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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 crude and attributable mortalities. Anidulafungin belongs to the class of echinocandins that are currently recommended as initial therapy for invasive candidiasis. Inadequate antifungal dosing relates with treatment failures and the emergence of resistance while it may put the

patients at risk of toxicity. Though the pharmacokinetics of anidulafungin are very 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. We therefore assess the pharmacokinetics of anidulafungin in a group of critically ill patients and compare our findings with those of already published studies.

Material/methods: Critically ill ICU patients treated intravenously with 200 mg anidulafungin as a loading dose and 100 mg daily as a maintenance dose were eligible. A pharmacokinetic curve was drawn on day 7 of treatment through sampling 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 C_{max} (T_{max}), the area under the 24h time-concentration (AUC_{0-24}) and the half-life ($t_{1/2}$) were then estimated. The variability of pharmacokinetic parameters were calculated with the coefficient of variation ($CV=SD/mean$).

Results: Anidulafungin concentration data were obtained from 13 ICU patients (10 males/3 females) hospitalized in Attikon and Hippokrateion General Hospitals of Athens. Their median (range) age, body mass index (BMI) and total were 65(41-83)y and 26(22-36) kg/m², respectively. On admission, their median(range) APACHE II and SOFA score were 26(13-40) and 10(7-16), respectively. The median (range) VD and CL were 27(15-60)L and 1.2(0.5-10.9)L/h. The median (range) AUC_{0-24} , C_{max} , T_{max} and $t_{1/2}$ were 74.21(16.7-194.4) mg·h/l, 7.6(2.5-17.1) mg/l, 1.67(1.67-3)h and 20(1-34)h respectively. The AUC_{0-24} exhibited considerable interindividual variability ($CV\%=60.2$) mainly because of the variation in CL ($CV=140\%$) rather than in Vd ($CV=43\%$) with 23% of our patients achieved a rather low AUC_{0-24} (<50 mg·h/l). Spearman correlation analysis showed statistically significantly correlation between SOFA score and CL ($r_s=-0.92$, $p=0.001$) and between VD and BMI ($r_s=0.78$, $p=0.001$).

Conclusions: Anidulafungin demonstrated considerable interindividual pharmacokinetic variability In ICU patient which was higher than previously documented (Liu et al AAC2013, Bruggeman et al AAC2016). The low drug exposures observed in some patients raises a question regarding the need of dose optimization beyond the case of extreme obesity.