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Population Pharmacokinetics of Continuous Infusion Ceftazidime

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Abstract

Objective: The purpose of this study was to develop and validate a model that predicts clearance and steady-state ceftazidime concentrations during continuous infusion.

Design: This was a prospective clinical observational trial. Two models describing drug clearance during the continuous infusion of ceftazidime to infected patients were developed. The first model included inter- and intraindividual variability (IIV) while the second extended the first model by including interoccasional variability (IOV).

Setting: This was a study of patients in a US hospital between January and June 1996.

Patients and participants: The analysis included 39 patients aged >18 years with infections at various sites.

Interventions: Patients received ceftazidime as either a 1000 or 2000mg loading dose followed by a continuous infusion of 1000 to 4000 mg/day. Serum samples were collected under approximate steady-state conditions and ceftazidime concentrations were analysed using high performance liquid chromatography. The models were fitted to the data using a nonlinear mixed effects model as implemented in the NONMEM program.

Results: 75 serum concentration measurements were included in the analysis. The routinely available clinical variables bodyweight, age, gender and serum creatinine were found to be statistically independent predictors of ceftazidime clearance. The IIV model was cross validated yielding a mean prediction error (with a 95% confidence interval) of –0.51 mg/L (–2.5 to 1.4 mg/L) and a mean absolute prediction error of 6.5 mg/L (5.3 to 7.8 mg/L).

Conclusion: We have developed and validated a model to estimate ceftazidime concentrations during continuous infusion using commonly available clinical information. Additional work is needed to compare outcomes of patients receiving continuous and intermittently administered ceftazidime, and to define the optimal target steady-state ceftazidime concentrations during continuous infusion.

Ceftazidime is a parenterally administered cephalosporin with inhibitory and/or bactericidal activity against *Pseudomonas aeruginosa* and many Enterobacteriaceae isolates.[1] Ceftazidime is commonly used in the treatment of nosocomial pneumonia and infections associated with neutropenic

fever.[2] Like other β-lactam antibiotics, ceftazidime exhibits time-dependent bacterial killing as opposed to concentration-dependent killing.[3]

Comparisons between continuous infusion and intermittently infused ceftazidime have suggested that continuous infusion is more efficient as it provides a superior serum bactericidal activity while using equal or lower daily dosages.[4-6] Previous studies have examined the kinetics of intermittently or continuously administered ceftazidime in healthy volunteers with and without renal compromise and in patients with presumed infection as well as various disease states.[7-29] Novel *in vitro* explorations into the pharmacodynamics of ceftazidime have also been reported.[30,31]

This study was a prospective clinical observational trial of continuous infusion ceftazidime. The purpose was to develop and validate a model that predicts clearance and steady-state ceftazidime concentrations during continuous infusion. This study used the nonlinear mixed effect model as implemented in the NONMEM program for pharmacostatistical analysis.[32]

Materials and Methods

Patients, Sampling and Analyses

Ceftazidime concentration data were obtained at Metropolitan Hospital in Grand Rapids, Michigan, in the USA. This study was a collaborative effort between the Hospital's Infectious Disease, Pharmacy, Medicine, Laboratory and Nursing departments. The study was coordinated by the Pharmacy's Therapeutic Drug Monitoring Service (TDMS). 39 patients with 75 serum concentration measurements were included in the analysis.

The Institutional Review Board of Metropolitan Hospital approved the study with the understanding that no additional phlebotomies beyond those considered part of routine patient care would be performed. Patients were excluded from the study if they were younger than 18 years of age, pregnant or lactating, allergic to cephalosporins or had CNS infections. Patients referred to the TDMS for ceftazidime continuous infusion management between January 1 and June 1 1996 were included in the study.

The Fortaz® brand of ceftazidime (Glaxo Wellcome Inc., Research Triangle Park, NC, USA) was used in all patients. Loading doses were either 1000 or 2000mg and were diluted in 50 to 100ml of 5% dextrose or normal saline and infused by gravity over 15 minutes. The size of the loading dose was rather arbitrary and was generally determined by the ordering physician. A continuous infusion rate was calculated to attain steady-state serum concentrations (C^{ss}) equal to the higher of 24 mg/L [3 times the National Committee for Clinical Laboratory Standards (NCCLS) break-point for susceptibility] or 2 times the highest bacterial minimum inhibitory concentration (MIC) of concern for a given patient.[33] The formulas used to estimate ceftazidime clearance and volume of distribution, and hence infusion rates and approximate times to steady-state, were taken from Leroy et al.[7]. Maintenance doses of ceftazidime were diluted in 5% dextrose or normal saline and the administration rate was controlled via an infusion pump (Flo-Guard 6200; Baxter Co., Deerfield, IL, USA). Intravenous site patency and accuracy of ceftazidime administration rates were monitored by the Intravenous Team of the Nursing department.

