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Multiple-Dose Pharmacokinetics of Amikacin and Ceftazidime in Critically Ill Patients with Septic Multiple-Organ Failure during Intermittent Hemofiltration

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The pharmacokinetic parameters of amikacin and ceftazidime were assessed in four patients undergoing hemofiltration for septic shock. The parameters were assessed during hemofiltration and in the interim period. The concentration-time profiles of these two drugs in plasma, urine, and ultrafiltrate were investigated after intravenous perfusion (30 min). In all cases a 1-g dose of ceftazidime was administered; for amikacin, the dosage regimen was adjusted according to the patient's amikacin levels (250 to 750 mg). Concentrations of drug in all samples were assayed by high-performance liquid chromatography with UV detection for ceftazidime and by enzyme multiplied immunoassay for amikacin. The elimination half-life ($t_{1/2}$) and the total clearance of amikacin ranged from 31.1 to 138.2 h and from 5.4 to 8.9 ml/min, respectively, during the interhemofiltration period in anuric patients. Hemofiltration substantially decreased the $t_{1/2}$ (3.5 ± 0.49 h) and increased the total clearance (89.5 ± 11.8 ml/min). The hemofiltration clearance of amikacin represented 71% of the total clearance, and the hemofiltration process removed, on average, 60% of the dose. During hemofiltration, the elimination $t_{1/2}$ of ceftazidime (2.8 ± 0.69 h) was greatly reduced and the total clearance increased (74.2 ± 11.2 ml/min) compared with those in the interhemofiltration period (9 to 43.7 h and 7.4 to 16.8 ml/min, respectively). About 55% of the administered dose was recovered in the filtrate, and the hemofiltration clearance of ceftazidime was 46 ± 14.3 ml/min. A redistribution phenomenon (rebound) in the amikacin and ceftazidime concentrations in plasma (35 and 28%, respectively) was reported after hemofiltration in two patients. The MICs for 90% of the most important pathogens were exceeded by the concentrations of the two drugs in plasma during the whole treatment of these patients.

The association between acute renal failure and sepsis is frequent (4, 12, 22, 23, 25). In this setting, many bacterial species have been implicated as etiologic pathogens, i.e., *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and other members of the family *Enterobacteriaceae*. In patients with multiple-organ failure induced by sepsis, the combination of edema, acute renal failure, acute respiratory distress syndrome, and hemodynamic instability is frequent, and hemofiltration may be the only way for correcting edema and metabolic disorders of acute renal failure (4, 19). Indeed, hemofiltration was usually performed in patients with septic shock and/or multiple-organ failure for its good hemodynamic tolerance. Hemofiltration can be performed either intermittently or continuously. Intermittent hemofiltration is a well-established tool in nephrologic therapy, whereas continuous methods have become valuable and accepted methods in critical care units.

Another problem in septic patients undergoing hemofiltration is to determine the best-adapted method for administering antibiotics. In these patients, the combination of cephalosporins and aminoglycosides is widely used. Ceftazidime is a cephalosporin with exceptionally high activity against a wide spectrum of bacteria. It is highly stable to a wide range of β-lactamases and is bactericidal. It may therefore offer a

TABLE 1. Patient characteristics

Patient no.	Sex[a]	Age (yr)	Ht (cm)	Isolated strain	Pathology
1	M	58	180	Unknown[b]	Alcoholic cirrhosis, digestive hemorrhage, infected ascites
2	M	78	175	*P. aeruginosa*	Postoperative course of bowel necrosis
3	F	75	160	*P. aeruginosa*	Postoperative course of rectal cancer, postoperative pneumonia
4	F	32	160	*Klebsiella pneumoniae*	Alcoholic hepatitis, acute respiratory distress syndrome

[a] M, male; F, female.
[b] Treatment with cefotaxime before admission.

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TABLE 2. Dosage regimen[a]

Patient no. and day	Time (h:min)	Hemofiltration:		Amt of drug administered (mg)		Creatinine (μmol/liter)	Blood urea (mmol/liter)	Amt of ultrafiltrate (liters)[b]	Wt (kg)
		Start	End	Ceftazidime	Amikacin				
Patient 1									
1	14:00			1,000	750				
1	16:02	*				140	24		89.0
2	01:30		*			96	16.7	43.4	90.2
2	02:00			1,000	750				
2	14:00			1,000	675				
3	02:00			1,000	675				
3	08:00			1,000	675				
3	10:30	*				104	21.9		91.0
3	19:50		*			102	19.4	46.0	91.4
3	20:00			1,000	675				
4	08:00				675				
4	20:00			1,000	675	107	22.6		92.8
5	08:00				675				
5	20:00				675				92.8
6	08:00			1,000	675				
6	10:40	*				131	31.5		92.9
6	13:15		*					12.8	93.4
Patient 2									
1	11:00			1,000	650				
1	13:45	*				684	45		86.5
2	00:00		*	1,000	650	336	27.7	55.0	80.7
3	06:00			1,000	400				
3	08:00	*				469	42.1		80.2
3	17:15		*			308	29	44.0	77.0
3	18:00			1,000	400				
6	04:00			1,000	700				
6	08:00	*				462	58.2		75.7
6	20:00		*			168	16.2	56.0	75.0
9	06:00			1,000	700				
9	10:15	*				436	46		72.3
9	20:00		*			154	16.9	48.0	71.7
12	06:00			1,000	250				
12	10:00	*				448	36.6		70.5
12	18:22		*			104	13.6	48.0	70.4
Patient 3									
1	16:00			1,000	500				
1	18:40	*				376	50.2		80.3
2	07:00		*			224	31	40.0	75.7
2	13:30			1,000	500				
2	16:20	*				235	35.9		75.3
3	04:20		*			115	13.4	45.0	70.2
3	14:00			1,000	500				
4	09:30			1,000	500				
4	13:00	*				259	45.4		71.7
4	23:00		*			126	21.2	42.0	70.1
5	07:00			1,000	500				
5	09:00	*				165	29.5		71.4
5	19:00		*			99	13.4	37.5	69.2
Patient 4									
1	14:00			1,000	500				
1	16:00	*				344	58.5		67.5
1	22:55		*			196	27.5	38.0	65
1	23:00			1,000	500				
4	08:00			1,000	500				
4	10:00	*				183	44.7		62.5
4	16:30		*			153	29.6	35.0	62.5
4	17:00			1,000	500				

