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PK/PD to improve treatment of critically ill patients

POPULATION PHARMACOKINETICS OF CEFTAZIDIME AND CEFEPIME IN SEPTIC SHOCK PATIENTS DURING CONTINUOUS RENAL REPLACEMENT THERAPY

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Objectives: The objective of this study was to develop a population pharmacokinetic model for patients in septic shock undergoing continuous renal replacement therapy (CRRT) and treated with cefepime or ceftazidime. This model was then used to perform dosing simulations.

Methods: In this observational pharmacokinetic study, multiple blood samples were taken of intravenous cefepime or ceftazidime. Blood samples were analysed using a validated ultra HPLC–tandem mass spectrometry technique. Population pharmacokinetic analysis and dosing simulations were performed using non-linear mixed-effects modeling. Both antibiotics were administered as a 30-minute infusion of 2 g twice daily after a loading dose of 2 g. CRRT was performed through a double-lumen catheter inserted into a large vein. 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*, which is 8 mg/L for both antibiotics. The threshold for toxicity for cefepime was set at 70 mg/L.

Results: Sixty-one blood samples were collected from 13 patients on cefepime, and 77 from 14 patients on ceftazidime. For cefepime, a one-compartmental model with between-subject variability) for both the clearance and the volume of distribution was chosen. The ultrafiltration rate, standardized to the median of 1500 mL/hour, was included as a covariate on both clearance and volume of distribution. For ceftazidime, a two-compartment model with BSV for the volume of distribution of both the central and the peripheral compartment was chosen. The dialysate flow rate, standardized to the median of 2000 mL/hour, was supported as a covariate on the volume of distribution of the central compartment. The mean clearance of cefepime was 4.54 L/h and the mean volume of distribution was 40.7 L. For ceftazidime, the mean clearance was 3.1 L/h and the mean volume of distribution was 76.3 L.

Dosing simulations for cefepime showed an important influence of dialysis settings. If the ultrafiltration rate is 1000 mL/hour or less, cefepime 2 g twice daily resulted in accumulation and potentially toxic peak concentrations. One gram 2 times daily resulted in adequate concentrations. However, if the ultrafiltration rate is 2000 mL/hour, cefepime given as 2 g twice daily was needed to obtain adequate concentrations.

All tested dosages for ceftazidime (1g 4 times daily, 1 gram two times daily, 2 g three times daily, 2 g two times daily and continuous infusion of 3 g) resulted in adequate plasma concentrations for the tested dialysate flow rates of 1000, 2000 and 3000 mL/hour.

Conclusion: This study is the first population pharmacokinetic study of ceftazidime and cefepime during CRRT in critically ill patients and describes the important influence of dialysis settings on the antibiotic concentrations.