Serum samples for ceftazidime analysis were obtained with routine morning phlebotomies. Samples were ordered only if laboratory work was already scheduled and at least 5 estimated half-lives (based on the formula in Leroy et al.[7]) had elapsed since the beginning of the continuous infusion. For a given patient, the time between any 2 ceftazidime concentration measurements was approximately an integral multiple of 24 hours.

Serum ceftazidime concentrations were measured by high performance liquid chromatography. An aliquot of serum was mixed with an aliquot of internal standard (cephacetrile). Acetonitrile was used to precipitate serum proteins. The mixture was then vortex-mixed, centrifuged and washed twice prior to autosampling onto the chromatography column. Chromatography was performed with a Shimadzu system including a LC-10AT pump,

SPD-10A detector, Sil-10A autosampler and a SCL-10A controller. A Supelco LC-8-DB column was used with 4% acetonitrile in phosphate buffer (pH 7) as the mobile phase. The flow rate was 1.5 ml/min and the detector wavelength was set at 300nm. The assay inter-day coefficients of variation (CV) were 12.1, 5.0 and 5.6% at 5, 25 and 200 mg/L, respectively. The lower limit of quantification was 5 mg/L. No attempt was made to determine the serum protein binding of ceftazidime.

Serum creatinine was measured at least once for each patient. The Synchron CX Jaffe rate method for serum creatinine determination (Beckman Instruments, Naguabo, PR, USA) was used. The inter-day assay CV values were 5.4 and 1.7% at 70.7 μmol/L (0.8 mg/dL) and 344.8 μmol/L (3.9 mg/dL), respectively.

Demographic variables [height in inches, bodyweight (WT) in kilograms, gender (SX) and age in years (AGE)] were determined from admission data. Four patients exhibited bodyweight fluctuations of at least 5kg during treatment (i.e. those requiring diuresis or large volumes of fluid replacement) and a stable pre-admission bodyweight was used for these patients. Residence in the intensive care unit (ICU) or the ventilator dependency unit (VDU) were each recorded as dichotomous variables. The primary suspected site of infection was determined from the attending physician's progress notes and was recorded as a categorical variable with the possible values of respiratory tract, urinary tract, skin structure or blood stream. For an individual, each day that a ceftazidime concentration was obtained was considered to be a distinct occasion. NONMEM V was used for pharmacostatistical analysis.[34]

Pharmacostatistical Model

Total serum concentrations of ceftazidime were modelled with a 1-compartment open model with first order elimination kinetics, parameterised in terms of total body clearance in L/h (CL) and volume of distribution in litres (Vd). Many models were explored; the 2 best models we were able to develop are described below:

$$CL_{tv} = \theta_1 \cdot (WT/70)^{\theta_2} \cdot \frac{SX \cdot (60/AGE)^{\theta_3}}{(CRMAX/88.4)} \quad \text{(Eq. 1)}$$

where CL_{tv} is the typical value of clearance and SX is an indicator variable such that if the patient is male the value is 1 and if female the value is θ_4.

CRMAX is defined as the serum creatinine (μmol/L) if the serum creatinine is $\geq\theta_5$ and θ_5 if the serum creatinine is $<\theta_5$.

