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Population pharmacokinetics and dosing simulations of cefepime in septic shock patients receiving continuous renal replacement therapy

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ABSTRACT

The aim of this study was to describe the population pharmacokinetics of cefepime in septic shock patients requiring continuous renal replacement therapy and to determine whether current or alternative dosing regimens can achieve PK/PD targets. In this observational PK study, 62 samples from 13 patients were analysed using non-linear mixed-effects modelling. Different dosing regimens were evaluated using Monte Carlo simulations with ultrafiltration flow rates (UFRs) of 1000, 1500 and 2000 mL/h. The probability of target attainment was calculated against a conservative (60% $T_{>MIC}$) and a higher PK/PD target (100% $T_{>MIC}$) against an MIC of 8 mg/L, the clinical susceptibility breakpoint for *Pseudomonas aeruginosa*. A one-compartment model with between-subject variability (BSV) on clearance and volume of distribution (V_d) described the data adequately. UFR was supported as a covariate on both parameters. Typical values for clearance and V_d were 4.4 L/h (BSV 37%) and 40.9 L (BSV 20%), respectively. Dosing simulations showed failure to achieve both a conservative and a higher PK/PD target using a dose of 1 g q12h for patients treated with a high UFR (≥1500 mL/h). The dose of 2 g q8h or 1 g q6h leads to optimal target attainment for high UFR. One gram q8h is optimal for low UFR (≤1000 mL/h). We found important variability in PK parameters. Dosing simulations show that a dose of 2 g q8h or 1 g q6h is needed to ensure rapid achievement of adequate levels if the UFR is ≥1500 mL/h and 1 g q8h for low UFR (≤1000 mL/h).

1. Introduction

Septic shock is a leading cause of mortality and morbidity in intensive care units, with hospital mortality as high as 40% [1]. Timely and adequate antibiotic therapy is essential to maximise survival and is therefore highly recommended in the Surviving Sepsis Campaign guidelines [2–4].

β-Lactam antibiotics are used as first-line therapy in this setting because of their potent bactericidal activity and wide therapeutic window. These antibiotics are considered to be time-dependent, which means that the duration of the dosing interval for which the concentration exceeds the minimum inhibitory concentration (MIC) of the pathogen is the best descriptor of bacterial killing. In vitro and animal pharmacodynamic (PD) models have shown that for cephalosporins, a time that the drug concentration exceeds the MIC (%$T_{>MIC}$) between two administrations of 60–70% was associated with maximal killing [5], whilst retrospective studies in critically ill patients suggest that higher targets such as 100% $T_{>MIC}$ might be needed to treat life-threatening infections [6–8]. However, several studies have shown that the pharmacokinetic (PK) behaviour of these hydrophilic antibiotics is profoundly disturbed in critically patients owing to different pathophysiological changes [9]. A higher volume of distribution (V_d) and either an increased or decreased clearance compared

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with healthy volunteers has been shown in numerous studies. As such, low concentrations have been reported in sepsis and may lead to treatment failure and the development of antimicrobial resistance [10].

Acute kidney injury is a common complication of sepsis and may lead to accumulation of hydrophilic drugs, which are mainly renally excreted. Although not very common, toxicity from β-lactam antibiotics may occur and is associated with high concentrations [11]. Extracorporeal circuits such as those used for continuous renal replacement therapy (CRRT) may further complicate pharmacokinetics. Indeed, recent studies showed a wide variability in antibiotic concentrations during CRRT, with many patients having low concentrations early in therapy and accumulation occurring in the following days [11–13]. Unfortunately, there is relatively little clinical data on drug removal by CRRT; moreover, it is unclear how the specific CRRT settings, such as ultrafiltration flow rate (UFR) and dialysis flow rate, influence drug concentrations. Current recommendations on antibiotic dosing during CRRT are based on studies that included a limited sample size of patients who received different types of CRRT [14].

