ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1992, p. 1404–1411
0066-4804/92/071404-08$02.00/0

Vol. 36, No. 7

Endotracheal and Aerosol Administrations of Ceftazidime in Patients with Nosocomial Pneumonia: Pharmacokinetics and Absolute Bioavailability

FRANÇOISE BRESSOLLE,[1]* JEAN-EMMANUEL DE LA COUSSAYE,[2] RIHAB AYOUB,[3] DAVID FABRE,[3] ROBERTO GOMENI,[4] GILBERT SAISSI,[2] JEAN-JACQUES ELEDJAM,[2] AND MARC GALTIER[3]

Département de Pharmacocinétique, Faculté de Pharmacie, Université de Montpellier I, 34060 Montpellier Cedex 1,[1] Département d'Anesthésie Réanimation,[2] and Laboratoire de Pharmacocinétique, Pharmacie Carrémeau,[3] Centre Hospitalier Universitaire, 30006 Nimes, and SIMED, S. A., 94008 Créteil Cedex,[4] France

Received 9 December 1991/Accepted 21 April 1992

Pharmacokinetic studies on ceftazidime, an aminothiazole cephalosporin with a wide spectrum of antibacterial activity, including activity against *Pseudomonas aeruginosa*, were performed in patients with nosocomial pneumonia. The concentration-time profiles of ceftazidime in plasma, urine, and bronchial secretions of 12 patients were investigated after intravenous (i.v.) (n = 12), endotracheal (n = 10), and aerosol (n = 5) administrations. In all cases a 1-g dose was administered. Concentrations of drug in all samples were assayed by high-performance liquid chromatography with UV detection. The elimination of the drug from the blood followed a biexponential (i.v. administration) or a monoexponential (endotracheal and aerosol administrations) decay, with an elimination half-life of 6 h and a total body clearance of 4.2 liters/h. The apparent volume of distribution was 0.36 liter/kg of body weight. Renal clearance of the drug accounted for 58% of the total clearance; 66% ± 17.7%, 33.5% ± 17.3%, and 6.59% ± 3.45% of the administered dose were eliminated in urine as parent drug after i.v., endotracheal, and aerosol administrations, respectively. The absolute bioavailabilities were 0.47 and 0.08 for endotracheal and aerosol administrations, respectively. Very high concentrations were found in bronchial secretions after local administration. The MICs for 90% of the most important pathogens responsible for nosocomial infections were exceeded by concentrations in bronchial secretion for up to 12 h after i.v. infusion and for up to 24 h after endotracheal and aerosol administrations.

Nosocomial pneumonia is associated with high levels of mortality and is a well-recognized complication in hospitalized patients, particularly those cared for in intensive care units (ICUs) (13, 21). The problem is particularly severe in intubated patients receiving mechanical ventilation. Patients with tracheostomies, especially when they are unconscious and cannot collaborate in obtaining adequate bronchial drainage, have a high incidence of bronchopulmonary infections caused by *Pseudomonas aeruginosa* and other gram-negative enteric bacilli. These organisms are the most troublesome nosocomial infections in the ICU and are often resistant to many antibiotics (15). The concentrations of antibiotics in respiratory secretions following parenteral administration are sufficient to suppress the normal bacteria flora but cannot generally inhibit the growth of bacilli responsible for hospital-acquired infections (15). Topical administration of antimicrobial agents results in very high local concentrations. This approach has been studied extensively as prophylaxis against pneumonia in humans, with mixed results (10, 12, 18, 19).

Ceftazidime is a cephalosporin with exceptionally high activity against a wide spectrum of bacteria. It is highly stable against a wide range of β-lactamases and is bactericidal. It may therefore offer a wider spectrum of activity and a low incidence of toxicity. Ceftazidime was found to be safe and effective in a variety of serious infections, many of which were due to *P. aeruginosa* (5, 6).

Studies of the pharmacokinetics of ceftazidime in human volunteers show a half-life ($t_{1/2}$) of 1.8 h and about 90% recovery in urine (14). Penetration into extracellular fluids is equal or superior to those of other cephalosporins (22).

The aim of this study was to determine the pharmacokinetic profile of ceftazidime after endotracheal and aerosol administrations in intubated patients with gram-negative pulmonary infections and to compare the computed pharmacokinetic parameters with those determined after intravenous (i.v.) administration. In addition, the kinetic profile of ceftazidime in bronchial secretions was assessed.

MATERIALS AND METHODS

Patients. This study was carried out in 12 patients (9 males, 3 females; mean age, 63 ± 13 years) admitted to an ICU for major gastrointestinal surgery. All the patients were mechanically ventilated and developed nosocomial pneumonia. This clinical situation required nursing care procedures consisting of thorough suctioning of tracheobronchial secretions with a cannula every 1 to 2 h; this procedure also allowed samples of bronchial secretions to be taken at precise times. The characteristics of the patients used in this study are summarized in Table 1.

Each patient received a physical examination before inclusion in the study. Nosocomial pneumonia was defined by its occurrence at least 4 days following admission to the ICU, elevated temperature (>38.5°C), leukocystosis (>10 × 10^9 liter^{-1}), purulent sputum at least 3 days before the trial, and lung infiltration on chest X ray. Pneumonia was con-

* Corresponding author.

