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Pharmacokinetics of Teicoplanin in Renal Failure

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By using a highly specific chromatographic technique, the effect of renal failure on the pharmacokinetics of the six main components of teicoplanin, taken individually or as a whole, was assessed for over 120 h after administration of a 3-mg/kg intravenous dose to healthy volunteers (group 1, $n = 6$) and to noninfected patients with moderate (group 2, $n = 6$) or severe (group 3, $n = 7$) renal failure. In subjects with normal renal function, total teicoplanin was mainly excreted in urine and its concentrations in plasma could be adequately fitted to a three-compartment model. Renal failure did not affect the model or the distribution of teicoplanin but strongly decreased its renal clearance (9.3, 3.2, and 0.6 ml/h per kg, respectively, for the three groups of subjects), in close relationship with the creatinine clearance ($r = 0.973$, $n = 18$, $P < 0.001$). The cumulative urinary excretion of unchanged total teicoplanin was decreased (50, 21, and 5% of the given dose for groups 1 to 3) and the terminal half-life was enhanced (62, 96, and 111 h for groups 1 to 3) by renal impairment. The relative behavior of the six major components was only slightly affected by renal failure. Consequently, the dosage regimen adjustment could be based on the total teicoplanin concentration, and simulations with the mean estimated pharmacokinetic parameters suggest that the 6-mg/kg daily dose, known to be effective in patients with normal renal function, could be given every 2 and 3 days in patients with moderate and severe renal insufficiency, respectively.

Teicoplanin is a new glycopeptidic antibiotic related to vancomycin (9, 19), which is made of at least 21 components classified into group A3, a main A2 group, and a minor group of related substances on the basis of their increasing lipophilicity (2, 4; Gruppo Lepetit-Merrell Dow, Internal report, Milan, Italy, 26 November 1982).

Teicoplanin activity is restricted to gram-positive growing bacteria, in which it specifically blocks their cell wall synthesis (9, 15, 19). Slight differences have been demonstrated in the in vitro activity, as well as in the in vivo activity and toxicity in mice, of the five main components of the A2 group. As a trend, both the activity and toxicity increase with lipophilicity (2, 4).

Previous pharmacokinetic studies, using microbiological methods for assessing drug concentrations, showed that, in healthy volunteers, teicoplanin pharmacokinetics was linear over a range of 2- to 6-mg/kg intravenous (i.v.) doses. Teicoplanin exhibited a two- to four-phase pharmacokinetic profile, and its terminal half-life ($t_{1/2}$) ranged from 33 to 190 h, depending on the last sampling time. Within 4 to 5 days, 40 to 50% of a single i.v. dose was recovered in urine. Renal clearance (CL_R) was low and represented ca. one-half to two-thirds of total clearance (CL). CL was not affected by repeated dosing (11, 12, 16, 18; T. B. Tjandramaga, L. Verbist, I. De Lepeleire, R. Verbesselt, and P. J. De Schepper, Third World Conf. Clin. Pharmacol. Exp. Ther., abstr. no. 1525, p. 294, 1986).

Teicoplanin seems a promising alternative to vancomycin for the following reasons. (i) It does not seem ototoxic and appears less nephrotoxic in animals and seems to be well tolerated in humans. (ii) It is highly active. (iii) It can be administered intramuscularly. (iv) Its slow elimination rate allows a once-a-day treatment (3, 9, 11, 18, 19). In the present work, the effect of renal failure on the pharmacokinetics of the six major components of teicoplanin, taken separately or as a whole, was determined by using a specific high-performance liquid chromatographic technique.

(This work was presented in part at the Third World Conference on Clinical Pharmacology and Experimental Therapeutics, Stockholm, Sweden, 27 July to 1 August 1986.)

MATERIALS AND METHODS

Subjects. Six healthy volunteers were included in the control group (G 1). Noninfected patients with renal failure, who needed prophylaxis against gram-positive bacteria, were divided into two groups according to their creatinine clearance (CL_{CR}): six with moderate renal impairment (for G 2, CL_{CR} from 48 to 64 ml/min per 1.73 m^2) and seven with severe renal failure (for G 3, CL_{CR} from 5 to 22 ml/min per 1.73 m^2) (Table 1). All subjects underwent a thorough physical examination and a complete blood and urine analysis before the study. We excluded those subjects with hepatic or cardiac disease, known drug hypersensitivity, or poor general status. During the 48 h preceding the study, the G 1 subjects avoided any drug intake, and only the absolutely necessary treatments were maintained in the patients (diuretic and antihypertensive drugs, mainly). The study protocol was approved by the Hospices Civils de Lyon Ethical Committee, and informed consent was obtained from the subjects.

Protocol. Subjects who had fasted overnight received at 8 a.m., 1 h after a light breakfast, a single i.v. dose of 3 mg of teicoplanin per kg (batch 8403A01; Gruppo Lepetit-Merrell Dow) injected over 2 to 3 min. The first standardized meal was allowed 4 h after the dose, and adequate hydration was ensured throughout the study. Blood samples were drawn into heparinized plastic containers before and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 32, 48, 56, 72, 80, 96, 104, and 120 h after

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TABLE 1. Characteristics of the subjects included in the study[a]

