The pharmacokinetics of micafungin, particularly its weight-based clearance rate, varies by age group. Comparison of single dose studies in adult, pediatric, and infant patient populations shows micafungin clearance in premature infants > 1000 g to be ~1.7 times that of children ages 2 to 8 years and ~ 2.6 times that of adults and children ages 9 to 17 years [19,23,26]. Another pharmacokinetics study showed higher micafungin clearance in infants immediately after birth compared to infants 3 to 8 weeks old [26,29]. Higher clearance rates in young infants may be attributable to differences in plasma protein binding by micafungin.

The wide discrepancy in weight-based clearance between infants and adults suggests higher weight-based doses in infants are required to achieve comparable systemic exposure levels.

6. Conclusions

Studies of micafungin in adults and older children show micafungin to be well-tolerated.

Recent studies in premature infants have explored safety of micafungin at weight-adjusted doses higher than previously studied in older patients. The concern for HCME and the increased clearance of micafungin in infants indicate that higher doses are potentially needed to achieve effective systemic

exposure levels. Doses up to 15 mg/kg in premature infants were well-tolerated in these small trials. Doses of 10 mg/kg provide adequate systemic exposure levels to treat suspected HCME in an animal model [27].

7. Expert opinion

Although results from several trials of micafungin in infants have shown the drug to be well-tolerated, these trials are small and safety was assessed in infants that received a maximum of 5 days of antifungal therapy. Only 25 of the infants for whom safety was reported received > 3 mg/kg/day [30,34]. Safety following extended periods of administration and long term safety in this population is unknown.

We believe recommended dosing in adults should not be extrapolated to infants. Currently, recommended dose of micafungin for treatment for invasive candidiasis in adults is 100–150 mg daily [35]. The propensity for HCME in infants requires effective drug concentrations in the CNS, and the increased weight-based clearance of micafungin in infants requires relatively higher doses in infants compared with older patients. A recent study combining pharmacokinetic data from the 3 trials in infants found that micafungin exhibits linear pharmacokinetics for doses ranging from 0.75 to 15 mg/kg [36]. In addition, the study suggests that infant doses of 10 mg/kg/day result in over 80% of patients having systemic exposure levels with near-maximum fungicidal effect in the CNS.

There are no antifungal drugs approved for invasive candidiasis in the United States for use in infants < 3 months of age. Management is limited by a lack of trials studying the efficacy, pharmacokinetics, safety, and dosing of antifungals in this population. Optimal agent and length of therapy for neonatal candidiasis is unknown. Previous antifungal efficacy studies are limited to case series or9.

Article Highlights

- Micafungin is an echinocandin antifungal with an excellent safety profile in adults but lacks large safety studies in infants.
- Higher micafungin doses per kg in infants show favorable safety profiles and are well-tolerated in small studies.
- Infants may require higher systemic exposure levels of micafungin because of increased concern for hematogenous Candida meningoencephalitis.
- Infants require higher doses per kg of micafungin because of increased clearance.
- Recent safety and pharmacokinetic trials in infants may help guide optimal dosing.

This box summarizes key points contained in the article

References

1. Benjamin DK Jr, Stoll BJ, Fanaroff AA, et al. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. Pediatrics. 2006 Jan; 117(1):84–92. [PubMed: 16396864].

2. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics. 2002 Aug; 110(2 Pt 1):285–91. [PubMed: 12165580].

3. Benjamin DK Jr, DeLong ER, Steinbach WJ, et al. Empirical therapy for neonatal candidemia in very low birth weight infants. Pediatrics. 2003 Sep; 112(3 Pt 1):543–7. [PubMed: 12949281].

4. Friedman S, Richardson SE, Jacobs SE, et al. Systemic Candida infection in extremely low birth weight infants: short term morbidity and long term neurodevelopmental outcome. Pediatr Infect Dis J. 2000 Jun; 19(6):499–504. [PubMed: 10877162].

5. Kawaguchi C, Arai I, Yasuhara H, et al. Efficacy of micafungin in treating four premature infants with candidiasis. Pediatr Int. 2009 Apr; 51(2):220–4. [PubMed: 19405920].

6. Odio CM, Araya R, Pinto LE, et al. Caspofungin therapy of neonates with invasive candidiasis. Pediatr Infect Dis J. 2004 Dec; 23(12):1093–7. [PubMed: 15626944].

7. Smith PB, Steinbach WJ, Cotten CM, et al. Caspofungin for the treatment of azole resistant candidemia in a premature infant. J Perinatol. 2007 Feb; 27(2):127–9. [PubMed: 17262048].

8. Wagner C, Graninger W, Presterl E, et al. The echinocandins: comparison of their pharmacokinetics, pharmacodynamics and clinical applications. Pharmacology. 2006; 78(4):161– 77. [PubMed: 17047411].

9. Warnock DW. Trends in the epidemiology of invasive fungal infections. Nippon Ishinkin Gakkai Zasshi. 2007; 48(1):1–12. [PubMed: 17287717].

10. Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med. 2002 Dec 19; 347(25):2020–9. [PubMed: 12490683].

11. Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med. 2007 Jun 14; 356(24):2472–82. [PubMed: 17568028].

12. Tawara S, Ikeda F, Maki K, et al. In vitro activities of a new lipopeptide antifungal agent, FK463, against a variety of clinically important fungi. Antimicrob Agents Chemother. 2000 Jan; 44(1):57– 62. [PubMed: 10602723].

13. Ikeda F, Wakai Y, Matsumoto S, et al. Efficacy of FK463, a new lipopeptide antifungal agent, in mouse models of disseminated candidiasis and aspergillosis. Antimicrob Agents Chemother. 2000 Mar; 44(3):614–8. [PubMed: 10681327].

14. Messer SA, Diekema DJ, Boyken L, et al. Activities of micafungin against 315 invasive clinical isolates of fluconazole-resistant Candida spp. J Clin Microbiol. 2006 Feb; 44(2):324–6. [PubMed: 16455878]

15. Pfaller MA, Boyken L, Hollis RJ, et al. In vitro susceptibility of invasive isolates of Candida spp. to anidulafungin, caspofungin, and micafungin: six years of globalsurveillance. J Clin Microbiol. 2008 Jan; 46(1):150–6. [PubMed: 18032613]

16. CLSI. Document M27-A3. 3. Wayne, PA: Clincal and Laboratory Standards Institute; 2008. Method for antifungal disk diffusion susceptibility testing of yeasts; approved standard.

17. Sakaeda T, Iwaki K, Kakumoto M, et al. Effect of micafungin on cytochrome P450 3A4 and multidrug resistance protein 1 activities, and its comparison with azole antifungal drugs. J Pharm Pharmacol. 2005 Jun; 57(6):759–64. [PubMed: 15969931].

18. Van Burik JA, Ratanatharathorn V, Stepan DE, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis. 2004 Nov 15; 39(10):1407–16. [PubMed:15546073].

19. Hiemenz J, Cagnoni P, Simpson D, et al. Pharmacokinetic and maximum tolerated dose study of micafungin in combination with fluconazole versus fluconazole alone for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant. Antimicrob Agents Chemother. 2005 Apr; 49(4):1331–6. [PubMed: 15793107]

20. De Wet N, Llanos-Cuentas A, Suleiman J, et al. A randomized, double-blind, parallel-group, dose- response study of micafungin compared with fluconazole for the treatment of esophageal candidiasis in HIV-positive patients. Clin Infect Dis. 2004 Sep 15; 39(6):842–9. [PubMed: 15472817]

21. Sirohi B, Powles RL, Chopra R, et al. A study to determine the safety profile and maximum tolerated dose of micafungin (FK463) in patients undergoing haematopoietic stem cell transplantation. Bone Marrow Transplant. 2006 Jul; 38(1):47–51. [PubMed: 16715107]

22. Mycamine (package insert). Deerfield, IL: Astellas Pharma; 2005.

23. Seibel NL, Schwartz C, Arrieta A, et al. Safety, tolerability, and pharmacokinetics of Micafungin (FK463) in febrile neutropenic pediatric patients. Antimicrob Agents Chemother. 2005 Aug; 49(8):3317–24. [PubMed: 16048942].

24. Kusuki S, Hashii Y, Yoshida H, et al. Antifungal prophylaxis with micafungin in patients treated for childhood cancer. Pediatr Blood Cancer. 2009 Oct; 53(4):605–9. [PubMed: 19533659]

25. Freire, AAA.; Stevenson, P.; Undre, N. Pharmacokinetics of micafungin in pediatric patients with invasive candidiasis and candidemia. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2007 Sept 17–20; Chicago, IL. 2007. abstract A-772.

26. Heresi GP, Gerstmann DR, Reed MD, et al. The pharmacokinetics and safety of micafungin, a novel echinocandin, in premature infants. Pediatr Infect Dis J. 2006 Dec; 25(12):1110–5. [PubMed: 17133155].

27. Hope WW, Mickiene D, Petraitis V, et al. The pharmacokinetics and pharmacodynamics of micafungin in experimental hematogenous Candida meningoencephalitis: implications for echinocandin therapy in neonates. J Infect Dis. 2008 Jan 1; 197(1):163–71. [PubMed: 18171300].

28. Smith PB, Walsh TJ, Hope W, et al. Pharmacokinetics of an elevated dosage of micafungin in premature neonates. Pediatr Infect Dis J. 2009 May; 28(5):412–5. [PubMed: 19319022].

29. Kawada M, Fukuoka N, Kondo M, et al. Pharmacokinetics of prophylactic micafungin in very- low-birth-weight infants. Pediatr Infect Dis J. 2009 Sep; 28(9):840–2. [PubMed: 19636279].

30. Benjamin DK Jr, Smith PB, Arrieta A, et al. Safety and pharmacokinetics of repeat-dose micafungin in young infants. Clin Pharmacol Ther. 2010 Jan; 87(1):93–9. [PubMed: 19890251].