TABLE 1. Patient data

Patient no.	Sex[a]	Wt (kg)	Ht (cm)	Age (yr)	Serum creatinine (μmol/liter)[b]	CL_{CR} (ml/min)[c]
1	M	118	183	58	135	35
2	M	84	170	62	70	96
3	M	92.4	165	61	102	46
4	M	77.5	166	65	41	139
5	M	82.4	182	41	65	102
6	M	61	170	53	54	112
7	F	69.5	160	67	44	108
8	M	80.3	168	84	104	33
9	M	66	160	58	101	62
10	F	122	165	43	57	107
11	M	64	160	48	75	40
12	F	72.2	156	82	94	50
Mean ± SD		82.4 ± 19.8	167 ± 8.4	60 ± 13.4	78.5 ± 28.7	77.5 ± 36.8

[a] M, male; F, female.
[b] Normal serum creatinine values, 45 to 106 μmol/liter.
[c] Normal CL_{CR} values, 120 ± 20 ml/min.

firmed by fiber-optic bronchoscopy with double-sheathed microbiological brushes (9). All the patients enrolled in the study met all of these criteria. The status of each patient was ascertained by standard laboratory tests, including liver function tests (bilirubin, prothrombin time, alanine aminotransferase, aspartate aminotransferase), creatinine clearance (CL_{CR}; computed from serum creatinine and 24-h urine collection data), as well as urinalysis and urine microscopy.

Patients were excluded from the study if they fulfilled any of the following criteria: patients were not mechanically ventilated; patients were <18 years of age; or patients had respiratory distress syndrome, severe impairment of renal function (CL_{CR}, <30 ml/min), hepatocellular impairment (Childs Pugh score of B or C), and known hypersensitivity to β-lactam antibiotics.

Among the patients, six subjects had a normal renal function (CL_{CR}, >80 ml/min), and the six other subjects had mildly impaired renal function (CL_{CR}, 30 to 80 ml/min).

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

Drug administration and dose. All patients received a 30-min i.v. infusion of 1 g of ceftazidime by an infusion pump. Ceftazidime was also instilled into the tracheas of 10 of the patients while they were in the supine position. Endotracheal administration was performed through a plastic catheter that was deeply inserted into the trachea. The position of the catheter (1 cm before the carina) was controlled by using a portable chest roentgenogram and was in a similar location for each patient. Ceftazidime (1 g) was diluted in 20 ml of water and was slowly injected into the trachea over a 30-min period by an infusion pump. Five patients received 1 g of ceftazidime in 20 ml of water by aerosol therapy. Aerosol therapy was performed by using an ultrasonic aerosol (particle size, ~1 μm; DP 100; DP Medical, Meylan, France) that was placed into the inspiratory part of the ventilator (Servo 900 C,D; Siemens, St. Denis, France), near the endotracheal tube.

An interval of at least 48 h was allowed between the administration of the i.v., endotracheal, and aerosol doses. The order of administration was randomly assigned.

For all patients, before endotracheal and aerosol administrations, tracheobronchial secretions were obtained by suction through the endotracheal tube to obtain pretreatment samples and to clear the respiratory tract of secretions as much as possible before drug administrations. No saline or any other fluid was introduced.

The patients were treated with an aminoglycoside (tobramycin, 4 mg/kg of body weight per day, or amikacin, 15 mg/kg/day) in combination with ceftazidime.

Samples. Blood samples for drug assay were drawn into EDTA tubes by direct veinipuncture or through an indwelling catheter inserted into an antecubital vein for repeated blood sampling. Samples were collected from the arm contralateral to the arm used for drug administration (i.v. infusion) immediately before and at 10, 20, 30, 40, 50, 60, and 90 min and 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 h after each administration. Plasma samples were obtained by centrifugation at 3,000 × *g* for 10 min. The samples were then stored at −20°C, with quality-control samples prepared from human plasma.

The total urine output, collected at discrete intervals, was obtained from an indwelling catheter before dosing and at 0 to 1, 1 to 2, and about each 2 h until 24 h after drug administration. The collection bottles were kept in a refrigerator except during voiding. At the end of each interval, the total volume of urine was measured and recorded. The urine sample was shaken thoroughly, and two 25-ml aliquots of the sample were transferred to vials and were stored at −20°C with quality-control samples until analysis.

Distal bronchial secretions were withdrawn by suction through the endotracheal tube by using a single-use, protected blind distal bronchial catheter (mucus extractor; 50 cm; CH 16; Vygon, Ecouen, France) and traps before and at 2, 4, 6, 8, 10, 12, and 24 h after drug administration. At each sampling time, a new catheter was positioned (10 cm deep). Samples were immediately frozen at −20°C until analysis.

Assay of ceftazidime. The concentrations of ceftazidime in plasma, urine, and bronchial secretions were assayed by high-performance liquid chromatography (HPLC) with UV detection by using a Dupont spectro-flow variable wavelength UV detector that was operated at 254 nm and that was fitted with a standard 12-μl quartz cell. The method used was proposed by Ayrton (2) and was modified as follows. Plasma (0.5 ml) and urine (50 μl) were analyzed after treatment with acetonitrile and centrifugation (2,000 × *g* for 10 min).

The bronchial secretions (50 to 100 mg) were liquefied by

adding 1 ml of Digest Eur (Eurobio Laboratories, Paris, France) and were then shaken for 15 min. The supernatant was removed after centrifugation (1,000 × *g* for 10 min), and the same assay procedures as the ones used for plasma and urine samples were used for the supernatant (i.v. administration) or serial dilutions of the supernatant (endothracheal and aerosol therapies).

