Title

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Abstract

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Objective: Limited data exist on the effects of extracorporeal membrane oxygenation (ECMO) on pharmacokinetics of cefepime in critically ill pediatric patients. The objective was to describe cefepime disposition in children treated with ECMO using population pharmacokinetic modeling.

Design: Multi-center, prospective observational study

Setting: The pediatric and cardiac intensive care units of six sites of the Collaborative Pediatric Critical Care Research Network.

Patients: Seventeen critically ill children (30 days to < 2 years old) on ECMO who received cefepime as standard of care between Jan 4, 2014 and August 24, 2015 were enrolled.

Interventions: None.

Measurements/Results: A pharmacokinetic model was developed to evaluate cefepime disposition differences due to ECMO. A two-compartment model with linear elimination, weight effects on clearance (CL), inter-compartmental clearance (Q), central volume of distribution (V1), and peripheral volume of distribution (V2) adequately described the data. The typical value of clearance in this study was 7.1 mL/min (1.9 mL/min/kg$^{0.75}$) for a patient weighing 5.8kg. This value decreased by approximately 40% with the addition of renal replacement therapy. The typical value for V1 was 1170 mL. In the setting of blood transfusions, V1 increased by over 2-fold, but was reduced with increasing age of the ECMO circuit oxygenator.

Conclusion: Cefepime clearance was reduced in pediatric patients treated with ECMO compared to previously reported values in children not receiving ECMO. The model demonstrated that the age of the ECMO circuit oxygenator is inversely correlated to V1. For free cefepime, only 14 of the 19 doses (74%) demonstrated a *fT*_MIC of 16 mg/L, an appropriate target for the treatment of pseudomonal infections, for greater than 70% of the dosing interval. Pediatric patients on ECMO might benefit from the addition of therapeutic drug monitoring of cefepime to assure appropriate dosing.

Keywords

ECMO; pediatrics; population pharmacokinetics; cefepime

Introduction

Extracorporeal membrane oxygenation (ECMO) can provide patients with severe cardiopulmonary failure partial or complete respiratory or cardiac support for days to weeks. This is accomplished by draining blood from the body into an extracorporeal circuit and pumping it across a membrane lung that oxygenates the blood and eliminates carbon dioxide.(1) There are two types of ECMO circuits: (i) veno-venous (VV) ECMO provides support for the lungs whereas (ii) veno-arterial (VA) ECMO provides support for both the heart and lungs. The ECMO system introduces variables that increase drug variability, which are inherent to the circuit itself, as well as the systemic inflammation that results from the use of the circuit. Sequestration of drugs in the circuit, increased volume of distribution (Vd), and decreased clearance (CL) are the major pharmacokinetic (PK) changes associated with ECMO.(2, 3). Neonatal and adult studies have reported significant alterations in antibiotic, sedative, and analgesic disposition.(4, 5) The amount of drug sequestration is

influenced by many factors including the age of the circuit components, the circuit priming volume as well as the type of pump, oxygenator, and tubing.(6–9) Patient factors such as systemic inflammation, hemo-dilution, bleeding, transfusion requirement, organ dysfunction, and renal replacement therapy (RRT) add to the challenges of appropriate drug administration during ECMO.(10, 11) In addition, individual hospitals and intensive care units (ICU) use different techniques when building their respective ECMO circuits. The extent to which these factors can alter the variability in drug disposition has not been quantified to date and remains poorly characterized.

Cefepime, a fourth-generation cephalosporin, is a bactericidal agent that has broad spectrum of activity against both gram-positive and gram-negative bacteria, including activity against pseudomonas, making it a commonly used antibiotic in this population for suspected or known gram-negative infections.(12). The pharmacodynamic (PD) relationship historically thought to be predictive of cefepime efficacy is the percentage of time of the dosing interval that the free drug concentration remains above the minimum inhibitory concentration (MIC) of the infecting organism ($fT\_$MIC).(13) Numerous *in vivo* animal studies with various cephalosporins have suggested that a $fT\_$MIC target of 50 to 70% is required to achieve maximal reductions in the numbers of colony forming units of gram-negative bacteria.(14) However, the data available from evaluations of cephalosporin PD have been less decisive and are discordant with the findings of *in vivo* animal studies. Published reports of studies examining cefepime PD in patients with gram-negative infections found the ratio of the minimum cefepime concentration to the MIC (C_{min}/MIC) to be the parameter best associated with a microbiological response, while another study defined the ratio of the area under the concentration time curve to the MIC (AUC/MIC) to be the most predictive.(15–17) Moreover, when the $fT\_$MIC for total drug was evaluated, investigators found that targets of 90 to 100% were required for predictable microbiological success.(15, 17) These studies demonstrated that cefepime concentrations as high as 4–$6.6 \times$ MIC are required for bactericidal activity, (17, 18) but these higher concentrations have also been associated with neurotoxicity.(19) Overall, there is still no consensus on optimal dosing, but rather it is generally accepted to target a $fT\_$MIC of 70– 90% according to the suspected pathogen.

