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

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Background

Whilst commonly performed in ICUs, renal replacement therapies (RRTs) differ in their solute clearances. There is a paucity of data on ciprofloxacin clearances in different RRT techniques. The aim of this study was to describe the population pharmacokinetics of ciprofloxacin during equal doses of continuous venovenous haemofiltration (CVVHF) and continuous venovenous haemodiafiltration (CVVHDF) in critically ill patients.

Methods

Study population

Patients eligibility:

- 400 mg of ciprofloxacin IV 8 or 12-hourly
- CVVHF or CVVHDF

Up to ten blood samples collected over one dosing interval: H0, H1, H1.5, H2, H2.5, H3,H3.5, H4, H8 and H12 if 12-hourly dosing.

Sample Handling, Storage and Measurement

- Blood stored at -80°C after centrifugation
- Analysis performed at the Burns Trauma and Critical Care Research Centre, The University of Queensland, Australia, for analysis.
- Ciprofloxacin concentrations in plasma determined by HPLC with fluorescence following criteria of the US FDA's guidance for industry on bioanalysis

Population pharmacokinetic modelling

- One and two compartment models developed with the Non Parametric Adpative Grid Algorithm within Pmetrics software package for R (Los Angeles, CA, USA).
- Elimination from the central compartment, inter-compartmental distribution (two compartment model) into the peripheral compartment were modelled as first-order processes using differential equations.
- Goodness of fit assessed by regression, observed-predicted plot, coefficients of determination and log likelihood values.
- Probability of target attainment (PTA) of AUC/MIC 125 and fractional target attainment (FTA) against MIC distribution for *A. Baumannii, K.pneumoniae, E.Coli* and *P.aeruginosa* were calculated based on Monte Carlo simulations

Statistical Analysis

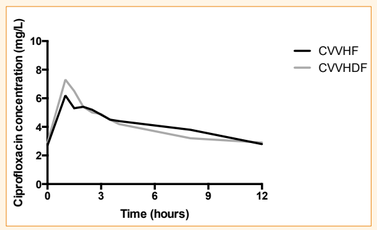
- Mean (SD) or median (IQR)
- Scatter graph and Pearson correlation
- Mann-Whitney U-test, χ
-

Funded

Nimes University Hospital

Results

Observed mean ciprofloxacin concentration-time profiles for the sampling interval



Renal replacement therapy settings during ciprofloxacin sampling interval

RRT parameters	CVVHDF (n=8)	CVVH (n=10)	p-value
Arterial pressure (mmHg)	-33 (-65 to -7)	-75 (-96 to -23)	0.3
Trans-membrane pressure (mmHg)	52 (24-72)	80 (50-97)	0.2
Venous return pressure (mmHg)	117 (78-133)	117 (86-132)	0.9
Blood flow rate (mL/min)	200 (200-200)	250 (200-275)	0.1
Fluid removal (mL/day)	640 (103-1593)	1155 (227-1958)	0.5
Reinfusion flow rate (mL/kg/h)	19 (13-20)	34 (22-37)	0.026
Dialysate flow rate (mL/kg/h)	15 (15-16)	NA	NA
Filtration ratio (%)	12 (8-14)	19 (15-20)	0.009
Actual time of RRT (min)	720 (697-720)	697 (631-708)	0.1
Effective time of RRT (%)	100 (97-100)	97 (94-99)	0.2

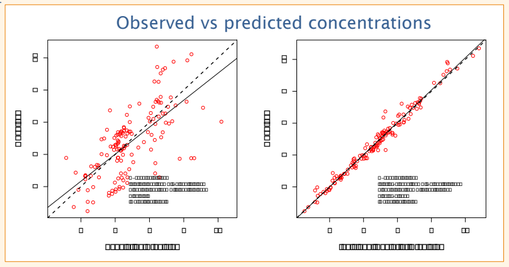
Mean population parameters estimates from the final model:

- two compartment model
- weight is the only covariate retained in the final model

	Mean	SD	CV	Median
Clearance (L/h)	10.7	5.3	49.6	8.5
$V_{central}$ (L)	21.3	11.3	53.2	17
Kcp (/h)	10.9	4.3	39.6	12.3
Kpc (/h)	2.3	1.8	74.8	2.0

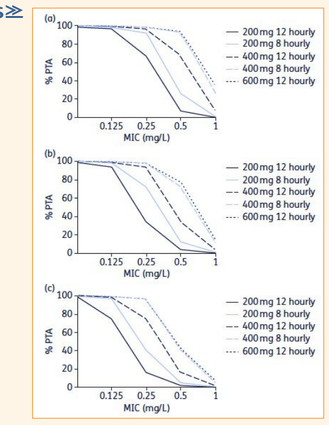
kcp –rate constant for drug distribution from the central to peripheral compartment
kpc –rate constant for drug distribution from the peripheral to central compartment

Diagnostic plots for the final covariate model



Data are expressed in mg/L

Monte Carlo simulations and PTA of achieving AUC/MIC 125 for various dosing regimens and weights



50kg (a), 90kg (b), 140kg (c)

Fractional target attainment

Body weight (kg)	iv dose/frequency	*A. baumannii*	*K. pneumoniae*	*E. coli*	*P. aeruginosa*
50	200 mg 12 hourly	65.8	90.3	96.5	70.1
	200 mg 8 hourly	78.1	93.2	97.9	78.9
	400 mg 12 hourly	86.7	95.5	98.6	86.2
	400 mg 8 hourly	93.3	97.6	99.3	92.5
	600 mg 12 hourly	94.0	97.8	95.0	93.2
90	200 mg 12 hourly	53.3	87.8	96.9	62.0
	200 mg 8 hourly	69.2	91.3	98.1	73.0
	400 mg 12 hourly	80.3	93.7	98.9	80.8
	400 mg 8 hourly	88.9	96.2	99.0	88.3
	600 mg 12 hourly	89.8	96.5	93.5	89.1
140	200 mg 12 hourly	40.7	84.6	93.5	50.3
	200 mg 8 hourly	56.8	88.8	95.5	64.9
	400 mg 12 hourly	70.9	91.7	97.1	74.2
	400 mg 8 hourly	82.8	94.4	98.4	82.8
	600 mg 12 hourly	83.0	94.4	98.4	83.1

Doses achieving the a priori target of AUC/MIC 125 against at least 85% of isolates are shaded grey

Conclusion

- High pharmacokinetic variability of ciprofloxacin during CVVH and CVVHDF
- Therapeutic drug monitoring required
- High dosing regimens (400 mg 8-hourly) if difficult-to-treat pathogens are suspected regardless RRT modalities