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Biafungin (CD101), a Novel Echinocandin, Displays an Uncommonly Long Half-life in Multiple Species

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ABSTRACT

Background: The echinocandins are an important class of antifungal agents, but are administered once daily by intravenous (IV) infusion. An echinocandin that offers a convenient and more economic dosing schedule is desired.
Biafungin is a highly stable echinocandin for intermittent IV administration. The compound was found to have a long half-life ($T_{1/2}$), which may greatly reduce costs even as an IV therapy through less frequent dosing, allowing earlier discharges for patients with negative fungal cultures who are clinically stable. The $T_{1/2}$ of biafungin in rats, dogs, and monkeys was compared to that of anidulafungin, which has the longest $T_{1/2}$ of the approved echinocandins.

Methods: The pharmacokinetics of biafungin and anidulafungin were compared in Sprague Dawley rats, beagle dogs, and cynomolgus monkeys. In each study, single-dose (2.8 mg/kg) pharmacokinetic (PK) parameters were evaluated over 72 h. In the rat, PK parameters were determined in three animals each after IV bolus administration. In the dog, a crossover design was used with four animals and administration by IV slow push. In the monkey, a crossover design was used with three animals and administration by IV slow push. For each of these studies, concentrations were determined by quantitative LC/MS/MS from extracted plasma and comparison to a standard curve. Pharmacokinetic parameters were calculated using noncompartmental analyses.

Results: The $T_{1/2}$ and clearance in the rat were 30 h and 44 mL/h/kg for biafungin and 22 h and 64 mL/h/kg for anidulafungin, respectively. Differences were more pronounced in dogs: $T_{1/2}$ and clearance were 53 h and 19 mL/h/kg for biafungin and 12 h and 47 mL/h/kg for anidulafungin, respectively. Differences were most pronounced in monkeys: $T_{1/2}$ and clearance were 40 h and 18 mL/h/kg for biafungin and 8 h and 302 mL/h/kg for anidulafungin, respectively.

Conclusions: Biafungin displays a long $T_{1/2}$ and slow clearance relative to other echinocandins in multiple species, with the differences trending more pronounced in higher species. These findings warrant further investigation of biafungin as a potential once-weekly or less frequently dosed agent, enabling earlier hospital discharges and expansion of echinocandin use to indications where daily infusion is impractical.

BACKGROUND

Systemic fungal infections are important complications in patients receiving solid organ transplant, hematopoetic stem cell transplant, cancer chemotherapy, long-term antibiotics, immunosuppressive drugs, and associated medical conditions. Echinocandins and azoles have been the most commonly utilized therapeutic classes for these patients. However, increasing drug resistance and drug interaction/tolerability issues with azoles limit their utility.

Since their introduction in 2001, the echinocandins have become increasingly important. They have very few drug interactions, a low incidence of resistance, and no dose adjustments based on renal function. However, the three approved echinocandins are all administered once daily by intravenous (IV) infusion. An echinocandin that offers a convenient and more economic dosing schedule is desired.

Biafungin (formerly SP 3025) is a highly stable echinocandin originally designed for IV and oral administration. The compound was found to be comparable to the approved echinocandins in terms of MIC/MEC against panels of recent *Candida* and *Aspergillus* clinical isolates.[1] The compound was also found to have a long half-life ($T_{1/2}$), which could help reduce costs even as an IV therapy due to earlier discharges for patients with negative fungal cultures who are clinically stable. Herein is presented the single-dose pharmacokinetics of biafungin in rats, dogs, and monkeys compared to that of anidulafungin, which has the longest $T_{1/2}$ of the approved echinocandins.

METHODS

The single-dose pharmacokinetics of biafungin and anidulafungin were compared in Sprague Dawley® rats, beagle dogs, and cynomolgus monkeys (Table 1). Animals received biafungin or anidulafungin as an IV bolus (rat) or as a 10-minute infusion (dog and monkey). For each of these studies, whole blood samples (K_3EDTA anticoagulant) were collected up to 72 h after dosing. The samples were centrifuged at 5 ° C within 30 min of collection, and plasma was stored at -70 ° C until analysis. Levels of biafungin and anidulafungin in the plasma samples were measured by quantitative LC/MS/MS analysis compared to a calibration curve and an internal standard. Pharmacokinetic parameters were calculated from the plasma concentration-time data using standard noncompartmental methods and utilizing WinNonlin analysis software.

