Clinical Pharmacokinetics of Cefamandole and Ceftazidime Administered by Continuous Intravenous Infusion

J. Berkhout,^{1,2} L. G. Visser,^{1*} P. J. van den Broek,¹
J. A. M. van de Klundert,² and H. Mattie¹

*Department of Infectious Diseases¹ and Department of Medical Microbiology,²
Leiden University Medical Center, Leiden, The Netherlands*

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In view of the results of animal studies as well as theoretical considerations, continuous administration of β -lactam antibiotics should be superior to intermittent administration because of the close relationship between efficacy and the duration of time in which the concentration of unbound antibiotics in plasma remains above the MIC. The aim of the present study was to establish the pharmacokinetic parameters of cefamandole and ceftazidime for patients receiving these cephalosporins by continuous infusion. The interindividual differences in the concentrations in plasma at the steady state were mainly attributable to variations in renal function, as estimated by the rate of creatinine clearance. Using these results, we derived formulas for both cephalosporins that can be used to determine on an individual basis the total daily dose needed to obtain a therapeutic concentration in plasma. These formulas were tested with a group of subsequent patients and proved to be practical and fairly reliable. For some patients, a correction for a possible underestimation of the renal clearance at presentation might be required.

For β -lactam antibiotics, the maximal bactericidal effect is reached in vitro at relatively low concentrations. Increasing the concentration further does not appear to have any additional effect (3). This means that the range within which the antimicrobial effect is concentration dependent is rather narrow. This knowledge can be used for optimizing dosing regimens.

In experimental infections in granulocytopenic animals, the antimicrobial effect of β -lactam antibiotics was closely related to the duration of time that the concentration of the drug in plasma remained above the MIC (1, 2, 5, 7, 9, 11, 12, 14).

The half-life of most β -lactam antibiotics in humans is relatively short and is often not longer than 2 h. Doubling the dose prolongs by only one half-life of the drug the time during which the concentration in plasma remains above the effective concentration. To obtain a maximal effect in patients with serious infections, therefore, a more efficient way to keep the concentration in plasma from falling below the MIC long before the end of the dose interval would be to decrease the dose interval rather than to increase the dose. If this were to lead to very frequent dosing, continuous infusion of the drug would be preferable to intermittent administration.

To properly treat patients by continuous infusion of antibiotics, the pharmacokinetics during this procedure, in particular in relation to renal function, should be known. Cefamandole and ceftazidime are often used for the treatment of serious gram-negative infections, with the choice depending on the expected or established sensitivity of the causative microorganism.

The present study was undertaken to establish the pharmacokinetics of those two antibiotics during continuous infusion.

As a first step, we determined the relationship between concentration in plasma, renal clearance, and nonrenal clearance. To validate these results, they were used to obtain predicted concentrations in plasma for a subsequent group of patients.

MATERIALS AND METHODS

Patients. Between May 1996 and January 1997, 16 patients were treated with cefamandole and 14 patients were treated with ceftazidime by continuous infusion. The choice of the antibiotic was based on the guidelines for antimicrobial therapy followed in our hospital, but the patients gave informed consent to change intermittent intravenous administration to continuous infusion. The Hospital Review Committee approved the study protocol. The most frequent indications for therapy were sepsis, invasive otitis externa, and pneumonia. For a second group of patients, the doses were based on the findings for the first group. This so-called evaluation group consisted of consecutive patients who received cefamandole ($n = 21$) or ceftazidime ($n = 6$) between May 1998 and August 1999. This evaluation group was similar to the first group with respect to age, rate of creatinine clearance, and type of infection. Patients whose body weights had not been recorded or whose creatinine concentrations in serum at the steady state had not been determined were excluded from the study.

