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Short Communication

Population pharmacokinetics of cefepime in febrile neutropenia: implications for dose-dependent susceptibility and contemporary dosing regimens

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ABSTRACT

Alterations in cefepime pharmacokinetic (PK) exposure and decreased bacterial susceptibility increase the risk of treatment failure. The impact of susceptible-dose-dependent (SDD) minimum inhibitory concentrations (MICs), i.e. 4–8 μg/mL, on target attainment rates for cefepime in febrile neutropenia (FN) is unclear. We sought to identify optimal cefepime regimens against SDD cefepime MICs in FN using a modelling and simulation approach. Creatinine clearance (CL_{Cr}) and body surface area (BSA) covariate-adjusted models of clearance were evaluated. Monte Carlo simulations representing 10 000 patients were completed to assess various dosing strategies (i.e. 3–8 g/day infused over 0.5–24 h, replaced every 6–24 h) and predict probabilities of target attainment (PTAs) for unbound cefepime. Nine patients received cefepime 2 g every 8 h (q8h) (0.5-h infusion). A two-compartment PK model with BSA- and CL_{Cr}–adjusted clearance was fit to the data. Mean population values for total clearance (6.3 ± 1.1 L/h), intercompartmental clearance (6.9 ± 2.8 L/h), and central (14.8 ± 3.8 L) and peripheral (10.9 ± 4.6 L) distribution volumes were all estimated with <50% CV. Simulated dosing regimens of 3–4 g/day administered as continuous infusions and doses of 2 g administered q6h (0–5 h infusion) to q8h (4-h infusion) achieved ≥90% PTA at MICs up to 8 μg/mL. Simulated regimens of 1 g q8h (4-h infusion) or 1 g q6h (0.5-h infusion) achieved ≥90% PTA only against MICs up to 4 μg/mL. High-dose prolonged infusion or more frequent cefepime regimens may be necessary to treat FN organisms with SDD MICs.

1. Introduction

Antimicrobial resistance among Enterobacteriaceae has forced the re-evaluation of cefepime susceptibility breakpoints. Increasing cefepime minimum inhibitory concentrations (MICs) are associated with higher rates of in-hospital mortality among cefepime-treated patients [1–5]. The Clinical and Laboratory Standards Institute (CLSI) defines Enterobacteriaceae MIC susceptibility breakpoints as follows: susceptible, ≤2 μg/mL; susceptible-dose-dependent (SDD), 4–8 μg/mL; and resistant, >8 μg/mL [6]. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretive criteria for Enterobacteriaceae have dramatically lower MIC breakpoints of 1 μg/mL and 4 μg/mL for susceptibility and resistance, respectively [7]. Thus, MICs within the SDD range are likely to require more aggressive dosing to yield ideal activity.

Correspondingly, patient populations with altered pharmacokinetics are expected to have variable probabilities of achieving pharmacokinetic/pharmacodynamic (PK/PD) targets for cefepime. Because the duration that the unbound cefepime concentration remains above the MIC ($fT_{>MIC}$) is the PK/PD efficacy target for β-lactams such as cefepime [8], decreasing cefepime $fT_{>MIC}$ significantly contributes to negative outcomes [9]. For high-risk patients, the cefepime $fT_{>MIC}$ should minimally exceed 60–70% of the dosing interval to reduce the risk of mortality in the setting of severe infection [8,9].

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We have previously described cefepime pharmacokinetics using a parametric approach among patients with neutropenic fever receiving standard dosing regimens [10]. The purpose of our previous investigation was to provide treating clinicians with initial estimates of cefepime pharmacokinetics that could be used to guide dosing; however, robust simulations were not evaluated at that time. In the present analysis, we sought to expand upon our initial study through the development of a non-parametric population pharmacokinetic (PK) model that could be used to simulate cefepime dosing strategies associated with optimal $fT_{>MIC}$ attainment against SDD MICs.

2. Materials and methods

2.1. Population, sample procurement and sample analysis

Patients with neutropenic fever ($n = 9$) receiving cefepime had venous blood collected (up to 11 time points per patient) [10]. All concentrations were obtained after a dose at steady-state and prior to the subsequent dose given (i.e. on a single concentration–time curve). Demographics and covariates (e.g. age, weight and serum creatinine) were obtained. Creatinine clearance (CL_{Cr}) was calculated for each patient [11] at the time of PK sampling. The study was approved by the Institutional Review Board at each investigator's primary institution. Serum cefepime concentrations were determined using liquid chromatograph–tandem mass spectrometry (LC-MS/MS) as previously described [10]. The lower limit of quantification for the assay was 10 ng/mL in a 100 μL sample for injection. For the present analysis, a linear curve was generated for relevant concentrations, and the assay was linear between 0.3 μg/mL and 80 μg/mL with 103–101% accuracy and 6.4–3.9% precision.