Data regarding the impact of ECMO on cefepime disposition is warranted given the need for therapeutic concentrations to ensure efficacy while also minimizing toxicity. Unlike antibiotics such as many aminoglycosides and vancomycin, cefepime dosing is not guided by therapeutic drug monitoring. As such, concentrations achieved with standard dosing are not routinely assessed. Achievement of target concentrations may not occur, especially in clinical scenarios such as ECMO where drug disposition may be impacted. The aim of this study was therefore to provide preliminary data on cefepime disposition in pediatric patients receiving ECMO therapy, specifically with regards to site dependent differences in management.

Materials and Methods

This multicenter observational PK study was conducted at hospitals in the Collaborative Pediatric Critical Care Research Network (CPPCRN). The project was approved by each institution's Institutional Review Board and the Data Coordinating Center at the University

of Utah and informed consent was obtained from parents/guardians before any study procedure commenced. Patients receiving ECMO therapy were screened daily for eligibility. Inclusion criteria included patients aged 30 days to < 2 years, receiving ECMO therapy and intravenous cefepime for the treatment of known or suspected gram negative infections based on the decision of the clinical care team. Exclusion criteria included treatment with ongoing massive blood product transfusion for hemorrhage, RRT, therapeutic plasma exchange, or previous enrollment in this study. A later protocol revision allowed subjects receiving RRT to be enrolled due to its frequent utilization during ECMO, enabling and assessment of its impact on cefepime PK and improved the study generalizability. Once eligibility criteria were met, the parent(s) or legal guardian(s) were approached for consent.

Cefepime could have been prescribed every 6, 8, 12, 18, or 24 hours. For each subject, target PK samples (n=10) were collected based on the dosing interval for one or two cefepime doses separated in time by at least 24 hours. Separating the two cefepime doses by at least 24 hours instead of consecutive doses allowed evaluation of cefepime disposition due to any potential impact of circuit age within each subject. Hypothetically, older circuits are exposed to more medications and potential drug-binding sites may became saturated. A maximum of 20 mL (1 mL per sample) could be collected from lumens not used to administer cefepime. After collection, samples were transferred to labeled lithium heparinized tubes and placed immediately on ice.

Plasma Sample Analysis

Plasma was separated from blood by centrifuging samples at 2500 rpm for 10 minutes and then stored at −80°C. The cefepime concentrations in plasma samples were determined using a validated high-performance liquid chromatography and tandem mass spectrometry assay. Samples were processed on ice due to the limited stability of cefepime in plasma at room temperature.(20) Plasma samples (50 μL) were mixed with 200 μL internal standard solution (250 ng/mL cefepime-d3 in acetonitrile), vortexed and centrifuged at 4000 rpm for 20 min. Next, 150 μL of the supernatant was transferred to a clean 96-well plate and 10 μL was injected for analysis. Chromatographic separation was achieved using a Kinetex PFP column (4.6 × 50 mm, 2.6 μm 100 A; Phenomenex, Torrance, CA), with mobile phase A consisting of 5 mM ammonium acetate in water (pH 5.0) and mobile phase B consisting of 5 mM ammonium acetate in 90/10 acetonitrile/water. Cefepime and cefepime-d3 were detected using an API4000 mass spectrometer (AB Sciex, Redwood City, CA). The lower limit of quantitation for the cefepime plasma assay was 5 ng/mL with an assay range of 5–10,000 ng/mL. The intraday precision based on the standard deviation of replicates of quality control samples ranged from 2.9% to 4.8% with accuracy ranging from 91% to 107%. The interday precision based on the standard deviation of replicates of quality control samples based on 3-day validation ranged from 4.7% to 9.2% with accuracy ranging from 98% to 108%. Cefepime was stable in human plasma under assay and storage conditions. Since the Kinetex PFP column was no longer available, the assay was validated with Kinetex F5 column (4.6 × 50 mm, 2.6 μm 100 A; Phenomenex, Torrance, CA) for further analysis of plasma and ultrafiltrate samples.

