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Paper Poster Session
PK/PD of agents against Gram-negatives

Comparative effect of equal dose of continuous veno-venous haemofiltration and continuous veno-venous haemodiafiltration on ciprofloxacin population pharmacokinetics in septic patients

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Background: Continuous venovenous haemofiltration (CVVHF) and continuous venovenous haemodiafiltration (CVVHDF) are two common renal replacement therapy (RRT) modalities. Ciprofloxacin is a commonly used antibiotic for difficult-to-treat infections for which little data is available to guide dosing for different types of RRT. A target area under the concentration time curve from 0-24 hours (AUC_{0-24}) to minimum inhibitory concentration (MIC; AUC_{0-24}/MIC) ratio of 125 mg.h/L is associated with maximal clinical cure. The objective of this study was to compare the population pharmacokinetics of ciprofloxacin during CVVHF and CVVHDF and develop a population pharmacokinetic model from which future robust dosing recommendations could be developed.

Material/methods: This was an ethically approved observational prospective study at a tertiary referral hospital. Patients with a clinical indication for ciprofloxacin and prescribed either CVVHF (30 mL/kg/h) or CVVHDF (15 mL/kg/h + 15 mL/kg/h) were eligible for participation. Patients were administered 400mg IV 8- or 12-hourly. Up to ten blood samples were collected over one dosing interval and analysed by a validated chromatographic method. Clinical and demographic characteristics of the patient as well as data relating to RRT and infection were collected. A non-parametric population pharmacokinetic analysis was undertaken using Pmetrics (available at www.lapk.org). One and two compartment linear models with and without covariates were compared using model diagnostics used to confirm the most appropriate model. Statistical analysis was performed using SPSS (version 22).

Results: Eighteen sampling intervals were included (8 CVVHDF; 10 CVVHF) from 11 patients with 6 patients having sampling during both RRT modalities. The mean (SD) age, weight and sequential organ failure assessment (SOFA) score were 65.1 (18.7) years, 84.7 (31.6) kg and 11.7 (3.3) respectively. A two compartment linear model best described the data. Increasing patient weight was the only covariate associated with increasing drug clearance. The mean (SD) parameter estimates were clearance 10.7 (5.5) L/h, volume of the central compartment 21.3 (11.6) L, intercompartmental clearance constants from central to peripheral (Kcp) 10.9 (4.5) L/h and peripheral to central

compartments (Kpc) 2.3 (1.8) L/h. After accounting for patient weight, CVVHF was associated with a 1.7% higher mean ciprofloxacin clearance than CVVHDF, although the difference was not significant (P=0.43).

Conclusions: The present study indicates a high pharmacokinetic variability of ciprofloxacin during CVVHF and CVVHDF. Sub-optimal achievement of therapeutic targets occurs at the EUCAST breakpoint MIC of 0.5-1.0 mg/L using current doses. Dose adjustment should occur based on patient weight when mg/kg doses are used of either CVVHF or CVVHDF.