Subject	Sex	Age (yr)	Wt (kg)	Ht (cm)	CL_{CR} (ml/min)
G 1					
A	Female	30	49	161	113
B	Male	28	67	164	118
C	Female	34	48	160	97
D	Male	33	77	180	112
E	Female	34	56	170	92
F	Male	62	60	167	111
Mean ± SEM		37 ± 6	60 ± 5	167 ± 4	107 ± 5
G 2					
G	Male	65	66	167	50.8
H	Male	40	71	172	61.7
I	Male	57	70	168	63.2
J	Female	49	55	160	43.0
K	Female	46	56	162	57.8
L	Male	60	66	171	65.5
Mean ± SEM		53 ± 4	64 ± 3	167 ± 2	57.0 ± 3.6
G 3					
M	Male	52	71	168	13.3
N	Male	74	67	167	5.6
O	Female	47	67	156	13.7
P	Male	36	67	170	23.0
Q	Male	60	73	172	7.0
R	Female	55	51	160	9.4
S	Female	51	88	177	10.6
Mean[b] ± SEM		57 ± 4	69 ± 5	167 ± 4	9.9 ± 1.4

[a] G 1, Normal renal function; G 2, mild renal insuffiency; G 3, severe renal insufficiency.
[b] Subject P excluded (see Results for details).

teicoplanin administration. The samples were kept at 4°C and centrifuged at the same temperature within 2 h. Plasma was stored at −20°C until analysis. Urine was collected before and from 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, and 96 to 120 h after teicoplanin administration. As soon as a fraction was completed, the urine volume and pH were measured and portions were stored at −20°C.

Measurement of teicoplanin. Teicoplanin was assayed by a sensitive and highly selective high-performance liquid chromatographic method (E. Riva, N. Ferry, A. Cometti, G. Cuisinaud, G. G. Gallo, and J. Sassard, J. Chromatogr., in press). Teicoplanin was isolated and quantitatively recovered from a 2-ml plasma or urine sample by affinity chromatography, which involved the selective binding of teicoplanin to a matrix bearing the D-alanyl-D-alanine group previously immobilized by ε-amino caproic acid to Sepharose (5). After this isolation step, the sample extract was chromatographed on a Nucleosil C18 (5-μm) column to ensure the separation of the major teicoplanin components. With a linear-gradient elution profile, at least 15 components were separated with a mixture of 0.01 M sodium dihydrogen phosphate buffer, pH 4.9, and acetonitrile as the mobile phase, delivered at a flow rate of 1.3 ml/min. All the components were detected at 240 nm. Figure 1 shows a typical chromatogram obtained from a standard solution of teicoplanin. With the assumption of identical extraction and detection for all the separated components and with extracted external standards, quantitation of total teicoplanin was based on the sum of the peak areas of the six major components (Fig. 1), which represented 93% of the sum of the peak areas after direct injection of a teicoplanin solution. The linearity of the method was checked between 0.5 and 50 mg/liter. The limit of detection, based on a signal-to-noise ratio of 3:1, was found to be 0.1 mg/liter of plasma or urine. At this concentration, only the

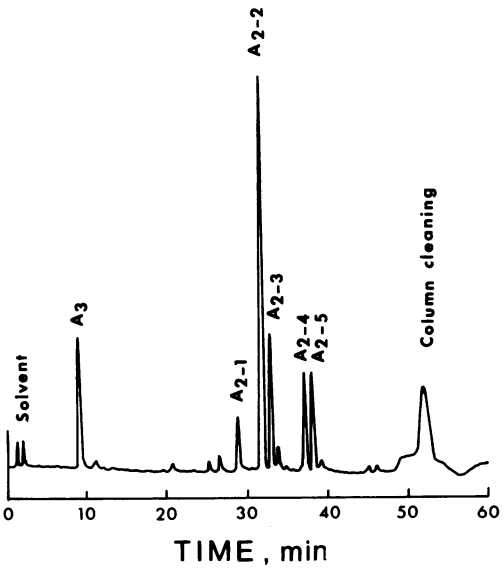

FIG. 1. Typical chromatogram obtained from a standard solution of teicoplanin showing the six major components used for quantitation (A3, A2-1, A2-2, A2-3, A2-4, and A2-5).

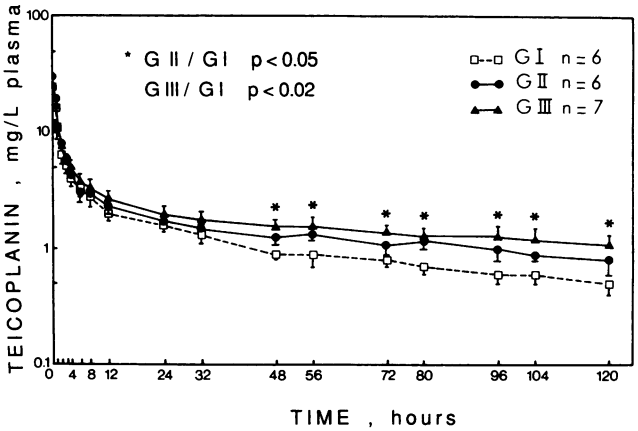

FIG. 2. Mean (± standard error of the mean) teicoplanin concentrations in plasma after a single 3-mg/kg i.v. dose in healthy volunteers (□) and in patients with moderate (●) and severe (▲) renal failure.

peak corresponding to the A2-2 component could be measured. The within-day precision was 6.8 and 4.4% in plasma and 6.2 and 4.4% in urine for concentrations of 2 and 20 mg/liter, respectively. The between-day coefficient of variation was 8.6 and 4.8% in plasma for concentrations of 2 and 20 mg/liter, respectively, and 8.9 and 4.1% in urine for concentrations of 2 and 50 mg/liter, respectively. The amounts corresponding to each of the six major components were calculated with: (i) the ratio of the area under each individual peak compared with that obtained in the external standards for the component being considered and (ii) the proportion of the component in teicoplanin, i.e., its peak area expressed as a percentage of the sum of the peak areas of the detected components in a solution of the batch of teicoplanin given to the patients (see Table 3).