Plasma Protein Binding Assessment

A previous study demonstrated concentration independent plasma protein binding of 21% ($fu = 0.79 \pm 0.09$) for cefepime based on ultrafiltrate-dialysate samples from patients.(21) Since cefepime is not stable in plasma at 37^0C, the equilibrium dialysis method could not be utilized.(20) We therefore evaluated an ultrafiltration method that had been successfully used for other cephalosporin antibiotics.(22, 23) The cefepime plasma assay was cross-validated for the analysis of ultrafiltrate samples to measure total plasma and ultrafiltrate concentrations in a single assay. Twenty representative plasma samples were processed by ultrafiltration of 170 μL of plasma with a Spin-X ultrafiltrate membrane (10,000 molecular weight cutoff; Corning Inc, Lowell, MA) at 4^0C for 30 minutes to measure unbound cefepime. However, the measured concentrations of cefepime in ultrafiltrate samples were higher (112%) than the concentrations in the corresponding plasma samples. To further evaluate the limitation of the ultrafiltration method to measure cefepime free fraction, cefepime plasma standards (100 μg/mL) were subjected to ultrafiltration. The concentration measured in an ultrafiltrate sample was 102 μg/mL and the residual plasma was 36.6 μg/mL. It was determined that during ultrafiltration, cefepime concentration in the upper reservoir decreased and cefepime concentration in the ultrafiltrate increased compared to the starting plasma concentration. This is likely due to the dissociation of bound cefepime and equilibration during ultrafiltration.(24) Therefore, the ultrafiltration method could not be used for accurately measuring plasma protein binding of cefepime, and the free fraction could not be determined. As a result, the free fraction was assumed to be 80% of the total based on previous reports and which has been successfully implemented. (21)

Pharmacokinetic Analysis

Initial concentration time plots were constructed using linear interpolation between two measured concentrations to produce an approximated concentration value every five minutes. This concentration time profile was used to calculate the percent of the dosing interval that was above a target MIC. This was performed for both the total and free concentrations. A target MIC of 16 mg/L was used based on published evidence that this represents the MIC90 of cefepime against pseudomonas.(25)

Cefepime disposition was estimated using a population pharmacokinetic analysis (NONMEM software, version 7.2, ICON Gaithersburg, MD). All models were run with the first-order conditional estimation with interaction. Goodness-of-fit diagnostics and graphical displays were generated in R (www.r-project.org). The goodness of fit from each run was assessed by examining the following criteria: visual evaluation of diagnostic plots, parameter precision, successful minimization, changes in Akaike Information Criteria (AIC) which is based on the minimum objective function value (OFV), and the size of interindividual and residual variabilities for the specified model.

Various compartmental disposition models were investigated. Unexplained random variability of parameters between individuals was described using an exponential variance model. Additive, proportional, and combined (additive and proportional) residual error models were considered during the model building process. The effect of weight on clearance (CL), intercompartmental clearance (Q), central (V1) and peripheral (V2) volumes

of distribution were investigated by allometric scaling: $TVP = \theta_{TVP} * (WT_i/WT_{ref})^{\theta_{allometric}}$ where TVP is the typical value of the parameter, θ_{TVP} is the population value for the typical subject, WT is the weight of each subject i and a reference weight which was set at the median weight for the cohort, 5.8 kg. The impact of size is represented by $\theta_{allometric}$, which is a power parameter and is fixed at 0.75 for CL and Q and 1 for volumes.(26)

Covariates were pre-specified and included in the model based on prior knowledge, clinical interest, and physiologic plausibility of their potential effects. The following hypotheses were evaluated via estimation of covariate effects: (1) blood transfusions (BT) may increase circulating volume and therefore may increase V1; (2) tube coating (TC) would decrease V1 since many ECMO circuits are constructed of tubing that is coated to prevent binding of circulating drugs to the circuit tubing; (3) oxygenator age may impact V1 as newer oxygenators may have less of the surface area bound by circulating drugs whereas older oxygenators may have saturated their surface areas; and (4) renal dysfunction would result in a decrease in systemic CL since cefepime is primarily renally cleared. Creatinine values (SCr) were evaluated as surrogates for renal dysfunction. Additionally, if RRT was used, cefepime CL could be increased if drug was filtered off during RRT, or alternatively decreased if drug not filtered and accumulates with renal dysfunction. Dichotomous covariates (BT, TC, and RRT) were evaluated as multiplicative covariate models specified as $TVP = \theta_{TVP} * (\theta_{COV})^{COV_{yes/no}}$ where TVP is the typical value of the parameter, θ_{TVP} is the population parameter estimate and θ_{cov} is the effect of the covariate. In the event that the covariate was not present (equal to 0), $(\theta_{COV})^{COV_{yes/no}}$ is equal to 1 and there is no effect of that covariate on the parameter. Continuous covariates (serum creatinine and oxygenator age in days) were evaluated using power models where $TVP = \theta_{TVP} * (covariate\ value)^{\theta_{covariate}}$ where the covariate value is the value at the time the PK samples were obtained and $\theta_{covariate}$ is the effect of that covariate on the parameter of interest. In order to assess impact of potentially correlated covariates on parameter estimates and model stability, univariate exclusion of covariates was conducted.

