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Original Article

Micafungin Effectiveness in Treating Pediatric Patients with Proven Candidemia

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ABSTRACT

Aim: Micafungin is one of three currently available echinocandin for the treatment of candidiasis and candidemia. We aimed to discuss the effectiveness of micafungin and any possible side effects in the treatment of proven candidemia in children.

Materials and Methods: In this study, children who were treated with micafungin for proven candidemia between May, 2017 and October, 2019 were included. The time to achieve negative culture, liver and renal functions as well as blood counts were recorded using the hospital data system.

Results: Forty-five patients (52.3%) who received micafungin for proven candidemia were included in this study. The median age of the children who received micafungin due to invasive candidiasis (IC) was 4 months (range: 12 days to 216 months). Of these 45 IC patients, 10 (22.2%) were neonates, 19 (42.2%) were infants, 11 (24.4%) were between 1 and 5 years old, and 5 (11.1%) were between 10-18 years old. The median duration of micafungin treatment to culture negativity for *C. albicans* related candidemia episodes was shorter (6 days, 1-26 days) than *non-albicans Candida* spp. related candidemia episodes (7 days, 1-35 days) (p=0.10). Culture negativity could not be achieved at the end of the 14th day of micafungin treatment in 15 of the 45 (33.3%) candidemia episodes. The most commonly isolated *Candida* spp. in patients with treatment failure was *C. parapsilosis* (n=6), followed by *C. albicans* (n=5), *C. guilliermondii* (n=1), *C. tropicalis* (n=2) and *C. tropicalis* and *C. guilliermondii* co-infection (n=1) respectively. None of the patients developed side effects due to micafungin treatment.

Conclusion: Micafungin was found to be safe and effective for the treatment of culture proven candidemia in pediatric patients, including neonates.

Keywords: Micafungin, effectiveness, safety, candidemia, antifungal resistance, pediatric patients

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Introduction

Invasive fungal infections (IFIs) caused by *Candida* spp. are important causes of morbidity and mortality in both immunocompromised and hospitalized patients. Candidemia is one of the most common cause of pediatric health care-associated bloodstream infections in the world (1-4).

Due to the emergence of treatment resistance to broad spectrum triazole antifungals, new treatment options for IFIs are required. Echinocandins provide clinicians with an alternative treatment option as they are well tolerated, have rapid antifungal activity, favorable pharmacokinetics and some of them do not require a loading dose. Micafungin is an echinocandin with demonstrated effectiveness for the treatment of invasive candidiasis (IC) and for the prophylaxis of *Candida* infection in patients undergoing allogeneic hematopoietic stem cell transplantation, or in those who are expected to have neutropenia for ≥10 days (5,6).

Micafungin is a non-competitive, concentration-dependent inhibitor of the enzyme 1,3-b-D-glucan synthase and, consequently, inhibits the synthesis of 1,3-b-D-glucan (an integral component of the fungal cell wall, which is not present in mammalian cells). Micafungin was approved by the European Medicines Agency in 2008 for the treatment of IC, for the prophylaxis of *Candida* infection in patients undergoing allogeneic haematopoietic stem cell transplantation or for patients who are expected to have neutropenia (absolute neutrophil count <500 cells/μL) for 10 or more days for children (including neonates) and adolescents <16 years of age (7).

Micafungin is well-tolerated by pediatric patients. The incidence of treatment-related adverse events is lower in pediatric patients (8,9). The most frequently reported treatment-related adverse events are nausea (2.8% of subjects), elevated alkaline phosphatase (2.7%), phlebitis (2.5%), vomiting (2.5%), elevated aspartate aminotransferase (AST) levels (2.3%), hypokalemia (2.1%), fever (2.1%), and elevated alanine aminotransferase (ALT) levels (2%) (9). However, there are limited data available regarding the effectiveness and safety of micafungin in children (10-14).

The aim of the current study was to evaluate the effectiveness and tolerability of intravenously administered micafungin for proven IC in pediatric patients.

Materials and Methods

Patient Selection and Study Design

All children, including neonates, who were hospitalized in the pediatric wards of University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, and who had received micafungin due to proven IC between May, 2017 and October, 2019 were included in this retrospective study. The patients' risk factors, underlying diseases, type of unit of hospitalization, routine laboratory assessments of biochemistry (serum concentrations of liver enzymes, bilirubin, creatinine, urea, albumin, electrolytes) and blood counts as well as the daily doses and durations of micafungin treatment, concomitant antibiotics, clinical responses and adverse effects were obtained from their electronic medical records. Biochemical parameters such as serum concentrations of liver enzymes, bilirubin, creatinine, urea, albumin, and electrolytes were recorded in order to evaluate the safety of micafungin.