Pharmacokinetic analysis. (i) Total teicoplanin. The total teicoplanin concentrations in plasma (C) were fitted to a three-compartment open model, with elimination from the central compartment. The use of this model resulted in a good fit of the data. Considering the relatively small number of datum points and the length of the study, the data were not fitted to a four-compartment model. With a nonlinear least-squares regression program developed on an HP-9825 desk computer, the exponential slopes (λ_1, λ_2, and λ_z) and coefficients were thus estimated for each individual. A $1/C$ weighting factor was selected because the assay reproducibility was better at high concentrations of teicoplanin and it resulted in a better fit of the data than the $1/C^2$ factor did. The following pharmacokinetic parameters were classically derived from the exponential parameters: the intercompartment distribution rate constants (k_{12}, k_{21}, k_{13}, and k_{31}), the total elimination rate constant (k_{el}), the area under the plasma concentration-time curve (AUC), the AUC from time zero to infinity ($AUC_{0-\infty}$), $t_{1/2}$, CL, the volume of the central compartment, the volume of distribution of the terminal phase, and the volume of distribution at steady-state levels (8).

To separately evaluate CL_R, the AUC under the experimental values, from 0 to 120 h (AUC_{0-120}), was calculated by using the log-linear trapezoidal rule. For more accurate calculations, the initial concentration in plasma was estimated by log-linear regression over the first three datum points (the correlation coefficient ranged from 0.934 to 1.000, considering all the subjects). CL_R was thus calculated as the ratio of the cumulative urinary excretion (CUE) of unchanged teicoplanin (CUE_{0-120}) over AUC_{0-120}. Nonrenal clearance was obtained as the difference between CL, previously derived, and CL_R. The renal elimination rate constant was calculated as CL_R over volume of the central compartment (8).

(ii) Six major components of teicoplanin. A simplified analysis was performed for each major component of teicoplanin. AUC_{0-120}, CUE_{0-120}, and CL_R were estimated as for total teicoplanin. AUC_{0-120}, and CUE_{0-120} were expressed as a percentage of the sum of the corresponding AUC or CUE of the six components (AUC%S and CUE%S). CUE_{0-120} was also expressed as a percentage of the administered dose of each component, which was calculated by using its proportion in the given teicoplanin (CUE%D).

Pharmacokinetic simulation for total teicoplanin. Concentrations in plasma and CUE values after repeated i.v. bolus administration were computed for each group on the basis of the mean values of the volume of the central compartment and the rate constants that we estimated in the first step from the single 3-mg/kg i.v. dose data. This simulation used ADAPT (6), a program which we implemented on a Harris 880 computer.

Statistical analysis. The data were individually treated. Results were expressed as the mean (± standard error of the mean) and compared as unmatched data by the one-sided nonparametric Wilcoxon test.

RESULTS

Pharmacokinetics of total teicoplanin. The evolution over time of mean total teicoplanin concentrations in plasma and CUE values are shown in Fig. 2 and 3. Table 2 summarizes the estimated pharmacokinetic parameters. Because of incomplete blood sampling, one patient (P) from G 3 had to be excluded from the pharmacokinetic analysis.

In subjects with normal renal function, teicoplanin kinetics was correctly described by a three-compartment model. Its $t_{1/2}$ was long, 62 h (from 50 to 78 h). Its CL was low, 15.7 ml/h per kg (12.0 to 21.0). Teicoplanin was essentially eliminated unchanged in the urine, with a CL_R value of 9.3 ml/h per kg (7.2 to 12.7), which represented ca. 10% of CL_{CR}. After 120 h, only 50% (34 to 84) of the dose was excreted as unchanged teicoplanin.

Renal insufficiency did not affect the three-phase profile in

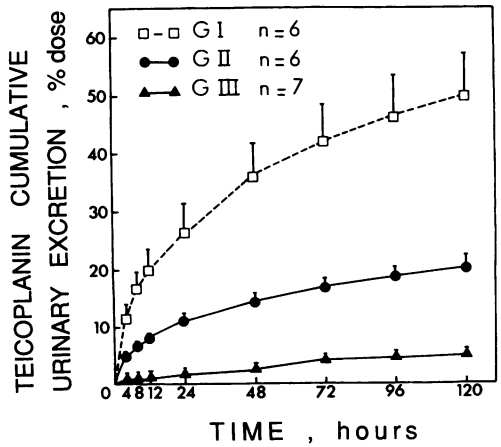

FIG. 3. Mean (± standard error of the mean) CUE of teicoplanin as the percentage of a single 3-mg/kg i.v. dose in healthy volunteers (□) and in patients with moderate (●) and severe (▲) renal failure.

TABLE 2. Teicoplanin pharmacokinetic parameters[a]