[a] The drugs were given as a 30-min infusion.
[b] Amount of ultrafiltrate removed.

TABLE 3. Pharmacokinetic parameters for amikacin determined during hemofiltration and the interhemofiltration period[a]

Patient no. and period	C_{max} (mg/liter)	C_{min} (mg/liter)	Elimination half-life (h)			V_1 (liter/kg)
			Plasma	Ultrafiltrate	Urine	
1[b]						
Hemofiltration	32.7 ± 3.3 (3)[c]	2.65 ± 0.90 (3)	3.1 ± 0.3 (3)	2.9 ± 0.2 (2)	4 ± 0.9 (2)	0.231 ± 0.034 (3)
Interhemofiltration	35.4 ± 7.8 (8)	6.35 ± 0.80 (8)	4.8 ± 1.5 (8)		4.7 ± 2.2 (3)	0.193 ± 0.0665 (8)
2						
Hemofiltration	32.3 ± 9.9 (5)	3.98 ± 1.63 (5)	3.7 ± 0.5 (5)	3.4 ± 0.2 (3)	96.1 ± 5.2 (2)	0.229 ± 0.0307 (5)
Interhemofiltration	31.5 ± 2.6 (2)	10.9 ± 4.05 (2)	65.2 ± 3.2 (2)			0.220 ± 0.0146 (2)
3						
Hemofiltration	22.5 ± 4.79 (4)	3.38 ± 1.17 (4)	4.1 ± 1.5 (4)	4.0 ± 1.0 (4)	50.1	0.258 ± 0.0615 (4)
Interhemofiltration	24.3	13.9	31.1			0.260
4						
Hemofiltration	39.5 ± 3.95 (2)	6.2 ± 1.3 (2)	3.1 ± 0.6 (2)	2.8 ± 0.1 (2)	183.5	0.219 ± 0.0672 (2)
Interhemofiltration	31.7 ± 6.05 (2)	5.25 ± 0.95 (2)	138.2 ± 60.2 (2)		122.4 ± 81.4 (2)	0.240 ± 0.0255 (2)

[a] The parameters were computed by using Siphar software. Data are means ± standard deviations.
[b] The patient was treated with furosemide.
[c] Values in parentheses are number of data.
[d] Urinary excretion of amikacin was nil.

wider spectrum of activity and a low incidence of toxicity. Ceftazidime was found to be safe and effective for treating a variety of serious infections mainly caused by *P. aeruginosa* (5, 6). Aminoglycoside antibiotics are appropriate for use against this type of infection because of their broad gram-negative spectrum of activity. Elimination of ceftazidime and amikacin, which have low levels of protein binding (<20%) (2, 3, 20) and molecular weights of 637 and 582.6, respectively, is mainly via the renal route. The dosage regimens of these two drugs, which are primarily eliminated by the kidneys, must therefore be adjusted in patients with severe renal insufficiency to prevent the accumulation of the drug to toxic levels; moreover, the ototoxicities and nephrotoxicities of aminoglycosides suggest, for long-term intravenous treatment, a dosage regimen adjustment in patients with acute renal impairment.

The aim of the present study was therefore to assess the pharmacokinetics of amikacin and ceftazidime in patients undergoing intermittent veno-venous hemofiltration. The kinetics of these two drugs were investigated in plasma, urine, and ultrafiltrate. Kinetics were assessed during the hemofiltration period and during the period without hemofiltration. The second objective of the present study was to propose a suitable dosage regimen for the establishment of a safe and efficient drug level in these types of patients.

MATERIALS AND METHODS

Patients. The study was carried out on four patients (two males, two females; mean age, 60.8 ± 21.1 years) undergoing intermittent hemofiltration in a critical care unit for septic shock. The characteristics of the patients are summarized in Table 1. All patients were treated with the combination of ceftazidime and amikacin and were anuric or oliguric, despite furosemide infusion and hemodynamic support (i.e., vascular loading controlled by a pulmonary artery catheter, dobutamine, dopamine, and norepinephrine infusion). They were previously tracheotomized, mechanically ventilated with positive end expiratory pressure, and sedated with flunitrazepam and fentanyl infusion. For each patient, anamnesis data, physical examination, vital signs (blood pressure, heart rate, temperature, and weight), and standard laboratory tests, including liver function tests (bilirubin, prothrombin time, alanine aminotransferase, and aspartate aminotransferase) and renal function tests (blood urea nitrogen, and serum creatinine), were obtained or performed before and during the study. For all patients, hematocrit was maintained between 30 and 35%. All patients were negative for human immunodeficiency virus and hepatitis B virus.

The families of the patients were fully informed of the study design, and the patients were enrolled in the study after their families granted written informed consent. The protocol was approved by the local hospital ethics committee.

