Pharmacokinetics of Isepamicin during Continuous Venovenous Hemodiafiltration

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The objective of this study was to analyze the pharmacokinetics of isepamicin during continuous venovenous hemodiafiltration. Six patients received 15 mg of isepamicin per kg of body weight. The mean isepamicin concentration peak in serum was 62.88 ± 18.20 mg/liter 0.5 h after the infusion. The elimination half-life was 7.91 ± 0.83 h. The mean total body clearance was 1.75 ± 0.28 liters/h, and dialysate outlet (DO) clearance was 2.76 ± 0.59 liters/h. The mean volume of distribution was 19.83 ± 2.95 liters. The elimination half-life, DO clearance, and volume of distribution were almost constant. In this group of patients, the initial dosage of 15 mg/kg appeared to be adequate, but the dosage interval should be determined by monitoring residual isepamicin concentrations in plasma.

Isepamicin is a novel broad-spectrum aminoglycoside which possesses a high level of stability to aminoglycoside-inactivating enzymes (9). Acute renal failure is a serious and common complication in critically ill patients (6). Kidneys are rarely the only organs that fail: there is often a multiple-organ dysfunction syndrome (14). Continuous venovenous hemodiafiltration (CVVHD) has been introduced in intensive care units to provide a more stable, flexible form of dialysis (6, 12). Knowledge of the impact of continuous hemodiafiltration on the elimination of drugs and the pharmacokinetic profiles of drugs is essential to good clinical management (2, 7, 15). The aim of our study was to analyze the pharmacokinetics of isepamicin during CVVHD.

MATERIALS AND METHODS

Patients. Six patients were included in this study after giving written informed consent (Table 1). All patients were anuric.

Hemodiafiltration technique, samples, and dosages. Vascular access was obtained by introducing a central venous catheter into a femoral vein. Blood was pumped with a roller pump at 150 ml/min through a membrane hemofilter (Hemopan AN 69 S; Hospal Lyon France) (effective surface area, 0.6 m²). Standard dialysis fluid was delivered at 1,000 ml/h via a volumetric pump into the dialysate compartment of the filter.

Sample design and measurement of isepamicin. Isepamicin (15 mg/kg of body weight) was given as an intravenous infusion over a 30-min period. No patient received isepamicin before the test dose was given. This antibiotic was administered to treat septic shock in association with cefazidime (2 g) every 8 hours. Cefazidime was never administered during isepamicin infusion.

Blood samples were collected from the venous intravenous line 0.47, 0.50, 0.57, 1, 3, 5, 7, and 12 h after the beginning of infusion. Ultrafiltrate (UF) and dialysate (dialysate outlet [DO]) samples were collected simultaneously. The isepamicin concentrations in serum samples and in aliquots of DO and UF were measured by a fluorescence polarization immunomassay (TDx; Abbott, Rungis, France) (16). Serum and DO came from the same biological matrix, and all the results presented for the serum could be used for the DO. The values of accuracy and precision in serum could be used to validate the assay for the DO. The method was linear for concentrations from 1 to 50 mg/liter, the mean extraction coefficient was 98%, and the limit of quantification was less than 1 mg/liter for each fluid.

Between-day and within-day coefficients of variation (CV) were calculated from three concentrations of isepamicin. Between-day CVs for isepamicin concentrations of 5, 15, and 25 mg/liter were 3.6, 2.3, and 1.5%, respectively, for plasma and 3.8, 2.7, and 1.6%, respectively, for UF. Within-day CVs for isepamicin concentrations of 5, 15, and 25 mg/liter were 1.8, 0.85, and 1.1%, respectively, for plasma and 2.5, 0.8, and 1.5%, respectively, for UF. None of the associated drugs interfered with isepamicin dosage.

Pharmacokinetic analysis. The pharmacokinetic analysis was performed with P-PHARM software (SIMEED, Criteil, France). The population characteristics of the pharmacokinetic parameters (i.e., means and variances) were calculated by a parametric method based on an expectation-maximization algorithm (10).

Each iteration was composed of two steps. The E step (expectation step) consisted of estimating the pharmacokinetic parameters of each individual by the Bayesian method, given the current estimate of the population parameters. The M step (maximization step) consisted of estimating the population pharmacokinetic parameters by maximum likelihood, given the current estimate of the individual parameters and using a first-order expansion of the model about the individual parameters. The choice of the parametrization of the model is free. The distribution of each parameter can be assumed to be normal or log-normal. Residual error was assumed to be additive to the concentration.