Micafungin doses of 4-10 mg/kg in neonates and 2-4 mg/kg in children with IC were used (15). The efficacy end-point was defined as being alive and fungal free [based on improvement of clinical symptoms and laboratory findings (culture)].

Case Definitions

Candidemia is defined as the presence of the growth of any *Candida* species in at least one blood culture obtained by either peripheral venipuncture or through an indwelling central venous catheter (CVC). When the same isolate is detected in a peripheral blood culture and catheter-drawn blood culture obtained at least 2 hours apart, candidaemia is considered as a CVC related bloodstream infection. Time to mycological eradication represents the number of days from the initiation of treatment to the first day of blood culture negativity for *Candida* species. Treatment failure was defined as death within 14 days of the initiation of therapy or ≥1 positive blood culture for *Candida* spp. 14 days or more after the initiation of antifungal therapy. If a patient died due to a different identifiable cause, this death was not seen as treatment failure.

Death which ensues within 30 days of the onset of candidemia with no apparent alternative cause is recognized as a candidemia-attributable mortality.

For the assessment of any potential side effects, the following standard values were applied: AST, normal range 25-85 U/L; alanine ALT, normal range 12-93 U/L.

Statistical Analysis

All statistical analyses were performed using the SPSS package program for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA). Continuous data are expressed as mean±standard deviation and categorical variables are reported as percentages. The distribution of continuous variables was assessed by the Kolmogorov-Smirnov test. Probable associations among categorical variables were evaluated by the chi-squared test or Fisher's exact test. Fisher's exact test was applied if more than 20% of the categories have expected frequencies less than 5. Parametric and non-parametric continuous variables were analyzed by the independent t-test and the Mann-Whitney u test, respectively.

The inferential statistical analysis between the baseline values as well as the maximum and minimum parameters and the parameters at the cessation of antifungal treatment were carried out by Wilcoxon matched-pairs and were analyzed by the Friedman two-way analysis of variance by ranks, due to non-normally distributed values in at least one group or day, making a parametric analysis of variance (ANOVA) for repeated measures not appropriate. The analyses of the hepatic and kidney parameters are presented as median (minimum-maximum). P-values of ≤0.05 were defined as significant.

This study was approved by the Ethics Committee of University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (date: 10.12.2019, approval no: 13399118-799).

Results

In this study, 86 children in total with a median age of 3 months (9 days-17 years), had received micafungin. Fifty-eight (67.4%) of the patients were male (Female/Male ratio=0.48). Forty-five patients (52.3%) who had received micafungin for proven candidemia were included in this study. The median age of the children who received micafungin due to IC was 4 months (range=12 days-216 months). Of these 45 IC patients, 10 (22.2%) were neonates, 19 (42.2%) were infants, 11 (24.4%) were between 1-5 years old, and 5 (11.1%) were between 10-18 years old. Four of the 10 (40%) neonates were premature. Ten (22.2%) patients had been hospitalized in the neonatal intensive care unit, 16 (35.6%) patients in the pediatric intensive care unit, 9 (20%) patients in the surgical intensive care unit, 5 (11.1%) patients in the hematology-oncology unit, 1 (2.2%) in the pediatric infectious diseases ward and the other 4 (8.8%) patients in general pediatric wards at the time of micafungin treatment. There were 27 children with underlying diseases including a history of intra-abdominal surgery (n=13), congenital heart disease (n=3), hemato-oncological disease (n=5), and immune deficiency (n=6). The baseline characteristics of these patients are presented in Table I.

Twenty-five (55.6%) IC patients had been receiving fluconazole treatment before switching to micafungin treatment. Twenty-three (51.1%) *Candida* spp. cases were resistant to fluconazole, which was the reason for switching to micafungin treatment. Fourteen (31.1%) *Candida spp.* were *C. albicans*, and the thirty-one (68.9%) were *non-albicans Candida* spp. The most commonly isolated *Candida* spp. was *Candida parapsilosis (C. parapsilosis)* (n=15) followed by *C. albicans* (n=14), *C. tropicalis* (n=5), *C. glabrata* (n=4), *C. guilliermondii* (n=3), *C. krusei* (n=2), and *C. pelliculosa* (n=1). Additionally, *C. guilliermondii* and *C. tropicalis* were isolated concomitantly in 1 patient (Figure 1).