Administration of antibiotics. Cefamandole (cefamandole nafate; Eli Lilly, Nieuwegein, The Netherlands) or ceftazidime (ceftazidime pentahydrate; Glaxo Wellcome, Zeist, The Netherlands) was dissolved in saline or distilled water according to the manufacturer's instructions and administered intravenously by means of a syringe infusion pump (Adquiment, Medical Instrument Division, Rotterdam, The Netherlands). Syringes with freshly dissolved antibiotics were inserted every 6 h. The standard daily dose of cefamandole was 4 g. The standard daily dose of ceftazidime was 1.5 g, but when an infection with *Pseudomonas aeruginosa* was suspected, the standard daily dose was 3 g (or a dose adjusted to renal function). To determine the concentration of cefamandole or ceftazidime in plasma, two blood samples were taken 1 h apart (by veni puncture, from the arm opposite to that used for infusion of the antibiotic) at least 6 h after initiation of treatment by continuous infusion. The second sample was taken to verify that a near steady state had been reached. After the second sample was taken, the dose was doubled to obtain information about the relationship between dose and concentration at a higher dose range (up to 8 g of cefamandole and 3 to 6 g of ceftazidime per day) and, at least 6 h later, two blood samples were again taken 1 h apart.

In the evaluation group, a loading dose was given and total daily doses were adjusted to changes in renal function to reach target concentrations in plasma (12 mg/liter for cefamandole and 6 or 12 mg/liter for ceftazidime). The next day,

* Corresponding author. Mailing address: Department of Infectious Diseases, Leiden University Medical Center, C5-P-41, P.O. Box 9600, 2300 RC Leiden, The Netherlands. Phone: 31 71 526 2613. Fax: 31 71 526 6758. E-mail: L.G.Visser@lumc.nl.

two blood samples were taken 1 h apart to verify that the steady state had been reached. Samples were centrifuged and stored at 4°C for determination of antibiotic concentrations.

Measurements. Total concentrations in plasma were measured by high-performance liquid chromatography within 24 h after taking the sample. An aliquot of serum was mixed with acetonitrile (Merck, Darmstadt, Germany) to precipitate serum proteins. The mixture was then vortex mixed, centrifuged for 5 min at $1,200 \times g$, washed with dichloromethane, and centrifuged again for 5 min at $1,200 \times g$ prior to sampling onto the chromatography column. Chromatography was performed with a system including a constant flow pump (model 1000; Sykam, Analytica BV, Rijswijk, The Netherlands), a Rheodyne model 7125 injection valve equipped with a 20- μ l sample loop (Chrompack, Middelburg, The Netherlands), a stainless steel column (length, 10 cm; internal diameter, 3 mm), and a Spectroflow 773 absorbance detector (Kipp & Zonen, Delft, The Netherlands) operating at a wavelength of 254 nm. Chromatograms were registered on a BD 42 recorder (Kipp & Zonen). Using a pressurized slurry technique, the column was packed with 5- μ m particle-size Hypersil ODS (Shandon SPL, Cheshire, United Kingdom). Calibration plots were constructed after the addition of known amounts of cefamandole or ceftazidime to plasma, and concentrations of the samples were calculated by interpolation of the calibration plots. Previous experience with this assay showed a variability of less than 10% between measurements made within 24 h (unpublished data) and a lowest level of detection of 0.1 mg/liter.

For a limited number of patients, plasma protein binding of the antibiotic was determined by equilibrium dialysis in a Dianorm dialysis apparatus (Diachema AG, Zurich, Switzerland).

Creatinine concentrations in serum were determined with a Technicon-SMAC multichannel autoanalyzer (Technicon Instruments, Tarrytown, N.Y.). Creatinine clearance was estimated from age, sex, body weight, height, and concentration of creatinine in serum according to the method of Hallynck et al. (6).

Pharmacokinetic models. Under steady-state conditions during continuous infusion, the concentration of the antibiotic in plasma was determined by the dose and plasma clearance according to the following equation:

$$C = R_0/CL \quad (1)$$

in which C is concentration in plasma, R_0 is rate of administration, and CL is plasma clearance of the antibiotic. β -Lactam antibiotics are cleared from plasma by renal and nonrenal elimination. Therefore,

$$CL = CL_R + CL_{NR} \quad (2)$$

in which CL_R is the renal clearance and CL_{NR} is the nonrenal clearance of the antibiotic. Since renal clearance is dependent on the number of functional nephrons, it is proportional to the glomerular filtration rate, which is given by the calculated creatinine clearance rate:

$$CL_R = \alpha \times CL_{CR} \quad (3)$$

in which α is a constant.

