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

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Introduction: 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. The objective of this study was to compare the population pharmacokinetics of linezolid during continuous venovenous haemofiltration (CVVHF, 30 mL.kg^{-1}.h^{-1}) and continuous venovenous haemodiafiltration (CVVHDF, 15 mL.kg^{-1}.h^{-1} + 15 mL.kg^{-1}.h^{-1}). We then sought to perform Monte Carlo dosing simulations to determine doses that best achieve pharmacodynamic targets for these patients.

Methods: Patients with a clinical indication for linezolid and prescribed either CVVHF or CVVHDF were eligible for participation in this prospective pharmacokinetic study. Patients were administered 600mg IV 12-hourly. Seven blood samples were collected over one dosing interval (H0, H1, H1.5, H2, H4, H8 and H12). Population pharmacokinetic analysis was undertaken using Pmetrics and Monte Carlo simulations evaluated achievement of a pharmacodynamics target of an area under the concentration-time curve from 0-24 hours to minimum inhibitory concentration (AUC_{0-24}/MIC) of 80.

Sample Handling, Storage and Measurement
Blood samples were immediately placed on ice and centrifuged within 60-minutes at 3000 rpm, for 10-minutes then stored at -80°C. An HPLC-UV assay was used to measure linezolid concentrations in plasma.

Statistical analysis: Continuous data are presented as the mean (SD) or median [IQR]. Categorical data are presented as counts (%). Comparisons used Mann Whitney and chi-square tests as appropriate. Correlation was assessed by means of a scatter graph and Pearson correlation coefficient (r). Differences in linezolid clearance by CVVHF and CVVHDF were analysed using a Students t-test. A *P*-value < 0.05 was considered as statistical significance, and all analyses were performed using SPSS version 21 (Chicago, IL, USA).

Results: 9 CVVHDF and 8 CVVHF were performed in 13 patients. Pulmonary and intra-abdominal infections were the main causes of sepsis. The MIC of the Gram-positive pathogen was always 2 mg.l^{-1}.

RRT therapy
The characteristics of RRT are shown in Table 1.

Parameters	CVVHDF (n=9)	CVVHF (n=8)	p-value
Time RRT session-admission (days)	1 [0-2]	4 [1-13]	0.1
Arterial pressure (mmHg)	-30 [-57:-6]	-37 [-70:27]	0.9
Trans-membranar pressure (mmHg)	39 [29-58]	63 [19-88]	0.5
Venous return pressure (mmHg)	89 [76-105]	101 [81-115]	0.4
Blood flow rate (ml.minute^{-1})	200 [165-200]	200 [185-245]	0.5
Fluid removal (ml.h^{-1})	130 [6-620]	2110 [1530-3900]	0.009
Substitution flow rate (ml.kg^{-1}.h^{-1})	16 [13-17]	22 [22-23]	NA
Dialysis flow rate (ml.kg^{-1}.h^{-1})	15 [15-17]	NA	NA
12-hour diuresis (ml.kg^{-1}.h^{-1})	0.1 [0.0-0.25]	0.05 [0.0-0.55]	0.6

Table 1

Pharmacokinetics of linezolid
A two compartment linear model best described the data. The model was considered acceptable according to the goodness of fit evaluations (Figure 1.)

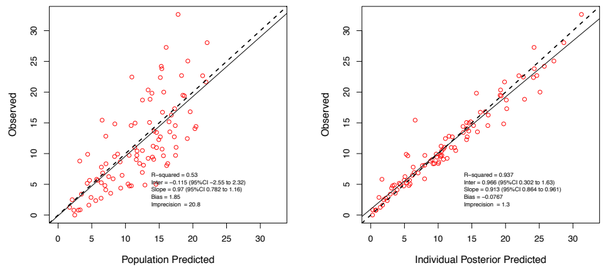


Figure 1. Diagnostic plots for the final covariate model.

CVVHDF was associated with a 20.5% higher mean linezolid clearance than CVVHF, although the difference was not significant (5.9 vs 4.5 L.h^{-1}, p=0.39).

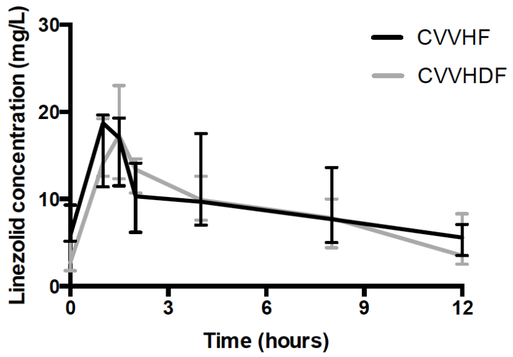
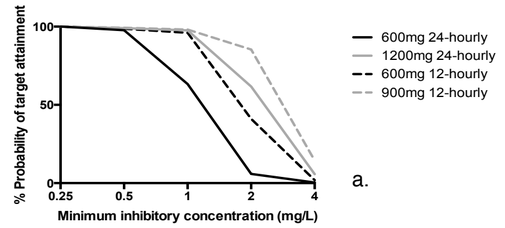


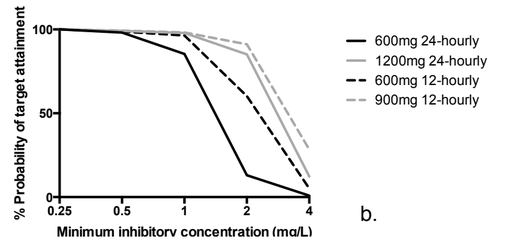
Figure 2. The median observed linezolid concentration-time profile in critically ill patients receiving CVVHF or CVVHDF.

The mean (SD) parameter estimates were clearance 3.8 (2.2) L.h^{-1}, volume of the central compartment 26.5 (10.3) L, intercompartmental clearance constants from central to peripheral (Kcp) 8.1 (12.1) L.h^{-1} and peripheral to central compartments (Kpc) 3.6 (4.0) L.h^{-1}. The mean AUC_{0-24} was 227.9 (115.0) mg.h.L^{-1}.

Dosing simulations
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.



a.



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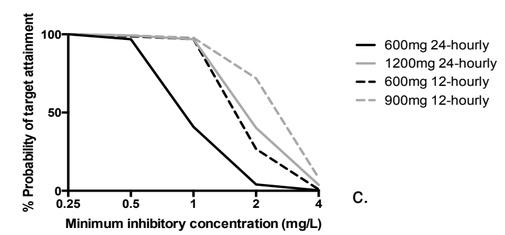

c.

Figure 3. Monte Carlo dosing simulations for various doses and PTA for achieving an AUC/MIC ≥80 during the first 24 hours of treatment for a patient with a SOFA score of 13, and a total body weight of 60 kg (a), 90 kg (b) and 120 kg (c).

Conclusions: The present data indicates **profound pharmacokinetic variability** of linezolid during **CVVHF and CVVHDF. Sub-optimal achievement of therapeutic targets** occurs at the EUCAST breakpoint MIC of **2 mg/L using 600mg IV 12-hourly**.