The median duration of micafungin treatment in the 45 IC cases was 14 days (3-36 days). The median duration of

Table I. The demographic and clinical characteristics of the patients

Age**	4 months (range: 12 days-216 months).
Gender (male/female)*	31/14 (68.9 vs. 31.1, F/M: 0.45)
Prior fluconazol treatment*	25 (55.6)
Neonatal intensive care unit (n, %)*	10 (22.2)
Term*	6 (60)
Preterm*	4 (40)
Gestational week (weeks)	35 (min.: 26/max.: 40)
Gender (male/female)*	8/2 (M/F: 4)
Hospital ward*	
Neonatology	10 (22.2)
Pediatric intensive care unit	16 (35.6)
Surgical intensive care unit	9 (20)
Oncohematology	5 (11.1)
Others	5 (11.1)
Underlying disease***	
Intra-abdominal surgery	13
Congenital heart disease	3
Hematological malignancy	5
Primary immune deficiency	6
*: n (%) **: Median (minimum-maximum)	***= n

micafungin treatment to culture negativity for candidemia episodes was 6.5 days (1-35 days). Culture negativity could not be achieved in 2 patients. Two patients with IC [*C. parapsilosis* (n=1) and *C. albicans* (n=1)] died, one due to IC and the other due to concomitant gram negative bacterial sepsis. The median duration of micafungin treatment to culture negativity *for C. albicans* related candidemia episodes was shorter (6 days, range: 1-26 days) than *non-albicans Candida* spp. related candidemia episodes (7 days, range: 1-35 days) (p=0.10). Culture negativity could not be achieved at the end of the 14th day of micafungin treatment in 15 (33.3%) of the 45 IC episodes. The most commonly isolated *Candida* spp. in those patients with treatment failure was *C. parapsilosis* (n=6), followed by *C. albicans* (n=5), *C. guilliermondii* (n=1), *C. tropicalis* (n=2) and *C. tropicalis* and *C. guilliermondii* coinfection (n=1). One patient