The concentration- versus-time data for isepamicin in serum, DO, and UF were analyzed by a nonlinear mixed-effect modeling approach. An open two-compartment pharmacokinetic model with zero-order input was used to describe isepamicin kinetics. The choice was based on previous studies on the disposition of isepamicin (8). Time design and blood samples were optimized with the theory of D optimality (4). The prior mean parameter vector (necessary to begin the D optimality) was the vector (60, 15) (60 ml/min for total body clearance and 15 liters for the volume of distribution [Vf]). These parameters were determined for the serum, DO, and UF samples.

TABLE 1. Clinical characteristics of the six patients and mean individual UF rates during the collection of samples

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Ht (cm)</th>
<th>Wt (kg)</th>
<th>Sex</th>
<th>SAPS</th>
<th>UF rate (ml/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mean ± SD</td>
</tr>
<tr>
<td>1</td>
<td>47</td>
<td>172</td>
<td>80</td>
<td>M</td>
<td>15</td>
<td>540 ± 200</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>176</td>
<td>98.6</td>
<td>F</td>
<td>19</td>
<td>558 ± 212</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>165</td>
<td>55</td>
<td>F</td>
<td>30</td>
<td>576 ± 225</td>
</tr>
<tr>
<td>4</td>
<td>73</td>
<td>172</td>
<td>97</td>
<td>M</td>
<td>28</td>
<td>660 ± 106</td>
</tr>
<tr>
<td>5</td>
<td>74</td>
<td>149</td>
<td>39.8</td>
<td>F</td>
<td>12</td>
<td>628 ± 206</td>
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<tr>
<td>6</td>
<td>88</td>
<td>160</td>
<td>60</td>
<td>F</td>
<td>10</td>
<td>769 ± 192</td>
</tr>
</tbody>
</table>

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1 M, male; F, female.
2 SAPS, simplified acute physiologic score.
The sampling design of the theory of D optimality was used to obtain the output, plasma central compartment, and DO and UF values. In order to obtain a population estimate of the elimination half-life, which is a key parameter of clinical use, the data were also analyzed by fitting them to a bicompartamental model implemented as the usual integrated equation, with the slope of the terminal phase.

The pharmacokinetic model used, a two-compartment pharmacokinetic model, had the following characteristics: linearity, heteroscedastic (Y^2) measurement error variance, a 0.001 Marquardt precision on parameters, and a 0.001 relative parameter change for gradient calculation. The results of analysis were judged with weighted sum of squares, number of iterations, values of Akaike criterion, and Bayesian objective function.

The sieving coefficient (Sc) related the ratio of solute concentration in the UF to that in the plasma and is the mathematical expression of the solute's ability to convectively permeate the membrane: Sc = 2C_{UF}(C_{P} + C_{DO}), where C_{UF} is the isepamicin concentration in the UF and C_{P} (arterial) and C_{DO} (venous) are the filter inlet (plasma) and outlet (dialysate) isepamicin concentrations, respectively (11).

### RESULTS

Means and standard deviations for serum, DO, and UF isepamicin concentrations obtained in CVVHD patients are listed in Table 2. The peak serum isepamicin concentration (mean ± standard deviation) occurring between 0.5 and 1 h after infusion was 62.88 ± 18.20 mg/liter (range, 37.08 to 90.44 mg/liter). The average remaining isepamicin concentration 12 h after the beginning of infusion was 20.16 ± 6.48 mg/liter (range, 12.52 to 27.28 mg/liter).

The individual pharmacokinetic parameters of the bicompartamental model calculated by the Bayesian method are listed in Table 3. The mean UF rates for each patient during the study are reported in Table 1. The elimination half-life was 7.91 ± 0.83 h (range, 6.47 to 8.87). The mean total body clearance was 1.75 ± 0.28 liters/h, and the DO clearance was 2.76 ± 0.59 liters/h. The mean V was 19.83 ± 2.95 liters. The mean Sc was estimated at 0.65 ± 0.11 (range, 0.48 to 0.81).

### DISCUSSION

Reviews of isepamicin activity demonstrate MICs at which 90% of the isolates are inhibited ranging from 1.1 to 8.5 mg/liter for members of the family Enterobacteriaceae, making isepamicin slightly more potent than amikacin (9).