A steel chromatographic column (150 by 4.6 mm) was packed with 3-μm Nucleosil C18 particles (SFCC, Neuilly Plaisance, France). The mobile phase 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) and was used at a flow rate of 1.5 ml/min. The analytical column was kept at 50°C. Under these conditions, ceftazidime had a retention time of 5.5 min, and the internal standard (cephalexin) had a retention time of 8.5 min. None of the samples of serum, urine, or bronchial secretions taken before entry into the study showed peaks at the retention time of ceftazidime or the internal standard.

This method was validated according to Good Laboratory Practice guidelines. 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 (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.

Pharmacokinetic analysis. The data were modeled by using the SIPHAR software on an IBM PS 50 microcomputer by the nonlinear least-squares method (11). After extravascular administrations, ceftazidime plasma concentration-versus-time curves were modeled for each patient by using a one- or a two-compartment open model with either a first-order or a zero-order rate of absorption by using the weighted term $1/y^2$. The choice of the model and the order of the absorption kinetic was done 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 (CV) of each parameter, defined by the formula CV = 100 × SD/*P*, where SD is the standard deviation, and *P* is the parameter value (SD was computed by using the variance-covariance matrix); and the scatter of the plot of the residuals and the standardized residuals (normalized to the variance model) against time and against computed values and the correlation matrix. The value of CV may give an indication of the accuracy of the estimate. If CV is >20 to 30%, the lack of accuracy may be considered too large to be accepted. Comparison between competing models was made by using the 2-log likelihood, the Akaike test, the Leonard test, and the Schwartz test (11).

All the pharmacokinetic parameters were evaluated after a simultaneous fitting of the plasma and urine data, which allowed a better estimation of renal excretion kinetic properties. The simultaneous fit was performed by a weighted nonlinear least-squares procedure with a weight equal to $1/y^2$. The renal clearance (CL_R) of ceftazidime was estimated from the slope of the plot of the excretion rate versus the plasma drug concentration at the midpoint of the drug excretion intervals. A *t* test was performed to compare the computed intercept with the expected theoretical value (zero). If the slope of the line was statistically significantly different from zero ($P < 0.05$) and the intercept was not significantly different from zero, the simultaneous fitting of plasma and urine data can be, a priori, reasonably performed. The following model was used:

$$C_p = \sum_{i=1}^{N} Ci \exp(-\lambda_i t)$$

$$A_u = \sum_{i=1}^{N} CL_R\ C_i[1 - \exp(-\lambda_i t)]/\lambda_i$$

where C_p is the concentration of drug in plasma, C_i and λ_i are the coefficients and exponents of the exponential model; A_u is the cumulative amount excreted in the urine up to time *t*, *N* is the number of exponential terms describing the model equation, and CL_R is renal clearance.

The drug concentrations in the bronchial secretions were separately modeled according to a one- or a two-compartment model with first-order input and output rates.

The highest observed concentration was designated C_{max}. The time of the C_{max} relative to the time of dosing was designated T_{max}. The total area under the curve (AUC) was obtained by linear trapezoidal approximation with correction to time infinity by dividing the last observed datum point by the terminal elimination rate constant (λ_2). The total clearance (CL) was evaluated by the following: F_{A_u} × dose/AUC, where F_{A_u} is absolute bioavailability. The apparent volume of distribution at steady state (V_{ss}) was evaluated as follows: V_{ss} = CL · (MRT − *T*/2), where *T* is the infusion duration (or absorption) after the zero-order input rate and MRT is the mean residence time, and V_{ss} = CL · (MRT − $1/k_a$), where k_a is the apparent rate constant of absorption after the first-order input rate. After extravascular administration, CL and V_{ss} were corrected by F_{A_u}. MRT, a noncompartmental parameter, was determined by the ratio of AUMC to AUC corrected for the infusion period, where AUMC is defined as the area under the first moment curve (MRT = AUMC/AUC + *T*/2) (24).

An estimate of the total amount of drug (A_u) excreted in the urine was calculated from the amount recovered after 24 h ($A_{u_{24}}$), as follows: $A_u = A_{u_{24}}/(1 - \exp^{-\lambda_2 \times 24})$. The ratios of AUC and A_u after extravascular and i.v. administrations were used to calculate the fraction of the administered dose which was absorbed or the absolute bioavailability F_{AUC} (F_{A_u}). When a better fit was obtained with zero-order input, the rate of absorption was computed as follows: F_{A_u} × dose/T_{max}.

Statistical analysis. Results in the text are presented as mean ± SD. Statistical comparisons of the pharmacokinetic parameters T_{max}, C_{max}, AUC, $t_{1/2}$ of elimination ($t_{1/2\beta}$), F_{AUC}, and A_u between the two local administrations were performed by a nonparametric Friedman test. Statistical comparison of $t_{1/2\beta}$ between plasma and bronchial secretions was performed by using a paired *t* test. A *P* value of less than 0.05 was taken as the threshold of probability.