Results

Seventeen infants from six participating CPCCRN sites were treated with cefepime, and enrolled in the trial between Jan 4, 2014 and August 24, 2015. Indications for cefepime administration include suspicion/rule-out sepsis (n=3), prophylaxis for surgery or ECMO (n=9), active infection (n=3), acute respiratory failure in a burn patient (n=1), and unknown (n=1). Cohort demographics including ECMO specific characteristics are listed in Table 1. One subject was treated with VV ECMO while the others were all treated with VA. Details of the sampling schedule employed for the subjects are in Table 2. The number of samples, number of cefepime doses per subject (one or two), study covariates, including BT, TC, oxygenator age, and RRT are presented in Supplemental Table 1. Eleven subjects received a blood transfusion during a sampling period (Supplemental Table 2). Fourteen subjects were treated with coated ECMO circuits and two subjects were treated with RRT. Oxygenator age during PK sampling ranged from one to six days. Limited PK sampling occurred in Subject 4 (2 of 10 planned samples), and subject 11 (6 of 10). Furthermore, cefepime concentrations were not detectable in Subject 6. The reason for this could not be determined. Subject 9 demonstrated low concentrations and upon review of the medical record and discussions

with the investigative team it was identified that throughout the sampling period there were multiple issues with fluctuating ECMO flows and hemodynamics, which was caused by a clot obstructing the entire atrial cannula. The ECMO circuit was changed 90 minutes after the final sample was obtained.

Determination of percent of time above MIC is presented in Supplemental Table 1. Subjects 4, 6, 9, and 11 were not included in this analysis. For total cefepime, 16 of the 19 doses (84%) demonstrated a fT_MIC of 16 mg/L for greater than 70% of the dosing interval. For free cefepime (based on 20% protein binding), 14 of the 19 doses (74%) demonstrated a fT_MIC of 16 mg/L for greater than 70% of the dosing interval (again excluding Subjects 4, 6, 9 and 11).

Concentration time curves per subject are provided in Figure 1. For the population PK model, subject 6 was excluded from analysis because of no detectable cefepime concentrations. The base PK model was developed using 196 samples from 16 subjects based on clinically-driven dosing decisions. A total of 22 doses were evaluated. Six of the 16 subjects underwent PK sampling for two doses separated in time by at least 24 hours while the remaining 10 subjects were sampled for only one dose.

A two-compartment model with linear elimination, with weight allometrically scaled on CL, Q, V1, and V2 resulted in improved goodness-of-fit based on all criteria, relative to a one-compartment model. Progression of model development and the quantitative effects of each covariate on PK parameters are described in Supplemental Table 3 which includes the assessment of BT, TC, RRT effects, serum creatinine (SCr) and then the addition of oxygenator age on cefepime PK parameters. Initially the effect of BT, TC, creatinine, oxygenator age, and RRT were independently evaluated. Next, covariates were added to the model in combinations to determine if there was collinearity between the covariates, indicated by a change in the covariate effect when alone in the model as compared to a model that contained additional covariates. The covariates were deemed to not be collinear. The covariate effect of TC on V1 was estimated at 10.9 when alone in the model, and reduced to 1.6 with other covariates. However, the value of 10.9 was imprecise with a 95% CI of −11.6 to 33.4, and therefore we did not deem this change to represent collinearity with other covariates. The addition of RRT and creatinine as a covariate on CL, and BT, TC, and oxygenator age on V1 resulted in a 30 point reduction in both OFV and AIC, without a successful covariance step. The removal of the intersubject variability term on Q (which was estimated to be very small) resulted in an additional 15 point reduction in both measures and successful execution of the covariance step. Confidence intervals for covariate effects demonstrated poor precision with 95% CI crossing the null value except for the estimate of BT on V1 and RRT on CL in the final model.

Final estimates for population model typical values, covariate effects, and variability parameters, along with the asymptotic normal 95% confidence intervals, are shown in Table 3. A proportional error model was used to describe the random residual variability. Creatinine demonstrated a narrow range of only 0.1–0.9 mg/dL. Despite this narrow range, serum creatinine values were included in the model to account for renal function in this

population. Observed versus population and individual predicted concentrations for the full covariate PK model are presented in Figure 2.

