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Safety, Effectiveness, and Exposure-Response of Micafungin in Infants: Application of an Established Pharmacokinetics Model to Electronic Health Records

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Abstract

Micafungin is used off-label in the United States to treat invasive candidiasis in neonates. We used an established pharmacokinetic model to determine micafungin exposures for 46 courses in 39 hospitalized infants. In this small cohort of infants, micafungin exposure was not associated with laboratory markers of liver toxicity, death, or failure of microbiological clearance.

Keywords

Micafungin; safety; exposure; infants

INTRODUCTION

Mortality of invasive candidiasis (IC) in extremely premature infants is as high as 30% (1, 2). Standard of care for treatment of IC in the United States includes amphotericin B deoxycholate, lipid formulations of amphotericin B deoxycholate, or fluconazole. However, due to concerns for toxicity (amphotericin B deoxycholate) or resistance among certain *Candida* species (fluconazole), echinocandins are increasingly used in infants (3).

Micafungin is an echinocandin and is US Food and Drug Administration (FDA)-approved in the United States for use in adults and children >4 months of age (4), though the European Medicines Agency has approved micafungin as a recommended treatment option in neonates (5). The safety of micafungin has been evaluated in small studies including infants <120

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Conflicts of Interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

days of age with few adverse effects reported (6). A small pharmacokinetic (PK) study in infants showed that a dose of 10 mg/kg every 24 hours achieved desired therapeutic and safe exposures (area under the curve [AUC]₀₋₂₄ target of 166.5 mg*h/L) (7). However, the effectiveness and safety of micafungin in infants and the relationship between exposure and these outcomes have not been evaluated in larger cohorts of infants.

To evaluate these relationships, large clinical trials would need to be conducted, which are not feasible in this vulnerable population. Alternative approaches, including the use of electronic health records, can be leveraged to obtain answers to these questions. The objective of this study was to evaluate the safety, effectiveness, and the exposure-response relationship of micafungin in infants <120 days of age using a combination of electronic health records and simulated drug exposure.

MATERIALS AND METHODS

Included infants were exposed to micafungin prior to day of life 120 at one of 348 neonatal intensive care units (NICUs) managed by the Pediatrix Medical Group (Sunrise, FL) between 2006–2015. Data on multiple aspects of care were entered into a shared electronic health record to generate admission and daily progress notes and discharge summaries, and then transferred to the Pediatrix Clinical Data Warehouse for quality-improvement and research purposes (8). From this database, the following elements were extracted: dosing frequency, including total daily dose of micafungin; gestational age; daily weights; microbiological culture data; and laboratory values (alanine transaminase [ALT], aspartate aminotransferase [AST], and direct bilirubin). Infants missing dosing information for micafungin were excluded from analyses relating exposure to safety and effectiveness. Clinical characteristics were reported, and analyses were performed at the course level.

Drug exposure simulations were performed using a previously published population PK model in young infants (7). Using simulated concentrations in each infant, AUC from 0 to 24 hours (AUC₀₋₂₄) was generated on each day after initiating micafungin. Micafungin doses 9 mg/kg/day were considered to be therapeutic, and doses <9 mg/kg/day were considered to be underdosed (7).

Values 3 times the upper limit of normal for AST (>360 U/L), ALT (>135 U/L), and direct bilirubin (>1.4 mg/dL) were considered laboratory adverse events. Laboratory adverse events were recorded if they occurred on a day that micafungin therapy was given. Unadjusted comparisons between groups were performed using Fisher's exact test. Univariable generalized estimating equations (GEEs) were used to evaluate the association of micafungin AUC₀₋₂₄>166.5 mg*h/L and >249.8 mg*h/L (which represents 1.5 times the target AUC₀₋₂₄), with elevated AST, ALT, and direct bilirubin levels for each day. These AUC₀₋₂₄ values were chosen based on a recent study that used 166.5 mg*h/L as the therapeutic target (7). Multiple observations per infant were accounted for using GEE. P-values of <0.05 were considered statistically significant. Analyses were performed using Stata 14.1 (College Station, TX).

Based on culture data, treatment courses were divided into 3 groups: 1) definite IC, defined as a positive culture for *Candida* obtained during micafungin therapy or 7 days prior to start of micafungin therapy from sterile body fluid (blood, suprapubic or catheterized urine, cerebrospinal fluid, abscess, or peritoneal fluid); 2) probable IC, defined as a positive culture for *Candida* obtained during micafungin therapy or 7 days prior to start of micafungin therapy from another location (trachea, non-sterile urine, rectum, skin, umbilical cord); and 3) no IC, defined as either no positive cultures or unknown source. The proportion in each group in which the infant experienced death (defined as all-cause mortality prior to hospital discharge) or microbiological clearance (defined as a negative blood culture on the last blood culture obtained prior to the end of therapy) was determined and compared using Fishers' exact test.

RESULTS

A total of 116 infants received 130 courses of micafungin. The median gestational age (GA) was 25 weeks (25th–75th percentiles: 24–27 weeks), median birth weight (BW) was 748 g (25th–75th percentiles: 591–940 g), and 77% of courses were prescribed to infants <1000 g BW. Median micafungin course duration was 12 days (25th–75th percentiles: 8–25 days); of note, 20 courses are missing the end date. Dosing data were available for 46 courses in 39 infants. Doses ranged from 2–15 mg/kg/day. The median doses for the underdosed and therapeutic subgroups were 6 mg/kg/day (25th–75th percentiles: 5.5–7 mg/kg/day) and 10 mg/kg/day (10–10.5 mg/kg/day), respectively. The majority of the courses (31/46, 67%) were therapeutic. The median AUC₀₋₂₄ was 224 mg*h/L (25th–75th percentiles: 167–295 mg*h/L).