RESULTS

Pharmacokinetic parameters after i.v. infusion. For all patients, a simultaneous fit of the plasma and urine data was performed by using a two-compartment open model with first-order transfers among compartments and first-order elimination rate constants. Figure 1 shows a plasma concentration-versus-time profile with urine data for one patient. The pharmacokinetic parameters for individual patients are given in Table 2. The mean concentration of the individual plasma samples peaked at 58.6 ± 10.0 mg/liter at the end of infusion. The mean $t_{1/2}$ values of the distribution (λ_1) and elimination (λ_2) phases were 0.50 ± 0.25 and 6.11 ± 2.48 h,

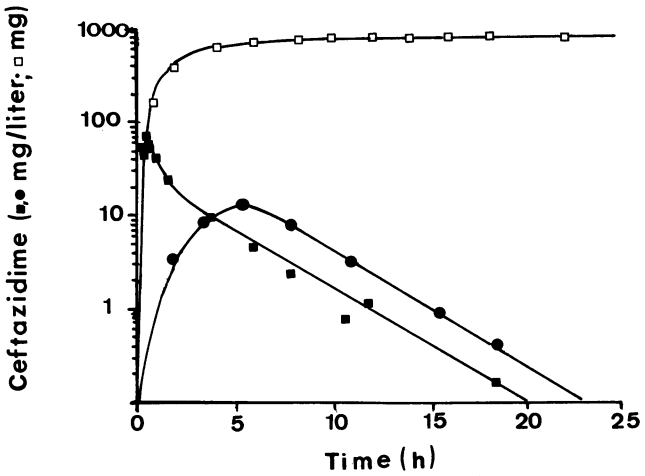

FIG. 1. Kinetics of ceftazidime in plasma (■), bronchial secretions (●), and urine (□) after i.v. administration to patient 4.

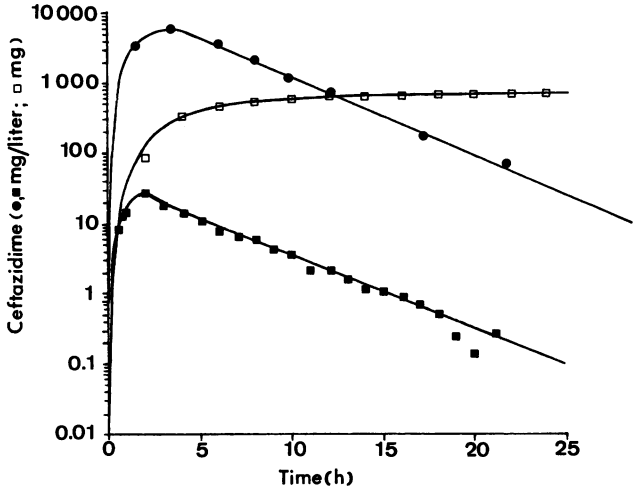

FIG. 2. Kinetics of ceftazidime in plasma (■), bronchial secretions (●), and urine (□) following a 1-g dose given endotracheally to patient 4.

respectively. The mean values of V_{ss} and CL were 0.358 ± 0.105 liter/kg and 4.23 ± 1.94 liters/h, respectively.

The estimated A_u was 66% ± 17.7%. Urinary elimination of ceftazidime was related to the degree of impairment of the renal function, since 62.6 to 95.6% of the dose was recovered unchanged in nonuremic patients and 37 to 71.1% was recovered in patients with mild renal insufficiency. Mean CL_R was 2.45 ± 1.31 liters/h; it decreased from 3.44 ± 0.808 liters/h (n = 6) in normal subjects to 1.46 ± 0.896 liter/h (n = 6) in subjects with mildly impaired renal function.

Pharmacokinetic parameters after endotracheal administration. Ten patients received ceftazidime by the endotracheal route. A one-compartment open model with first- or zero-order input and first-order elimination adequately described the observed data. For four patients (patients 2, 3, 4, and 6), a better fit was obtained when the data were analyzed with a zero-order rate of absorption (k_0 = 204.6 ± 213.8 mg/h); for the other patients, the data were consistent with a first-order rate of absorption ($t_{1/2}$ of absorption = 0.951 ± 0.548 h).

The ceftazidime plasma concentration-versus-time profile with urine data for one patient is presented in Fig. 2. Pharmacokinetic parameters for individual patients are given in Table 3. The mean peak concentration in plasma was 11.9 ± 7.70 mg/liter, which was reached after 2 to 8 h, depending on the patient. This C_{max} was about fivefold lower than that obtained at the end of infusion; however, the level in plasma at 4 h postdose was only twofold higher after i.v. than after endotracheal administration (18.8 ± 8.28 and 9.45 ± 5.61 mg/liter, respectively). The apparent $t_{1/2\beta}$ of 6.16 ± 2.94 h was in the same range as that obtained after i.v. administration (F = 1.042; P = not significant). The mean values of V_{ss}, CL, and CL_R were 0.356 ± 0.0996 liter/kg, 4.65 ± 2.95 liters/h, and 2.72 ± 1.31 liters/h, respectively. These values were of the same order of magnitude as the values found after i.v. administration; no statistically significant differences were detected.

The unchanged recovery of ceftazidime in urine accounted for 33.5% ± 17.3% of the administered dose. The absorption coefficient determined with reference to the i.v. administration was F_{AUC} = 0.473 ± 0.268 when it was determined from plasma data and F_{A_u} = 0.475 ± 0.219 when it was determined from urine data.

