

ASSESSMENT OF THE PHARMACOKINETICS (PK) OF ANIDULAFUNGIN (ANID) IN PATIENTS WITH INVASIVE ASPERGILLOSIS (IA) RECEIVING CONCOMITANT LIPOSOMAL AMPHOTERICIN B (LAMB).

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Objective:

Combination antifungal therapy for the treatment of invasive aspergillosis has arisen due to high mortality rates and rising incidence in high risk populations. Sparse clinical PK data on the concomitant use of echinocandins and amphotericinB exist. ANID is an echinocandin being studied for serious fungal infections. ANID is chemically degraded, not metabolized, and not excreted renally. ANID has low potential to interfere with the elimination of other drugs. An investigation of potential clinical PK interactions was performed by comparing the PK of ANID in patients with IA receiving concomitant LAmB to that observed in other patient populations.

Methods:

Patients with IA were enrolled in an open label non-comparative study of intravenous ANID (100 mg/day) and LAmB (AmBisome[®], Gilead; 3 to 5 mg/kg/day). Patients were treated until the resolution of signs and symptoms, for a maximum of 90 days. Plasma samples obtained at steady-state on separate days, at various sampling intervals post-dose, were assayed for ANID. Data were combined with data from patients with invasive and esophageal candidiasis (CAN), analyzed using a population PK analysis (nonlinear mixed effects modeling), and PK parameters were compared.

Results:

A two-compartment population PK model was established that described the steady-state PK of ANID. The model was developed using 600 ANID plasma concentrations collected from 225 patients from four recent patient studies. Seven patients with IA, receiving concomitant LAmB, were included in the analysis. Overall, the population PK model showed little impact due to any intrinsic or extrinsic factors, such as patient demography, concomitant medications, or disease. Patient weight and gender were found to be covariates on the model, but had little clinical importance, accounting for less than 20% of the intersubject variability. Patients with IA receiving concomitant LAmB had similar PK parameters as patients with CAN who did not receive concomitant LAmB, as shown in the table (parameter means +/- SD).

	CL (L/h)	Vss (L)	t1/2 (h)
Patients w/ IA	0.84 (0.23)	34.4 (1.7)	30.6 (7.2)
Patients w/ CA	1.01 (0.35)	33.4 (4.8)	25.5 (7.4)

Conclusions:

Patients with IA receiving concomitant LAmB had no observable differences in ANID PK compared to other patients with serious *Candida* infections. This is consistent with the elimination mechanism of ANID.