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Pharmacokinetics of Habekacin in Patients with Renal Insufficiency

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The pharmacokinetics of habekacin, a new semisynthetic aminoglycoside antibiotic, were investigated in six healthy subjects and 25 uremic patients (six of whom were on hemodialysis) after administration of a single 3-mg/kg dose. Six healthy subjects received the 3-mg/kg dose both intramuscularly (i.m.) and intravenously (i.v.) (1-h infusion). Uremic patients were given the 3-mg/kg dose as an i.m. injection, except for the hemodialysis patients, who received the dose as a 1-h i.v. infusion. Afther the i.m. injection, the peak concentrations in serum were higher and the times to peak levels were longer in patients with renal impairment than in healthy subjects. The elimination half-life in serum increased in relation to the degree of renal impairment, from 2 h in normal subjects to 32 h in patients with creatinine clearances of less than 10 ml/min. Renal impairment did not significantly modify the apparent volume of distribution. After the same 3-mg/kg dose as a 1-h i.v. infusion in six hemodialysis patients, the elimination half-life averaged 48 and 5 h off and on a 4- to 5-h hemodialysis session, respectively. The habekacin pharmacokinetic data appeared to be similar to those of the other available aminoglycoside antibiotics.

Habekacin [1-*N*-(*S*)-4 amino-2-hydroxybutyryl dibekacin] is a new semisynthetic aminoglycoside antibiotic that is obtained by acylation of dibekacin in a reaction analogous to that used to produce amikacin (3). The antibacterial activity of habekacin was roughly comparable to that of amikacin against *Pseudomonas aeruginosa* and several gentamicin- and tobramycin-resistant organisms (A. Thabaut and M. Meyran, Program Abstr. 25th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 206, 1985). Resistance patterns of both antibiotics were found to be similar (8). Like other aminoglycoside antibiotics, habekacin is excreted almost exclusively in urine as the active compound by glomerular filtration and tubular reabsorption. Therefore, it was essential to investigate the pharmacokinetic properties of habekacin in patients with various degrees of renal insufficiency.

MATERIALS AND METHODS

Subjects. Thirty-one subjects were selected for the study after informed written consent was obtained and approval was given by the Ethical Comittee, University of Rouen. A total of 6 subjects had normal renal function, and 25 subjects, 6 of whom were hemodialysis patients, had chronic renal impairment of various degrees. None of the subjects received any antibiotic in the month preceding the study, and none of them had a documented history of drug allergy.

The 25 patients with chronic renal failure (age range, 26 to 76 years; weight range, 43 to 92 kg) were divided into the following four groups on the basis of glomerular filtration rate, as determined by endogenous creatinine clearance (CL_{CR}): group 1, mild renal impairment ($n = 6$; CL_{CR}, > 30 ml/min); group 2, moderate renal impairment ($n = 7$; $10 < CL_{CR} < 30$ ml/min); group 3, severe renal impairment ($n = 6$; CL_{CR}, < 10 ml/min); group 4, hemodialysis patients ($n = 6$). The physical characteristics of the subjects are given in Table 1.

Study design. All subjects fasted overnight before the study and for 2 h after habekacin administration. Healthy subjects received a single intramuscular (i.m.) dose of 3 mg/kg and after a 1-week washout period the same dose as a 1-h intravenous (i.v.) infusion. Patients in groups 1, 2, and 3 were given a single i.m. dose of 3 mg/kg; hemodialysis patients (group 4) received the same dose as a 1-h i.v. infusion. It was not possible to inject habekacin i.m. in these patients, because anticoagulant was used during the hemodialysis session. Two hours after administration all subjects had breakfast, and thereafter food and drink were allowed ad libitum.