Species	Test Article	N=	Dose Level (mg/kg)	Dose Conc. (mg/mL)	Dose Volume (mL/kg)	Dose Route	Blood Draw Volume (mL)
Sprague Dawley Rat	Biafungin	3M	2.8	2.8	1	IV Bolus	0.25
	Anidulafungin	3M	2.8	2.8	1	IV Bolus	0.25
Beagle Dog	Biafungin	4M	1.4	3.36	0.417	IV (10 min)	1.0
	Anidulafungin	4M	1.4	3.02	0.464	IV (10 min)	1.0
Cynomolgus Monkey	Biafungin	3M	2.8	2.8	1	IV (10 min)	1.0
	Anidulafungi	3M	2.13	2.13	1	IV (10 min)	1.0

Table 1. Study parameters in the rat, dog, and monkey.

RESULTS

- The plasma concentration-time curves for biafungin and anidulafungin after IV administration in Sprague Dawley rats are shown in Figure 1. The $T_{1/2}$, Vz, and CL for biafungin were 30 h, 1.6 L/kg, and 44 mL/h/kg, respectively. For anidulafungin, they were 22 h, 1.6 L/kg, and 64 mL/h/kg, respectively.

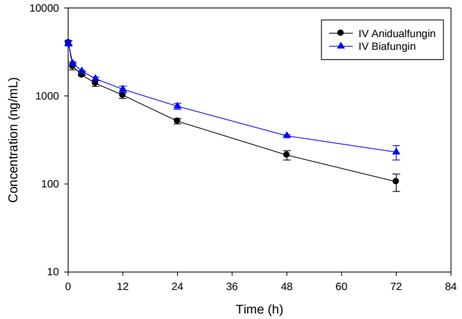

Figure 1. Plasma concentration-time curves for biafungin and anidulafungin in Sprague Dawley rats. Six naïve rats (two groups of three) received a single dose (2.8 mg/kg) of either biafungin (blue triangle, ▲) or anidulafungin (black circle, ●). Each point on the graph is an average from three animals ± SEM.

RESULTS cont.

- The plasma concentration-time curves for biafungin and anidulafungin after IV administration in beagle dogs are shown in Figure 2. The $T_{1/2}$ and CL for biafungin were 53 h and 19 mL/h/kg, respectively. For anidulafungin, they were 12 h and 47 mL/h/kg, respectively.

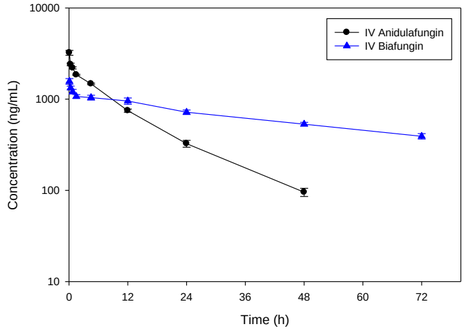

Figure 2. Plasma concentration-time curves for biafungin and anidulafungin in beagle dogs. Four non-naïve dogs received a single dose (1.4 mg/kg) of either biafungin (blue triangle, ▲) or anidulafungin (black circle, ●) in a crossover fashion. Each point on the graph is an average from four animals ± SEM.

- The plasma concentration-time curves for biafungin and anidulafungin after IV administration in cynomolgus monkeys are shown in Figure 3. The $T_{1/2}$, Vz, and CL for biafungin were 40 h, 0.9 L/kg, and 18 mL/h/kg, respectively. For anidulafungin, they were 8 h, 0.8 L/kg, and 302 mL/h/kg, respectively.