TABLE 2. Pharmacokinetic parameters of ceftazidime in individual patients after i.v. infusion

Patient no.	$t_{1/2}$ (h)		MRT (h)	V_{ss} (liter/kg)	CL (liters/h)	CL_R (liters/h)[a]	A_u (%)
	Distribution	Elimination					
1[b]	0.319	5.09	7.54	0.330	5.37	2.83	57.4
2	0.383	3.96	5.85	0.246	3.61	2.14	65.4
3[b]	0.450	6.13	8.66	0.308	3.33	2.04	71.1
4	0.933	2.52	2.52	0.234	6.76	4.42	84.8
5	1.02	4.30	4.40	0.373	7.35	4.14	70.1
6	0.585	5.84	6.06	0.638	6.40	3.29	62.6
7	0.416	4.90	6.38	0.388	4.23	3.14	89.9
8[b]	0.387	7.95	11.0	0.385	2.80	1.42	62.5
9[b]	0.567	6.50	8.33	0.430	3.41	1.47	47.6
10	0.184	5.02	8.64	0.318	4.58	3.53	95.6
11[b]	0.352	10.2	14.8	0.342	1.53	0.514	37.0
12[b]	0.499	10.8	15.5	0.303	1.41	0.511	48.3
Mean ± SD	0.50 ± 0.25	6.11 ± 2.48	8.31 ± 3.88	0.358 ± 0.105	4.23 ± 1.94	2.45 ± 1.31	66.0 ± 17.7

[a] The mean ± SD CL_{CR} was 5.02 ± 2.56 liters/h.
[b] Patients with mildly impaired renal function.

TABLE 3. Pharmacokinetic parameters of ceftazidime in individual patients after endotracheal administration

Patient no.	C_{max} (mg/liter)	T_{max} (h)	k_0 (mg/h)	$t_{1/2}$ (h)		MRT (h)	V_{ss} (liter/kg)	CL (liters/h)	CL_R (liters/h)[a]	A_u (%)	F_{AUC}	F_{A_u}
				Absorption	Elimination							
2	7.76	3.8	67.4		7.91	9.01	0.300	3.10	1.70		0.256	
3[b]	15.0	6.0	164.3		8.55	11.3	0.232	2.22	1.51	35.0	0.727	0.493
4	27.2	2.0	517.9		3.00	4.89	0.326	6.54	3.92	65.9	0.802	0.777
5	3.27	2.0		0.776	2.98	5.32	0.360	8.11	5.62	12.7	0.153	0.181
6	0.17	4.0	68.6		2.95	5.00	0.372	10.6	3.21	21.5	0.205	0.343
7	16.5	4.1		0.883	4.36	7.95	0.345	2.74	2.62	44.9	0.684	0.499
8[b]	4.27	4.0		0.315	5.54	9.11	0.380	4.31	2.77	16.6	0.180	0.266
9[b]	7.79	4.0		1.95	7.89	12.2	0.525	3.38	2.04	19.6	0.405	0.411
10	16.2	2.0		1.32	6.66	10.5	0.220	2.55	2.66	44.1	0.816	0.461
12[b]	16.7	8.0		0.47	11.8	17.4	0.504	2.40	1.15	40.9	0.497	0.847
Mean ± SD	11.9 ± 7.7	4.0 ± 1.9	204.6 ± 213.8	0.951 ± 0.548	6.16 ± 2.94	9.27 ± 3.88	0.356 ± 0.0996	4.65 ± 2.95	2.72 ± 1.31	33.5 ± 17.3	0.473 ± 0.268	0.475 ± 0.219

[a] The mean ± SD CL_{CR} was 4.65 ± 2.21 liters/h.
[b] Patients with mildly impaired renal function.

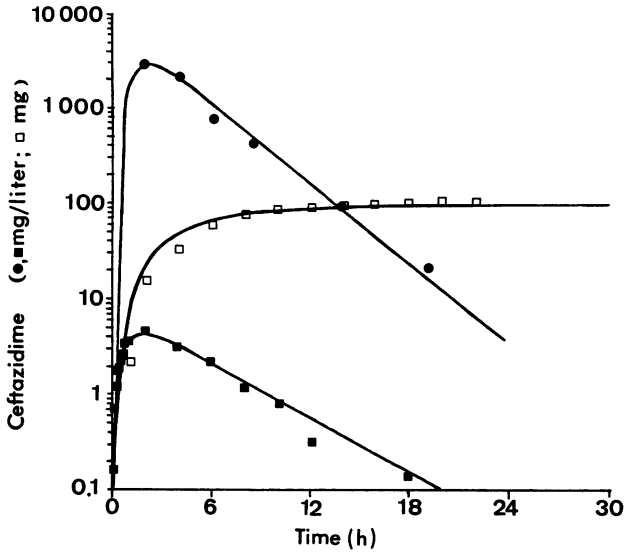

FIG. 3. Kinetics of ceftazidime in plasma (■), bronchial secretions (●), and urine (□) following a 1-g dose given by aerosol to patient 4.

Pharmacokinetic parameters after aerosol administration. Five patients (patients 1 to 5) were treated by aerosol therapy. A one-compartment open model with first-order input and output rates adequately described the observed data (Fig. 3). Pharmacokinetic parameters for individual patients are presented in Table 4. The mean C_{max} was 2.24 ± 1.52 mg/liter. The apparent absorption $t_{1/2}$ and $t_{1/2\beta}$ were 0.735 ± 0.546 and 4.35 ± 2.45 h, respectively. The mean V_{ss}, CL, and CL_R were 0.358 ± 0.0608 liter/kg, 6.50 ± 2.80 liters/h, and 3.34 ± 0.595 liters/h, respectively. The estimated A_u was 6.59 ± 3.45%. The absorption coefficients determined from plasma and urine data with reference to i.v. administration were F_{AUC} = 0.102 ± 0.0834 and F_{A_u} = 0.0954 ± 0.0527.