As the data were collected under steady-state conditions, multicompartment models were not explored and the Vd could not be estimated. We set the Vd as equal to 0.23 L/kg as reported by Leroy et al.[7]

Bodyweight is regarded as time invariant; however, serum creatinine is allowed to vary with time within an individual. Five patients exhibited serum creatinine changes of at least 44.2 μmol/L (0.5 mg/dL) during their treatments. Two modelling approaches were explored (see the Discussion section), one allowing only inter- and intraindividual variability (IIV) and the other allowing interindividual, interoccasional and intraindividual variability (IOV). Clearance is allowed to vary randomly between patients, and between occasions as follows:

$$CL = CL_{tv} \cdot \exp(\eta + \kappa) \quad \text{(Eq. 2)}$$

where η is a interindividual random effect of mean 0 and variance ω^2, and κ is an interoccasion random effect of mean zero and variance π^2. The structural form in equation 2 is from Karlsson and Sheiner.[35] In this form, the η model the differences in CL between patients and the κ model the between-occasion differences in CL within a given patient. The difference between the j^{th} measured concentration in the i^{th} patient ($Cobs_{ij}$) and its respective prediction ($Cpred_{ij}$) was modelled with a exponential error model as follows:

$$Cobs_{ij} = Cpred_{ij} \cdot \exp(\varepsilon) \quad \text{(Eq. 3)}$$

The random variable ε is assumed to be statistically independent of both η and κ, and to be distributed with mean 0 and variance σ^2. First order and first order conditional estimation were used for the IIV and IOV models, respectively.[34]

Table I. Patient characteristics

Characteristic	Median or frequency	Interquartile range
Sample size (male/female)	39	(20/19)[a]
Age (y)	62	51-77
Bodyweight (kg)	69	59-81
Height (cm)	165	163-175
Creatinine (μmol/L) [range]	79.6	26.5-282.9
Ventilator dependency unit	10	
Intensive care unit	12	
Infusion rate (mg/h) [range]	83	41-167
Concentration determinations (range)	2	1-3
Duration (days)	6	3-9
Ceftazidime concentration (mg/L)	26	17-32

a Counts.

The solution to this problem was accomplished with the NONMEM program by minimising an objective function with respect to the fixed effects parameters (the θ_i), the interindividual random effect variance ω^2, the interoccasion random effect variance π^2 and the intraindividual random effect variance σ^2.[10] A fixed effect parameter was considered to be statistically significant ($p < 0.05$) if inclusion in the model resulted in a drop in the objective function of 4 or more. This criteria is based on the objective function having an approximate chi-squared distribution with 1 degree of freedom.

A Sun Ultra 30 workstation running the Solaris 2.6 operating system and a 4.0 FORTRAN compiler was used for the NONMEM runs (Sun Microsystems, Mountain View, CA, USA).

Model Evaluation

In order to assess objectively the predictive capability of our model, a cross-validation was undertaken.[36] The 39 patients used for the development were randomly divided into 5 groups: 4 groups with 8 patients and 1 with 7 patients. The IIV model (see the Results section) was fitted to the data from 4 of the groups and parameter estimates were obtained. These parameter estimates were then used to generate serum ceftazidime concentration predictions for the remaining patients in the fifth group. This process was repeated 4 more times so that predictions could be generated for all 39 patients. Prediction errors were calculated by subtracting each predicted ceftazidime concentration from the observed ceftazidime concentration. Bias and precision were assessed using mean error and mean absolute error, respectively.

Results

Patient Characteristics

39 patients (20 males) with a total of 75 serum concentrations were included in the analysis. 11 patients had only 1 ceftazidime concentration obtained, 19 patients had 2 concentrations and 9 patients had 3 concentrations. Suspected primary infectious diagnosis was as follows: pneumonia, 26; urosepsis, 8; skin structure infection, 4; sepsis of unknown origin in 1 patient. Table I contains summary statistics on patient characteristics.

Parameter Estimates

The parameter estimates for the pharmacostatistical models, along with confidence intervals (CI) for the parameters, are shown in table II. The fixed effect estimates (θ) were similar for both the

Table II. Parameter estimates. 95% confidence intervals[a] are shown in parentheses

Parameter (relation)	IIV	IOV
θ_1 (constant) [L/h]	4.54 (3.90-5.18)	4.73 (4.1-5.36)
θ_2 (bodyweight on CL)	0.67 (0.37-0.97)	0.7 (0.4-1.05[b])
θ_3 (age on CL)	0.31 (0.05-0.39[b])	0.34 (0.05-0.65[b])
θ_4 (gender on CL)	0.78 (0.66-0.90)	0.77 (0.66-0.88)
θ_5 (creatinine on CL) [μmol/L]	79.6 (76.1-83.2)	75.2 (64.6-85.8)
ω^2	0.033 (0.013-0.053)	0.25 (0.0072-0.27)
π^2	NE	0.032 (0.005-0.059)
σ^2	0.029 (0.016-0.042)	0.0034 (0-0.028[b])

a Confidence intervals were constructed as estimate ± 2 × standard error of estimate (truncated below at zero for variances) except where indicated.

b Profile likelihood method used to construct confidence interval.

