Population Pharmacokinetics of Ceftazidime in Intensive Care Unit Patients: Influence of Glomerular Filtration Rate, Mechanical Ventilation, and Reason for Admission

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The aim of this study was to develop a population-pharmacokinetic model of ceftazidime in intensive care unit patients to include the influence of patients' characteristics on the pharmacokinetics. Forty-nine patients for model building and 23 patients for validation were included in a randomized study. They received ceftazidime at 2 g three times a day or as 6 g per day continuously. A NONMEM pharmacokinetic model was constructed, and the influences of covariates were studied. The model was validated by a comparison of the predicted and observed concentrations. A final model was elaborated from the whole population. Total clearance (CL) was significantly correlated with the glomerular filtration rate (GFR) calculated by modification of the diet in renal disease (MDRD), the central volume of distribution (V1) with intubation, and the peripheral volume of distribution (V2) with the reason for admission. The mean pharmacokinetic parameters were as follows: CL, 5.48 liters/h, 40%; V1, 10.48 liters, 34%; V2, 32.12 liters, 59%; total volume, 42.60 liters, 45%; and intercompartmental clearance, 16.19 liters/h, 42%. In the polytrauma population (mechanically ventilated), the time above the MIC at steady state never corresponds to 100% for discontinuous administration, and the target concentration of five times the MIC was reached with a 6-g/day dose only for patients with an MDRD of <150 ml/min. We showed that the GFR-MDRD, mechanical ventilation, and the reason for admission may influence the achieved concentrations of ceftazidime. Our model allows the a priori dosing to be adjusted to the individual patient.

Ceftazidime is a broad-spectrum cephalosporin generally used in the treatment of severe Pseudomonas aeruginosa infections. Since ceftazidime exhibits time-dependent killing of gram-negative bacteria in vitro or in critically ill patients, studies involving continuous administration of cephalosporin confirm that the steady-state concentration in blood should be four to five times higher than the bacterial MIC (6, 27). When the MIC is not available, the European breakpoint is used to calculate the target concentration (8). In patients with sepsis syndrome, ceftazidime plasma concentrations after a 2-g dose of ceftazidime every 8 h or 4 g by continuous infusion may be inadequate (42).

Intensive care unit (ICU) patients represent a highly heterogeneous population ranging from young trauma patients to elderly medical patients and postsurgical patients. This heterogeneity is well known to produce high variability in pharmacokinetic parameters, as was previously demonstrated for the clearance and the total volume of distribution (15, 26, 36). Ceftazidime pharmacokinetics in critically ill patients is altered by an increased volume of drug distribution and a longer elimination half-life (16).

In order to determine interindividual pharmacokinetic variability and the influence of some patient characteristics on the pharmacokinetics of ceftazidime, we conducted a population pharmacokinetic study to develop and validate a model to enable an adequate individual dosing strategy to be put in place (3). We used rich data collected in a prospective study comparing continuous infusion versus intermittent administration of ceftazidime, along with the demographic, clinical, and biological characteristics of these ICU patients. This study used the nonlinear mixed-effect model as implemented in the NONMEM program for pharmacostatistical analysis (4).

MATERIALS AND METHODS

A prospective, open, and randomized population study of the pharmacokinetics of ceftazidime was carried out with ICU patients, following the agreement of the Toulouse Ethical Committee. Ceftazidime plasma concentration data were obtained and analyzed in the Laboratoire de Pharmacocinétique et Toxicologie Clinique of the Purpan Hospital in Toulouse, France.

Patients. A total of 72 patients hospitalized in the ICU of the Rangueil University Hospital (Toulouse, France) were included. To be enrolled in the study, patients had to meet the following inclusion criteria: (i) an inpatient stay in the ICU, (ii) over 18 years old, and (iii) presenting with P. aeruginosa nosocomial pneumonia or bacteremia with a strain thought to be sensitive to ceftazidime. Informed consent was obtained from the relatives of all patients. Before the study, the population was randomized according to the mode of administra-
tion: continuous administration of ceftazidime with or without a loading dose and discontinuous administration.

The following demographic, clinical, and biological parameters were collected as possible covariates: age, gender, body weight, height, etiology of admission, mechanical ventilation, serum creatinine, proteins, blood urea nitrogen, leukocyte counts, hemoglobin, C-reactive protein, and simplified acute physiology scores (SAPS I and II).

