Title: Dose optimisation of cefotaxime in critically ill patients: a population pharmacokinetic study

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Background**:**

Cefotaxime is a beta-lactam antibiotic used in critically ill patients to treat infections. Literature data on the pharmacokinetics (PK) of cefotaxime in these patients are lacking. A two-centre prospective, observational study in critically ill patients was undertaken. The aim of this study was to describe the PK of cefotaxime and propose a dosing regimen in critically ill patients.

Materials/methods:

Critically ill patients treated with cefotaxime dosed 1g q6h or q4h were included. Five samples were drawn per patient during one dosing interval. PK parameters were estimated using NONMEM. Monte Carlo simulations (n=5000) were performed using Miclab 2.36 (Medimatics, NL) to determine Probability of Target Attainments (PTA). The percentage of patients reaching 100% *f*T>MIC was used to compare different dosing regimens for *Enterobacterales* and *S. aureus*.

Results:

92 patients (57 males), median age (range) of 64 (23-85) years, weight 76 (45-150) kg and creatinine clearance 57 (4-347) ml/min were included. A total number of 437 observations were analyzed. The best structural model was a two-compartment model with a combined error, and interindividual variability (IIV) on clearance (CL), central volume (V1), and intercompartmental clearance (Q). Correlations between IIV were included. CL increased with higher CKD-EPI (creatinine clearance) and higher albumin concentration and could explain 48% of IIV on CL. The estimates population parameters were 7.08 ml/min for CL; 15.7 L for V1; 25.0 L for V2 and 4.81 L/h for Q. For *Enterobacterales* (ECOFF 0.25 mg/L), 100% of patients reached the target with 1g q6h (15 minutes infusion time). For *S. aureus* (ECOFF 4 mg/L) a PTA of 64.2% and 88.8% was reached for the regimen 1g q6h and 1g q4h, respectively. With an increased dose of 2g q4h 97.3% of critically ill patients reached the target for *S. aureus*.

Conclusions:

In critically ill patients, cefotaxime PK is best described by a two-compartment model with CKD-EPI and albumin concentration as covariates influencing clearance. All dosing regimens are adequate to treat *Enterobacterales*. However, this study indicates that for *S. aureus* the dosing regimen needs to be increased to 2g q4h administered over 15 min.

Keywords:

cefotaxime; critically ill; pharmacokinetics; dose optimisation