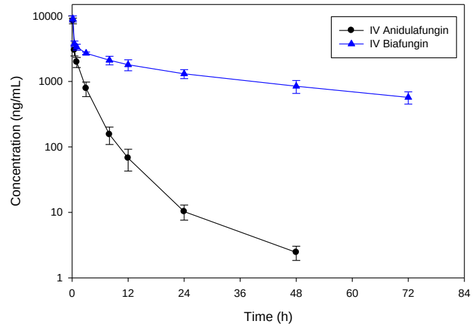

Figure 3. Plasma concentration-time curves for biafungin and anidulafungin in cynomolgus monkeys. Three non-naïve monkeys received a single dose of either biafungin (2.13 mg/kg; blue triangle, ▲) or anidulafungin (2.8 mg/kg; black circle, ●) in a crossover fashion. Each point on the graph is an average from three animals ± SEM. Anidulafungin levels were below the quantitation limits after 48 h.

RESULTS cont.

- Species comparisons of half-lives and clearance for biafungin and anidulafungin are shown graphically in Figures 4 and 5. Interestingly, the rat was the species in which anidulafungin had the longest half-life, whereas for biafungin it was the shortest.

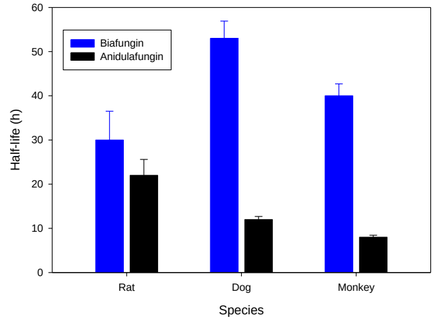

Figure 4. Half-lives of biafungin and anidulafungin in various species. Blue bars (biafungin) and black bars (anidulafungin) represent the average half-lives ± SEM in Sprague Dawley rats (N=3), beagle dogs (N=4), and cynomolgus monkeys (N=3).

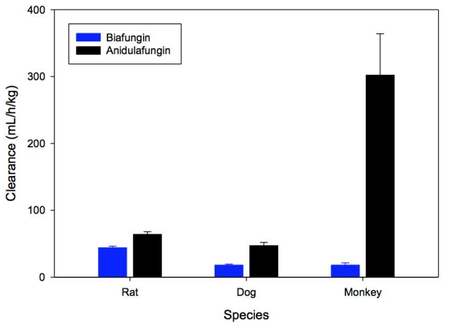

Figure 5. Clearance of biafungin and anidulafungin in various species. Blue bars (biafungin) and black bars (anidulafungin) represent the average clearance ± SEM in Sprague Dawley rats (N=3), beagle dogs (N=4), and cynomolgus monkeys (N=3).

RESULTS cont.

- Table 4 indicates the half-lives observed in this study for biafungin and anidulafungin in the context of values reported elsewhere for caspofungin, micafungin, and anidulafungin. Biafungin consistently displayed a longer half-life than what has been observed for any of the approved echinocandins in each species evaluated.

Organism	Half-life (h)			
	Caspofungin	Micafungin	Anidulafungin	Biafungin
Rat	6-7[2]	5[5]	18-19[6], 22*	30
Dog	NA	NA	12*, 15-16[7]	53
Monkey	5-6 (rhesus)[2]	NA	8*	40
Chimpanzee	5-8[2]	NA	30*[8]	81[8]
Man	9-11[3,4]	10-17[3,4]	24-26[3,4]	-

*Tested as comparator to biafungin

Table 4. Half-lives of biafungin and the three approved echinocandins in multiple species. In studies of biafungin, anidulafungin was routinely used as the comparator because it consistently exhibits the longest half-life of the approved echinocandins. The values marked with an asterisk (*) were obtained in direct comparison to biafungin. Other listed values are those reported in the literature as indicated.

CONCLUSIONS

- Biafungin exhibits a long half-life and a slow clearance compared to other echinocandins in multiple species.
- In this set of species the differences in half-life and clearance trended greater in larger animals, and they were particularly pronounced in the primate.
- The volumes of distribution for biafungin and anidulafungin showed no distinguishable trend across the species tested.
- The differences in half-life and clearance seen in the dog and monkey warrant further investigation of biafungin to determine if it could potentially be dosed weekly in the clinical setting.

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