Lean body weight was estimated according to the James formula (14, 18). The glomerular filtration rate (GFR) was estimated from creatinine clearance calculated by the Cockcroft-Gault method with total body weight and lean body weight (9, 20, 31). The Kirkpatrick creatinine clearance and modification of the diet in renal disease (MDRD) (20, 21) were also calculated. A baseline model was constructed, and then the influences of all the above-mentioned demographic and biological covariates were studied.

Drug administration. The 72 patients entered into this study received ceftazidime by three modes of administration: (i) an infusion of 2 g over 30 min three times a day (n = 22), (ii) 6 g continuously administered via an electric syringe over 24 h (n = 22), or (iii) a 2-g loading dose over 30 min followed by 6 g continuously administered (n = 28).

Blood sampling and measurements. Venous blood samples were collected in dry tubes (Vacutainer, France). During continuous infusion, blood was sampled on the first day at 0, 0.5, 1, 4, 8, 12, and 24 h. From the patients receiving a loading dose, samples were taken at 0, 0.25, 0.5, 1, 4, 8, 12, and 24 h. For intermittent administration, blood was sampled at 0, 0.5, 1, 4, 8, 8.5, 12, 16, 16.5, 20, and 24 h. A total of 443 measurable serum concentrations versus time were available.

Blood samples were immediately sent to the pharmacokinetics laboratory and centrifuged at 3,100 rpm at +4°C, and the sera were frozen at −20°C until they were assayed. Drug concentrations were measured by high-performance liquid chromatography with UV detection as described previously (10).

Statistical analysis. At the end of the clinical part of the study, whatever the mode of administration of ceftazidime, an anteriori randomization was carried out for two-thirds of the patients (group 1, 49 patients with 300 ceftazidime concentrations different from zero) for model building and one-third of the patients (group 2, 23 patients with 143 measurable ceftazidime concentrations) for validation of the model.

The quantitative covariates of the two groups were compared by using Student’s t test, and the qualitative covariates were compared by the chi-square test.

Pharmacokinetic model building. The population pharmacokinetic analysis was carried out using the NONMEM (3) and Visual-NM computer programs.

The first group of patients was used to model the pharmacokinetics of ceftazidime. A one- versus a two-compartment model were evaluated to describe the pharmacokinetics. Proportional, additive, and mixed error models were evaluated to describe the interindividual variability. The choice of the model was based on the lower value of the objective function. The pharmacostatistical model was fitted to the data to obtain the population parameters (the mean and variance of each parameter), in terms of total body clearance (CL), distributional volumes (V1 and V2) volumes of distribution in liters, and central (V1) and peripheral (V2) volumes of distribution. Individual pharmacokinetic parameters were obtained by using the Bayesian maximum a posteriori estimator. They were reported with their coefficients of variation estimated from the NONMEM standard errors of estimate. Their interindividual variability was given by the omega terms and the intraindividual variability by sigma.

Secondarily, the influence of each covariate was examined in the structural model with a 0.05 level of significance for the likelihood ratio test. The resulting pharmacostatistical model was refined by independently deleting each covariate with 0.001 as the level of significance for the likelihood ratio test. We then looked at the correlation matrix and standard errors of estimates in order to delete the less precisely estimated parameters in the final model, including all the selected covariates for all the parameters. When a high correlation (abs(τ) ≥ 0.7) was observed between the estimates for two parameters, the less significant one was eliminated from the model. The result of this step was designated the intermediate model.

Validation. The second group of 23 patients was used to validate the intermediate-model construction. Based on the defined intermediate-model parameters, ceftazidime serum concentrations were simulated for this second group.

The predictive performance of our model was evaluated by comparing the measured concentrations (C_{obs}) with the predicted concentrations (C_{pred}). The bias was calculated as C_{bias} = C_{obs} − C_{pred} the prediction error (PE) as the bias reported to the C_{pred}, and the absolute prediction error (APE) as the absolute value of the PE. The median prediction error (MDPE) (the median of the PE), the median absolute prediction error (MDAPE) (the median of the APE), and the average fold error (APE) were used to analyze the predictive performance of our model (34). As the number of samples was different from one patient to another, the MDPE and MDAPE were also calculated for each individual and reported as mean and standard deviation.

Total model. The two populations were mixed together after the validation process. Population and individual parameters were then reevaluated for the whole population to produce the final model.

Simulation. The total model was used to perform simulations for polytrauma patients with mechanical ventilation as a function of the GFR estimated by MDRD.

RESULTS

Patient characteristics. Seventy-two patients with a total of 443 measurable serum ceftazidime concentrations were included in the study: 49 for construction of the model and 23 for validation. Figure 1 shows the repartition of the measured concentrations over 24 h according to the dosage regimen. Table 1 contains summary statistics for the patient characteristics. No statistical difference was observed between the two groups.