Parameter	Mean[b] ± SEM (n = 6)		
	G 1	G 2	G 3
λ_1[c] (per h)	2.54 ± 0.56	2.66 ± 0.39	3.41 ± 0.61
λ_2[c]	0.232 ± 0.047	0.308 ± 0.066	0.298 ± 0.041
λ_z[c]	0.011 ± 0.001	0.0081 ± 0.0010**	0.0066 ± 0.0007***†
$t_{1/2}$ (h)	62 ± 5	96 ± 19**	111 ± 15***†
k_{12} (per h)	1.290 ± 0.311	1.215 ± 0.226	1.764 ± 0.386
k_{21}	0.693 ± 0.154	0.828 ± 0.181	0.916 ± 0.158
k_{13}	0.549 ± 0.149	0.713 ± 0.109	0.845 ± 0.153
k_{31}	0.046 ± 0.005	0.047 ± 0.003	0.057 ± 0.006
k_{el}[d]	0.208 ± 0.029	0.168 ± 0.031	0.130 ± 0.024
k_{1r}[e]	0.126 ± 0.023	0.051 ± 0.008**	0.009 ± 0.002***‡
V_1[f] (liter/kg)	0.086 ± 0.016	0.066 ± 0.009	0.069 ± 0.009
V_z[g]	1.43 ± 0.21	1.29 ± 0.13	1.31 ± 0.19
V_{ss}[h]	1.13 ± 0.17	1.11 ± 0.13	1.17 ± 0.17
CL (ml/h per kg)	15.7 ± 1.3	10.1 ± 1.2**	8.8 ± 1.8**
CL_R	9.3 ± 0.8	3.2 ± 0.5***	0.6 ± 0.1***‡
CL_{NR}[i]	6.4 ± 1.5	7.0 ± 1.0	8.2 ± 1.8
$AUC_{0-\infty}$ (mg · h/liter)	197 ± 15	320 ± 42***	409 ± 72**
AUC_{0-120}	159 ± 15	207 ± 20	232 ± 33
CUE_{0-120} (% dose)	50 ± 8	21 ± 2***	5 ± 1***‡

[a] Observed after a single 3-mg/kg i.v. dose injected over 2 to 3 min in healthy volunteers (G 1) and in patients with moderate (G 2) or severe (G 3) renal failure.
[b] Values for indicated group compared with G 1 (**, $P < 0.01$; ***, $P < 0.005$) and with G 2 (†, $P < 0.05$; ‡, $P < 0.005$).
[c] Exponential slopes calculated by a nonlinear least-squares regression program.
[d] Total elimination rate constant.
[e] Renal elimination rate constant.
[f] Volume of distribution of the central compartment.
[g] Volume of distribution of the terminal phase.
[h] Volume of distribution at steady-state levels.
[i] Nonrenal clearance.

plasma. G 2 and 3 differed significantly from G 1 in their concentrations in plasma only 48 h after teicoplanin administration. G 2 and 3 never differed significantly in their concentrations in plasma. Distribution was not affected by renal failure, as indicated by the values of the distribution volumes. The essential change was the significant decrease in CL_R: 3.2 ml/h per kg (1.4 to 4.3) in patients with moderate renal failure and only 0.6 ml/h per kg (0.3 to 0.7) in those with severe renal insufficiency. The percentage of the dose excreted unchanged in the urine decreased to 21% (14 to 27) in G 2 and to 5% (3 to 7) in G 3 patients. Comparing the ratio of CL_R to CL with these percentages, we did not get urinary recovery up to infinity. As nonrenal clearance was not significantly enhanced by renal failure, there was a significant increase in $t_{1/2}$, which reached 96 h (67 to 187) in G 2 and 111 h (84 to 181) in G 3 patients. The upper value of the range in G 2 and 3 was from one subject who differed markedly from the others (I in G 2 and O in G 3). There is uncertainty about the $t_{1/2}$ value estimated for these two subjects, as the value is larger than the study length. Without these two subjects, $t_{1/2}$ ranges from 67 to 94 h in G 2 and from 84 to 106 h in G 3. Figure 4 shows the close relationship observed between CL_R of teicoplanin and CL_{CR} ($r = 0.973$, $n = 18$, $P < 0.001$), as well as the significant correlation between CL and CL_{CR} ($r = 0.639$, $n = 18$, $P < 0.01$). CL was significantly lowered by renal failure, although this decrease was not significant between G 2 and 3, with a mean value of 10.1 ml/h per kg (6.6 to 13.2) in G 2 and 8.8 ml/h per kg (4.5 to 14.9) in G 3.

Pharmacokinetics of the six major components of tei-

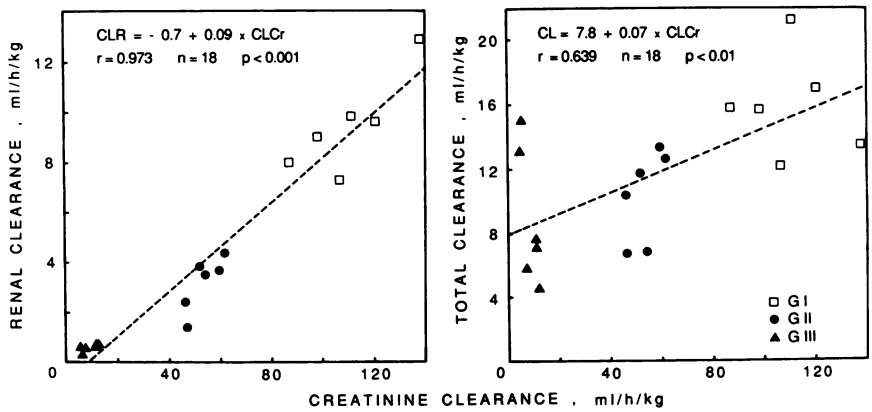

FIG. 4. Relationship between CL and CL_R (CLR) of teicoplanin and the CL_{CR} (CLCr) observed in healthy volunteers (□) and in patients with moderate (●) and severe (▲) renal failure after a single 3-mg/kg i.v. dose.