Hemofiltration. Intermittent pump-driven veno-venous hemofiltration was performed by using a Gambro pump apparatus (MMA-2 NR 683; AB Instrumenta, Lund, Sweden). An FH 88 H fiber hemofilter (Gambro; Dialysatoren GmbH & Co. KG, Hechingen, Germany) was used. The filter consists of a bundle of capillary hollow fibers (inside diameter, 215 μm; number of fibers, 12,200). The active layer is a permeable membrane made of polyamide. This membrane contains pores which permit the passage of water and solutes with molecular masses of up to 10,000 Da. To maintain patient fluid balance, a volume of physiologic replacement solution (sodium, 140 meq/liter; chloride, 110 meq/liter; bicarbonate, 35 meq/liter; calcium, 3.5 meq/liter; magnesium, 1.5 meq/liter) was filtered to eliminate particles and then infused at a rate similar to the ultrafiltration rate. The total reinfusion volume was arbitrary and was based on about 0.5 liter/kg of body weight. The flow rate of the blood pump was 300 ml/min.

Drug administrations and doses. All patients received a 30-min intravenous infusion of 1 g of ceftazidime in combination with amikacin via an infusion pump. The dosage regimen was adjusted according to the patient's amikacin levels, as shown in Table 2.

Samples. Arterial blood samples (2 ml) for drug assay were drawn into EDTA tubes through a 3-F (1-mm-diameter) arterial Teflon catether (Plastimed, Saint Leu la Forêt, France) for repeated blood sampling. Samples were collected immediately before and after infusion of antibiotics, at the start of hemofiltration (Table 2), every 2 h until the end

TABLE 3—*Continued*

V (liter/kg)	CL (ml/min)	CL_{HF} (ml/min)	CL_R (ml/min)	CL_{NR} (ml/min)	% Hemofiltration	% Drug excreted in urine
0.453 ± 0.0642 (3)	101.1 ± 29.3 (3)	52.0 ± 6.8 (2)	36.0 ± 7.61 (2)	20.8 ± 13.7 (2)	23.9 ± 4.0 (2)	25.0 ± 8.0 (2)
0.392 ± 0.0791 (8)	48.8 ± 21.4 (8)		46.7 ± 10.3 (3)	12.7 ± 8.07 (3)		15.9 ± 3.1 (3)
0.469 ± 0.137 (5)	73.5 ± 9.0 (5)	59.7 ± 14.4 (3)	0.893 ± 1.13 (3)	8.24 ± 3.29 (2)	68.7 ± 14.6 (3)	0.823 ± 0.916 (3)
0.433 ± 0.0762 (2)	5.4 ± 0.5 (2)		0	5.4 ± 0.5 (2)		0
0.487 ± 0.0459 (4)	94.6 ± 18.7 (4)	73.2 ± 16.9 (4)	0.458 ± 0.915 (4)[d]	12.8 ± 7.64 (4)	61.6 ± 12.0 (4)	0.435 ± 0.87 (4)[d]
0.521	8.9		0	8.9		0
0.369 ± 0.001 (2)	88.7 ± 13.5 (2)	56.8 ± 8.58 (2)	8.73 ± 4.16 (2)	23.2 ± 17.9 (2)	52.7 ± 12.2 (2)	6.35 ± 1.06 (2)
0.435 ± 0.058 (2)	16.0 ± 15.8 (2)		13.8 ± 12.1 (2)	2.38 ± 3.37 (2)		18.6 ± 11.6 (2)

of hemofiltration (Table 2), and every 2 h until the next dose. During the interhemofiltration periods, samples were collected immediately before and at the end of infusion and every 2 h until the next dose. Plasma samples were obtained by centrifugation at 1,500 × *g* for 10 min. The samples were then stored at −20°C along with quality control samples prepared from human plasma until analysis.

Ultrafiltrate was obtained every 2 h during the hemofiltration periods.

When the urine data were available, the total urine output was taken from an indwelling catheter every 2 h.

The total volumes of ultrafiltrate and urine samples were measured and recorded at the end of each interval. The samples were homogenized, and two 2-ml aliquots were transferred to vials and were stored at −20°C along with quality control samples prepared in free urine until analysis.

Assay method. The concentrations of ceftazidime in plasma, ultrafiltrate, and diluted urine (1/10 to 1/100) were assayed by high-pressure liquid chromatography (HPLC) with UV detection (254 nm). This method has been validated in our laboratory according to Good Laboratory Practice guidelines (3).

A steel chromatographic column (100 by 4.6 mm) was packed with 3 μm Nucleosil C18 particles (Société Française de Chromato Colonne, Neuilly Plaisance, France). The mobile phase, which contained 5 parts of acetonitrile and 95 parts of citrate buffer (citric acid, 0.75 g/liter; sodium citrate, 2 g/liter; adjusted to pH 5 with 2 M NaOH), was used at a flow rate of 1.5 ml/min. The analytical column was kept at 50°C. Under these conditions, ceftazidime showed a retention time of 5.5 min and the internal standard (cephalexin) showed a retention time of 8.5 min. None of the samples of plasma, hemofiltrate, or urine taken before drug administration showed peaks at the retention time of ceftazidime or the internal standard. Quality control samples were included in each analytic sequence to verify the stability of the study samples during storage and the accuracy and precision of ceftazidime analysis. The inter- and intraday reproducibilities of the HPLC assay, as well as its within-run precision at high and low concentrations (recovery of spiked samples), were determined; the coefficient of variation was <10% for a concentration range from 0.25 to 100 μg/ml. The limit of quantification was 0.25 μg/ml.