CL = total body clearance; **IIV** = interindividual and intraindividual variability model; **IOV** = interindividual, intraindividual and interoccasional variability model; **NE** = not estimated.

IIV and IOV models; therefore, in the remainder of this section only the estimates for the IIV model will be described.

The multiplicity factor relating female gender to clearance was 0.78 (θ_4). The CRMAX function maps serum creatinine onto itself if the serum creatinine concentration is greater than or equal to 79.6 μmol/L, otherwise CRMAX maps the serum creatinine to the number 79.6 (θ_5). This function maps the serum creatinine concentration in μmol/L to a dimensionless quantity.

The fixed effects parameter θ_5 used in the CRMAX relationship was estimated by NONMEM, not arbitrarily fixed by the authors. θ_2 indicates that clearance increases nonlinearly with bodyweight. θ_3 indicates that clearance decreases nonlinearly with age. A visual indication of goodness of fit of our IIV model to the data can be seen in figure 1. Figure 1 shows predictions for typical individuals ($\eta = 0$).

Model Evaluation

The cross validation technique (see the Materials and Methods section) was used with the 75 ceftazidime concentrations and the estimates from the IIV model. The mean error (95% CI) was –0.51 (–2.5 to 1.4) mg/L. Using a 2-sided t-test to explore the null hypothesis of zero bias results in a p-value of 0.6. This statistic is minimally informative because of the possibility of a type II error. Perhaps the best indication of the lack of bias is seen in the scatterplot in figure 2. The mean absolute error (95% CI) was 6.5 (5.3 to 7.8) mg/L. Observed versus predicted ceftazidime concentrations for the cross validation are displayed in figure 2. Figure 2 shows predictions for typical individuals (i.e. $\eta = 0$).

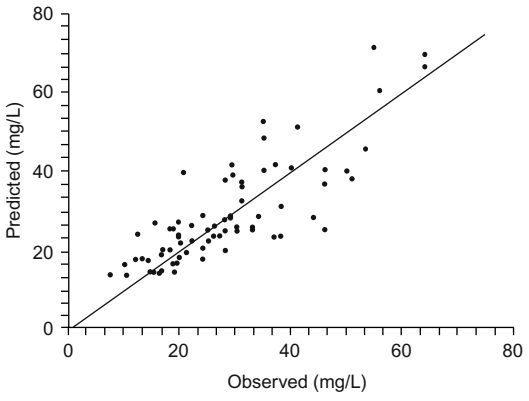

Fig. 1. Scatterplot of predicted versus observed serum concentrations of ceftazidime for inter- and intraindividual variability (IIV) model.

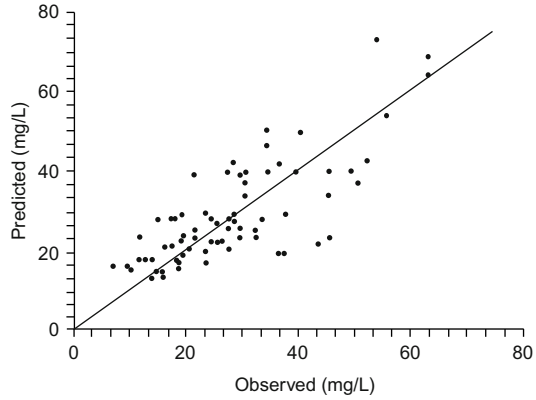

Fig. 2. Scatterplot of predicted versus observed serum concentrations of ceftazidime for cross validation of inter- and intraindividual variability (IIV) model.

Discussion

We were unable to detect any effect of height, site of infection or residence in the VDU or ICU on the CL of ceftazidime.

Our finding that ceftazidime clearance depends on the patient's serum creatinine, bodyweight, age and gender is in agreement with previously published reports which studied the relationship between ceftazidime clearance and measured or estimated creatinine clearance.[7-11,14,16,17,19-22,24-26,28]

We found a 'maximiser function' useful for modelling the impact of low serum creatinine values on ceftazidime clearance. The idea of transforming creatinine values to a fixed value if they fall below the fixed value when estimating creatinine clearance is controversial.[37,38] The value often referenced for this serum creatinine cutoff is 88.4 μmol/L. It has been suggested that a values below this should be transformed to 88.4 μmol/L

when evaluating the Cockcroft-Gault formula.[37,38] This concept is intuitively appealing because very low serum creatinine values (i.e. <45 μmol/L) can be misleading to the extent of overestimating renal function and drug clearance.