Population model. The pharmacokinetic parameters of ceftazidime were estimated in the first group from 300 measurable serum ceftazidime concentrations.

The open two-compartment pharmacokinetic model with first-order elimination was chosen to describe the concentration-versus-time data for ceftazidime in serum. The first-order conditional-estimates method was used to determine the pharmacokinetic parameters: CL; V1; Q, describing ceftazidime exchange between central and peripheral compartments; and V2.

A proportional-error model was the most accurate for residual and interpatient variability.

The linear regression between the individual C_{obs} and the concentrations (C_{pred}) predicted by the pharmacokinetic analysis according to a two-compartment model with a proportional-error model was as follows: C_{pred} (mg/liter) = 0.8903 (C_{obs}) + 8.348 (r = 0.8533).

This model had an objective function of 1,818 and a residual variability of 18%. The mean pharmacokinetic parameters, their 95% confidence intervals (CI), and the precision of their estimation were as follows: CL, 4.62 liters/h (CI, 3.74 to 5.50; precision, 10%); V1, 10.7 liters (CI, 7.88 to 13.50; precision, 13%); intercompartmental clearance, 12.8 liters/h (CI, 9.2 to 16.4; precision, 14%); and V2, 44.9 liters (CI, 25.5 to 64.3; precision, 22%).

The influences of covariates were examined one by one in this structural model.

For CL, the reason for admission, mechanical ventilation, SAPS II, the Cockcroft clearance based on total body weight and lean body weight, the Kirkpatrick clearance, and the MDRD statistically decreased the objective function and the interindividual variability described by omega. For V1 and V2, the statistically significant covariates were, respectively, mechanical ventilation and the reason for admission. After independent deletion, the model was as follows: TVCL = \( \theta_1 + \theta_2 \times \text{MDRD} \), with MDRD in ml/min; TVV1 = \( \theta_3 \) for patients without mechanical ventilation; TVV1 = \( \theta_4 \) for patients with mechanical ventilation; TVQ = \( \theta_5 \); TVV2 = \( \theta_6 \) for polytrauma etiology; TVV2 = \( \theta_7 \) for postoperative etiology; and TVV2 = \( \theta_8 \) for medical etiology, where TVCL, TVV1, TVQ, and TVV2 are typical values, respectively, for
The objective function was reduced from 1,818 to 1,730 ($P < 0.0001$) and the residual variability from 18% to 12%.

Validation. We used this model to analyze the patients in the validation group. We predicted their serum concentrations, and then we compared them with the observed results. The means ± standard deviations (SD) for the 143 observed

![FIG. 1. Mean (±SD) ceftazidime concentrations (mg/liter) versus time in 72 ICU patients.](image-url)
(50.54 ± 40.87 mg/liter) and predicted (51.04 ± 38.97 mg/liter) ceftazidime serum concentrations were not significantly different. The success of this population prediction was shown by the bias (−0.5 mg/liter, corresponding to a PE of 1%, a population MDPE of −2%, an APE of 30%, an MDAPE of 24%, and an AFE of 1.15). For the individuals, the mean of the MDPE was 15% and the mean of the MDAPE was 33%. From these parameters, we concluded the validation of our model.

**Total model.** The two groups were mixed together to obtain a total model. The final estimates are shown in Table 2. Figure 2 shows the correlation between $C_{\text{pred}}$ and $C_{\text{obs}}$ according to the following equation: $C_{\text{pred}}$ (mg/liter) = 0.897 ($C_{\text{obs}}$) + 6.8822 ($r = 0.8857$).

The means of each pharmacokinetic parameter in the total population were as follows: CL, 5.48 ± 2.20 liters/h; V1, 10.48 ± 3.61 liters; V2, 32.12 ± 18.89 liters; total volume of distribution, 42.60 ± 19.32 liters; and distribution clearance, 16.19 ± 6.78 liters/h.

The mean ± SD for the 443 observed (47.99 ± 38.90 mg/liter) and predicted (49.93 ± 39.40 mg/liter) ceftazidime serum concentrations were not significantly different. In the total population, the absolute bias was −1.94 mg/liter, corresponding to a PE of −2%, a population MDPE of −6%, an APE of 30%, an MDAPE of 26%, and an AFE of 1.11. For the individuals, the mean of the MDPE was 2% and the mean of the MDAPE was 28%. These results demonstrated the success of the model. These parameters for the total population are representative of those estimated for the different administration groups.

