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Biafungin (CD101), a Novel Echinocandin, Displays a Long Half-life in the Chimpanzee, Suggesting a Once-Weekly IV Dosing Option

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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 could be administered once weekly could facilitate earlier hospital discharges and could expand usage to indications where daily infusions are impractical. Biafungin is a highly stable echinocandin for once-weekly IV administration. The compound was found to have a spectrum of activity and potency comparable to other echinocandins. In chimpanzees single dose pharmacokinetics of IV and orally administered biafungin were compared to IV anidulafungin, which has the longest half-life ($T_{1/2}$) of the approved echinocandins.

Methods: The pharmacokinetics of biafungin and anidulafungin were compared in *Pan troglodytes*. Six healthy adult female chimpanzees (three groups of two) received a single dose of either IV biafungin (1.0 mg/kg, 1 h infusion), oral biafungin (10 mg/kg, bolus gavage), or IV anidulafungin (1.0 mg/kg, 1 h infusion). Blood draws were collected over 22 days in animals receiving biafungin and over 10 days for anidulafungin. Quantifications of biafungin and anidulafungin were performed using qualified LC/MS/MS and LC/MS methods, respectively. Pharmacokinetic parameters were calculated using noncompartmental analyses.

Results: After IV administration, the $T_{1/2}$ and clearance for biafungin in the chimpanzee were 81 h and 3.41 mL/h/kg, whereas for anidulafungin the observed values were 30 h and 25.2 mL/h/kg, respectively. The oral bioavailability of biafungin was 4.5%, but exposures were high ($AUC_{0\text{-}inf}$ of ~137,000 ng*h/mL) and persisted after a single dose. The apparent $T_{1/2}$ after oral administration was longer than after IV administration (99 h vs 81 h). The T_{max} after oral administration occurred late (24 h).

Conclusions: Biafungin has a $T_{1/2}$ nearly 3-fold longer and a clearance over 7-fold slower than those for anidulafungin in the chimpanzee. Despite a low oral bioavailability, slow clearance leads to high AUCs after a single oral dose. These results suggest that biafungin could potentially be administered in patients once weekly as an IV infusion, enabling earlier hospital discharges and expansion of use to situations 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 class 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, Figure 1) is a highly stable echinocandin in development for weekly IV 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] Additionally, it was found to have a long half-life ($T_{1/2}$) and slower clearance compared to other echinocandins in multiple species.[2] If these features of biafungin enable once-weekly dosing, costs may be lowered due to earlier discharges for patients with negative fungal cultures who are clinically stable. Further, an echinocandin that could be dosed weekly rather than daily may extend the use of this class into indications where uses of the currently approved echinocandins are impractical. Herein we report the single dose pharmacokinetics in chimpanzees of IV and orally administered biafungin compared to IV anidulafungin, which has the longest half-life of the approved echinocandins.

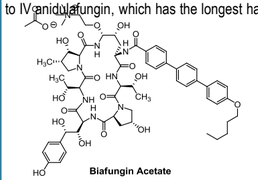

Figure 1 (left). Structure and molecular weight of biafungin acetate.

METHODS

Six healthy adult female chimpanzees (*Pan troglodytes*, three groups of two) received a single dose of either IV biafungin, oral biafungin, or IV anidulafungin (Table 1). Blood draws (10 mL) were collected in K_2EDTA tubes pre-dose, midpoint of infusion (IV only), end of infusion (IV only), at 2, 4, 8, 12, 24, 48, 72 h, and after 5, 7, and 10 d. For biafungin, blood was also drawn after 15 and 22 d. Samples were centrifuged at 5 ° C within 30 min of collection, and plasma was stored at -70 ° C until analysis. Quantifications of biafungin and anidulafungin were performed using qualified LC/MS/MS and LC/MS methods, respectively. Comparisons were made to standard curves and quality control samples. Noncompartmental pharmacokinetic parameters were calculated using Excel.

Test Article	N =	Dose Level (mg/kg)	Dose Conc. (mg/mL)	Dose Volume (mL/kg)	Dose Route	Flush Volume
Biafungin	2F	1.0	0.77	1.3	IV (60 min infusion, 5% dextrose)	2 mL (5% dextrose)
Biafungin	2F	10	10	1.0	Oral gavage (5% citric acid)	10 mL water
Anidulafungin	2F	1.0	0.77	1.3	IV (60 min infusion, 5% dextrose)	2 mL (5% dextrose)

Table 1. Dosing groups and details of administration of biafungin and anidulafungin to chimpanzees.

