Considerable interindividual variability of anidulafungin pharmacokinetics in critically ill ICU patients

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BACKGROUND

Invasive candidiasis represents a significant problem in the intensive care units (ICU) and is associated with high mortality. Anidulafungin belongs to the class of echinocandins that are currently recommended as initial therapy for invasive candidiasis.

Inadequate drug concentrations may result in treatment failures and emergence of resistance while high drug concentrations may put the patients at risk of toxicity. Though the pharmacokinetics of anidulafungin are well defined in non-critically ill patients, doses established in other cohorts of patients or in healthy volunteers may be inappropriate for the severely ill patient who tend to have an array of pathophysiological changes that can cause antifungal PK alterations.

AIM OF THE STUDY

We assessed the pharmacokinetics of anidulafungin in a group of critically ill patients and basic pharmacokinetic parameters were correlated with other covariates..

METHODS

Critically ill ICU patients treated empirically or targeted intravenously with 200 mg anidulafungin as a loading dose and 100 mg daily as a maintenance dose were eligible. Samples were collected on day 7 of treatment at predefined time points (0, end of infusion, 2, 4, 8, 12 and 24 hours post infusion). The concentration data were obtained from a fully validated HPLC-fluorescence plasma assay method.

The volume of distribution (Vd) and clearance (CL) were calculated with non-parametric analysis with iPhoenix® 6.4 pharmacokinetic software (www.certara.com) and correlated with age, body mass index (BMI), APACHE II, SOFA score (spearman correlation analysis).

The derived pharmacokinetic parameters maximum concentration (C_{max}), time of Cmax (T_{max}), the area under the 24h time-concentration (AUC_{0-24}) and the half-line ($t_{1/2}$) were then estimated. The variability of pharmacokinetic parameters were calculated with the coefficient of variation (%CV=SD/mean*100).

RESULTS

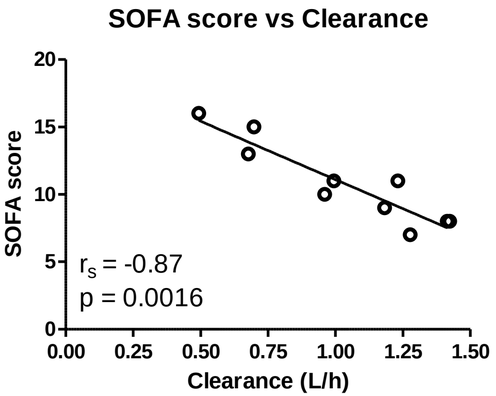
- Anidulafungin concentration data were obtained from **13** ICU patients (**10** males, **3** females) (**Table 1**).
- The **AUC_{0-24}** exhibited considerable interindividual variability (**CV=60%**) mainly because of the variation in **CL** (**CV=146%**) (**Table 2**).
- **23%** of our patients achieved a rather low **AUC_{0-24} (<50 mg·h/l)**.
- **SOFA score** and Clearance (**CL**) showed statistically significant correlation (r_s=-0.87, p=0.0016) (**Figure 1**).
- **Volume of distribution** (**Vd**) and **BMI** showed statistically significant correlation (r_s=0.79, p=0.0014) (**Figure 1**).

Table 1. Patients Characteristics

	MEDIAN	RANGE
Age (yrs)	65	41-83
Body Mass Index (kg/m^2)	26	22-36
APACHE II $_{adm}$	26	13-40
SOFA score $_{adm}$	10	7-16

Table 2. Pharmacokinetic Data

PK parameter	MEDIAN	RANGE	CV
AUC_{0-24} (mg·h/l)	85.1	16.7 - 194.4	60%
C_{max} (mg/l)	8.4	2.5 - 17.1	49%
T_{max} (h)	1.7	1.6 - 3.0	20%
$t_{1/2}$ (h)	18.2	1 – 34	43%
Vd (L)	30	14.8 – 60.4	43%
CL (L/h)	1.8	0.5 – 10.9	146%



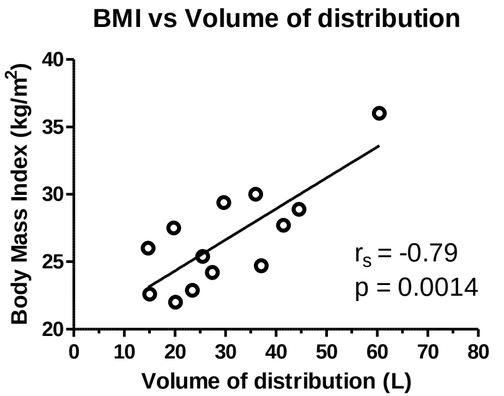


Figure 1. Correlation between clearance (CL) of anidulafungin and SOFA score and between Volume of Distribution (Vd) anidulafungin and Body mass index (BMI).

CONCLUSIONS

- ✓ Anidulafungin demonstrated considerable interindividual pharmacokinetic variability in ICU patient which was higher than previously documented (Liu et al AAC 2013, Brüggemann et al AAC 2016).
- ✓ The low drug exposures observed in some patients raises a question regarding the need of dose optimization beyond the case of extreme obesity.