Title: Large variability of unbound active fraction of ceftriaxone in contrast to ciprofloxacin in plasma of critically ill patients

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Background: Traditional antibiotic dosing is not designed for critically ill patients. Severe illness, frequent hypoalbuminemia, and renal failure results in aberrant pharmacokinetics. Protein binding of drugs may vary significantly in critically ill patients, which can lead to high drug clearance and therefore low plasma concentrations and therapeutic failure. Additionally, bound fractions of antibiotics have no therapeutic effect. For ceftriaxone and ciprofloxacin the unbound fractions have been described as 5-15% and 60-70%, respectively. However, data on protein binding of these antibiotics are scarce in critically ill patients. Our objectives were to determine unbound fractions of ceftriaxone and ciprofloxacin in critically ill patients, and to determine predictors affecting the unbound fractions.

Materials/methods: Samples were obtained from an ongoing multicentre randomized controlled trail (DOLPHIN) at the intensive care units. Peak and trough samples were collected at 1, 3, and 5 days after initiation of antibiotic therapy. Total and unbound concentrations were determined with a validated mass spectrometry (LC-MS/MS) method. For unbound fractions, we used linear regression to find predictors (p-value <0.10). These predictors were used in a multivariate linear regression (stepdown) for each predictor (p-value <0.05).

Results: A total of 38 patients (137 samples) receiving ceftriaxone or ciprofloxacin were included. Unbound fractions that exceeded more than 3 standard deviations (outliers) were removed from analysis (N=20). The median (IQ25-IQ75) unbound fractions were 20.2 (15.4-29.4)% and 71.1 (69.4-76.5)% in peak concentrations for ceftriaxone and ciprofloxacin, respectively. For trough concentrations the fractions were 12.3 (8.5-20)% and 69.1 (66.8-73.5)%. Using multivariate analysis, decreased serum albumin, increased serum creatinine, and septic shock were found to be positive predictors for the percentage of unbound fraction of ceftriaxone trough concentration. Septic shock was the major predictor. No patient characteristics were identified as predictors for unbound fractions of ciprofloxacin.

Conclusions: In contrast to the moderately and fairly constant bounded ciprofloxacin, the fraction of unbound concentration was extremely variable in ceftriaxone and especially for trough concentrations, higher than previously reported, resulting in fluctuations in effective exposure. At the moment unbound fraction is not considered when dosing ceftriaxone, but therapeutic drug monitoring unbound trough concentrations might increase the likelihood of therapeutic success.