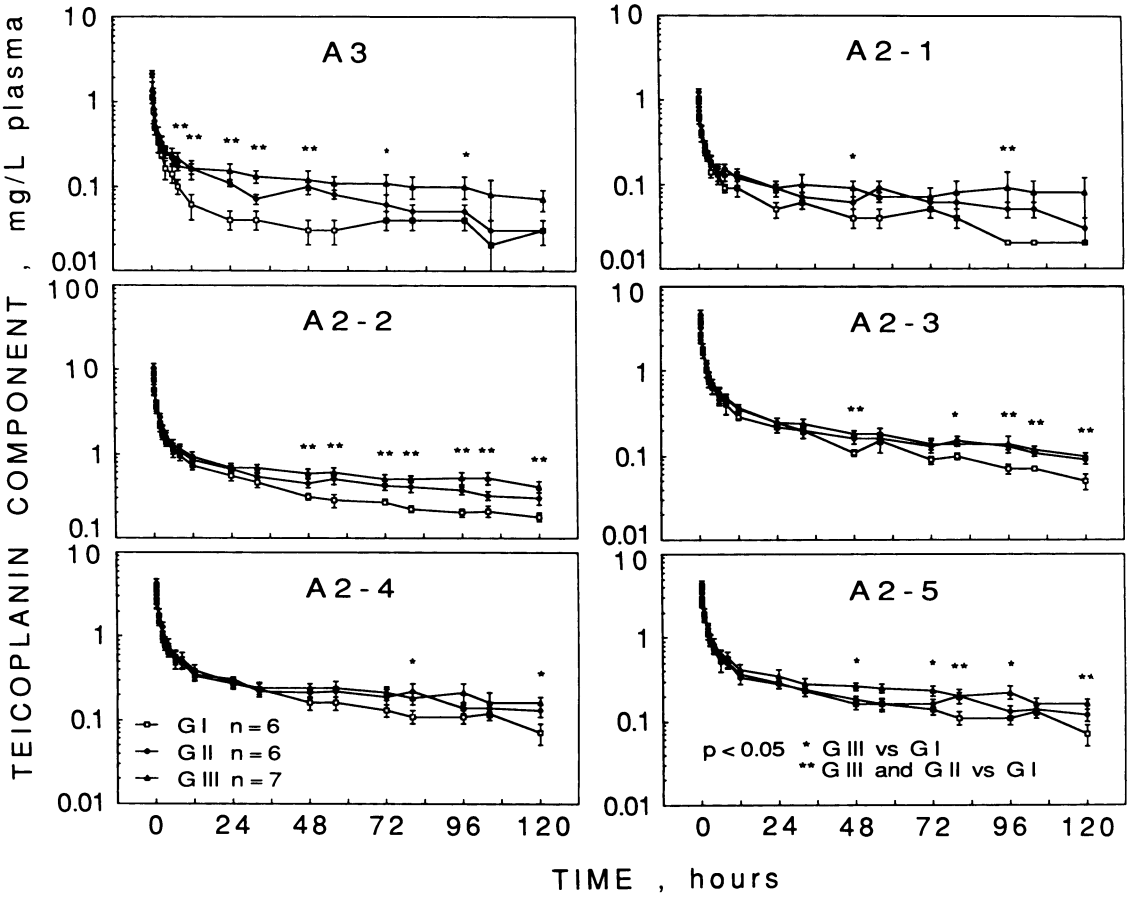

FIG. 5. Mean (± standard error of the mean) concentrations of the six major components of teicoplanin in plasma after a single 3-mg/kg i.v. dose of teicoplanin in healthy volunteers (□) and in patients with moderate (◆) and severe (▲) renal failure.

TABLE 3. Pharmacokinetic characteristics of the six major components of teicoplanin[a]

Parameter	Group	Mean[b] ± SEM of component (n = 6)					
		A3	A2-1	A2-2	A2-3	A2-4	A2-5
Proportion in teicoplanin[c]		11.5 ± 0.2	5.5 ± 0.1	40.3 ± 0.2	13.7 ± 0.1	11.4 ± 0.1	10.2 ± 0.1
AUC_{0-120} (mg · h/liter)	1	6.2 ± 0.6	6.7 ± 0.6	55.0 ± 5.1	22.9 ± 2.5	27.0 ± 3.1	28.5 ± 3.2
	2	11.7 ± 0.9**	9.7 ± 1.2*	73.5 ± 7.3*	28.1 ± 2.6	32.5 ± 3.5	30.8 ± 3.1
	3	15.8 ± 3.2*	11.9 ± 3.1	85.3 ± 11.7	28.7 ± 3.7	33.5 ± 6.7	37.4 ± 5.4
AUC%S	1	4.4 ± 0.6	4.7 ± 0.4	37.8 ± 0.9	15.6 ± 0.5	18.3 ± 0.5	19.3 ± 1.1
	2	6.4 ± 0.5*	5.2 ± 0.5	39.4 ± 0.6	15.1 ± 0.8	17.4 ± 0.6	16.5 ± 0.6*
	3	7.1 ± 0.9*	5.3 ± 0.8	40.8 ± 1.0*	13.9 ± 0.7	15.1 ± 1.7*	17.8 ± 0.6
CUE%S	1	20.4 ± 1.0	6.5 ± 0.2	44.6 ± 0.6	11.3 ± 0.2	9.4 ± 0.3	7.8 ± 0.7
	2	22.2 ± 1.6	7.3 ± 0.3*	45.8 ± 1.0	10.0 ± 0.2**	8.6 ± 0.5	6.1 ± 0.2*
	3	18.6 ± 2.3	7.6 ± 0.6	47.4 ± 1.7	9.8 ± 0.8	9.6 ± 1.2	7.0 ± 1.0
CUE%D	1	70.1 ± 2.7[d]	56.6 ± 8.3	51.9 ± 6.8	39.0 ± 6.1	39.2 ± 5.6	35.9 ± 5.4
	2	36.9 ± 3.9**	26.1 ± 3.1**	22.1 ± 2.2**	14.1 ± 1.4**	14.7 ± 1.5**	11.6 ± 1.1**
	3	8.0 ± 1.5**	6.6 ± 0.8**	5.8 ± 0.9**	3.5 ± 0.7**	3.9 ± 0.4**	3.1 ± 0.3**
CL_R (ml/h per kg)	1	47.1 ± 5.3	13.8 ± 1.4	11.4 ± 1.0	7.0 ± 0.6	5.0 ± 0.4	3.9 ± 0.4
	2	11.6 ± 2.1**	4.9 ± 1.0**	3.9 ± 0.6**	2.2 ± 0.3**	1.7 ± 0.3**	1.2 ± 0.2**
	3	1.5 ± 0.1**	0.9 ± 0.1**	0.8 ± 0.1**	0.5 ± 0.1**	0.5 ± 0.2**	0.3 ± 0.1**

