Anidulafungin in children: Experience in a tertiary care children's hospital in Argentina

María T. Rosanova, M.D.[a], Claudia Sarkis, M.D.[a], Florencia Escarra, M.D.[a], Carolina Epelbaum, M.D.[a], Norma Sberna, Pharmacists[b], Susana Carnovale, M.D.[c], Carlos Figueroa, M.D.[d], Rosa Bologna, M.D.[a] and Roberto Lede, M.D.[e]

ABSTRACT
The experience using anidulafungin for the treatment of invasive fungal infections in pediatrics is limited.
In this article, we describe our experience in 55 children. Anidulafungin was administered intravenously at a loading dose of 3 mg/kg once daily, followed by 1.5 mg/kg every 24 hours over a mean period of 14 days (range: 7-22 days). Patients' median age was 114 months old (interquartile range: 32-168 months old). All patients had underlying diseases. Among patients with bone marrow transplant, the difference in white blood cell count, transaminase levels, and renal function at baseline and at the end of anidulafungin administration was not significant. No adverse events were reported and no patient died from an anidulafungin-related cause. Anidulafungin may be considered an alternative for the prophylaxis or treatment of invasive fungal infections in pediatrics but methodologically robust studies are needed to confirm this.
Key words: *anidulafungin, children, invasive fungal infections.*

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INTRODUCTION

Invasive fungal infections (IFIs) are an increasingly more relevant health problem associated with a high rate of morbidity and mortality.[1]

Echinocandins, the latest class of antifungals introduced in the market, have a distinct mechanism of action: they act by inhibiting 1,3 beta-D glucan synthesis and damaging cell walls without affecting human cells because these lack 1,3 beta-D-glucan.[2-5] These novel therapeutic options have been used in the adult population but experience in the pediatric setting, especially with anidulafungin, is limited.

Anidulafungin has been the latest echinocandin introduced in the market; its pharmacokinetic profile is different from that of the other echinocandins. It is not metabolized by the liver but undergoes more than 90% of slow degradation in plasma by nonspecific peptidases that open the molecular ring and form a substrate that is subjected to tertiary degradation by plasma proteases.[5] Anidulafungin does not rely on renal excretion and does not interact with immunosuppressive agents.[5-8]

It shows an excellent *in vitro* activity against *Candida* spp. and *Aspergillus* spp., including fluconazole- and amphotericin B-resistant strains.[1,6]

Given anidulafungin's metabolism and excretion, no dose adjustment is required for patients with mild, moderate or severe liver or renal failure, turning it into an appealing drug for the prophylaxis and/or treatment of IFIs in transplant patients.

Mild or moderate infusion-related adverse effects were reported in children, including discomfort, facial erythema and flushing, fever, and low blood pressure.[2]

In spite of anidulafungin's favorable features, the experience in pediatrics is limited.

OBJECTIVE

The objective of this descriptive-prospective study was to describe our experience using anidulafungin in a pediatric population.

MATERIAL AND METHODS

In the setting of a public, tertiary care children's hospital, and given the temporary lack of lipid formulations of amphotericin, anidulafungin was indicated as prophylaxis or treatment between January and June of 2016 to 55 patients with proven, probable, or possible IFI, together with a follow-up protocol. Following an adequate bibliographic review, and after having assessed the lack of interactions and the scarce reports of

a. Department of Infectious Diseases, Hospital de Pediatría "Prof. Dr. Juan P. Garrahan", Autonomous City of Buenos Aires, Argentina.
b. Pharmacy Department, Hospital de Pediatría "Prof. Dr. Juan P. Garrahan", Autonomous City of Buenos Aires, Argentina.
c. Department of Microbiology, Hospital de Pediatría "Prof. Dr. Juan P. Garrahan", Autonomous City of Buenos Aires, Argentina.
d. Department of Bone Marrow Transplant, Hospital de Pediatría "Prof. Dr. Juan P. Garrahan", Autonomous City of Buenos Aires, Argentina.
e. Universidad Abierta Interamericana (UAI), Buenos Aires, Argentina.

E-mail address:
María T. Rosanova, M.D.: margris2@yahoo.com.ar

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adverse effects, the hospital's Drug Committee approved anidulafungin for its off-label use.

Lab tests: The monitoring of biochemical parameters included, at the beginning and end of treatment, white blood cell count (cells/mm^3), transaminase levels (U/L), bilirubin (mg/dL), and creatinine (mg/dL) in all patients.

Definitions: IFIs were defined according to the criteria established by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG).[9]

Proven IFI: Positive histopathology based on a biopsy with associated tissue lesion or positive microbiological culture obtained from a sterile area with clinical or radiological features compatible with infection.

Probable IFI: Presence of a host factor plus a mycological criterion plus a clinical feature.

Possible IFI: Presence of host factors and clinical evidence of IFI, but absence of positive mycological criteria.

Dosage: Anidulafungin was administered intravenously at the recommended dose (loading dose of 3 mg/kg once daily, followed by 1.5 mg/kg every 24 hours, both as prophylaxis and treatment). All possible or probable drug-related adverse events were recorded.