The nonparametric test for C_{max}, AUC, F_{AUC}, and A_u indicated a statistically significant difference between the observations after aerosol administration compared with those after endotracheal administration. There was no significant difference between the two extravascular administrations for $t_{1/2\beta}$ and T_{max}; however, individual values of T_{max} showed lower values after aerosol administration than after endotracheal administration for two of four patients.

Penetration into bronchial secretions. Large variations among individuals were noted in the concentrations of drug in bronchial secretions.

After a 1-g i.v. infusion, the bronchial secretion concentration-versus-time curves were consistent with a one-compartment model. The peak concentration in bronchial secretions was obtained between 2 and 10 h postdose, depending on the patient, with a noticeable value of 12.4 ± 6.48 mg/liter. The concentrations of ceftazidime in bronchial secretions then decreased slowly ($t_{1/2\beta}$ = 6.53 ± 2.54 h) and were still relatively high at 20 h (Fig. 1). The ratios between concentrations in bronchial secretions and simultaneous plasma concentrations in plasma (B/P) were 0.10 to 0.50 at 2 h postdose and 1.27 ± 0.13 (range, 0.30 to 3.54) at the time of the peak concentration in bronchial secretions. The B/P ratio was plotted against time; a statistically significant straight line could be fitted to these data (r = 0.60; P < 0.001). The calculation of the AUCs of the concentration in

the bronchial secretions and the concentration in plasma yielded a mean B/P ratio of 0.764 ± 0.40.

After endotracheal administration, the results were consistent with a one- (five patients) or a two-compartment model. The mean of the peak concentration in bronchial secretions of 13 g/liter (range, 2.5 to 23 g/liter) was reached between 2 and 6 h. The concentration of ceftazidime in bronchial secretions then decreased with a different rate constant, depending on the patient ($t_{1/2}$ = 2 to 10 h), and was still relatively high at 12 and 24 h (mean values, 320 and 57 mg/liter, respectively). The B/P ratios were much higher during 12 h postdose (>500). It was about 60 at 18 h and 15 at 24 h. The mean ratio of bronchial AUC/plasma AUC was 1,018.7 ± 936.2. A kinetic of ceftazidime in bronchial secretions is shown in Fig. 2.

After i.v. and endotracheal administrations, the paired *t* test did not show any statistically significant difference between the $t_{1/2\beta}$ of drug from plasma and bronchial secretions.

After aerosol therapy, a one-compartment model was used. The concentrations of the antibiotic in the bronchial secretions were measured at different intervals for only two of five patients (patients 4 and 5). A kinetic is presented in Fig. 3. For patients 4 and 5, at each sample collection time, the B/P ratios were in the same range after endotracheal and aerosol administrations. The ratios of bronchial AUC/plasma AUC were 459.7 and 1,076.4 for patients 4 and 5, respectively.

DISCUSSION

The $t_{1/2\beta}$ found in this study (2.5 to 11 h) is higher than that found in healthy volunteers (1.8 h) and patients with mildly impaired renal function (3.74 ± 0.75 h) (20). The value of V_{ss} (0.22 to 0.638 liter/kg) is considerably different from those obtained by Leroy et al. (20) in normal and uremic subjects (0.25 liter/kg); moreover, this result is in the same range, with the same interpatient variability, as those reported by Turner et al. (25) (0.456 liter/kg) and Kercsmar et al. (17) (0.394 liter/kg) in patients with cystic fibrosis. CL ranged from 3.6 to 7.3 liters/h in nonuremic patients and from 1.4 to 5.3 liters/h in patients with mildly impaired renal function; for 3 patients (patients 4 to 6), CL was in the same range as that reported in healthy subjects (20). Large interpatient variations in pharmacokinetic parameters were observed. In the present study, the patients were treated with ceftazidime in association with tobramycin or amikacin. This drug association could not explain the variabilities of the pharmacokinetic parameters; indeed, in contrast to cefsulodin, another cephalosporin that is efficient against *Pseudomonas* strains, the concentration of ceftazidime in plasma is not influenced by the combined treatment with tobramycin (23). Kelly et al. (16) suggested that these variations may be caused by the degree of right-sided heart failure present in the patient during the period of treatment. These variabilities could also be due to hemodynamic status and pathological conditions in hospitalized patients in ICUs and could explain the difference between CL_R of ceftazidime and CL_{CR} in some patients.

The various concentrations of drug in bronchial secretions reported in this study might not be related to the underlying pathology, but similar variations have been observed frequently in other studies (4), probably because of several of the following host factors: degree of respiration, tissue inflammation, volume of bronchial secretions, fibrosis, edema, and the underlying extrapulmonary pathology. These factors are difficult to evaluate and may vary consid-

TABLE 4. Pharmacokinetic parameters of ceftazidime in individual patients after aerosol therapy

Patient no.	C_{max} (mg/liter)	T_{max} (h)	$t_{1/2}$ (h)		MRT (h)	V_{ss} (liter/kg)	CL (liters/h)	CL_R (liters/h)[a]	A_u (%)	F_{AUC}	F_{A_u}
			Absorption	Elimination							
1	2.86	1	0.246	8.00	11.1	0.402	4.62	2.50	9.93	0.193	0.173
2	0.79	1	1.65	2.06	4.17	0.289	11.2	3.57	2.86	0.014	0.0437
3[b]	1.32	2	0.423	5.69	9.05	0.438	5.26	3.06	4.61	0.0413	0.065
4	4.60	2	0.604	3.16	5.06	0.320	4.49	3.48	10.6	0.188	0.125
5	1.65	1	0.753	2.86	5.16	0.343	6.95	4.09	4.94	0.075	0.0704
Mean ± SD	2.24 ± 1.52	1.4 ± 0.55	0.735 ± 0.546	4.35 ± 2.45	6.91 ± 3.00	0.358 ± 0.0608	6.50 ± 2.80	3.34 ± 0.595	6.59 ± 3.45	0.102 ± 0.0834	0.0954 ± 0.0527

[a] The mean ± SD CL_{CR} was 5.02 ± 2.56 liters/h.
[b] Patient with mildly impaired renal function.

erably in individual patients. The pH, the purulence, and the ionic composition of bronchial secretions could also explain these variations (1).