2.2. Pharmacokinetic models

The Nonparametric Adaptive Grid (NPAG) algorithm [12,13] within the Pmetrics v.1.5.0 package [13] for R [14] was utilised to conduct the population PK/PD analysis. Multiple physiologically relevant compartmental population PK models were tested. Covariate effects were evaluated using a backward stepwise regression of covariates on PK parameters. Pre-planned analyses were conducted to evaluate the impact of calculated CL_{Cr} [11] and body surface area (BSA) on cefepime clearance (Model 1). Clearance was linearly scaled to both CL_{Cr} and BSA, standardised to 120 mL/min and 1.73 m^2, respectively. In addition, cefepime clearance was limited using a non-linear Hill-type function [15] to evaluate potential saturability of cefepime clearance (Model 2, not shown). Differential equations for the covariate-adjusted, two-compartment PK model (Model 1) were:

$$\frac{dX_1}{dt} = \text{RateIV} + \left(\frac{Q}{V_p}\right) \times X_2 - \left(\frac{CL_T}{V_c} + \frac{Q}{V_c}\right) \times X_1 \quad (1)$$

$$\frac{dX_2}{dt} = \left(\frac{Q}{V_c}\right) \times X_1 - \left(\frac{Q}{V_p}\right) \times X_2 \quad (2)$$

$$CL_T = CL_R \left(\frac{CLCr}{120}\right) \times \left(\frac{BSA}{1.73\,m^2}\right) \quad (3)$$

where CL_T is the total cefepime clearance rate (L/h), CL_R is the renal cefepime clearance rate (L/h), V_c is the central cefepime volume of distribution (L), V_p is the peripheral cefepime volume of distribution (L) and Q is the intercompartmental cefepime clearance rate (L/h).

Assay error [standard deviation (SD)] and process noise were accounted for using an error polynomial as a function of the measured concentration, Y (i.e. $SD = C_0 + C_1 Y$) with C_0 and C_1 inputs of 0.7 and 0.15, respectively. The inverse of the observed variance (SD^2) was used as the first estimate for observation weighting [13]. Residual error was estimated using the multiplicative gamma (i.e. error = γ^*SD), which was given a starting value of 2. The best-fit model was determined by the rule of parsimony and Akaike's information criterion (AIC) score. The final PK model was used to generate the simulations (see Section 2.3). Goodness-of-fit and predictive performance of the competing models were evaluated as previously described [16], with model performance and validity assessed via simulation, generation of normalised prediction distribution errors, and construction of visual predictive checks. Median Bayesian posterior parameter estimates for each patient enabled calculations of posterior-predicted cefepime concentrations for each study patient. A non-compartmental analysis of the posterior-predicted cefepime concentration–time profiles was conducted to facilitate comparison of the individual-predicted cefepime exposures in our patients with PK estimates reported in previous studies.

2.3. Simulations and probability of target attainment (PTA)

For simulations, a covariate-based sampling method was employed to evaluate exposures predicted by the covariate-adjusted PK model [13,17]. The distributions of covariate values sampled were constrained to fall within the observed values in the original patient population (e.g. BSA range 1.7–2.2 m^2 and CL_{Cr} range 108–220 mL/min) using a truncated simulation strategy. Monte Carlo sampling of parameters and covariate values from the weighted, multivariate, unimodal distribution generated a population with 10 000 parameter sets. From the simulated population, concentration–time profiles were generated for cefepime regimens of 3–8 g/day in 0.5-h increments. Simulated doses were infused over 0.5, 2, 4 or 24 h and were replaced every 6, 8, 12 or 24 h. Predicted concentrations were corrected for protein binding (i.e. 80% unbound drug [18]) and were evaluated against a PK/PD target of $fT_{>MIC} \geq 68\%$ [9] across doubling MICs from 1–64 μg/mL over the first 24 h of therapy.

3. Results

3.1. Demographics

A total of nine patients contributed 93 concentrations, with eight of nine patients contributing 11 samples in a 24-h period after steady-state (i.e. ≥48 h after treatment initiation). Patients within the PK cohort had a mean ± SD weight of 82.5 ± 7.6 kg, a mean ± SD BSA of 1.95 ± 0.14 m^2 and a mean ± SD calculated CL_{Cr} of 149 ± 35.5 mL/min (range 108.8–220.3 mL/min). Patients ranged in age from 33–65 years (mean 54.4 years).

3.2. Pharmacokinetic model selection and parameters

Measured cefepime concentrations ranged from 1.30–160 μg/mL. For Model 1, the NPAG-fitted linear-clearance population model identified nine support points. The population PK model produced good fits of the observed concentrations ($R^2 = 91.3\%$), with low bias and imprecision (0.67 μg/mL and 9.66 $\mu g^2/mL^2$, respectively; Fig. 1A left). Likewise, the Bayesian individual posterior fits of the observed data were excellent ($R^2 = 95.7\%$, bias = –0.03 μg/mL, imprecision = 0.998 $\mu g^2/mL^2$; Fig. 1A right). Predictive checks of Model 1 revealed that ca. 5% ($n = 5/93$) of observations fell outside of the respective 95% confidence bands of the prediction intervals (Fig. 1B). Model 2 also produced good population and posterior fits with highly acceptable predictive checks (data not shown). Model 2 was more complex than Model 1 but was not significantly more explanatory, as indicated by a marginally higher AIC value (556 vs. 551.7, respectively; $P = 0.55$). Thus, Model 1 was selected as the final PK model for simulations.