Substitution of equation 3 into equation 1 leads to the following equation:

$$C = R_0/CL_{NR} + \alpha \times CL_{CR} \quad (4)$$

Statistical analysis. In the first group of patients, the best estimates of CL_{NR} (and of α for the model with or without the contribution of nonrenal elimination) were obtained by nonlinear regression analysis using the average of the measured values of C and the calculated creatinine clearance (CL_{CR}) values (in milliliters/minute) and using NONLIN software (Systat, Evanston, Ill.). The proportion of the total variation of C that can be explained by the pharmacokinetic model is indicated by the squared multiple regression coefficient (r^2). The predictive value of the resulting equations was tested in the evaluation group by comparing the observed and predicted values of C . The mean differences and the 95% limits (i.e., $1.96 \times$ standard deviation [SD]) of the differences between the observed and predicted values of C were calculated to indicate the extent of agreement.

RESULTS

Between May 1996 and January 1997, cefamandole was studied with 16 patients and ceftazidime was studied with 14 patients. Two patients from the cefamandole group were excluded from analysis because blood was not drawn according to the study protocol. The patient characteristics for this first group are summarized in Table 1.

TABLE 1. Patient characteristics

Characteristic	Cefamandole		Ceftazidime	
	First group	Evaluation group	First group	Evaluation group
No. of patients	14	20	14	6
No. of males/no. of females	9/5	5/15	11/3	4/2
Age in yr ^a	56 (26–90)	58 (25–82)	63 (38–83)	68 (31–81)
CL _{cr} in ml/min ^a	61 (19–90)	74 (21–143)	86 (49–142)	56 (20–99)
Body wt in kg ^a	72 (59–99)	72 (50–124)	77 (51–93)	73 (50–90)

^a Mean (range).

Cefamandole concentrations in plasma of the second samples were slightly higher for 9 of the 14 patients receiving the low dose (average difference $\pm$ standard error of mean, 2.5% $\pm$ 2.3%) and for 9 of the 11 patients receiving the high dose (11.2% $\pm$ 6.1%); however, these differences were not statistically significant (P values were 0.29 and 0.10, respectively). Likewise, ceftazidime concentrations in plasma of the second samples were somewhat higher for 12 of the 14 patients receiving the low dose (5% $\pm$ 2.8%) and for 6 of the 11 patients after receiving the high dose (–1.5% $\pm$ 2.9%); again, these differences were not statistically significant (P values were 0.10 and 0.62, respectively). These findings indicate that most samples were collected in near steady state.

There was considerable variation in the steady-state concentrations in plasma for patients receiving the same daily dose of antibiotic. For example, when cefamandole was administered at a total daily dose of 4 g, the average concentrations ranged from 11.8 to 43.5 mg/liter while a total daily dose of 3 g of ceftazidime resulted in 11.6 to 48.8 mg/liter (Fig. 1).

Fitting equation 4 to the data for all patients receiving cefamandole leads to a negligible value for CL_{NR} (–0.63) (95% confidence interval [CI], –1.24 to –0.03 ml/min) and a value for α of 2.24 (95% CI, 1.81 to 2.67). By omitting CL_{NR} from equation 4, a value of 1.89 (95% CI, 1.70 to 2.08) was calculated for α .

For ceftazidime, the value according to equation 4 of CL_{NR} was also negligible (0.41 ml/min; 95% CI, –1.05 to 1.87); the value of α was 0.90 (95% CI, 0.52 to 1.83). After dropping CL_{NR} from equation 4, the estimate for α was 1.01 (95% CI, 0.89 to 1.13). The variation in the concentrations of cefamandole and ceftazidime in plasma was mainly attributable to the variation in the rate of creatinine clearance ($r^2 = 0.80$ and 0.70, respectively).