**TABLE 2. Objective function, pharmacokinetic parameter thetas, interindividual variability omegas, and intraindividual variability sigma (CV%) in the basic, intermediate and total model**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Basic model (n = 49)</th>
<th>Intermediate model (n = 49)</th>
<th>Final model (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective function</td>
<td>1,818</td>
<td>1,730</td>
<td>2,588</td>
</tr>
<tr>
<td>Theta 1 (liters/h)</td>
<td>4.62 (10%)</td>
<td>2.20 (21%)</td>
<td>2.24 (27%)</td>
</tr>
<tr>
<td>Theta 2</td>
<td>0.023 (18%)</td>
<td>0.024 (23%)</td>
<td></td>
</tr>
<tr>
<td>Theta 3 (liters)</td>
<td>10.70 (13%)</td>
<td>22.30 (15%)</td>
<td>18.90 (10%)</td>
</tr>
<tr>
<td>Theta 4 (liters)</td>
<td>9.24 (13%)</td>
<td>9.02 (9%)</td>
<td></td>
</tr>
<tr>
<td>Theta 5 (liters/h)</td>
<td>12.80 (14%)</td>
<td>14.20 (13%)</td>
<td>15.20 (13%)</td>
</tr>
<tr>
<td>Theta 6 (liters)</td>
<td>44.90 (22%)</td>
<td>77.40 (14%)</td>
<td>57.10 (12%)</td>
</tr>
<tr>
<td>Theta 7 (liters)</td>
<td>27.50 (17%)</td>
<td>25.70 (18%)</td>
<td></td>
</tr>
<tr>
<td>Theta 8 (liters)</td>
<td>15.50 (20%)</td>
<td>13.60 (26%)</td>
<td></td>
</tr>
</tbody>
</table>

**Interindividual variability**

| Omega CL     | 0.23 (30%)           | 0.08 (28%)                | 0.09 (24%)          |
| Omega V1     | 0.22 (95%)           | 0.19 (74%)                | 0.12 (86%)          |
| Omega Q      | 0.56 (80%)           | 0.51 (68%)                | 0.50 (38%)          |
| Omega V2     | 0.84 (47%)           | 0.17 (133%)               | 0.11 (116%)         |

**Intraindividual variability**

| Sigma        | 0.05 (18%)           | 0.05 (12%)                | 0.05 (13%)          |

**PES**

| Mean PE | −0.5% | 0.04% | −2% |
| Mean APE| 39%   | 32%   | 30% |
| Median PE| −11%  | −4%   | −6% |
| Median APE| 31%  | 27%   | 26% |
| AFE    | 1.15  | 1.09  | 1.11 |

*See the text for the equation describing the total model.*

**FIG. 2. Scatter plot of $C_{\text{pred}}$ versus $C_{\text{obs}}$ in the total population (n = 72).**
Simulation. The simulated ceftazidime concentrations are shown in Fig. 3 as a function of the GFR estimated by MDRD between 30 and 180 ml/min for patients with mechanical ventilation. In the polytrauma population assisted by mechanical ventilation, the time above the MIC (\(T_{\text{MIC}}\)) at steady state never corresponds to 100% for discontinuous administration. This target is reached with a 6-g/day dose only for patients with an MDRD lower than 150 ml/min.

DISCUSSION

By adopting the method of NONMEM, we investigated the quantitative relationships between pharmacokinetic parameters, clearance and volume of distribution, and physiologic features in ICU patients treated with ceftazidime. The interest of the population approach lies (i) in the potential explanation by covariates of a part of the interindividual variability of the pharmacokinetic parameters and (ii) in obtaining better individual estimates.

The data collected in this study were best described by a two-compartment pharmacokinetic model, which is in accordance with most of the previous observations (10, 11, 28). In agreement with the literature on ICU patients, our work shows that there is very high interindividual variability for V1, V2, and CL (38, 41).

Our study showed an increase in the total volume of distribution compared with that of healthy volunteers (35, 41). This is in accordance with antibiotic pharmacokinetic studies of ICU patients, especially for ceftazidime (29). The increase in the total volume of distribution was reported to be correlated with body weight, the severity of illness, and the status of the trauma (16, 38, 39). The tissue edema induced by sepsis or by fluid resuscitation is also involved in the modification of the volume of distribution and could act as a reservoir from which ceftazidime slowly returns to the circulation (11, 23, 25).