[a] Observed after a single 3-mg/kg i.v. dose of teicoplanin injected over 2 to 3 min in healthy volunteers (G 1) and in patients with moderate (G 2) or severe (G 3) renal insufficiency.
[b] Values for indicated component compared with G 1 (*, $P < 0.05$; **, $P < 0.005$).
[c] Determined over 15 injections of a teicoplanin solution (batch 8403A01; 20 mg/liter).
[d] For this value, n = 5 (see text for details).

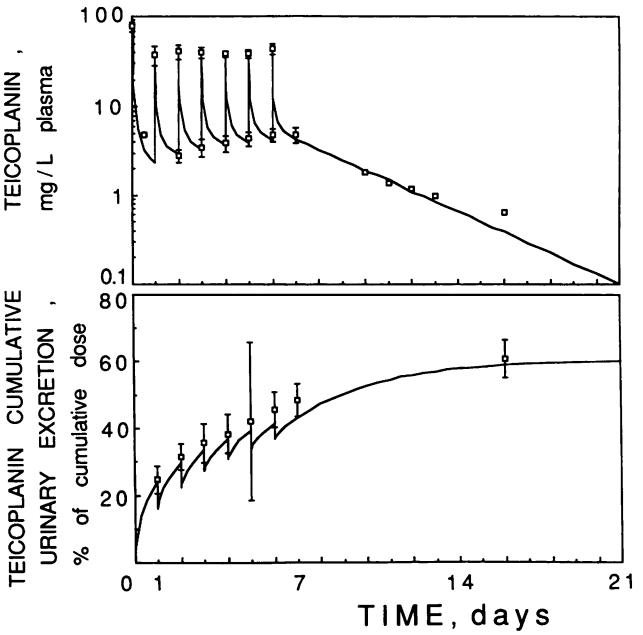

FIG. 6. Teicoplanin concentrations in plasma and CUE values in healthy volunteers predicted by computer, with the mean pharmacokinetic parameters estimated after a single 3-mg/kg i.v. dose (—) and those observed by Tjandramaga et al. (Third World Conf. Clin. Pharmacol. Exp. Ther.) (□, mean [n = 6] ± standard deviation when available) after i.v. bolus dosing with 6 mg/kg on day 1, followed by 3 mg/kg per day for 6 days.

coplanin. Figure 5 shows the evolution, over time, of the mean concentrations of the six major components of teicoplanin in plasma, and Table 3 summarizes their mean pharmacokinetic characteristics.

In subjects with normal renal function, the pharmacokinetic behavior evolved, logically, from the most hydrophilic component, A3, to the most lipophilic, A2-5. CL_R decreased from 47.1 (36.7 to 65.5) to 3.9 ml/h per kg (2.9 to 5.6), and CUE%D decreased from 70.1 (63.2 to 76.6) to 35.9% (18.2 to 52.6). The first G 1 subject was excluded from the mean CUE%D of A3, for a value of 154%. This subject differed from the others by a high CL_R, and the abnormal CUE%D value observed could be explained by a transformation of one or more components into A3 by elimination of the glycone part. On the basis of the evolution of the concentrations in plasma and of the values for AUC%S, it appears that renal failure markedly influenced the elimination of only three components: A3, A2-2, and A2-3, representing 66% of the pure teicoplanin. However, the CUE%S values show that the relative urinary excretion of the six components did not change. The only component for which AUC%S increased, both in mild and severe renal insufficiency, was A3, a finding which indicates that there was a light relative accumulation of this component, which is logical because its elimination was mainly renal. Considering CUE%D, only A3 differed from total teicoplanin. The other components, which could be individually considered, did not behave differently.

Simulation of the total teicoplanin concentrations in plasma during treatment. To ascertain if the pharmacokinetic parameters derived from our single-dose study could be extrapolated to repeated-dose regimens, we compared the teicoplanin concentrations in plasma and values for urinary excretion, simulated with the parameters that we estimated in healthy subjects, with those measured by Tjandramaga et al. (Third World Conf. Clin. Pharmacol. Exp. Ther.) in volunteers repeatedly dosed. Figure 6 represents our simulation results and their mean datum points. The good agreement of the two is a reasonable indication of: (i) the validity of our mean estimated parameters to predict the repeated administration of teicoplanin and (ii) in teicoplanin accumulation, a low quantitative importance of the pharmacokinetic phase 4 described by these authors.