Cefepime is a fourth-generation cephalosporin with a broad spectrum of activity both against Gram-positive and Gram-negative pathogens, including *Pseudomonas aeruginosa*. Cefepime is commonly used as empirical or directed therapy for a variety of infections in critically ill patients. Adequacy of cefepime dosing during CRRT has previously been evaluated in studies with small cohorts of patients; however, a population PK approach for analysis was not used [15,16] and therefore these studies could not adequately describe the influence of CRRT settings on cefepime pharmacokinetics. Moreover, these studies sampled after having reached assumed steady-state and therefore could not evaluate cefepime pharmacokinetics during the early phase of treatment, where the risk of underdosing is the greatest. Therefore, the aim of this study was to describe the population pharmacokinetics of cefepime in septic shock patients requiring CRRT and to investigate whether PK/PD targets are achieved with current dosing strategies as well as to investigate the potential advantages of alternative dosing regimens.

2. Methods

2.1. Patients

In this study, data from two previously published PK studies were pooled, the details of which have been described elsewhere [11,12]. The first study was a PK study with blood sampling on multiple occasions [12]. The study was conducted according to the principles of the Declaration of Helsinki for human research and was approved by the local ethics committee. Informed consent was obtained from the patient if possible or from a legally authorised representative. The second study reviewed data that had been collected as part of routine treatment. Therefore, the ethics committee waived the need for informed consent because of its retrospective nature [11]. The inclusion criteria of the first study were as follows: age >18 years; diagnosis of severe sepsis or septic shock according to standard criteria; acute renal failure treated with CRRT; and receiving cefepime. Exclusion criteria were pregnancy, burns and cystic fibrosis. For the second study there were additional inclusion criteria, namely a residual creatinine clearance (CL_{Cr}) of <30 mL/min and at least one therapeutic drug monitoring sample taken during the CRRT treatment. An additional exclusion criterion was the use of extracorporeal membrane oxygenation (ECMO) therapy.

2.2. Drug administration

Patients received 2 g every 8 g (q8h) or every 12 h (q12h) based on guidelines for antibiotic dosing in critically ill patients receiving CRRT [14]. The dose was administered as a 30-min intravenous infusion.

2.3. Continuous renal replacement therapy

CRRT was performed according to local practice by insertion of a double-lumen catheter into the subclavian, femoral or internal jugular vein. Continuous venovenous haemodiafiltration (CVVHDF) or continuous venovenous haemofiltration (CVVHF) were performed using standard equipment (Prisma® or Prismaflex®; Gambro Hospal, Bologna, Italy) with a polyacrylonitrile cylinder (AN 69; Hospal, Meyzieu, France) haemofilter without special coating. Anticoagulation was performed using systemic heparin or citrate within the circuit. The blood flow rate was set around 130–150 mL/min and the UFR was adjusted to provide ≥15–20 mL/kg/h [11,12]. CRRT intensity was calculated as dialysate flow rate (mL/kg/h) + UFR (mL/kg/h).

2.4. Study procedures

In the first study, blood samples were drawn from the arterial line on the day of inclusion and then every second day during CRRT treatment whenever possible [12]. On each sampling day, blood samples were drawn immediately before antibiotic administration (0 h) and then at 1, 2 and 5 h and at 6 or 12 h (depending on the antibiotic regimen) after the start of the infusion. The exact sampling times were recorded. In the second study, two blood samples were drawn during the antibiotic elimination phase: 2 h after the end of infusion and just before administration of the next dose [11].

Samples were immediately put on ice and were sent to the clinical chemistry laboratory where they were centrifuged at 3000 rpm at 4 °C for 10 min. The supernatant was then removed and analysed using a validated high-performance liquid chromatographic technique as described elsewhere [12].

Additional data were obtained from the medical record and included participant demographics, clinical details, measures of illness severity and CRRT settings.

2.5. Pharmacokinetic analysis

The concentration–time data were analysed using non-linear mixed-effects modelling (NONMEM v.7.3; Globomax LLC, Hanover, MD). A Digital Fortran compiler was used and the runs were executed using Wings for NONMEM (http://wfn.sourceforge.net). The first-order conditional estimation (FOCE) method with interaction was used throughout the model building.

2.6. Model development

For the population PK analysis, the plasma concentrations were fitted to one-, two- or three-compartment linear models using subroutines from the NONMEM library. Between-subject variability (BSV) was evaluated using an exponential variability model. Various models for residual unexplained variability (RUV) were also tested.

2.7. Model diagnostics

Visual inspection of diagnostic scatterplots and the NONMEM objective function value (OFV) were used to evaluate goodness of fit. Statistical comparison of nested models was undertaken in the NONMEM program on the basis of a χ^2 test of the difference in