Discussion

In infants receiving ECMO, the PK model estimated a typical value of allometrically scaled clearance of 7.1 mL/min/5.8kg (1.9 mL/min/kg$^{0.75}$) for a subject not treated with RRT, BT, or TC. Cefepime PK parameters can be estimated using the model structure (shown in the legend of Table 3). The model suggests that CL is reduced in the presence of RRT. In addition, our model suggests that V1 is increased in the setting of blood transfusions and tube coating, while V1 is decreased with increasing oxygenator age. However, the covariate effects of TC and oxygenator age were not precise or statistically significant, but are presented to demonstrate that they may be important covariates in cefepime disposition if evaluated in a larger cohort. Each institution utilized similar ECMO components (tubing and oxygenators). Variability in ECMO management (blood transfusions, coating, and RRT) were accounted for during model development by the interindividual and residual variabilities (Table 3), representing inter-institutional variability.

Linear interpolation between observed concentrations allowed for the determination of the percent of the dosing interval above the target MIC. Specifically, linear interpolation only assumes linearity between two observed concentrations, but does not assume linearity across the whole profile of each subject, therefore does not affect clearance predictions produced by the population pharmacokinetic model. Five of the 19 doses evaluated achieved a *fT*_MIC of 16 mg/L of 70% for free concentrations. The target of 70% itself may not be sufficient, with some studies stating that the *fT*_MIC should be closer to 90%.(15, 17) This represents failures in target attainment in 26% of the doses. These failures occurred in both doses for Subject 2 and the single dose in Subject 8. The doses utilized for analysis in these subjects were the 1st and 4th cefepime dose for Subject 2 and the 3rd cefepime dose for Subject 8. This may suggest that standard dosing early in the treatment course, prior to achievement of steady state, may result in concentrations that do not achieve the target, and warrants the consideration of a loading dose. However, Subjects 5, 7, 15 and 17 also had early doses evaluated, and these doses achieved the target *fT*_MIC of 16 mg/L of 70% for both total and free concentrations.

Cefepime PK has been evaluated in pediatric patients who were not receiving ECMO following single and multiple 50 mg/kg doses on q8h and q12h schedules.(27) The mean (± SD) age of the patients was 3.6 (± 3.3) years, and ranged from 2.1 months to 11.2 years. Following a single intravenous dose, total body clearance averaged 3.3 (± 1.0) mL/min/kg. (28) In another study of neonates, infants and children who received cefepime without ECMO, CL was determined to be 2.59 mL/min/kg for children greater than 30 days. These CL values are higher than estimated in the ECMO population in the current study (1.9 mL/min/kg$^{0.75}$) (29), suggesting that CL is reduced while on ECMO. However, the steady state volume of distribution of 0.37 ± 0.07 L/kg (29) in the previously reported study is slightly smaller than the total volume of distribution (V1+V2) determined in this ECMO study (0.4 L/kg). This larger volume of distribution may contribute to the failure in achieving target concentrations, especially in the presence of blood transfusions and tube

coating where the total volume can increase substantially (1.0 L/kg). Even with an older oxygenator (~ 6 days as in this study) reduction in volume, the volume of distribution is still larger (0.7 L/kg) than the previously reported value. Overall, the volume of distribution of cefepime with the use of ECMO can increase almost 2.5-fold compared to the volume without the use of ECMO, thereby reducing the overall amount of cefepime available to be cleared.

Cefepime has been associated with a greater risk of mortality than other β-lactams in patients treated for severe sepsis. Cefepime's PK and efficacy were examined in a prospective non-interventional study of 21 consecutive ICU adult patients treated with cefepime for nosocomial pneumonia.(30) Patients (median age 55.1 years, range 21.8 to 81.2) received intravenous cefepime at 2 grams every 12 hours for creatinine clearance (CLCr   50 mL/min, and 2 grams every 24 hours or 36 hours for CLCr < 50 mL/minute. Seventeen first-doses and 11 steady states were measured. Plasma levels varied greatly between individuals, from two- to three-fold at peak-concentrations to up to 40-fold at trough-concentrations. Twenty-one of 21 (100%) patients had cefepime concentrations above the MIC for the pathogens recovered in that study (MIC   4 mg/L), but only 45 to 65% of them had appropriate coverage for potential pathogens with cefepime MIC   8 mg/L. Moreover, 2/21 (10%) patients with renal impairment (CLCr < 30 mL/minute) demonstrated accumulation of cefepime (trough concentrations of 20 to 30 mg/L) in spite of dosage adjustment. Both had symptoms compatible with non-convulsive epilepsy that were not attributed to cefepime-toxicity until plasma levels were disclosed to the caretakers and symptoms resolved promptly after cefepime was discontinued. The authors confirmed the suspected risks of hidden side effects and inappropriate PK/PD parameters (for pathogens with upper-limit MICs) in a population of ICU adult patients. In yet another study, high cefepime plasma concentrations were associated with neurological toxicity in febrile neutropenic patients with mild renal dysfunction.(19) Given these reports and observations, an approach to dosing that includes a philosophy of "just give more" places patients at risk of toxicities. Unfortunately, cefepime and additional β-lactam antibiotics do not have readily available therapeutic drug monitoring, leaving the prescriber to rely on best guesses in circumstances such as renal impairment and ECMO.