The concentrations of amikacin in plasma, ultrafiltrate, and urine were assayed by the enzyme multiplied immunoassay technique. The enzyme multiplied immunoassay system consists of a Syva 1500 pipetor dilutor, an S III spectrophotometer (340 nm), a CP-5000 clinical processor, and a vacuum receiver (Syva-bioMerieux, Dardilly, France). A 50-μl aliquot of plasma, urine or 1/10- to 1/100-diluted urine, and ultrafiltrate were analyzed. The inter- and intraday reproducibilities of the assay, as well as its within-run precision, were determined; the coefficient of variation was <10% for a concentration range from 2.5 to 50 μg/ml. The limit of quantification was 2.5 μg/ml.

Pharmacokinetic analysis. Individual pharmacokinetic parameters for amikacin and ceftazidime were estimated from plasma, urine, and hemofiltrate data by using Siphar software (11). This program allows determination of individual pharmacokinetic parameters during the hemofiltration and interhemofiltration periods. Subsequently, the total clearances (CLs), which were computed by using the Siphar software, were used as clinical descriptors in the software of Jelliffe et al. (13). This program allows the simultaneous fitting of all datum points for each patient, including those during hemofiltration and the periods without hemofiltration.

By using the Siphar software, during the hemofiltration and interhemofiltration periods, plasma concentration-versus-time curves of ceftazidime and amikacin were modeled for each patient by using a one- or two-compartment open model with a zero-order input rate and first-order distribution and elimination rates.

In order to take into account the residual levels of drugs in plasma before the previous dose, the concentrations in plasma at each sampling time were corrected as follows: $C_{corrected} = C_{observed} - C_{residual}$ and $C_{residual} = C_0 \exp^{-\lambda_2 t}$, where C_0 is the concentration in plasma before the next dose (minimum concentration in plasma [C_{min}]), λ_2 is the elimination rate constant computed on the log-transformed data on the terminal phase of the curve, and t is the time from the last drug intake.

The coefficients and exponents of the exponential equation were estimated by this program by the weighted least-squares method (weight, $1/C^2$). The choice of the model was made with respect to several criteria to assess the goodness of fit of the models to the experimental data. These criteria were as follows: the objective function, the coefficient of variation of each parameter, the scatter of the plot of the residuals and the standardized residuals (normalized to the variance model) against time and computed values, and

TABLE 4. Hemofiltration data[a]

Patient no.	QF (ml/min)	QB (ml/min)	Amikacin								Ceftazidime							
			S_c	E	F/P						S_c	E	F/P					
					HF1	HF2	HF3	HF4					HF1	HF2	HF3	HF4		
1	80.3 ± 13.5 (10)	300	0.65	0.26	0.72 ± 0.15 (5)	0.52 ± 0.19 (5)					0.48	0.19	1.04 ± 0.42 (5)	0.77 ± 0.20 (5)				
2	89.9 ± 12.7 (16)	300	0.78	0.34	0.78 ± 0.07 (6)	0.73 ± 0.02 (5)	0.69 ± 0.13 (5)				0.37	0.17	0.96 ± 0.22 (6)	0.78 ± 0.12 (5)	0.94 ± 0.2 (5)			
3	65.8 ± 14.9 (21)	300	1.0	0.39	1.40 ± 0.1 (6)	1.17 ± 0.25 (6)	0.76 ± 0.3 (4)	0.90 ± 0.19 (5)			0.70	0.23	1.14 ± 0.07 (6)	0.81 ± 0.12 (6)	0.98 ± 0.12 (4)	1.02 ± 0.11 (5)		
4	86.1 ± 14.7 (8)	300	0.60	0.26	0.63 ± 0.23 (4)	0.73 ± 0.07 (4)					0.77	0.33	0.78 ± 0.09 (4)	0.58 ± 0.11 (4)				

[a] QF, ultrafiltration flow rate; QB, blood flow rate; S_c, sieving coefficient; E, efficiency of extracorporeal elimination; F/P, ultrafiltrate/plasma concentration ratios, which is also an estimate of S_c; HF, hemofiltration; Values in parentheses are number of data.

the correlation matrix. Comparison between competing models was made by using the Akaike test (11).

The highest observed concentration in plasma was designated C_{max}. The elimination half-life was determined from the slope of the log-linear part curves, λ_2. The total area under the curve was obtained by linear trapezoidal approximation with correction to infinity by dividing the last observed datum point by the terminal elimination rate constant (λ_2). CL was evaluated by the following: dose/area under the curve. The volume of distribution of the central compartment (V_1) was evaluated by V_1 = dose/(C_1 + C_2), where C_1 and C_2 are coefficients of the exponential terms. The apparent volume of distribution (V) was calculated as the ratio of the CL to the apparent rate constant of elimination.

The total amounts of ceftazidime and amikacin eliminated in urine and ultrafiltrate on the days of hemofiltration and in urine, when available, on the days without hemofiltration were computed at each sampling time. The amount of drug (in percent) excreted in urine between two drug administrations was also calculated. A pharmacokinetic analysis of the excretion rate of the two drugs (elimination by hemofiltration and/or in urine) versus time curves (rate plot) was undertaken for each subject by using the same computer program.

The hemofiltration clearance (CL_{HF}) and the renal clearance (CL_R) of ceftazidime and amikacin were estimated from the slope of the plot of the excretion rate versus the drug concentration in plasma at the midpoint of the drug excretion intervals. The nonrenal clearance (CL_{NR}) was obtained by the following: $CL_{NR} = CL - (CL_{HF} + CL_R)$.