The results of this study confirm the high rate of extravascular diffusion of ceftazidime (4) and its excellent penetration into the respiratory tract. After i.v. infusion, the concentration of the antibiotic in the bronchial secretions exceeded the MIC for 90% of the most important pathogens (5) over a 2- to 12-h observation period; the corresponding concentrations in bronchial secretions were 9.13 ± 6.0 and 3.85 ± 1.37 mg/liter, respectively. The penetration of the drug from the blood into the bronchial secretions, i.e., the bronchial secretion AUC as a percentage of the concentration in plasma (76.4% ± 40%), is higher than those reported by several investigators in patients with severe pulmonary or extrapulmonary pathology (3, 4, 7, 8). Indeed, Davies et al. (7) reported a value of 10.8% after injection of a 1-g dose and 11.8% after a 2-g dose, whereas Erttmann et al. (8) reported a value of 17.6% after 2 g was given i.v. twice daily for 7 days. After a 2-g intravenous infusion, Berthelot et al. (4) reported a ratio between bronchial secretions and simultaneous concentrations in serum that increased from 9% at 1 h to 30% at 6 h; in the present study, the ratios found 2 h postdose were higher. These results suggest the effectiveness of ceftazidime in the treatment of severe respiratory infections.

The endotracheal administration of ceftazidime results in high and sustained levels of this drug within bronchial secretions during 24 h postdose; concentrations of drug in bronchial secretions above the MIC for 90% of strains tested were maintained up to hour 24. The absolute bioavailability by this route of administration was almost 50%. The levels of ceftazidime in plasma induced after endotracheal injection suggested efficient alveolocapillar diffusion. The endotracheal injection of ceftazidime might thus represent good antimicrobial therapy for the management of bronchopneumonias caused by gram-negative organisms. Indeed, this route of administration induces levels in both the alveoli and blood which are adequate for the prevention or interruption of upper airway colonization and, consequently, prevented a subsequent respiratory tract infection.

The aerosol therapy induced good levels of ceftazidime in bronchial secretions, while levels in plasma were lower than those after endotracheal injection. The mean absolute bioavailability computed after aerosol therapy was 10%.

Ceftazidime was generally well tolerated. No clinically adverse reaction attributable to local antimicrobial treatment was observed. The local tolerance to endotracheally administered ceftazidime was excellent.

On the basis of the pharmacokinetic data, our results suggest that ultrasonic aerosol administration must be avoided because of its low bioavailability. In contrast, taking into account the levels of ceftazidime in bronchial secretions and plasma, one could argue that the endotracheal route might be clinically relevant. Moreover, in comparison with the i.v. route, 1 g of ceftazidime provided very high local concentrations over a 24-h period. Nevertheless, further trials should be conducted to confirm the clinical efficiency of the endotracheal route.

ACKNOWLEDGMENTS

We gratefully acknowledge the support for this work provided by Glaxo Laboratories, Paris, France.

Special thanks are due to P. Prince for preparation of the manuscript.