Plasma binding of cefamandole and ceftazidime was determined for a limited number of consecutive patients. For cefamandole ($n = 10$), the median binding level was 68% (range, 62 to 75%) independent of the concentration. For ceftazidime ($n = 5$), it was 0% in all cases. Nonlinear regression analysis using equation 4 as the model showed that CL_{CR} was mainly responsible for the total concentration in plasma and that saturability of tubular elimination did not seem to play a role, because even at high concentrations the model fit well (Fig. 2).

Using the values for α thus calculated (with $\alpha = 1.89$ for cefamandole and 1.01 for ceftazidime) and after rearranging equation 4, the following formulas were derived to estimate the total daily doses needed to obtain the following concentrations in plasma: for cefamandole, 12 mg/liter (dose [g/24 h] =

FIG. 1. Mean steady-state concentrations of cefamandole and ceftazidime in plasma during continuous infusion for the first patient group.

$0.033 \times \text{CL}_{\text{CR}}$ [ml/min]); for ceftazidime, 6 mg/liter (dose [g/24 h] = $0.009 \times \text{CL}_{\text{CR}}$ [ml/min]) and 12 mg/liter (dose [g/24 h] = $0.017 \times \text{CL}_{\text{CR}}$ [ml/min]).

These concentrations in plasma were chosen to obtain concentrations of unbound antibiotic of three times the MIC for the most likely causative organisms (1 mg/liter for cefamandole and 2 mg/liter for ceftazidime [or 4 mg of ceftazidime/liter in cases of *Pseudomonas aeruginosa* infection]).

The evaluation group of patients received the estimated total daily dose of cefamandole or ceftazidime by continuous infusion after a loading dose of 200 mg of cefamandole or 100 mg of ceftazidime. Concentrations in plasma were predicted using equation 4 without including nonrenal clearance values in the calculation.

A total of 21 patients were treated with cefamandole. One patient was excluded from further analysis. The concentration in plasma determined for this patient was 144 mg/liter, suggesting that the plasma sample was obtained from the arm used for infusion of the antibiotic.

The mean predicted concentration of cefamandole in plasma of the remaining 20 patients was 13.75 mg/liter (SD, 2.29 mg/liter). The observed values were significantly lower

than the predicted values (mean difference, -2.49 mg/liter; 95% limits, -9.68 to 4.71 mg/liter; P value, 0.007) (Fig. 3, left panel). The mean observed concentration of cefamandole in plasma was 11.26 mg/liter (SD, 4.30 mg/liter). For 11 of the 20 patients, concentrations of cefamandole in plasma were below the target concentration of 12 mg/liter but no concentration in plasma was below the MIC for the expected causative micro-organism.

Six patients were treated with ceftazidime. The mean predicted concentration of ceftazidime in plasma was 11.34 mg/liter (SD, 4.38 mg/liter); the mean observed concentration in plasma was 9.18 mg/liter (SD, 3.75 mg/liter) (Fig. 3, right panel). The mean difference between observed and predicted concentrations in plasma was -2.15 mg/liter (95% limits, -8.43 to 4.13 mg/liter; P value, 0.16). For one of three patients not treated for a possible *P. aeruginosa* infection, concentrations of ceftazidime in plasma were below the target concentration of 6 mg/liter; for the remaining three patients, concentrations of ceftazidime in plasma were below the target concentration of 12 mg/liter. Concentrations in plasma were below the MIC for the expected pathogens for none of the patients.

FIG. 2. Relation between observed and predicted values of total concentrations of cefamandole and ceftazidime in plasma during continuous infusion for the first patient group. Total concentrations in plasma were predicted on the basis of creatinine clearance and dose according to the model $C = R_0/(\alpha \times \text{CL}_{\text{CR}})$ (Materials and Methods). The diagonal line represents values for $y = x$.