AST, ALT, and direct bilirubin values were obtained in 56/130 (43%), 62/130 (48%), and 59/130 (45%) courses, respectively. Of these, 5/56 (9%) courses had an abnormal AST value, 5/62 (8%) courses had an abnormal ALT value, and 44/59 (75%) courses had an abnormal direct bilirubin value. AUC₀₋₂₄>166.5 mg*h/L was not associated with elevated AST (P=0.23), ALT (P=0.33), or direct bilirubin (P=0.11). Similarly, AUC₀₋₂₄> 249.8 mg*h/L was not associated with elevated ALT (P=0.73) or direct bilirubin (P=0.23). No infants with AUC₀₋₂₄> 249.8 mg*h/L had an elevated AST.

Of the 130 micafungin courses, 65 (50%) were associated with definite IC, 13 (10%) were associated with probable IC, and 52 (40%) were associated with no IC. Of the positive cultures, 76% were obtained from blood, 10% from urine, 0.3% from the cerebrospinal fluid, and 14% from other sites. Mortality data were available for 101 infants (114 courses), and 33/101 (33%) infants died. Death occurred after 16/59 (27%) courses associated with definite IC, 2/10 (20%) courses associated with probable IC, and 19/45 (42%) courses associated with no IC. There was no difference in death or microbiological clearance according to IC group or micafungin dosing or exposure at a course level (Table 1).

DISCUSSION

This is the largest study to date exploring the safety and effectiveness of micafungin in infants. We leveraged a previously validated PK model and the availability of detailed

micafungin data in our cohort to evaluate the exposure-response relationship. The micafungin FDA label does not specifically address exposures associated with toxicity in children (4). In adults, doses resulting in $AUC_{0-24} > 663 \text{ mg}\cdot\text{h/L}$ may be associated with toxicity (4). Compared with adults, the simulated exposure in our population was lower and was not associated with increased liver toxicity.

Our findings are similar to those reported in a post-marketing surveillance study in 91 Japanese pediatric patients (9). In this study, the most common adverse effects observed were hyperbilirubinemia and abnormal hepatic function, but the 18 neonates included did not experience any adverse effects. Ten neonates included in the efficacy arm showed a clinical response rate of 90% measured by microbiological clearance and overall clinical improvement. While effectiveness in our study was lower than that observed previously (33% of infants in our study died), the majority of infants in our study were extremely premature and critically ill. The previous study did not specify the GAs or BWs of affected infants. In other small investigations, no adverse effects were associated with micafungin exposure in 12 infants supported with extracorporeal membrane oxygenation (10) or 18 infants who received high-dose micafungin for IC and meningoencephalitis (6). In the latter report, 14/18 (78%) of the infants had resolution of infection (6).

Our study has several limitations: we used observational data with a relatively small sample size, complete dosing and laboratory data were not available for every course, cultures were not always obtained to document microbiological clearance, and we did not consider other concomitant antifungals to which infants may have been exposed, which was likely to impact effectiveness. We were also unable to determine whether some of the lower doses were given for prophylaxis rather than treatment. Additionally, we were unable to adjust for potential confounders due to low numbers of infants in each exposure group. Due to the small sample size, we were unable to evaluate other dosing regimens (such as 4 mg/kg/day).

Our data suggest that increased exposure to micafungin was not associated with adverse laboratory effects, including hepatic toxicity, in this group of infants. This study also provides proof of concept of a new methodology for the use of electronic medical record data to study drug effectiveness and safety in infants. Further prospective studies are needed to confirm safety and effectiveness of micafungin in hospitalized infants.

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Table 1

Micafungin exposure-response relationships.

	AUC ₀₋₂₄ exposure				Dosing group	
	<166.5 mg* ^a /L (N=12)	166.5 mg* ^a /L (N=36)	<249.8 mg* ^a /L (N=36)	249.8 mg* ^a /L (N=12)	Therapeutic (N=31)	Underdosed (N=17)
Died	0/8 (0)	11/33 (33)	7/30 (23)	4/11 (36)	8/29 (28)	3/10 (30)
Microbiological Clearance	5/7 (71)	14/16 (88)	14/18 (78)	5/5 (100)	14/16 (88)	4/5 (80)
Elevated AST	1/8 (13)	1/22 (5)	2/24 (8)	0/6 (0)	0/18 (0)	2/12 (17)
Elevated ALT	2/8 (25)	2/24 (8)	3/24 (8)	1/8 (13)	1/20 (5)	3/12 (25)
Elevated direct bilirubin	7/8 (88)	13/20 (65)	15/21 (71)	5/7 (71)	10/17 (59)	10/11 (91)

Data presented as n/N (%). Total N is reported in column heading. Data are presented at the course level. AST, aspartate aminotransferase; ALT, alanine transaminase; AUC, area under the curve. Therapeutic dosing refers to 9mg/kg/day, and underdosing refers to <9mg/kg/day. All comparisons yielded differences that were non-significant by Fisher's exact test (p>0.05).