REFERENCES

1. **Aguilera, D., A. Coupry, L. Holzapfel, P. Karlin, D. Carrère-Debat, D. P. Giudicelli, and D. Gontier.** 1986. Etude des concentrations sériques et bronchiques au cours de l'administration continue de nétilmicine intratrachéale. Pathol. Biol. **35**:657–662.
2. **Ayrton, J.** 1981. Assay of ceftazidime in biological fluids using high-pressure liquid chomatography. J. Antimicrob. Chemother. **8**(Suppl. B):227–232.
3. **Bergogne-Bérézin, E., J. Pierre, G. Berthelot, H. Kafe, P. Even, C. Gilbert, D. Safran, and M. Sterm.** 1984. Diffusion bronchique des nouvelles β-lactamases antipseudomonas. Pathol. Biol. **32**: 421–425.
4. **Berthelot, G., E. Bergogne-Bérézin, P. Even, and M. Stern.** 1983. Penetration of ceftazidime into bronchial secretions, p. 1–10, part 64, 27. Proceedings of the 13th International Congress of Chemotherapy, Vienna.
5. **Daikos, G. K., J. Kosmidis, C. Stathakis, H. Giamarellou, E. Douzinas, and S. Kastanakis.** 1982. Ceftazidime: a new-broad spectrum antipseudomonal cephalosporin: in vitro activity, human pharmacokinetics and therapeutic efficacy, p. 499–501. *In* Current chemotherapy and immunotherapy. Proceedings of the 12th International Congress of Chemotherapy. American Society for Microbiology, Washington, D.C.
6. **Daikos, G. K., J. Kosmidis, C. Stathakis, H. Giamarellou, E. Douzinas, S. Kastanakis, and B. Papathanassiou.** 1981. Ceftazidime: therapeutic results in various infections and kinetic studies. J. Antimicrob. Chemother. **8**(Suppl. B):331–337.
7. **Davies, B. I., F. P. V. Maesen, and J. A. van Noord.** 1983. Treatment of chronic and recurrent respiratory infections with intramuscular ceftazidime. J. Antimicrob. Chemother. **12**(Suppl. A):1–8.
8. **Erttmann, M., U. Ullmann, and E. M. W. Koch.** 1990. Results of a clinical and pharmacokinetic study of ceftazidime in patients with postoperative pneumonia on assisted ventilation. J. Hosp. Infect. **15**(Suppl. A):55–59.
9. **Fagon, J. Y., J. Chastre, A. G. Hance, M. Guiguet, J. Trouillet, Y. Domart, J. Pieere, and C. Gilbert.** 1988. Detection of nosocomial lung infection in ventilated patients. Am. Rev. Respir. Dis. **138**:110–116.
10. **Feely, T. W., G. C. Du Moulin, J. Hedley-Whyte, L. S. Bushnell, J. P. Gilbert, and D. S. Feingold.** 1975. Aerosol polymyxin and pneumonia in seriously ill patients. N. Engl. J. Med. **293**:471–475.
11. **Gomeni, C., and R. Gomeni.** 1987. SIPHAR: an integrated computer system for statistical and pharmacokinetic data analysis, p. 507–516. *In* A. Serio, R. O'Moore, A. Tardini, and F. H. Roger (ed.), Proceedings of the 7th International Congress of Medical Informatics, Europe 87, Rome, Italy. European Federation for Medical Informatics, Rome.
12. **Greenfield, S., D. Teres, L. S. Bushnell, J. Hedley-Whyte, and D. S. Feingold.** 1973. Prevention of gram-negative bacillary pneumonia using aerosol polymyxin as prophylaxis. I. Effect on the colonisation pattern of the upper respiratory tract of seriously ill patients. J. Clin. Invest. **52**:2935–2940.
13. **Haley, R. W., D. H. Culver, J. W. White, W. M. Morgan, T. G. Emori, V. P. Munn, and T. M. Hooton.** 1985. The efficacy of infection surveillance and control programs in infection in US hospitals. Am. J. Epidemiol. **1217**:182–205.
14. **Harding, S. M., A. J. Monro, J. E. Thornton, J. Ayrton, and M. I. J. Hogg.** 1981. The comparative pharmacokinetics of ceftazidime and cefotaxime in healthy volunteers. J. Antimicrob. Chemother. **8**:263–272.
15. **Johanson, W. G., J. J. Seidenfeld, R. De Los Santos, J. J. Coalson, and P. Gomez.** 1988. Prevention of nosocomial pneumonia using topical and parenteral antimicrobial agents. Am. Rev. Respir. Dis. **137**:265–272.
16. **Kelly, B. H., R. Menendez, L. Fan, and S. Murphy.** 1982. Pharmacokinetics of tobramycin in cystic fibrosis. J. Pediatr. **100**:318–321.
17. **Kercsmar, C. M., R. C. Stern, M. D. Reed, C. M. Myers, D. Murdell, and J. L. Blumer.** 1983. Ceftazidime in cystic fibrosis: pharmacokinetics and therapeutic response. J. Antimicrob. Chemother. **12**(Suppl. A):289–295.

18. **Klastersky, J., R. Cappel, J. Noterman, J. Snoeck, C. Geuning, and E. Mouawad.** 1973. Endotracheal gentamicin for the prevention of bronchial infection in patients with tracheotomy. Int. J. Pharmacol. **4**:279–286.
19. **Klick, J. M., G. C. Du Moulin, J. Hedley-Whyte, D. Teres, L. S. Bushnell, and D. S. Feingold.** 1975. Prevention of gram-negative bacillary pneumonia using polymyxin aerosol as prophylaxis. II. Effect of the incidence of pneumonia in seriously ill patients. J. Clin. Invest. **55**:514–519.
20. **Leroy, A., F. Leguy, F. Borsa, G. R. Spencer, J. P. Fillastre, and G. Humbert.** 1984. Pharmacokinetics of ceftazidime in normal and uremic subjects. Antimicrob. Agents Chemother. **25**:638–642.
21. **Rubenstein, E., M. Green, M. Modan, P. Amit, M. Brenstein, and A. Rubinstein.** 1982. The effects of nosocomial infections on the length and costs of hospital stay. J. Antimicrob. Chemother. **9**(Suppl. A):93.
22. **Ryan, D. M., U. Mason, and S. M. Harding.** 1981. The penetration of ceftazidime into extravascular fluid. J. Antimicrob. Chemother. **8**(Suppl. B):283–288.
23. **Strandvik, B., A. S. Malmborg, H. Alfredson, and A. Ericsson.** 1983. Clinical results and pharmacokinetics of ceftazidime treatment in patients with cystic fibrosis. J. Antimicrob. Chemother. **12**(Suppl. A):283–287.
24. **Taburet, A. M., J. L. Steimer, D. Doucet, and E. Singlas.** 1986. Le temps de présence moyen dans l'organisme: un nouveau paramètre pharmacocinétique. Therapie **41**:1–10.
25. **Turner, A., S. J. Pedler, F. Carswell, G. R. Spencer, and D. C. E. Speller.** 1984. Serum and sputum concentrations of ceftazidime in patients with cystic fibrosis. J. Antimicrob. Chemother. **14**:521–527.