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Paper Poster Session V

Pharmacokinetics in various patient groups

The comparative effects of continuous venovenous haemofiltration vs continuous venovenous haemodiafiltration on the pharmacokinetics of linezolid in critically ill patients

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Objective: Continuous venovenous haemofiltration (CVVHF) and continuous venovenous haemodiafiltration (CVVHDF) are two common renal replacement therapy (RRT) modalities. Linezolid is a commonly used antibiotic for difficult-to-treat Gram-positive 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 80-120 mg.h/L is associated with maximal clinical cure. The objective of this study was to compare the population pharmacokinetics of linezolid during CVVHF and CVVHDF and develop a population pharmacokinetic model from which future robust dosing recommendations could be developed.

Methods: This was an observational prospective study at a tertiary referral hospital. Patients with a clinical indication for linezolid and prescribed either CVVHF or CVVHDF were eligible for participation. Patients were administered 600mg IV 12-hourly. Seven 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: Seventeen patients were included (9 CVVHDF; 8 CVVHF). The mean (SD) age, weight and sequential organ failure assessment (SOFA) score at the time of commencing RRT were 66.5 (10.6) years, 78.9 (27.1) kg and 12.8 (4.8) respectively. The urine output and the fluid removed by RRT during the 12-hour sampling period was 334 (580) mL and 671 (1058) mL respectively. A two compartment linear model best described the data. CVVHDF was associated with a 20.5% higher mean linezolid clearance than CVVHF, although the difference was not significant (P=0.39). Both increasing patient weight and decreasing SOFA score were associated with increasing drug clearance and were supported as covariates in the final model. The mean (SD) parameter estimates were clearance 3.8 (2.2) L/h, volume of the central compartment 26.5 (10.3) L, intercompartmental clearance constants from central to peripheral (Kcp) 8.1 (12.1) L/h and peripheral to central compartments (Kpc) 3.6 (4.0) L/h. The mean AUC_{0-24} was 227.9 (115.0) mg.h/L. Using the studied dose, 94% patients achieve a therapeutic AUC_{0-24}/MIC for an MIC of 1 mg/L, 69% for 2 mg/L and 24% for 4 mg/L.

Conclusions: The present data indicates profound pharmacokinetic variability of linezolid during CVVHF and CVVHDF with patient weight and level of sickness severity influencing drug disposition most prominently. Sub-optimal achievement of therapeutic targets occurs at the EUCAST breakpoint MIC of 2mg/L using 600mg IV 12-hourly.