Sampling. In subjects with normal renal function, blood samples were drawn at 0, 15, 30, 45, and 60 min and at 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 h after i.m. injection. Urine samples were collected six times: from 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, and 12 to 24 h after drug administration. Further blood samples were taken in uremic patients at 36 and 48 h for group 1 and at 72 h for groups 2 and 3. Four to five urine samples were collected at the following times, according to the degree of renal failure: 0 to 4, 4 to 8, 8 to 24, 24 to 48, and 48 to 72 h. Hemodialysis patients (group 4) were studied off and on a 4- to 5-h hemodialysis session, with at least a 1-week washout period betweeen the two studies. Blood samples were collected during 72 h after the i.v. infusion. In the study of hemodialysis patients, the 3-mg/kg i.v. dose of habekacin was administered 1 h prior to the beginning of the dialysis session. Blood samples were drawn at time 0 (before the infusion), 1 h (at the end of infusion, which was the beginning of dialysis), 1.5 h, 2 h, and each hour thereafter up to the end of the session, which lasted 4 to 5 h. Coil dialyzers (2308 CF 1511; Travenol, Maurepas, France) with single-pass dialysis were used. The blood flow rate was 300 ml/min, and the dialysate flow rate was 500 ml/min.

Antibiotic assay. Blood was collected in nonheparinized tubes and allowed to clot at room temperature. Serum and urine samples were stored frozen at −80°C until assay.

Habekacin concentrations in serum and urine were measured by fluorescence polarization immunoassay (FPIA) with an analyzer (TDX; Abbott Laboratories, North Chi-

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TABLE 1. Physical characteristics of patients[a]

Subject group	Age (yr)	Wt (kg)	Creatinine in serum (μmol/liter)	CL_{CR} (ml/min per 1.73 m^2)
Normal subjects (n = 6)	27.2 ± 4.7 (21–34)	64.3 ± 3.5 (60–69)	82.0 ± 8.1 (71–90)	147.1 ± 11.1 (135–164)
Group 1 (CL_{CR}, >30 ml/min; n = 6)	51.7 ± 13.9 (26–68)	70.8 ± 10.8 (53–82)	191.0 ± 60.3 (140–275)	51.5 ± 16.9 (36–76)
Group 2 (10 < CL_{CR} < 30 ml/min; n = 7)	56.3 ± 16.0 (34–75)	61.1 ± 19.2 (43–92)	354.0 ± 108.5 (185–515)	18.4 ± 5.2 (12–28)
Group 3 (CL_{CR}, < 10 ml/min; n = 6)	59.8 ± 16.2 (31–76)	68.4 ± 10.1 (52–83)	580.0 ± 126.5 (420–700)	8.8 ± 0.8 (8–10)
Group 4 (n = 6)	59.7 ± 11.4 (44–71)	64.4 ± 14.8 (46–90)	1,180.0 ± 264.0 (800–1,440)[b]	—[c]

[a] Values are means ± standard deviations; ranges are given in parentheses.
[b] Before hemodialysis.
[c] —, Anuric patients.

cago, Ill.). The intra- and interrun coefficients of variation were found to be 2.2 and 2.6%, respectively. The limit of sensitivity for the FPIA was 0.05 μg/ml. A good linear relationship was found betweeen FPIA and the microbiological assay (MA) when *Bacillus subtilis* ATCC 6633 was used as the test strain, as follows: concentration of FPIA = 0.9 (concentration of MA) + 0.8 (n = 95; r = 0.904; $P < 0.001$).

Creatinine concentrations in serum and urine were determined by the colorimetric method described previously (1).

Pharmacokinetic analysis. After the i.m. injection, the habekacin concentration in serum-time curves was best described by a two-compartment model, with first-order absorption and elimination. The linear least-squares regression method was used to determine the terminal elimination phase, and the absorption phase was estimated by using the method of residuals (Apple II personal computer). The following pharmacokinetic data of habekacin were calculated by using the equations described by Gibaldi and Perrier (2): theoretical peak serum level of drug in serum (C_{max}; in micrograms per milliliter); theoretical time to peak level (T_{max}; in hours); area under the serum concentration-time curve, extrapolated to infinity ($AUC_{0-\infty}$; in micrograms per hour per milliliter); terminal elimination half-life ($t_{1/2}$; in hours); apparent volume of distribution (V_{area}/F; in liters per kilogram), where $V_{area} = (F \times \text{dose})/(\text{AUC} \times \beta)$, and β is the elimination rate constant; total body clearance (CL_T/F; in milliliters per minute per 1.73 m^2), where $CL_T = (F \times \text{dose})/\text{AUC}$; renal clearance ($CL_R$; in milliliters per minute per 1.73 m^2), where $CL_R = (Ut_1 - t_2)/\int t_1 t_2 C\, dt$ in which U is the amount of habekacin excreted in urine during the interval from t_1 to t_2 in milligrams and $\int t_1 t_2 C\, dt$ is the area under the serum concentration-time curve during the same time interval. Bioavailability (F) of habekacin was found to be 0.95 to 1 in healthy subjects after the administration of the same 3-mg/kg dose to six subjects both i.m. and i.v.; these data were not determined in uremic patients.