In our model, V1 was influenced by mechanical ventilation, which is known to increase plasma renin activity, aldosterone, and antidiuretic hormone (2, 40).

\(V_2\) is a function of the reason for admission. Patients with a medical reason for admission presented a volume of distribution in the same order of magnitude as those of healthy subjects, but postoperative status and polytrauma status correspond to higher volumes of distribution.

From a theoretical point of view, for a given ceftazidime clearance, an increased volume of distribution induces an increase in the terminal half-life. If the drug is given as a continuous infusion, the time necessary to reach steady state is delayed and the \(T_{\text{MIC}}\) is reduced for the first administration. A loading dose would correct this, since the steady-state concentration is reached immediately. For discontinuous administration, the increase in the terminal half-life would correspond to an increased \(T_{\text{MIC}}\). However, the reported simulations show that this increase is not sufficient to show a \(T_{\text{MIC}}\) equal to 100% due to low ceftazidime concentrations. These results are not in accordance with those of Burgess and Frei (7). In fact, clearance is the relevant parameter for the steady-state concentration.

In our population, the mean ceftazidime clearance was lower than that reported in healthy volunteers. This observed ceftazidime clearance is in agreement with that reported for ICU patients (29) and burn patients (11), in septicemic melioidosis (1), and with very high variability. This is a consequence of the decreased GFR due to severe sepsis in part of our population (13). As seen in ICU patients, another part of our population had high clearances, which could result in very low concentrations of beta-lactams (22). According to Roos...
et al., in the absence of significant organ dysfunction, “supranormal” clearance of renally eliminated drugs could be explained by an increased renal preload (33).

After the independent deletion step, the GFR-MDRD was the most significant variable in ceftazidime clearance, and the omega result corresponding to interindividual variability was significantly reduced, as shown in Table 2. This is in accordance with the fact that ceftazidime is mainly eliminated by glomerular filtration (24).

The MDRD study formula (21) and the Cockcroft-Gault formula have great accuracy and precision with true GFR and can be applied to the healthy general population (19). Even if some authors found that these formulas were not optimal for recently admitted critically ill patients (17), the MDRD equation has been found superior to Cockcroft-Gault formulas in renal transplant recipients (30), for predicting aminoglycoside dosing recommendations (5), and in the general population (37).

Our population approach led us to perform simulations. The steady-state blood concentration should be four to five times higher than the MIC (6, 27). The breakpoint for P. aeruginosa is used as a sensitivity target when the MIC is not available. The European breakpoint corresponds to 8 mg/liter (8). To ensure effectiveness, it could be easily demonstrated with simulations that intermittent administration will not allow the target concentration to be reached, as shown in Fig. 3. After continuous administration, for strains with a MIC equal to or higher than 8 mg/liter in patients with a GFR-MDRD higher than 150 ml/min, this target would also not be reached with a standard dosage regimen. The simulation of other dosage regimens will provide individual solutions to these cases. For example, in polytrauma patients with mechanical ventilation and a GFR-MDRD at 180 ml/min after a 2-g loading dose, a 7-g daily dose by continuous infusion will be sufficient to reach the 40-ml/liter steady-state concentration target. In the same case, a 2-g dose six times a day would be required for discontinuous administration. This is in accordance with the fact that administration by continuous infusion is more effective than an intermittent dosing regimen (32) and with the results of De Ryke et al., who demonstrated that only high-dose ceftazidime regimens achieved bactericidal cumulative fractions of response greater than 90% against P. aeruginosa (12).

Conclusion. We have developed a model to estimate ceftazidime concentrations during continuous or intermittent administration that includes the influence of patient characteristics. In our work, interindividual and intraindividual variability can be explained by taking into account the GFR based on the MDRD for ceftazidime clearance, mechanical ventilation for V1, and the reason for admission for V2. Our model demonstrated that in young polytrauma patients with a high GFR-MDRD, the usual dosage regimen of 6 g/day, even in continuous infusion, would not be sufficient to reach a steady-state concentration higher than four to five times the MIC. Our model would allow us to propose the individualization of dosing, particularly in severe trauma patients with high clearances and high total volumes of distribution, which can lead to ceftazidime inefficacy. We use this model in clinical routine for ceftazidime drug monitoring associated with the MIC or the European breakpoint of P. aeruginosa.

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21. Levey, A. S., J. J. Bosch, J. B. Lewis, T. Greene, N. Rogers, D. Roth, et al., in the absence of significant organ dysfunction, “supranormal” clearance of renally eliminated drugs could be explained by an increased renal preload (33).