Isepamicin is completely eliminated via the renal route. Consequently, dosing in patients with renal insufficiency must be adjusted according to the degree of renal impairment (1). The pharmacokinetics of isepamicin are generally linear. Thus, peak plasma isepamicin concentrations and area under the plasma isepamicin concentration curve values are proportional to the administered dose, while clearance (1.1 to 1.3 ml/min/kg). V at steady state (0.23 to 0.29 liter/kg), and half-life (2 to 2.5 h) are independent of dose.

Suzuki et al. reported the usefulness of single-dose treatment with isepamicin against chronic complicated urinary tract infection (13). In this publication, laboratory and clinical experiments were performed (13). Concentrations of the drug in serum were assayed for patients after the administration of isepamicin at a dose of 400 mg by intravenous drip infusion for 30 or 60 min. Patients tested consisted of three groups with different degrees of renal function. When the peak and trough concentrations in the three groups were compared on days 1, 2, 5, and 6 of administration of the drug, no significantly different values were found.

Halstensen et al. evaluated the disposition of isepamicin in 30 subjects with various degrees of renal function (8). The V's of isepamicin were not significantly different among the five groups of patients. The total body clearance and renal clearance of isepamicin significantly decreased as creatinine clearance decreased. Hemodialysis augmented the total body clearance of isepamicin by approximately 25-fold. The amount of isepamicin recovered in the dialysate was 60.6% ± 15.8% of the dose administered. Concentrations in plasma increased 32.7% ± 22.9% over that measured at the end of hemodialysis.

Tod et al. studied the pharmacokinetics of isepamicin in 85 intensive care unit patients compared with those observed in 10 healthy volunteers (15). Isepamicin was given intravenously over 0.5 h at dosages of 15 mg/kg once daily or 7.5 mg/kg twice daily. Compared with healthy volunteers, the mean values of the pharmacokinetic parameters were profoundly modified in intensive care unit patients: the elimination clearance was reduced by 48%, the V in the central compartment was increased by 50%, the peripheral V was 70% higher, the distribution clearance was 146% lower, and the elimination half-life was 3.4 times longer. The interindividual variability in pharmacokinetic parameters was about 50% in intensive care unit patients.

Like hemodialysis, CVVHD diverts the patient’s blood into a hemofilter: a membrane across which material movements...
are achieved by convection. Hemodialysis requires similar hydrostatic pressures with a transmembrane osmotic gradient that favors diffusion (11). A knowledge of drug clearances during CVVHD is imperative, if pharmacological errors are to be avoided in these already fragile patients (3). Most drugs in clinical use are sufficiently small to pass through the pores in the filters used for CVVHD (2, 5).

Isepamicin pharmacokinetics have been studied during CVVHD to measure the amount of the drug that is removed. Serum, DO, and UF samples were collected during the entire dosing interval. The Sc relates the ratio of solute concentration in the UF to that in the plasma. The mean Sc in our study was 0.65 and ranged between 0.48 and 0.81. This coefficient value suggests that isepamicin has a very strong ability to convectively permeate the membrane. Aminoglycosides have a low V and a low degree of protein binding, which is usually less than 20%. In our patients, isepamicin had a low V (0.33 liter/kg of body weight) and a protein binding estimated at less than 20%. In our patients, V was variable, results ranging from 0.17 to 0.57 liter/kg, but this is usual for critically ill patients. The elimination half-life was 7.91 ± 0.83 h (range, 6.47 to 8.87 h) in our population. The mean DO clearance was 30.33 ml/min (range, 21.83 to 45.67 ml/min), and the similarity between an optimal drug removal was characterized by a mean Sc of 0.65.

The plasma drug levels in our patients for 15 mg/kg showed a mean maximum concentration of drug in serum of 62.88 mg/liter occurring between 0.5 and 1 h after infusion and a mean minimum concentration of drug in serum of 20.16 mg/liter 12 h after the infusion. Our data demonstrate that in CVVHD patients, the maximum concentration of drug in serum was lower and the half-life was longer, whereas the V is quite comparable to values for intensive care patients in the literature.

Conclusion. Because of isepamicin’s antimicrobial properties and serum half-life in our group of intensive care patients under CVVHD, the initial dosage of 15 mg/kg appeared to be adequate but the dosage interval should be determined by monitoring residual concentrations in plasma (goal of ≤1 to 2 mg/liter). Results demonstrated that the dosage interval in our group of patients was between 48 and 60 h.

REFERENCES