These results allowed us to perform similar simulations for our three groups of subjects to determine an appropriate dosage regimen. As recently reported (Teicoplanin Meeting, Merrell Dow, Strasbourg, France, March 1986), a daily 6-mg/kg dose, leading to trough concentrations of above 5 mg/liter, most often appeared clinically efficient in patients with normal renal function. Therefore, to reach such trough concentrations rapidly, our simulation study (Fig. 7) suggests a 3-day loading period with the following treatment: on day 1, two doses of 6 mg/kg every 12 h, rather than a single more important dose (because the possible toxicity of high peak levels has not been assessed) and, on days 2 and 3, a 6-mg/kg dose. On successive days, the following treatment was given: (i) in subjects with normal renal function, one 6-mg/kg dose every day, which, at steady-state levels, gave peak (0.5 h after dosing) concentrations of ca. 40 mg/liter and trough concentrations of ca. 10 mg/liter; (ii) in patients with moderate renal failure, one 6-mg/kg dose every 2 days, which, at steady-state levels, gave a peak concentration of 45 mg/liter and a trough concentration of 8 mg/liter; (iii) in

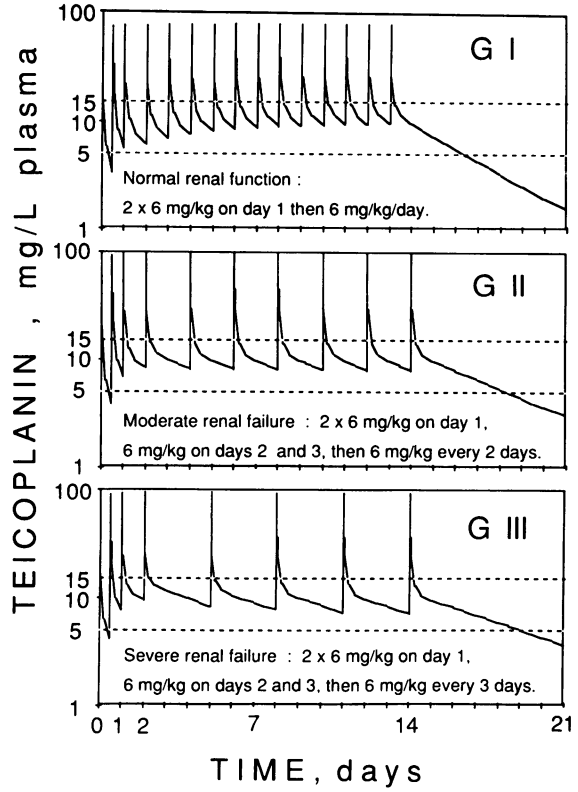

FIG. 7. Effect of dosage interval increase on teicoplanin concentrations in plasma. Concentrations were computed with the mean pharmacokinetic parameters estimated after a single 3-mg/kg i.v. dose and with repeated i.v. bolus dosing in healthy volunteers and in patients with moderate or severe renal failure.

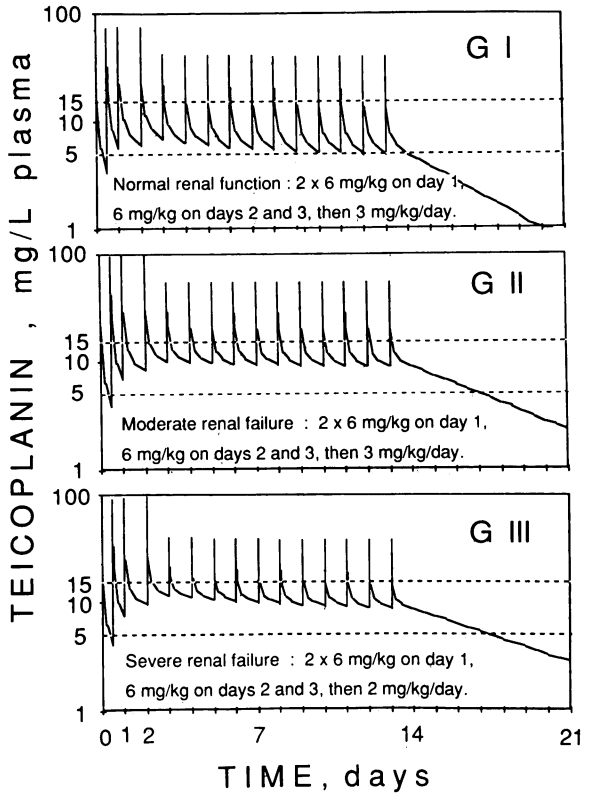

FIG. 8. Effect of dose reduction on teicoplanin concentrations in plasma. Concentrations were computed with the mean pharmacokinetic parameters estimated after a single 3-mg/kg i.v. dose and with repeated i.v. bolus dosing in healthy volunteers and in patients with moderate or severe renal failure.

patients with severe renal failure, one dose every 3 days, which, at a pseudo-steady-state level, gave peak concentrations decreasing from 37 to 36 mg/liter and trough concentrations from 8 to 7 mg/liter. Alternatively, it may be possible in these patients to maintain a 2-day interval between 6-mg/kg doses. Such a schedule led to peak concentrations of ca. 40 and trough levels of ca. 11 mg/liter.

Another possible regimen for patients with renal failure is to decrease the dose while maintaining the dosing interval used for patients with normal renal function. A dose reduction to 3 or 2 mg/kg per day in G 2 or 3 led to a similar trough (9 or 8 mg/liter) but lower peak levels (ca. 30 or 20 mg/liter) (Fig. 8). In G 3, a dose reduction to only 3 mg/kg per day provided steady-state peak levels of ca. 30 mg/liter and trough levels of ca. 12 mg/liter.