The CLs, which were computed by using the Siphar software, were then used as a clinical descriptor in the software of Jelliffe et al. (13). The data were modeled by the least-squares fitting procedures by using the Nelder-Mead simplex method (13). In this program, the rate constant for elimination (k_{el}) from the central compartment, which represents the total of renal and nonrenal excretory mechanisms and metabolic processes, was broken up into a nonrenal component or intercept (k_i) plus a slope (k_s) times drug clearance: $k_{el} = k_i + (k_s \cdot CL)$, where CL is the clinical descriptor. By this means, the k_{el} can be made to change from dose to dose with any changes in CL (i.e., CL_R and CL_{HF}) and all data on levels of drugs in plasma can be used, although the patient's functional status may have changed greatly.

The goodness of fit to the experimental data was assessed by using the objective function and the residuals between computed and experimental data. This program computed the microscopic rate constants (k_{cp} and k_{pc}), the volume of distribution of the central compartment (V_1), and k_{el}.

The sieving coefficient (S_c) of the membrane was computed as follows: $S_c = CL_{HF}/Q_F$, where Q_F is the ultrafiltrate flow rate.

The extraction ratio (E) was calculated from $E = CL_{HF}/QB\ (1 - Hct)$, where QB is the blood flow through the extracorporeal device, and Hct is the hematocrit.

Presentation of results. Results in the text are presented as means ± standard deviations.

RESULTS

Effects of hemofiltration on weight and endogenous compound elimination. The measured biochemical variables (i.e., serum creatinine and blood urea), the amount of ultrafiltrate removed, and the patients' net weight losses are given in Table 2. The decreases in serum creatinine and blood urea

resulting from the hemofiltration were 164.4 ± 118.5 μmol/liter and 20.2 ± 10.3 mmol/liter, respectively. Patients 2, 3, and 4 experienced weight losses during hemofiltration, while the weight of patient 1 increased. The amount of ultrafiltrate removed averaged 45 liters (35 to 56 liters) except during the last hemofiltration of patient 1, which was rapidly stopped because a cardiovascular collapse occurred.

Pharmacokinetic parameters determined by the Siphar software after intravenous infusion of amikacin. Statistical analysis of the fit of the model to the curves indicated that the data were consistent with a two-compartment body model. The goodness of fit as described by r^2 was typically >0.998 in 88% of the analytes, and the coefficient of variation of each parameter was less than 20%. This model typically produced a significant reduction in the objective function and in the statistical test. For each patient, mean pharmacokinetic parameters during the hemofiltration period and between two periods of hemofiltration are given in Table 3.

The intraindividual variability was low, with a coefficient of variation of <25% for most pharmacokinetic parameters.

The apparent elimination half-life of amikacin computed from plasma data ranged from 3.1 to 4.1 h during hemofiltration and from 31.1 to 138.2 h in the interhemofiltration period, except for patient 1, who was treated with furosemide and for whom the elimination half-lives determined during hemofiltration and between two hemofiltrations were very close. The V_1 averaged 0.23 liter/kg; the mean steady-state V was 0.445 liter/kg.

Elimination of amikacin in ultrafiltrate ranged from 24% (patient 1) to 69% (patient 2). The apparent elimination half-life determined from the variations of the excretion rate in the ultrafiltrate with time was close to that determined from the plasma data (2.8 to 4 h).

For patient 1, elimination of amikacin by the renal route (25%) and hemofiltration (24%) was equivalent. For the other patients, less than 10% amikacin was recovered in the urine. In patient 4 on the last day of treatment, a return of diuresis was noted and 26.8% of the dose was recovered unchanged in urine. For patient 1, the half-life of elimination evaluated from the urinary excretion rate was of the same order of magnitude as that determined from the plasma data (4.7 h). For the other patients, in some cases the urinary elimination half-life could be computed and varied from 50.1 to 183.5 h, depending on the patient; these values were close to those determined from the plasma data on the days without hemofiltration.

CLs computed from the plasma data during hemofiltration ranged from 74 to 101 ml/min; it was slightly greater than the sum of CL_R and CL_{HF}. The difference represents CL_{NR}, the values of which for the four patients in the present study were 20.8, 8.24, 12.8, and 23.2 ml/min. These values were greater than those computed during the interhemofiltration period (12.7, 5.4, 8.9, and 2.38 ml/min), especially for patient 4 (Table 3).

The ultrafiltration flow rate ranged from 80.3 to 89.9 ml/min for patients 1, 2, and 4 (Table 4); a lower value was found for patient 3 (65.8 ml/min). The mean S_c of amikacin and the extraction coefficient are listed in Table 4. The ultrafiltrate/plasma concentration ratio, which is also an estimate of S_c, was relatively constant during treatment for the four patients (Table 4).

After the hemofiltration procedure, an increase in the plasma amikacin concentration was observed for patients 2 and 3. The maximum rebound in the plasma amikacin concentration was observed to be from 1 to 13 h after hemofiltration. The maximum increase in the plasma amikacin concentration from the concentration observed immediately after hemofiltration was 37.2% ± 17.8% for patient 2 and 33.5% ± 4.97% for patient 3. For patient 4, a marked rebound was not observed. Patient 1 received a new drug administration immediately after stopping hemofiltration, so the rebound phenomenon was not detectable.

Pharmacokinetic parameters determined by the Siphar software after intravenous infusion of ceftazidime. After infusion, a two-compartment open model adequately described the observed data. The good agreement between the simulated and the experimental data and the coefficient of variation of the coefficient and of the exponent of the exponential term validated the choice of the model. Moreover, the model typically produced a significant reduction in the statistical test.

The mean ± standard deviation pharmacokinetic parameters obtained for each subject are presented in Table 5.

The intraindividual variability was less than 25% for most pharmacokinetic parameters.