The small sample size of this study limits its ability to adequately estimate all the factors that impact cefepime disposition. The cohort did not demonstrate renal insufficiency based on creatinine values despite two subjects undergoing treatment with RRT. Early implementation of RRT may have prevented serum creatinine to rise and the determination of renal insufficiency based on serum creatinine. In addition, the cohort was compromised of predominately VA ECMO patients, and therefore, differences between VA and VV could not be determined. Finally, the reasons that one subject had no detectable plasma cefepime concentrations and for failure to attain target concentrations in Subjects 2 and could 8 could not be determined. The subjects enrolled in this study were sedated on ECMO and potential neurological side effects were therefore not evaluated. These neurological side effects have been reported to occur in the setting of higher concentrations, which was not the case for the subjects enrolled in the study.

In conclusion, the results suggest that cefepime CL in infants receiving therapy with ECMO is reduced when compared to children who are not receiving ECMO, and the Vd is larger. CL may be reduced in the setting of RRT, and V1 may be increased during blood transfusions and in circuits that are coated. V1 is decreased as the oxygenator ages, and this effect was precisely estimated. For free cefepime, only 14 of the 19 doses (74%) demonstrated a *fT*_MIC of 16 mg/L for greater than 70% of the dosing interval, demonstrating inadequate dosing to treat pseudomonal infections. Although the current model provides insight into the effects of ECMO on the cefepime PK, larger studies should include subjects of all ages to identify the impact of covariates on drug disposition as a step toward precision dosing. Additionally, further studies are necessary to determine the exact *fT*_MIC percentage improves the clinical outcomes in this population. Alternatively, cefepime therapeutic monitoring should be considered in the clinical setting to improve the ability to achieve therapeutic targets and minimize the potential for toxicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Supplementary Material