In this study we did not attempt to estimate or measure renal creatinine clearance. Serum creatinine is used as a surrogate marker of renal function. A resultant 69-point drop in the NONMEM objective function occurred when the creatinine 'maximiser function' was added to the model. We have found this 'maximiser function' approach significant for estimating both ceftizoxime[39] and aminoglycoside (unpublished observation) clearance.

We tested, but could not support, the inclusion of an additive nonrenal clearance component in our model.

To apply the model clinically one needs to determine a target steady-state serum ceftazidime concentration for a given patient and/or pathogen. Once determined, both a loading dose and infusion rate can easily be calculated. Suppose a ceftazidime serum concentration of 24 mg/L is desired. If a male patient weighs 70kg, the Vd would be ~16L and an approximate loading dose would be 384mg (24 mg/L · 16L). If this patient also has a serum creatinine of 88.4 μmol/L and was 60 years old the CL_{tv} would equal 4.54 L/h for the IIV model. The CL_{tv} is used because in the absence of serum concentration measurements this is our best estimate for a given patient. This approach is equivalent to evaluating equation 2 with the interindividual random effect η and interoccasional random effect κ set equal to their mean values, which are zero. An approximate infusion rate would then equal 2615 mg/day (4.54 L/h · 24 mg/L · 24 h/day). In clinical practice, one would round these doses to more practical values such as a 500mg loading dose followed by a 3000 mg/day infusion. To use equation 2 when serum creatinine values are reported in mg/dL one would replace the quantity (CRMAX/88.4) by 0.9 if the serum creatinine is less than 0.9 mg/dL, otherwise (CRMAX/88.4) would be replaced by the serum creatinine value in mg/dL.

The importance of modelling IOV in population pharmacokinetic studies has been reported by Karlsson and Sheiner.[35] Failure to model IOV can result in biased parameter estimates as well as inclusion of noninformative parameters in a model.[35] While we have attempted to provide an estimate of IOV, some discussion relating to the complications of its estimation is warranted. The literature is not clear on what constitutes an occasion, and therefore the partition of a given patient's entire course of therapy into occasions is somewhat arbitrary. We chose to let each day of therapy on which a ceftazidime concentration was obtained be contained in an distinct occasion. When we attempted to estimate IOV with the first-order method, numerical difficulties complicated the estimation of intraindividual error variance (σ^2), necessitating the use of first-order conditional estimation (FOCE). When FOCE was used, the estimate of intraindividual error variance (σ^2) contracted to a value very close to that expected for the assay error at the middle and high ceftazidime concentrations and less than that seen at the lower ceftazidime concentration. Additionally, the CI for the effect of bodyweight on CL (θ_2) expands to include 1, suggesting that CL is simply a linear function of bodyweight. This last finding would support the work of Karlsson and Sheiner[35] suggesting that failure to model IOV results in model overparameterisation.

A review of other studies exploring ceftazidime population kinetics or the rational for continuous infusion of β-lactam antibacterials is beyond the scope of this present work. The interested reader is referred to the references and the excellent review by Craig.[40]

The limitations of this study include small sample size and lack of exploration of the impact of disease states, such as congestive heart failure, end-stage diabetes or haematological malignancies, on ceftazidime clearance. For example, advanced heart failure or end-stage diabetes could result in compromised renal function and lower ceftazidime clearance than seen in patients without these diseases. It could also be questioned whether

the patients selected to receive continuous infusion ceftazidime in our institution are representative of typical patients receiving ceftazidime.

In summary, we have developed and validated a model to estimate ceftazidime concentrations during continuous infusion using commonly available clinical information. A computer program incorporating the model described here is currently in use at Metropolitan Hospital to facilitate ceftazidime dosage calculations. Although optimal pharmacodynamic relationships using the continuous infusion technique for antimicrobial administration have yet to be fully evaluated in clinical practice, our study shows that the population pharmacokinetic approach can provide important information that is relevant to clinical care decisions.

Acknowledgements

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