During hemofiltration, the apparent elimination half-life, computed from plasma data, ranged from 2.0 to 3.6 h, according to the patient; these values were very close to those determined from the variation with time of the ceftazidime excretion rate in ultrafiltrate (2.6 to 3.2 h). For patient 1, who was treated with furosemide, the elimination half-life computed from plasma data in the interhemofiltration period (2.6 h) was of the same order of magnitude as that determined from the urine data (3.1 h); these two values were very close to those computed during hemofiltration (2 and 3.4 h). For the other patients, the elimination half-life of ceftazidime determined from plasma data declined from 9.0 to 44 h in the interhemofiltration period to 2.6 to 3.6 h during hemofiltration. The apparent elimination half-lives computed from urinary data during hemofiltration were in good agreement with those computed from plasma on the days without hemofiltration (9.9 to 63 h). V_1 averaged 0.18 liter/kg, and the V in equilibrated tissues was 0.37 liter/kg.

For patients 2 and 4, the CL computed from plasma data was close to the sum of CL_R and CL_{HF}. In these patients, elimination by the renal route and hemofiltration represented 90% of the CL; for the other subjects, this sum represented about 70% of the CL. The difference corresponds to CL_{NR}. Patient 1 had a CL_{NR} that was of the same order of magnitude during the hemofiltration and the interhemofiltration periods; during the hemofiltration period, the three other patients had CL_{NR}s that were about two times greater than those computed during the interhemofiltration period.

For patients 2 to 4, the fraction of ceftazidime removed by hemofiltration accounted for 45 to 70%; these patients still had some urine output, and they excreted 0.2 to 6.4% of the dose in urine, except for the last dose in patient 4, in whom a return of diuresis was observed, and 29% of the administered dose was recovered in the urine of patient 4. In patient 1, who was treated with furosemide, during hemofiltration, 37 and 15% of the administered dose were eliminated in ultrafiltrate and urine, respectively; during the interhemofiltration period, 30% of the administered dose was excreted in urine.

The mean S_c of ceftazidime and the extraction coefficient are reported in Table 4. The ultrafiltrate/plasma concentration ratio was relatively constant during treatment of the four patients in the present study (Table 4).

After the hemofiltration procedure, rises in plasma ceftazidime levels were observed for patients 2 and 3. The maximum rebound in the plasma ceftazidime concentration was observed to be from 1 to 13 h after the end of hemofiltration.

TABLE 5. Pharmacokinetic parameters for ceftazidime determined during hemofiltration and the interhemofiltration period[a]

Patient no. and period	C_{max} (mg/liter)	C_{min} (mg/liter)	Elimination half-life (h)			V_1 (liter/kg)
			Plasma	Ultrafiltrate	Urine	
1[b]						
Hemofiltration	44.9 ± 3.3 (3)[c]	1.0 ± 0.6 (3)	2.0 ± 0.4 (3)	2.6 ± 0.3 (2)	3.4 ± 0.1 (2)	0.213 ± 0.0121 (3)
Interhemofiltration	47.7 ± 3.1 (4)	9.0 ± 5.5 (4)	2.6 ± 0.9 (4)		3.1 ± 0.5 (3)	0.208 ± 0.0375 (4)
2						
Hemofiltration	62.7 ± 9.2 (5)	4.3 ± 3.3 (5)	3.6 ± 0.8 (5)	3.2 ± 0.7 (3)	62.9	0.167 ± 0.018 (5)
Interhemofiltration	52.1 ± 15.4 (2)	17.1 ± 3.3 (2)	43.7 ± 13.8 (2)			0.163 ± 0.013 (2)
3						
Hemofiltration	77.3 ± 21.4 (4)	4.06 ± 1.6 (4)	3.1 ± 1.1 (4)	3.1 ± 0.9 (4)	19.2	0.190 ± 0.0153 (4)
Interhemofiltration	98.5	39.2	18.4			0.128
4						
Hemofiltration	65.5 ± 5.8 (2)	6.6 ± 0.3 (2)	2.6 ± 0.1 (2)	2.5 ± 0.1 (2)	9.87	0.163 ± 0.0128 (2)
Interhemofiltration	102.0 ± 0.6 (2)	4.5 ± 2.0 (2)	9.0 ± 1.3 (2)		9.85 ± 2.53 (2)	0.173 ± 0.0233 (2)

[a] The parameters were computed by using Siphar software. Data are means ± standard deviations.
[b] The patient was treated with furosemide.
[c] Values in parentheses are number of data.
[d] Urinary excretion of ceftazidime was nil.

The maximum increase in drug concentration was 27.3% ± 15.8% for patient 2 and 29.0% ± 9.9% for patient 3. For patients 1 and 4, a marked rebound was not observed.

Pharmacokinetic parameters from plasma data. Individual pharmacokinetic parameters determined by using the software of Jelliffe et al. (13) are given in Table 6.

The V_1 values (0.228 ± 0.0211 liter/kg for amikacin and 0.183 ± 0.020 liter/kg for ceftazidime) were very close to the extracellular water volume in normal subjects (inulin space). The interindividual variability was not very high, with a coefficient of variation of less than 11%.

The distributions in peripheral tissues (k_{12}s) of 0.181 ± 0.0891 h for amikacin and 0.164 ± 0.176 h for ceftazidime were lower than the transfer rate constants from tissue to plasma (k_{21}s), 0.368 ± 0.290 and 0.632 ± 0.540 h, respectively.

Relationship between the CLs of amikacin and ceftazidime and two endogenous compounds. During hemofiltration, a significant inverse correlation between the CL of amikacin and the decrease in the concentrations of creatinine in serum ($r = -0.75$; $P < 0.01$) and blood urea ($r = -0.56$; $P < 0.05$) was found.