Supplementary Material Supp2.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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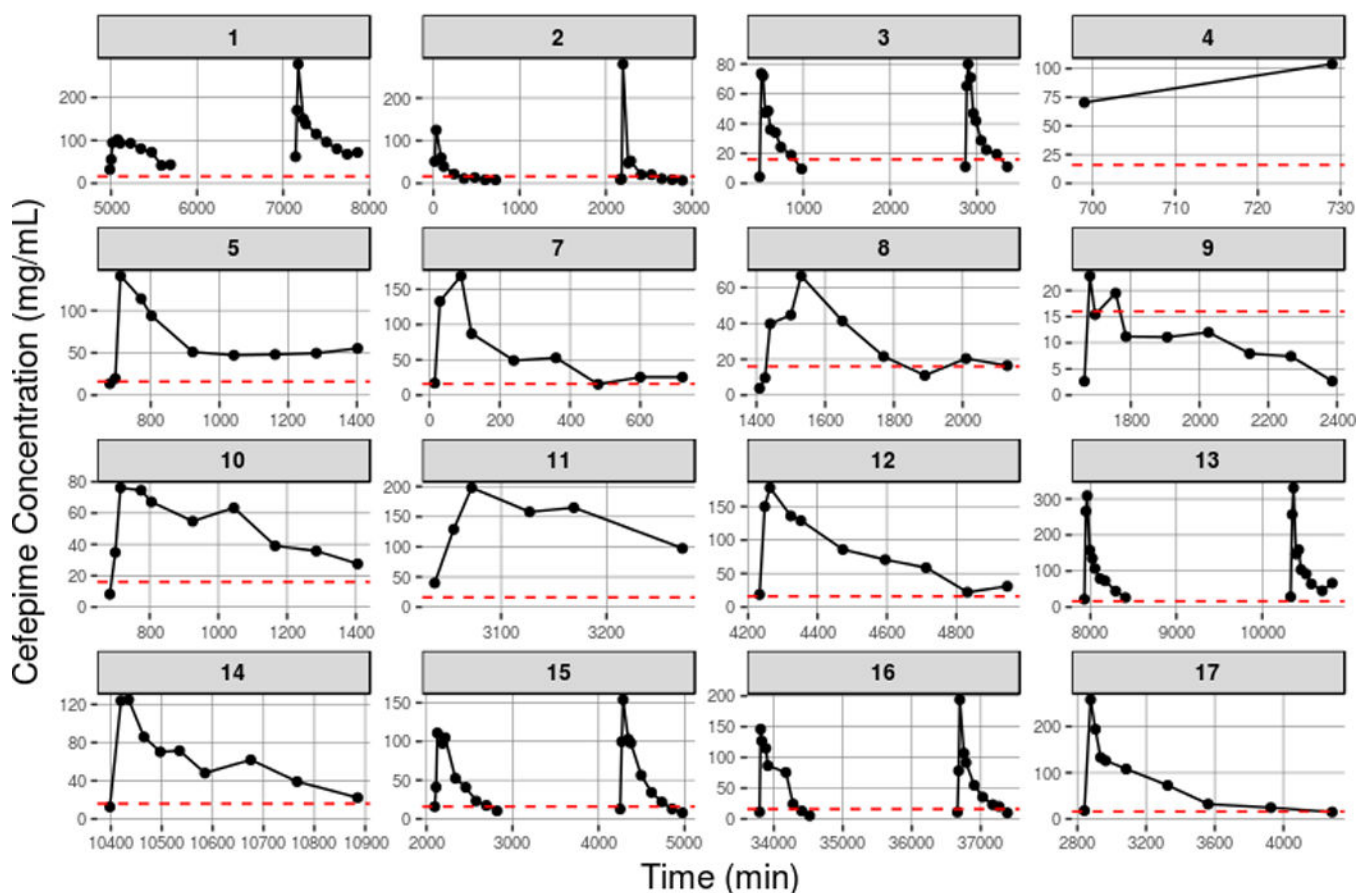
Figure 1. Concentration time plots for total concentrations.
Red dashed line represents MIC for pseudomonas of 16 mg/L. (25) Time 0 denotes the time
that the subject first received cefepime. Plasma concentrations represent when the dose that
was measured for the study was administered in reference to the first administered dose
(time (x axis) =0).
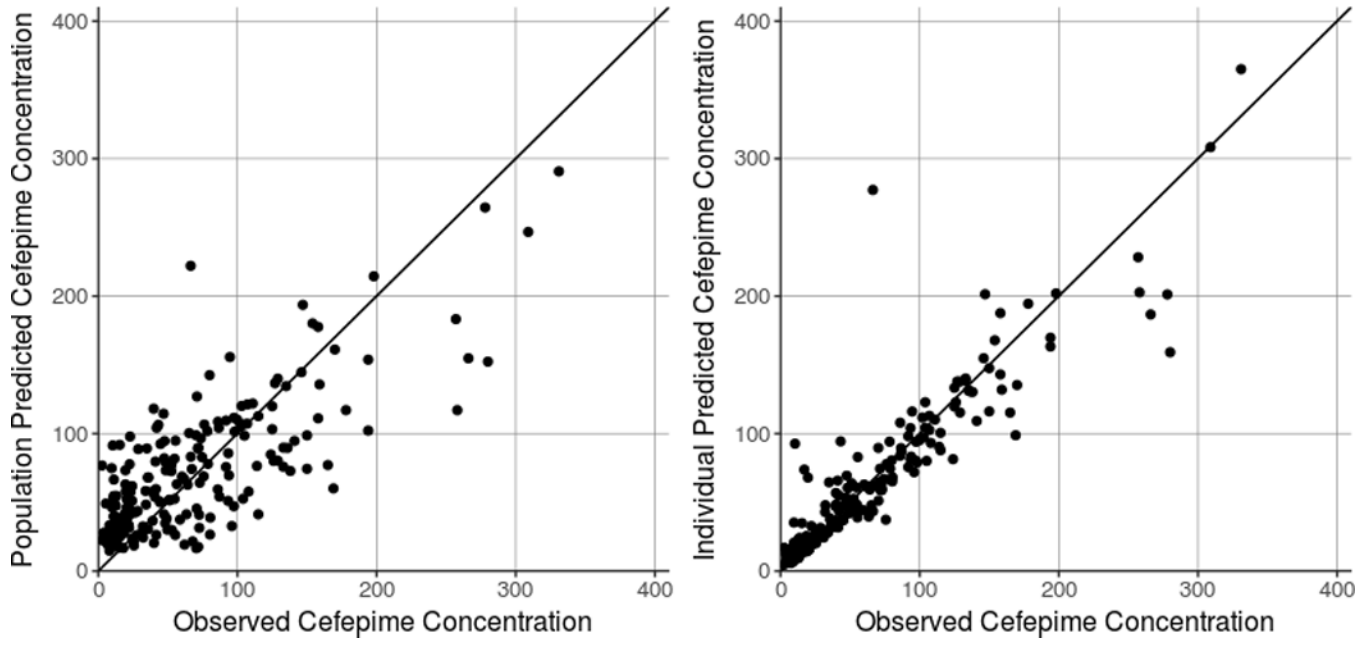
Figure 2.
Observed concentration vs. individual (left) and population (right) predicted plots.