The terminal elimination phase was investigated only after the 1-h i.v. infusion of the 3-mg/kg dose of habekacin.

Statistical analysis. Comparison of the pharmacokinetic data obtained in normal subjects and in the four groups of uremic patients was performed by using analysis of variance. P values of less than 0.05 were taken as the threshold of significance.

Linear relationships between the pharmacokinetic data of habekacin and the biological parameters of glomerular filtration rate data were established by using the linear least-squares regression method.

RESULTS

Subjects with normal renal function. After a single i.m. dose of 3 mg/kg, the mean C_{max} of habekacin in subjects with normal renal function was 7.85 ± 0.88 μg/ml and was obtained at a T_{max} of 0.67 ± 0.20 h. C_{max} values in serum were 1.31 ± 0.29 μg/ml at 6 h and were not detectable at 16 h. The $t_{1/2}$ was 2.10 ± 0.43 h. The V_{area}/F was 0.323 ± 0.034 liter/kg. The CL_T/F was 112.5 ± 19.0 ml/min per 1.73 m^2, and the CL_R value averaged 76.3 ± 13.6 ml/min per 1.73 m^2. A total of 69.7 ± 3.1% of the dose was recovered in an unchanged form in urine at 24 h (Table 2).

Patients with chronic renal impairment. Representative mean graphs of the serum concentration-time curves after the 3-mg/kg dose was administered to subjects with normal renal function and to uremic patients from each group are shown in Fig. 1. As renal function decreased, the average $t_{1/2}$ of habekacin increased to 8.69 ± 4.61, 19.47 ± 7.27, 31.64 ± 9.85, and 48.26 ± 19.86 h for uremic patients in groups 1, 2,

TABLE 2. Habekacin pharmacokinetic data in healthy subjects and uremic patients[a]

Subjects	C_{max} (μg/ml)	T_{max} (h)	AUC (μg · h/ml)	V_{area}/F (liter/kg)	$t_{1/2}$ (h)	Urinary excretion 24 h (% of dose)	Clearances (ml/min per 1.73 m^2)	
							CL_T/F	CL_R
Normal	7.85 ± 0.88 (6.5–9.0)	0.67 ± 0.20 (0.5–1)	28.11 ± 3.87 (21.7–32.1)	0.323 ± 0.034 (0.28–0.37)	2.10 ± 0.43 (1.5–2.7)	69.7 ± 3.1 (65–74)	112.5 ± 19.0 (97–146)	76.3 ± 13.6 (65–101)
Group 1 (CL_{CR}, > 30 ml/min)	11.42 ± 2.54 (9.1–15.4)	1.13 ± 0.70 (0.8–2)	123.10 ± 48.11 (63.3–177.4)	0.287 ± 0.050 (0.21–0.34)	8.69 ± 4.61 (4.1–14.9)	49.8 ± 7.1 (40–57)	30.8 ± 14.8 (16–55)	17.8 ± 7.8 (10–30)
Group 2 (10 < CL_{CR} < 30 ml/min)	11.39 ± 1.35 (9.5–13.4)	0.93 ± 0.12 (0.8–1)	239.00 ± 70.97 (144.5–347.2)	0.352 ± 0.052 (0.27–0.43)	19.47 ± 7.27 (11.5–34.1)	34.7 ± 8.2 (23–44)	14.0 ± 4.7 (8–20)	7.6 ± 2.5 (4–11)
Group 3 (CL_{CR} < 10 ml/min)	9.70 ± 2.69 (7.3–13.8)	1.67 ± 0.52 (1–2)	365.10 ± 52.80 (284.0–411.3)	0.374 ± 0.117 (0.26–0.56)	31.64 ± 9.85 (18.5–46.4)	20.4 ± 10.3 (9–38)	9.1 ± 1.3 (8–12)	4.1 ± 1.6 (3–7)
Group 4	12.97 ± 2.92 (9.5–17.0)[b]		671.40 ± 233.40 (443.4–970.7)	0.327 ± 0.059 (0.25–0.39)	48.26 ± 19.86 (25.8–85.6)		5.5 ± 1.9 (3–9)	

[a] Values are means ± standard deviations; ranges are given in parentheses.
[b] End of i.v. infusion.