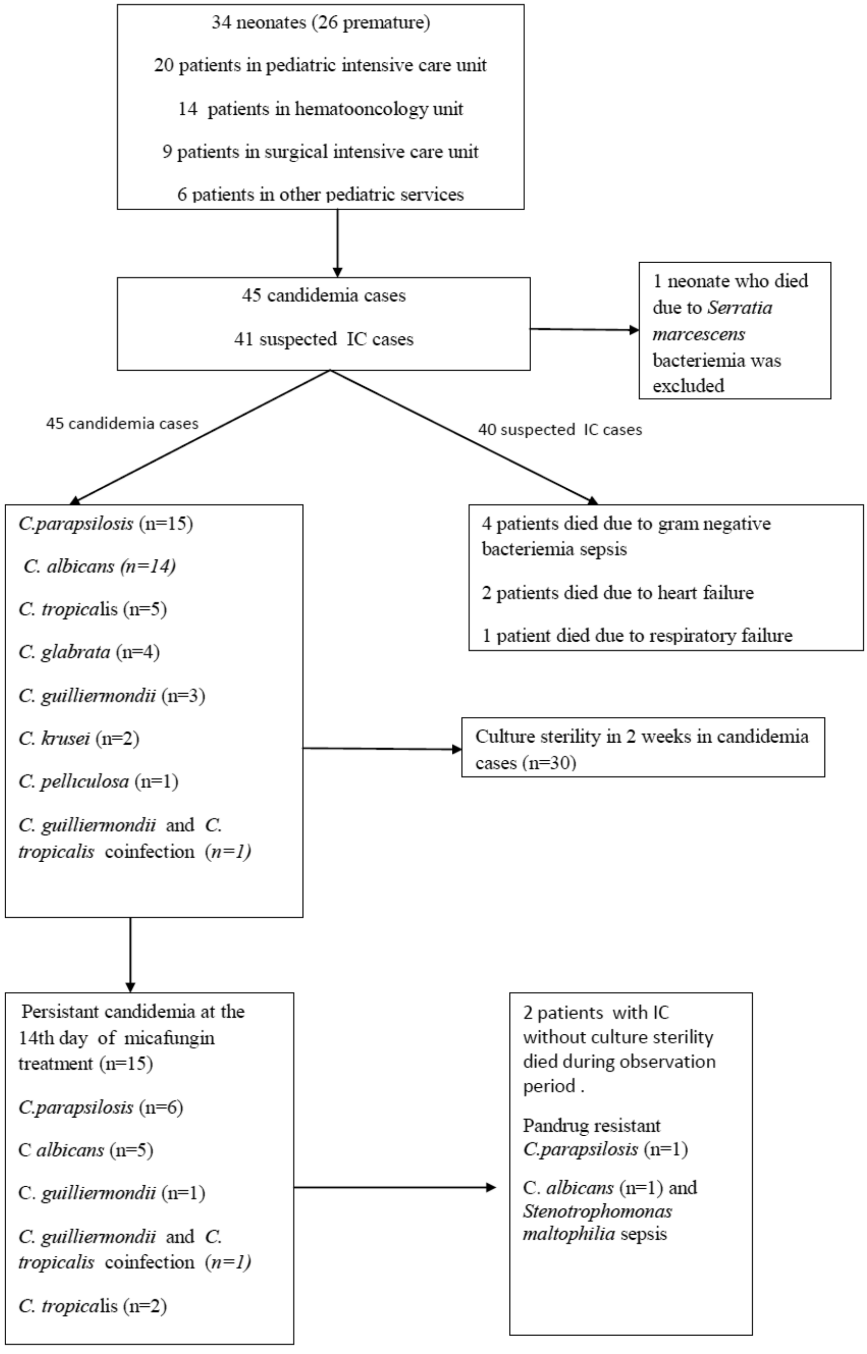

Figure 1. Outcomes of patients who received micafungin

with pan-drug resistant *C. parapsilosis* candidemia died during the observation period and this was attributed to treatment failure.

Non-albicans Candida spps. were more commonly isolated from patients with treatment failure at the 14th day of micafungin treatment (n=10, 66%).

The median serum thrombocyte value was statistically significantly higher at the end of micafungin treatment compared to the median value before treatment (p<0.001). Median thrombocyte values taken prior to micafungin treatment and at the end of micafungin treatment were 145x10^3/µL (15-772x10^3/µL) versus 272x10^3/µL (19-937x10^3/µL) respectively (Table II).

Safety

None of the patients had treatment interruption because of adverse drug reactions. Serum AST and ALT levels were higher in those IC patients with prior fluconazole treatment (Table II). Serum alanine aminotransferase levels were statistically significantly higher in the group who had received fluconazole treatment before switching to micafungin treatment (21.7%, p=0.005). Serum ALT levels in the group who had received fluconazole treatment before switching to micafungin treatment were statistically significantly decreased after switching to micafungin treatment (p=0.05).

Table II. Laboratory change before and after micafungin treatment

	Before micafungin treatment	After micafungin treatment	p-value
Serum AST (IU/L)	37 (8-885)	39 (7-685)	0.61
Serum ALT (IU/L)	27 (6-790)	27 (6-174)	0.11
Serum creatinine (mg/dL)	0.5 (0.3-8)	0.3 (0.5-5)	0.86
Serum sodium (mmol/L)	137 (123-147)	137 (130-164)	0.40
Serum potassium (mmol/L)	4.3 (2.6-5.7)	4.5 (2.7-5.1)	0.80
Hemoglobin (gr/dL)	9.7 (6.2-16.9)	9.7 (7-14.5)	0.68
Leucocyte (x10^3/µL)	9.2 (0.37-35.6)	10.6 (1.6-48.9)	0.13
Absolute neutrophil count (x10^3/µL)	4.2 (0.18-24.7)	4.1 (0.15-33.7)	0.74
Thrombocyte (x10^3/µL)	**129 (15-772)**	**250 (13-937)**	**<0.001**

Values are given as median (min.-max.)
AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, min.: Minimum, max.: Maximum

Discussion

In this study, our experience with intravenous micafungin treatment in 45 pediatric patients with proven IC were reviewed. *Non-albicans Candida* spp. have been more commonly isolated than *C. albicans* isolates in pediatric studies from our country (16-19). Fifteen (17.4%) patients died during the observation period but only 1 patient's death was attributable to candidemia due to *C. parapsilosis* candidemia.

Fourteen *Candida* spps. were resistant to all antifungals, minimum inhibitory concentration (MIC) for micafungin was the lowest which was the reason for the treatment choice. The increase in antifungal resistance of *Candida* spp. was thought to be the reason for persistent candidemia on the 14th day of micafungin treatment. However, culture negativity was achieved in 12 pan-drug resistant IC episodes after the 14th day of micafungin treatment. Two patients (one patient with a diagnosis of cerebral palsy and another with tetralogy of Fallot) died during candidemia episodes and culture negativity could not be achieved within 2 weeks in these 2 patients. *Candida parapsilosis* cultured in the blood culture of 1 of these 2 patients was resistant to all antifungals. In the other patient who was operated due to tetralogy of Fallot, *C. albicans* was the reason of candidemia but death was due to Gram-negative bacterial sepsis.

