Population PK of ceftazidime and cefepime in septic shock patients during CRRT

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Introduction and objectives

There is significant variability in antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy (CRRT). The objective of this study was to develop a population pharmacokinetic model for patients in septic shock undergoing CRRT and treated with cefepime or ceftazidime. This model was then used to perform dosing simulations.

Materials and Methods

In this observational pharmacokinetic study, serial blood samples of cefepime or ceftazidime were taken. Blood samples were analysed using a validated ultra HPLC–tandem mass spectrometry method. Population pharmacokinetic analysis and dosing simulations were performed using non-linear mixed-effects modeling.

Both antibiotics were administered as an 30-minute IV infusion of 2 g twice daily after a loading dose of 2 g. Characteristics of the CRRT were recorded for each patient at each blood sampling time. The pharmacokinetic target used for the dosing simulations was a trough plasma concentration exceeding the EUCAST breakpoint of *Pseudomonas aeruginosa*, (8 mg/L for both antibiotics). The threshold for toxicity for cefepime was set at a trough concentration of 70 mg/L after 1 week of therapy.

Results

Sixty-one blood samples were collected from 13 patients on cefepime, and 77 from 14 patients on ceftazidime.

Model characteristics :

Cefepime: one-compartment model with between subject variability (BSV) for both clearance (CL) and the volume of distribution (Vd). Ultrafiltration flow rate (UFR) standardized to the median 1500 mL/hour, was supported as a covariate for CL and Vd.

Ceftazidime: two-compartment model with BSV for the volume of central compartment (Vc) and volume of the peripheral compartment (Vp). Dialysate flow rate (DFR) standardized to the median 2000 mL/hour, was supported as a covariate on Vc.

Parameter estimates:

The mean cefepime CL was 4.5 L/h and the mean Vd was 40.8 L. For ceftazidime, the mean CL was 3.1 L/h and the mean Vd was 76.3 L.

Dosing simulations

Monte Carlo dosing simulations were undertaken (n=500 per dose). A dose was considered adequate if at least 95 % of the patients attained the target range (trough 8-70mg/L).

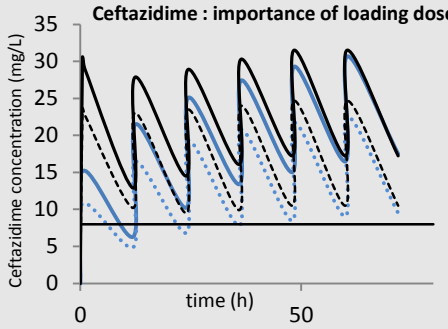
Parameter	Cefepime			
	Model	Bootstrap		
	Mean	Mean	95 % CI	
			2.5%	97.5%
Fixed effects				
Cl (L/h)	4.5	4.5	3.7	5.8
V (L)	40.8	40.7	34.3	49.3
Random effects BSV (% CV)				
Cl (L/h)	37.7	35.3	17.3	48.4
V (L)	21.2	17.8	0	26.5
Random error				
RUV (% CV)	20.4	19.4	9.4	28.9
RUV (SD, mg/L)	3.3	3.0	0	5.6

Parameter	ceftazidime			
	Model	Bootstrap		
	Mean	Mean	95 % CI	
			2.5 %	97.5 %
Fixed effects				
Cl (L/h)	3.1	3.1	3.0	3.2
Vc (L)	41.2	39.3	31.9	47.7
Vp (L)	32.5	37.0	15.8	88.8
Q (L/h)	3.3	3.6	2.0	6.4
Random effects BSV (% CV)				
Vd (L)	20.3	16.7	0	30
Vp (L)	149	138	16.7	285
Random error				
RUV (SD, mg/L)	8.4	7.9	1.4	18.1

Cl= Clearance, V= volume of distribution (1 compartment) Vc = Volume of distribution of the central compartment; Vp = Volume of distribution of the peripheral compartment; Q = Intercompartmental clearance; BSV = between subject variability; RUV = residual unexplained variability; CV = coefficient of variation, SD = standard deviation

Dosing simulations: Cefepime		
dose	UFR 1000	UFR 2000
2g q8h	Toxic	Adequate
2g q12h	Insufficient	Insufficient
1g q6h	Insufficient	Insufficient
1g q8h	Adequate	Insufficient
1g q12h	Insufficient	Insufficient
Cl 3g q24h	Adequate	Adequate
Cl 2g q24h	Adequate	Insufficient

Dosing simulations: Ceftazidime			
dose	DFR 0	DFR 1500	DFR 3000
1g q12h	Insufficient	Insufficient	Insufficient
1g q12h with loading dose	Adequate	Adequate	Adequate



Black: 1 g twice daily with 1 g loading dose
Blue : 1 g twice daily,
solid line = median concentration of 500 simulated patients, dotted line = 5th percentile
Black line : target

Conclusion

These preliminary data provide a useful insight into the pharmacokinetics of ceftazidime and cefepime during CRRT in critically ill patients with septic shock and describes the important influence of dialysis settings on the antibiotic concentrations. However, more patients are required to build a robust model with better clinical applicability.