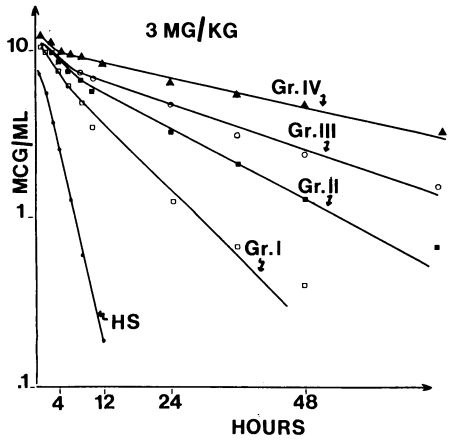

FIG. 1. Mean habekacin concentration (in micrograms per milliliter) in serum-time (in hours) curves in healthy subjects and in the four groups of uremic patients. Gr, Group.

3, and 4, respectively (Table 2). After the same i.m. dose as that given to normal subjects, the C_{max} of habekacin in serum significantly increased ($P = 0.01$) and the T_{max} was delayed in severe uremic patients ($P = 0.006$). Renal impairment did not statistically modify the apparent V_{area}: 0.32 ± 0.03 liter/kg in healthy subjects and 0.37 ± 0.12 liter/kg in patients with a CL_{CR} below 10 ml/min ($P > 0.10$) (Table 2). Urinary elimination was inversely related to the degree of renal impairment; 70% of the dose was recovered in urine at 24 h in healthy subjects, and only 20% of the dose was recovered in patients with severe renal impairment (group 3). Habekacin concentrations in urine remained above the MICs for the most susceptible bacteria during 24 h, however, in patients with a CL_{CR} below 10 ml/min. In hemodialysis patients, the habekacin $t_{1/2}$ averaged 48.26 and 4.71 h for patients off and on hemodialysis, respectively. Concentrations in serum decreased by approximately 60% during a 4- to 5-h hemodialysis session. CL_T averaged 58.3 ± 22.8 ml/min per 1.73 m^2 for patients on hemodialysis.

DISCUSSION

Pharmacokinetic data for habekacin are quite similar to those found for other available aminoglycoside antibiotics, particularly amikacin and dibekacin (4–7). In healthy subjects, kinetic data of habekacin were found to be similar for the two doses of 3 and 3.75 mg/kg and for the two routes of administration (i.m. and i.v.) (A. Leroy, G. Humbert, F. Borsa, and J. P. Fillastre, 25th ICAAC, abstr. no. 300, 1985). In uremic patients, the habekacin $t_{1/2}$ increased in relation to the severity of renal failure, from 2 h in normal subjects to 48 h in patients with end-stage renal dysfunction. The same findings have been observed for other aminoglycoside antibiotics, such as lividomycin, amikacin, sisomicin, and dibekacin (4–6). This increase in $t_{1/2}$ was particularly pronounced in patients with CL_{CR} values of less than 20 ml/min. Renal insufficiency did not significantly modify the V_{area} but increased the C_{max} of habekacin. Linear relationships between habekacin pharmacokinetic data and glomerular filtration rate data ($t_{1/2} = 0.052$ creatinine $- 0.040$ [$r = 0.830$]; $CL_T/F = 1.43\ CL_R + 3.75$ [$r = 0.997$]) provided a basis for dosage adjustment in subjects with renal function impairment. Thus, we recommend injection of a 3-mg/kg habekacin dose as the loading dose in all patients. In uremic patients, the habekacin $t_{1/2}$ could be evaluated from the following relationship: $t_{1/2}$ (in hours) = 0.05 × blood creatinine (μmol/liter). We propose injection of half the dose (i.e., 1.5 mg/kg) every $t_{1/2}$ ($t_{1/2}$ was calculated from the relationship described above). These schedules should be checked and adjusted, however, and the antibiotic concentrations in serum should be determined regularly to maintain effective and nontoxic levels in serum during treatment.

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