Data were processed using the Epi-Info 6.0 software. Continuous outcome measures were expressed as median and interquartile range (IQR) whereas categorical outcome measures, as absolute quantity and percent relative frequency.

RESULTS

All patients receiving anidulafungin were included (n: 55). Their median age was 114 months old (IQR: 32-168 months old). All patients had underlying diseases; bone marrow transplant (29 patients, 53%), liver transplant (9 patients, 16%), and other hematooncological diseases (7 patients, 13%) were the most common ones (see *Table 1*).

Treatment was administered over a mean period of 14 days (IQR: 7-22 days) and indicated as treatment for 27 patients (49%) and as prophylaxis for 28 patients (51%). IFIs were confirmed in 10 patients, and *Candida albicans* was the most commonly isolated fungus (*Table 1*).

Bone marrow transplant recipients accounted for the largest number of patients; mean values of biochemical parameters in this group were analyzed at the beginning and end of treatment. These included transaminase levels: 29.5 U/L and 32 U/L (*p*: 0.44); bilirubin: 0.35 and 0.30 mg/dL (*p*: 0.20); and creatinine: 0.52 and 0.60 mg/dL (*p*: 0.67). A wide variability was observed in white blood cell count on account of underlying diseases; however, the difference between the baseline value and that at the end of drug administration was not significant: median of 2810 cells/mm^3 and 5160 cells/mm^3, respectively (*p*: 0.07) (see *Table 2*).

In terms of effectiveness, it was observed that IFIs resolved in 100% of patients treated with anidulafungin, and that 100% of patients receiving the drug as prophylaxis did not develop an IFI in the 30-day follow-up.

No mild, moderate or severe adverse events were reported and no patient died from an

TABLE 1. *Characteristics of patients (n: 55)*

Outcome measure	
Age in months, median (IQR)	114 (32-168)
Underlying disease, n (%)	55 patients (100%)
Bone marrow transplant	29
Hematooncological disease	7
Liver transplant	9
Other	10
Immunosuppresive therapy, n (%)	50 patients (91%)
Anidulafungin indication	
Prophylaxis, n (%)	29 (53%)
Treatment, n (%)	26 (47%)
Documented fungus	10 patients (18%)
C. albicans (blood culture)	5 patients
C. parapsilosis (blood culture)	1 paciente
Aspergillus flavus (bronchoalveolar lavage)	2 patients
Trichosporon asahii (urine culture)	2 patients
Treatment duration	
Median (IQR)	14 días (7-22)

IQR: interquartile range.

anidulafungin-related cause. Follow-up at 30 days was complete, and no relapse or mortality associated with anidulafungin use was observed.

DISCUSSION

This study started due to the temporary lack of lipid formulations of amphotericin in our hospital. Anidulafungin use was based on the hypothesis that it may be better tolerated and that its effectiveness may not be inferior to that of other prophylaxis or treatment options. Its indication also considered that, unlike other antifungal agents, there were no known interactions between anidulafungin and immunosupressors, thus favoring its use in transplant patients, and that infusion-related adverse effects were less common and posed a lower cost compared to lipid formulations of amphotericin.[1,5,10-12]

In a phase II study, anidulafungin was administered to 24 children between 2 and 17 years old at a dose of 0.75 or 1.5 mg/kg of body weight per day; mild or moderate adverse effects were reported but only four cases were classified as possibly or probably drug-related.[2] These included discomfort, facial erythema and flushing, increased urea, fever, and low blood pressure, which were not observed in this series. These results demonstrated that bone marrow transplant recipients did not require discontinuing anidulafungin use due to adverse effects. Particularly, no cases of severe nephrotoxicity or hepatotoxicity directly attributed to drug use were reported. Transaminase levels remained stable or reduced during treatment.

White blood cell count varied in the studied population on account of patients' underlying disease; no significant alterations similar to those reported in the literature were confirmed.[2]

Either when indicated as prophylaxis or treatment, the success rates observed with anidulafungin were indicative of sufficient effectiveness, as reported in other patient series, especially adult patients.[1,11,13-15]

The limited literature regarding the pediatric population supports our findings on the safety and effectiveness of anidulafungin, and highlights the need for further studies to strengthen these statements.[1-3]

CONCLUSIONS

These findings warrant the need to plan methodologically adequate studies to prove the hypothesis that anidulafungin may be a valid alternative for the prophylaxis or treatment of IFIs in children. ■

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TABLE 2. *Course of biochemical parameters among patients with bone marrow transplant treated with anidulafungin (n: 29 patients)*

Biochemical parameters	Treatment initiation (median)	End of treatment (median)	*P*
Transaminase levels (IU/L)	29.5	32	0.44
Bilirubin (mg/dL)	0.35	0.30	0.20
Creatinine (mg/dL)	0.52	0.60	0.67
White blood cell count (cells/mm^3)	2810	5160	0.07