FIG. 3. Relation between observed and predicted values of the total concentrations of cefamandole and ceftazidime in plasma during continuous infusion for the evaluation group. In the right panel, closed circles represent the total concentrations of ceftazidime in plasma obtained for patients treated for a possible *P. aeruginosa* infection. The total concentrations in plasma were predicted on the basis of creatinine clearance and dose according to the model $C = R_0/(\alpha \times CL_{CR})$ (Materials and Methods).

DISCUSSION

Concentrations of cefamandole or ceftazidime in plasma during the steady state among patients who received a standard dose of one of these antibiotics by continuous infusion differed greatly. To a large extent, this variation is attributable to the variation in renal clearance. Although extreme values can be seen in cases of marked renal failure, our results indicate that in clinical practice, the concentration in plasma achieved at a given rate of administration can be predicted fairly accurately on the basis of the creatinine clearance alone.

Cefamandole is eliminated not only by glomerular filtration but also by tubular secretion (8) and to some extent by extrarenal mechanisms. In the present study, saturability of tubular elimination of cefamandole was not demonstrated and the contribution of nonrenal clearance to variations in concentrations in plasma was negligible. Ceftazidime is eliminated mainly by the kidney and to a much lesser extent by extrarenal mechanisms (13). Moreover, this renal elimination is almost exclusively accomplished by glomerular filtration (15). For our patients, we found a relationship between renal function and plasma clearance of ceftazidime similar to that found for healthy volunteers (10) as well as for a similar group of patients (4).

The predictive value of the two equations for both antibiotics was validated with a second group of patients. Statistical analysis showed that the observed concentrations in plasma for both patient groups treated with cefamandole or ceftazidime were significantly lower than the predicted values for these antibiotics. For the calculation of the creatinine clearance, the serum creatinine value on admission was used. For most patients, renal function improved significantly during the days following treatment (data not shown). Therefore, the differences between observed and predicted concentrations in plasma were most likely caused by an underestimation of the renal clearance rate on admission. The observed concentrations in plasma were lower than the preset target concentrations of three times the MIC for 55% of the patients treated with cefamandole and 67% of patients treated with ceftazi-

dime. However, concentrations in plasma were never below the MIC for the expected pathogens. On several occasions, the estimated total daily dose of cefamandole or ceftazidime was different from that actually given in the ward. Two of the 20 patients treated with cefamandole received only 88 and 83% of the calculated dose; 2 of the 6 patients treated with ceftazidime received 73 and 72% of the calculated dose. Besides the underestimation of the renal clearance, target concentrations were not reached in a number of patients because of underdosing.

However, these limitations do not argue against the principal conclusion that the concentration in plasma achieved at a given rate of administration can be predicted on the basis of the creatinine clearance alone. When one takes into account the consideration of underestimation of renal clearance, it might be prudent to increase the target concentration with two times the SD for the following predicted values: for cefamandole, 16 mg/liter (dose [g/24 h] = $0.044 \times CL_{CR}$ [ml/min]); for ceftazidime, 15 mg/liter (dose [g/24 h] = $0.022 \times CL_{CR}$ [ml/min]) and 21 mg/liter (dose [g/24 h] = $0.030 \times CL_{CR}$ [ml/min]).

Recently, Frame et al. (4) used a population study of pharmacokinetics to develop a model that predicts steady-state ceftazidime concentrations during continuous infusion. In their model, the parameters needed to estimate the creatinine clearance are incorporated separately, which makes it unnecessarily complicated.

Our formulas are based on an extensively validated method for estimation of the creatinine clearance (6). Besides, Frame et al. did not evaluate their results in a second group of patients. In our opinion, their model is too complicated for use in a clinical setting.

Our results made it possible to establish simple formulas for cefamandole and ceftazidime dosages (and to ignore nonrenal clearance of these antibiotics) which can easily be used in clinical practice to obtain a satisfactory estimate of the total daily dose needed for proper treatment of the individual patient by continuous infusion.

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