DISCUSSION

Using a new specific high-performance liquid chromatographic technique, instead of a microbiological assay, the results that we obtained concerning the pharmacokinetics of total teicoplanin in subjects with normal renal function were in good agreement with other i.v. single-dose (2 to 6 mg/kg) studies. Teicoplanin distribution was adequately described by a three-compartment model, as in two other studies of a similar length (4 days) in healthy volunteers (16, 18). MacNulty et al. (12) described their data by a two-compartment model but they sampled plasma only up to 49 h after injection of teicoplanin. The $t_{1/2}$ value of 62 h that we observed was comparable to the value of 49 h of Traina and Bonati (16) and the one of 47 h of Verbist et al. (18) after a single 3-mg/kg i.v. dose. After administration of a daily 3-mg/kg (6 mg/kg on day 1) i.v. dose over 7 days in healthy volunteers, Tjandramaga et al. (Third World Conf. Clin. Pharmacol. Exp. Ther.) found a four-phase profile and a $t_{1/2}$ of 190 h, with the last sample taken 10 days after the last dose. Both a three- and a four-compartment model resulted in a good fit of their data, and they had to statistically discriminate between the models. In addition, the good simulation of their repeated-dose data that we obtained with our mean G 1 parameters indicates that the phase 4 they observed might not be quantitatively critical in teicoplanin accumulation. Taking into account the large interindividual variability observed in all the studies, the other pharmacokinetic parameters of our study and previous studies (16, 18) corresponded well.

Renal failure did not change the pharmacokinetic behavior or the distribution of total teicoplanin, which still obeyed a three-compartment model. However, renal impairment strongly decreased the urinary elimination of teicoplanin, in close relationship with the glomerular filtration rate. Consequently, the $t_{1/2}$ was almost doubled in patients with severe renal insufficiency. In a six-day study of five patients with more severe renal impairment than our G 3 patients had, who also received a single i.v. 3-mg/kg teicoplanin dose, CL was lower, the volume of distribution at steady-state levels was identical, and $t_{1/2}$, logically, was longer (17). The pharmacokinetic differences between G 2 and 3 were significant only for CL_R and $t_{1/2}$. There was, for CL, an overlap between the three groups. This overlap was due to the high CL values observed for the two most impaired G 3 patients, who also presented the highest values for volume of distribution of the terminal phase and volume of distribution at steady-state levels for this group. Renal failure could decrease teicoplanin-plasma binding. However, this does not seem to be significant for most of the patients because the distribution volume values were not different between the three groups and the small increase of nonrenal clearance with the degree of renal failure was not significant.

The pharmacokinetics of the six major components of teicoplanin could be determined precisely because of the use of our specific chromatographic technique. It was found that, in healthy volunteers, the kinetic parameters of the six components were, logically, related to their lipophilicity. As lipophilicity increases from component A3 to A2-5, a decrease in CL_R (from 47 to 4 ml/h per kg) was observed. As a consequence, renal impairment significantly altered the pharmacokinetics of three of the less lipophilic components (A3, A2-2, and A2-3), while those of the two most lipophilic components (A2-4 and A2-5) remained unchanged. In patients with renal failure, only the A3 component was found to accumulate significantly; however, this accumulation is unlikely to be of clinical importance as the percentage of A3 in total teicoplanin was low (11.5). It was of interest to demonstrate that the relative pharmacokinetic behavior of the group A2 components was poorly affected by renal insufficiency, because the activity and the toxicity of these components have been reported to exhibit threefold variations in mice (2, 4). Therefore, the dosage adjustments required by renally impaired patients could be performed considering only total teicoplanin concentrations in plasma.

Significant therapeutic failures were observed with a 200-mg (ca. 3-mg/kg) i.v. or intramuscular daily dose in patients with normal renal function, with trough levels lower

than 5 mg/liter (3, 7, 10, 11; J. P. Stahl, P. Le Noc, E. Bernard, H. Etesse, et al., Teicoplanin Meeting, Merrell Dow, abstr. no. 15, 1986, Strasbourg, France; Y. Van Laethem, H. Goosens, S. Cran, J. P. Butzler, et al., Abstr. 14th Int. Congr. Chemother., p. 128, 1985). It is generally accepted (Merrell Dow Meeting) that trough concentrations in plasma have to remain above 5 mg/liter and that a 6-mg/kg per day regimen is clinically effective in patients with normal renal function. On this basis, the simulation of repeated doses with the mean pharmacokinetic parameters that we estimated in the three groups suggests the following regimens. As renal failure did not seem to influence teicoplanin distribution, the same loading regimen could be used for the three groups, i.e., two doses of 6 mg/kg given 12 h apart on day 1 and then one dose on days 2 and 3 in all the patients. This should be followed by one dose daily in patients with normal renal function. To maintain trough levels of ca. 10 mg/liter in patients with moderate or severe renal impairment, either the dosage interval could be increased (to 6 mg/kg every 2 or 3 days, respectively) or the dose could be reduced (to 3 or 2 mg/kg daily, respectively). As with vancomycin, the interval increase could be more appropriate as it also allows the achievement of high peak levels, which may be important for efficiency (1, 13, 14). For CL, there is a large variability among the patients with severe renal impairment. The above-described dosage regimens are general suggestions designed to give effective teicoplanin concentrations in plasma, while avoiding its potential nephrotoxic effects (3, 19). In some cases, e.g., our two severely impaired patients who exhibited normal CL values, the application of the proposed regimen may lead to low efficiency. This emphasizes the need for further studies to precisely determine the clinical efficiency of the dosage scheme derived from the present work.

In conclusion, with a highly specific chromatographic technique, the pharmacokinetics of the six main components which form teicoplanin was assessed in subjects with various degrees of renal function. It was demonstrated that, logically, renal insufficiency more markedly altered the elimination of the most hydrophilic component, which is mainly excreted by the kidney. However, because of its low concentration, this did not significantly alter the relative proportion of the different components of teicoplanin in patients with renal failure. Consequently, the dosage regimen adaptations could be scheduled on the basis of total teicoplanin concentrations in plasma. Since the $t_{1/2}$ of total teicoplanin was significantly increased in patients with renal impairment, the dosage of teicoplanin has to be reduced in these patients. Simulations allowed us to suggest that an appropriate reduction could be achieved by increasing the interval between doses. Further studies are needed to assess this hypothesis.

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