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Table 1.

Cohort demographics.

ID	Site [a]	Primary Diagnosis	Dose (mg/kg)	Dosing Interval (hours)	Weight (kg)	Age (months)	Gender	Ethnicity	ECMO Mode [b]	Pump Type
1	1	Congenital CV	50	q12	4.0	1.4	Male	Not Hispanic/Latino	VA	Roller
2	1	Congenital CV	50	q12	4.3	5.3	Male	Not Hispanic/Latino	VA	Roller
3	2	Respiratory failure	50	q8	6.3	7.6	Female	Not Hispanic/Latino	VA	Centrifugal
4	3	Congenital CV	50	q12	5.0	2.1	Male	Hispanic/Latino	VA	Centrifugal
5	4	Congenital CV	50	q12	6.9	8.0	Female	Not Hispanic/Latino	VA	Roller
6	4	Cardiac arrest	50	q12	3.3	2.9	Female	Not Hispanic/Latino	VA	Roller
7	4	Congenital CV	50	q12	9.7	22.2	Male	Not Hispanic/Latino	VA	Roller
8	4	Congenital CV	50	q12	7.3	8.0	Male	Not Hispanic/Latino	VA	Roller
9	4	Cardiac arrest	50	q12	3.8	2.4	Male	Not Hispanic/Latino	VA	Roller
10	4	Acquired CV	50	q12	8.0	3.3	Female	Not Hispanic/Latino	VA	Roller
11	2	Congenital CV	50	q12	5.3	4.1	Female	Not Hispanic/Latino	VA	Centrifugal
12	5	Congenital CV	50	q12	4.8	5.2	Male	Not Hispanic/Latino	VA	Centrifugal
13	5	Congenital CV	50	q8	7.5	6.3	Male	Hispanic/Latino	VA	Centrifugal
14	2	Congenital CV	50	q8	5.5	8.0	Male	Not Hispanic/Latino	VA	Centrifugal
15	1	Burn [f]	50	q12	10.0	12.3	Female	Not Hispanic/Latino	VA	Roller
16	6	Congenital CV	50	q12	3.3	1.3	Female	Not Hispanic/Latino	VV	Centrifugal
17	5	Congenital CV	50	q24	4.2	3.8	Female	Unknown	VA	Centrifugal

[a] CPCCRN site assignment

[b] Veno-arterial (VA) or veno-venous (VV)

[c] Subject 15 sustained burns over 73% of their body surface area

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Table 2.

Sampling Schedule.

| Dosing schedule | *Minutes after dose* | | | | | | | | | | | | Total number of samples |
	15	30	60	90	120	180	240	300	480	600	720	
q 8 hr	✓	✓	✓	✓	✓	✓	✓	✓	✓			10
q 12 hr	✓	✓	✓		✓		✓	✓	✓	✓	✓	10

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Table 3.

Parameter Estimates from the Final Cefepime Population PK Model

	PARAMETER	POINT ESTIMATE	RSE%
FIXED			
	CL (mL/min) for a 5.8kg individual	7.1	24.3%
	V1 (mL/5.8kg)	1170	46.3%
	Q (mL/min/5.8kg)	12.5	19.8%
	V2 (mL/5.8kg)	1130	26.8%
	RRT CL	0.60	25.6%
	SCr CL	-0.22 [**]	78.7
	BT OXYDAY V1	2.86	25.0%
	TC V1	1.37 [**]	56.9%
	OXYDAY V1	-0.29	66.0%
INTERINDIVIDUAL VARIABILITY			
	CL	54.5%	51.5%
	V1	73.8%	38.4%
	V2	47.3%	86.2%
RESIDUAL VARIABILITY			
	Proportional	30.4%	17.9%

Parameter estimates are for a typical individual of 5.8kg, with no RRT, no blood transfusion, uncoated tubing, and 0 oxygenator days. RSE is the relative standard error.

Interindividual and residual variability are presented as percent coefficient of variation calculated by the square root of the variance x 100.

[**] indicates 95% CI crosses null value.

CL (mL/min) $= 7.05*(WT/5.8)^{0.75} *0.60$ (if receiving RRT) $* (SCr)^{-0.22}$

In setting of no blood transfusions:

V1(mL) $=1170*(WT/5.58) *1.37$ (if tubing is coated)$*(oxygenator\ day)^{-0.29}$

In setting of a blood transfusion:

V1(mL) $=1170*(WT/5.58) *1.37$ (if tubing is coated) $* (oxygenator\ day)^{-0.29} * 2.86$

Q$=12.5*(WT/5.8)^{0.75}$

TVV2$=1130*(WT/5.8)$