Dosing Groups

IV Biafungin: Biafungin (77 mg, corrected for salt and water) was reconstituted with 100 mL of 5% sterile Dextrose for Injection. The active solutions were sterile filtered through a 0.2 µm filter, and the final concentration was confirmed by LC/UV analysis. Biafungin was infused at 1.3 mL/kg/h for 60 min with a syringe pump. The administration rate was 1 mg/kg/h.

Oral Biafungin: Biafungin (1500 mg, corrected for salt and water) was dissolved in 150 mL of 5% citric acid solution. The two animals received biafungin via oral bolus gavage through an esophageal tube.

IV Anidulafungin: Anidulafungin was obtained as the commercial product Eraxis® and was prepared per instructions from the most recent package insert (July 2012). Anidulafungin was infused at 1.3 mL/kg/h for 60 min with a syringe pump. The administration rate was 1 mg/kg/h.

RESULTS

Plasma Concentration-Time Curves: The plasma concentration-time curves for biafungin and anidulafungin after IV administration are shown in Figure 2.

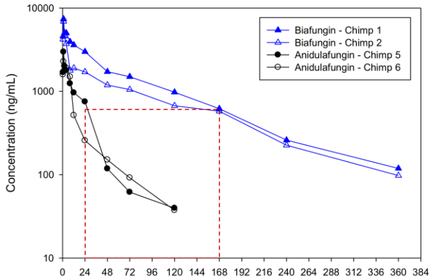

Figure 2. Plasma concentration-time curves of biafungin and anidulafungin in *Pan troglodytes*. Four non-naïve chimpanzees (two groups of two) received a single dose (1.0 mg/kg) of either biafungin (blue triangles) or anidulafungin (black circles) by intravenous infusion. Each point on the graph represents a sample from one animal. Anidulafungin levels had dropped below the quantification limits after day 5. The levels of biafungin remaining at day 7 (168 h) were approximately the same as the levels of anidulafungin at 24 h, as indicated by the red box.

The plasma concentration-time curves for IV and oral biafungin are shown in Figure 3. Although oral biafungin was administered at a 10-fold higher dose than IV biafungin, the C_{max} and AUC did not reach the levels achieved with the single IV dose.

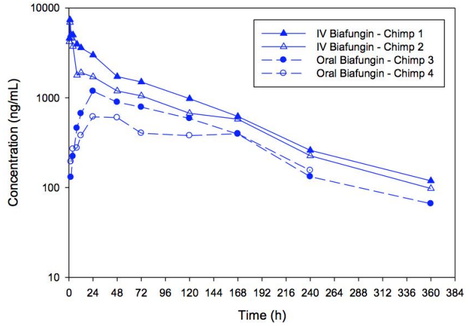

Figure 3. Plasma concentration-time curves of biafungin after IV and oral administration in *Pan troglodytes*. Four non-naïve chimpanzees (two groups of two) received a single dose of biafungin by IV (1.0 mg/kg, closed and open triangles) or oral (10 mg/kg, closed and open circles) administration. Each point on the graph represents a sample from one animal. The oral bioavailability of biafungin in the chimpanzee was about 4 – 5%.

RESULTS cont.

Differences in exposures among the three dosing groups are graphed in Figure 4. Despite the low oral bioavailability of biafungin, its exposures surpassed those of anidulafungin at these respective doses.

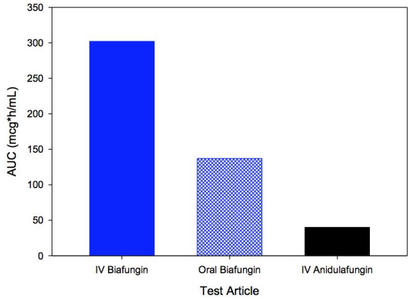

Figure 4. Bar graph illustrating the mean $AUC_{0\text{-}inf}$ observed after a single dose of IV biafungin (1.0 mg/kg), oral biafungin (10 mg/kg), and IV anidulafungin (1.0 mg/kg). At 10-fold greater dose, oral biafungin did not meet the exposure of a single IV dose of biafungin; however, it exceeded those of IV anidulafungin at these doses.