Micafungin treatment in neonates, including premature newborns, has not been extensively studied to date. In our study, treatment related side effects and treatment failure were not seen in neonates. In our study, all of the neonates were effectively treated with micafungin and all were culture-negative within 2 weeks. Benjamin and colleagues compared the efficacy, safety and pharmacokinetics of intravenous micafungin with intravenous amphotericin B deoxycholate in a phase 3, randomized, double-blind, multicenter, parallel-group, non-inferiority trial performed on infants between 2 and 120 days of age with proven IC. A total of 20 infants received micafungin, and 10 received amphotericin B deoxycholate. Although their study was terminated early due to low recruitment, fungal-free survival was observed in 12 out of the 20 [60%; 95% confidence interval (CI): 36-81%] infants treated with micafungin versus 7 of the 10 (70%; 95% CI: 35-93%) infants treated with amphotericin B deoxycholate (20).

Micafungin treatment in pediatric hematological malignancy is limited. In our study, 5 patients with hemato-oncological malignancy received micafungin and all of these patients were effectively treated. These results are similar to a study conducted in neutropenic patients. The

authors concluded that micafungin is effective against IC/candidaemia in those patients with neutropenia, irrespective of neutropenia duration or cultured *Candida* spp. (21).

In a study conducted on 8 pediatric patients using micafungin (≥3 doses) who had breakthrough candidemia (BC), the causative strains of BC were *C. parapsilosis* in seven of these patients. The authors concluded that immunocompromised patients may develop BC caused by micafungin-susceptible strains (21). In our study, persistent candidemia at the 14th day of micafungin treatment was seen in 15 cases with *Candida* spp., but culture negativity was achieved in 13 of these IC episodes.

In one study, micafungin was commenced for 174 courses in 148 patients, including 135 adults and 13 children aged under 18 years (10 of whom were under paediatric oncology care, 2 of whom were neonates and 1 was in general pediatric care). The authors concluded that micafungin was clinically effective for the treatment of IC and Aspergillus infections, and in line with our study results that micafungin usage did not increase the risk of liver dysfunction (12).

The development of the azole antifungals has enhanced treatment options for fungal infections and their reduced host toxicity has led to their widespread use. In our study, azole resistance of *C. albicans* and *non-albicans Candida* spp. were 50% and 61.9%, respectively. Consequently, with their extensive use, it is perhaps not surprising that resistance to these agents, particularly fluconazole, is encountered (22,23).

Echinocandins are fungicidal and have increased activity *in vitro* compared to amphotericin B deoxycholate and azoles against biofilms formed by *Candida* spp. Therefore, the most recent guidelines of the European Society of Clinical Microbiology and Infectious Diseases for the prevention and management of invasive infections in neonates and children support the increasing use of echinocandins in pediatric patients (24). In one study, conducted in 110 pediatric patients published in 2019, the authors concluded that micafungin was effective and well-tolerated as a prophylaxis against IFIs in pediatric onco-hematology patients and for curative purposes in pediatric and neonatal ICU patients, similar to our results (13).

Study Limitations

There are some limitations present in our study. As with any study with the sample size used in this study, the generalizability of our findings is limited. Additionally, this was a retrospective study, which has inherent limitations when compared to randomized clinical trials. Also, this study included all children, including neonates with different underlying diseases, co-morbidities and risk factors which might have caused bias for the outcome.

Conclusion

As a conclusion, micafungin was curative, especially in neonates, when used to treat IC. Pan-drug resistant candidemia was the reason of death for one patient included in our study. More aggressive treatment options should be chosen to treat pan-drug resistant IC cases. Additionally, in those centers with reports of emerging fluconazole resistant *Candida* spp. and *non-albicans Candida* spp., micafungin is a reliable and effective choice for empirical treatment for suspected candida infections of children.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (date: 10.12.2019, approval no: 13399118-799).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: K.Ö.A., Design: K.Ö.A., Data Collection or Processing: K.Ö.A., Analysis or Interpretation: K.Ö.A., Ş.Ç., H.A., N.B., İ.D., Literature Search: Writing: K.Ö.A., O.K., Ş.Ç., Ş.A., M.Ç., E.B., E.K., A.A.K., H.A., N.B., İ.D.

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