No correlation was found between the decrease in the concentration of blood urea and the CL of ceftazidime ($r = -0.39$; not significant). A significant inverse correlation between the CL of ceftazidime and the decrease in the concentrations of creatinine in serum was observed, however ($r = -0.69$; $P < 0.01$).

DISCUSSION

The present study demonstrated a profound difference between intermittent hemofiltration in comparison with hemodialysis and peritoneal dialysis. The elimination mechanism in hemofiltration differs from that in conventional dialysis treatment; diffusion processes, which play a role in peritoneal dialysis and hemodialysis, do not take place during hemofiltration, in which the filtration process is the only mechanism of elimination (23). The effect of intermittent hemofiltration on drug disposition has been evaluated for only a few compounds (1, 7, 8, 10, 15, 16, 23, 26). The present study demonstrated that hemofiltration can significantly remove ceftazidime and amikacin from the circulation of patients with severe renal disease. Hemofiltration significantly decreased the elimination half-life and increased the CL.

The elimination half-life of amikacin was markedly increased and the CL decreased in three anuric patients during the periods without hemofiltration; these two parameters were close to those computed in patients with terminal renal insufficiency: 86.5 h and 2.8 ml/min, respectively (20). During hemofiltration, the elimination half-life and CL_{HF} determined from plasma data (3.5 h and 60.4 ml/min, respectively) were different from previously reported data in patients on hemodialysis (5.6 h for dialysis half-life and 37.2 ml/min for dialysis clearance [20]) but were comparable to those found in subjects with normal kidney function (9). This is consistent with a greater efficiency of our method of hemofiltration in terms of extrarenal purification. Moreover, the pharmacokinetic parameters computed in the present study during intermittent hemofiltration were different from those computed by Armendariz et al. (1) after continuous veno-venous hemofiltration of amikacin. Those investigators reported a CL and an elimination half-life for amikacin of 10.5 ml/min and 29.7 h, respectively. In these four hemofiltered patients, the value of V in equilibrated tissues was greater than that computed in healthy subjects (0.445 liter/kg instead of 0.27 liter/kg) (9), but it was very close to that reported in patients with renal failure and patients during continuous veno-venous hemofiltration (1). Moreover, during the hemofiltration and interhemofiltration periods, the values of V_1 and V were in accordance, indicating that the delayed excretion does not influence the distribution of the drug.

Using the software of Jelliffe et al. (13), the mean V_1 (0.228 ± 0.0211 liter/kg) was very close to that reported by Jelliffe et al. (13) for a population of healthy subjects (0.22 ± 0.04 liter/kg). Moreover, the k_s of 0.00214 ± 0.00066 min/ml · h was two to three times lower than that in a population of healthy subjects (0.0056 ± 0.0018 min/ml · h) but very close to that reported in a population in a critical care unit (0.00245 ± 0.00049 min/ml · h) (13). By using the program of Jelliffe et al. (13), a Bayesian estimation of amikacin pharmacokinetic parameters with a minimum number of blood samples can be

TABLE 5—*Continued*

V (liter/kg)	CL (ml/min)	CL_{HF} (ml/min)	CL_R (ml/min)	CL_{NR} (ml/min)	% Hemofiltration	% Drug excreted in urine
0.363 ± 0.065 (3)	87.2 ± 6.1 (3)	42.4 ± 9.63 (2)	17.1 ± 5.75 (2)	27.2 ± 16.2 (2)	37.0 ± 7.0 (2)	15.0 ± 4.0 (2)
0.352 ± 0.0400 (4)	35.9 ± 8.15 (4)		15.0 ± 2.96 (3)	21.59 ± 3.58 (3)		29.8 ± 5.0 (3)
0.416 ± 0.0929 (5)	64.1 ± 7.6 (5)	53.3 ± 10.8 (3)	2.75 ± 0.915 (3)	14.8 ± 7.53 (3)	69.8 ± 18.0 (3)	3.07 ± 0.4 (3)
0.390 ± 0.0134 (2)	8.5 ± 2.5 (2)		0	8.5 ± 2.5 (2)		0
0.504 ± 0.0231 (4)	65.5 ± 6.1 (4)	45.9 ± 9.6 (4)	0.0425 ± 0.085[d]	17.8 ± 6.02 (4)	69.9 ± 20.5 (4)	0.055 ± 0.11 (4)[d]
0.365	7.4		0	7.4		0
0.282 ± 0.0240 (2)	79.8 ± 13.2 (2)	66 ± 8.6 (2)	3.7 ± 5.23 (2)	10.1 ± 5.17 (2)	44.9 ± 2.33 (2)	2.75 ± 4.39 (2)
0.303 ± 0.0346 (2)	16.8 ± 11.3 (2)		10.9 ± 12.6 (2)	5.88 ± 1.24 (2)		17.1 ± 16.8 (2)

used for the adaptative control of drug dosage during the interhemofiltration period.

During the treatment, in two cases, high C_{min}s were found when amikacin was administered during the interhemofiltration periods. During the hemofiltration and interhemofiltration periods, the C_{max}s were very close, with a mean value of 31.2 ± 5.2 mg/liter (n = 8); concentrations of amikacin of greater than 20 mg/liter were maintained during a very short time. Furthermore, in our study, the amikacin levels in plasma were much higher than the MICs for most potentially pathogenic bacteria.