Pharmacokinetic Parameters: A summary of the pharmacokinetic parameters of biafungin and anidulafungin is presented in Table 2.

Animal	Test Article	$AUC_{0\text{-}\infty}$ (ng*h/mL)	CL (mL/h/kg)	Vz (L/kg)	$T_{1/2}$ (h)	%F
1	Biafungin (IV)	353467	2.83	0.316	77.4	-
2		251103	3.98	0.483	84.1	-
Mean		**302285**	**3.41**	**0.400**	**80.7**	-
3	Biafungin (Oral)	154781	-	-	77.9	5.12
4		119609	-	-	119	3.96
Mean		**137195**	-	-	**98.7**	**4.54**
5	Anidulafungin (IV)	45107	22.2	0.795	24.9	-
6		35346	28.3	1.42	34.7	-
Mean		**40227**	**25.2**	**1.11**	**29.8**	-

Table 2. Individual and mean pharmacokinetic parameters from each dosing group after a single-dose administration of each test article in the chimpanzee.

After administration by 1-h infusion, biafungin exhibited a slow clearance (3.41 mL/h/kg) and a long half-life (80.7 h). The $AUC_{0\text{-}\infty}$ was ~302 µg*h/mL, and the Vz was 0.4 L/kg. The oral bioavailability of biafungin was ~4.5%, but exposures were high ($AUC_{0\text{-}inf}$ of ~137 µg*h/mL) and persisted after a single dose. Anidulafungin (1-h infusion) exhibited a faster clearance (25.2 mL/h/kg) and a shorter half-life (29.8 h) compared to biafungin in the chimpanzee. The mean $AUC_{0\text{-}\infty}$ was ~40 µg*h/mL, and the mean Vz was 1.11 L/kg. Elimination time curves were consistent between the two animals in each IV dosing group.

RESULTS cont.

Biafungin Levels and MIC_{90}/MEC_{90}: After the low IV dose (1 mg/kg), levels of biafungin remained above the previously observed MIC_{90}/MEC_{90} values for *Candida albicans*, *C. tropicalis*, *C. krusei*, *Aspergillus fumigatus*, *A. terreus*, *A. niger*, and *A. flavus* seven days after dosing (Figure 5).[1]

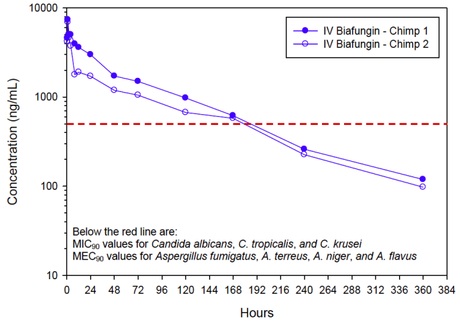

Figure 5. Plasma concentration-time curve for IV biafungin (1.0 mg/kg, blue lines) in relation to the MIC_{90} and MEC_{90} values for biafungin against common pathogens. For the organisms listed, the MIC_{90} and MEC_{90} values are all below the red line.[1] The circulating levels of biafungin remained above the MIC_{90}/MEC_{90} values for seven days after this low, single dose.

CONCLUSIONS

- The half-life of biafungin (81 h) measured in this study is nearly 3-fold longer than that of anidulafungin (30 h) in the chimpanzee.
- The clearance of biafungin (3.41 mL/h/kg) in the chimpanzee is over 7-fold slower than that of anidulafungin (25.2 mL/h/kg) in the same species.
- Biafungin has a longer half-life and a slower clearance in the chimpanzee than it has in the rat, dog, or monkey.
- Biafungin displayed low oral bioavailability (~4.5%) in the chimpanzee.
- Biafungin concentration in circulation remained above the MEC_{90}/MEC_{90} for many common fungal pathogens seven days after a single IV dose of 1.0 mg/kg.
- Once-weekly or less frequent IV dosing in patients is potentially feasible for biafungin and should be examined in future studies.

REFERENCES

1. ICAAC (2014) Poster M-1082.
2. ICAAC (2014) Poster A-693.

ACKNOWLEDGEMENTS

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