The elimination half-lives of ceftazidime during the interhemofiltration periods were substantially increased and the CLs were decreased except in patient 1, for whom a treatment with furosemide maintained a diuresis; these two pharmacokinetic parameters were not different from previously reported values (17) for patients on hemodialysis: 25.3 ± 4.14 h for the elimination half-life and 6.8 ± 0.7 ml/min for CL. During hemofiltration, the half-life of ceftazidime (2.8 ± 0.69 h [n = 4]; plasma data) was greatly reduced compared with that during the interhemofiltration period and was close to that found in patients during hemodialysis (2.8 h) (17); moreover, the CL (74.2 ± 11.2 ml/min [n = 4]) was of the same order of magnitude as that reported in normal subjects (17). The values of V_1 and V computed during hemofiltration and during the periods without hemofiltration were equivalent; we note, however, that the value of V in equilibrated tissues was greater than those found by Leroy et al. (17) in normal and uremic subjects. After multiple-dose administration, the intrapatient variability was low. During the treatment, the concentration of ceftazidime in blood exceeded the MICs for 90% of the most important pathogens tested (5), the C_{min}s ranged from 1 to 39.2 mg/liter, and the C_{max}s averaged 69 mg/liter (n = 8). Ceftazidime was well tolerated, and no severe side effects were noted.

The patients in the present study had a noticeable CL_{NR} which might be explained by the physical status of the patients with multiple-organ failure in the critical care unit. Indeed, fluids were lost through such means as gastric aspiration, diarrhea, abdominal tubes, and others which are difficult to quantify. Moreover, we observed that CL_{NR}s were higher during the hemofiltration than during the interhemofiltration periods. These findings were not in accordance with those found by Scarim et al. (24), who have recently reported that the CL_{NR} of vancomycin in patients with acute renal failure treated with continuous veno-venous hemofiltration is preserved. No rational explanation could be given except for patient 2, who underwent major gastric aspiration during the second hemofiltration, and patient 4, who experienced considerable diarrhea during the second hemofiltration.

During hemofiltration, a significant correlation between the CL of amikacin and the decrease in blood urea and serum creatinine was demonstrated. A high correlation was also found between the CL of ceftazidime and the decrease in serum creatinine. These findings were in accordance with the hemofiltration filters used. These filters were characterized by high porosities and higher S_cs than those for hemodialysis membranes for molecules in the middle molecular size range. Furthermore, during hemofiltration a higher blood flow rate than that during standard hemodialysis was used.

TABLE 6. Pharmacokinetic parameters computed by using the software of Jelliffe and colleagues[a]

Patient no.	Ceftazidime				Amikacin			
	V_1 (liter/kg)	k_s (min/ml · h)	k_{12} (h^{-1})	k_{21} (h^{-1})	V_1 (liter/kg)	k_s (min/ml · h)	k_{12} (h^{-1})	k_{21} (h^{-1})
1[b]	0.209	0.00315	0.420	1.27	0.212	0.00304	0.314	0.554
2	0.174	0.00281	0.0315	0.0714	0.217	0.00151	0.141	0.0897
3	0.162	0.00407	0.0674	0.868	0.259	0.00216	0.147	0.676
4	0.185	0.00345	0.139	0.319	0.226	0.00185	0.123	0.154

[a] See reference 13. k_s, slope; k_{12}, distribution in peripheral tissue; k_{21}, transfer rate constant from tissue to plasma.
[b] The patient was treated with furosemide.

The S_c is a measure of the relative permeability of the hemofiltration membrane for a given compound. The mean S_cs for amikacin and ceftazidime in the four patients studied ranged from 0.6 to 1 and from 0.37 to 0.77, respectively. For amikacin the S_c was very close to that found after continuous veno-venous hemofiltration (0.97 ± 0.16) (1). The average extraction coefficient found in the present study for ceftazidime (0.23 ± 0.061) was similar to those established for other beta-lactam antibiotics during hemodialysis and for cefoxitin during hemofiltration (8). For amikacin, the extraction coefficient was slightly greater than that for ceftazidime (0.31 ± 0.055).

Although the same hemofilter was used during the hemofiltration process and despite the deposition of blood components, especially protein, on the membranes during hemofiltration, an increase in the filtrate/plasma concentration ratios, as described by Rumpf et al. (23), was not observed.

In two subjects, a marked rebound was observed; the degree of the rebound ranged from 13 to 54% for amikacin and from 6 to 46% for ceftazidime, and the time to maximum rebound was highly variable. A similar phenomenon has been reported for other drugs after the hemofiltration procedure (7, 14, 18).

In the present study, ceftazidime and amikacin were given 2 h before the beginning of hemofiltration, so the distribution process of the drugs may have been completed. Thus, a full dose (i.e., 1 g of ceftazidime and 7.5 mg of amikacin per kg of body weight) seems to be suitable for the establishment of a safe, efficient, and nontoxic drug level during each hemofiltration period. The main problem is achievement of the desired peak and trough concentrations in plasma during the interhemofiltration period. Upon evaluation of plasma amikacin concentrations in individual patients during the period without hemofiltration, the C_{min} of amikacin averaged 14 mg/liter in two patients. Nevertheless, despite the in vivo postantibiotic effect of amikacin (21), we suggest that antibiotics should be given during the interhemofiltration period to efficiently treat severe infectious disease in these patients. On the basis of the results for the few patients in the present study and because of the large interpatient variability in the elimination rate constants during the interhemofiltration period, which was not dependent on residual diuresis, we can speculate that half of a dose might be administered at the end of the first hemofiltration. The monitoring of concentrations in plasma during the other interhemofiltration period should determine the next dosage regimen.

In conclusion, because minimal variability in the CL_{HF} was observed in the few patients in the present study, a full dose of antibiotics should be given during hemofiltration. However, the marked interpatient variability in the interhemofiltration elimination half-life and the degree of rebound justifies an individual approach to drug therapy in this patient population.

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