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Pharmacokinetics of Single- and Multiple-Dose Teicoplanin in Healthy Volunteers

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Teicoplanin, an investigational glycopeptide antibiotic related chemically and microbiologically to vancomycin, has in vitro and in vivo activity against gram-positive aerobic and anaerobic bacteria. We compared the single- and multiple-dose pharmacokinetics of intravenous teicoplanin in healthy volunteers. Serum and urine samples were collected for 35 days after single-dose (3 mg/kg) and 72 days after multiple-dose (3 mg/kg per day for 21 days) administration. A three-exponent equation with zero-order input was fitted to concentrations in serum. The mean half-lives ($t_{1/2}$s) were significantly different ($P = 0.0075$) after single- and multiple-dose administration (130 ± 14.9 and 176 ± 29.8 h, respectively). The clinically relevant $t_{1/2}$ obtained from multiple-dose data was approximately 61 h. Total and renal clearances determined at steady state were not statistically different, indicating that teicoplanin is eliminated almost entirely by renal mechanisms.

Teicoplanin, an investigational glycopeptide antibiotic produced by fermentation of *Actinoplanes teichomyceticus*, is a mixture of six structurally related components related both chemically and microbiologically to vancomycin (1, 2). Teicoplanin has in vitro and in vivo activity against gram-positive aerobic and anaerobic bacteria, including *Staphylococcus aureus* and *Staphylococcus epidermidis* (including methicillin-resistant strains), *Streptococcus faecalis*, and *Clostridium difficile*. Teicoplanin interferes with cell wall biosynthesis by inhibition of peptidoglycan polymerization and is bactericidal against susceptible bacteria (9).

Preliminary human and animal data suggest some potential advantages of teicoplanin. Administration by intravenous bolus or intramuscular injection does not appear to produce phlebitis or muscle necrosis. In addition, the half-life ($t_{1/2}$) of teicoplanin (approximately 48 h) appears from several single-dose pharmacokinetic studies to be considerably longer than that of vancomycin. Multiple-dose studies, however, reported a $t_{1/2}$ of approximately 96 h (12, 13). The purpose of the present study was to characterize the single- and multiple-dose pharmacokinetics of teicoplanin in healthy volunteers to resolve these discrepancies.

MATERIALS AND METHODS

Antibiotic. Teicoplanin was supplied by Merrell-Dow Research Institute, Cincinnati, Ohio (lots SB-C37955-SD and SH-C38464-SK), as a dry, sterile lyophilized powder (200 mg per vial) for reconstitution and intravenous administration and as a laboratory reference powder. Standards and quality-control samples were prepared in serum and urine and stored at −80°C for up to 4 months.

Volunteers. The study protocol was approved by the Hartford Hospital Institutional Review Board. After written, informed consent was obtained, six healthy volunteers (three men, three women) were selected for inclusion in the study on the basis of a normal physical examination and laboratory parameters (Table 1). No volunteer ingested caffeine, alcohol, or antibiotics for 72 h before the start of the study or had a history of hypersensitivity to vancomycin. Female volunteers were not pregnant.

Pharmacokinetic study design. (i) Phase 1: single-dose pharmacokinetics. Six healthy subjects were fasted overnight before and for 4 h after administration of a single 3-mg/kg intravenous dose of teicoplanin. Doses were administered in 25 ml of normal saline as a constant infusion into a forearm vein over 5 min.

Blood samples (7 ml) were obtained from a contralateral forearm vein before administration and at 5 (end of infusion), 10, 15, 30, and 45 min and 1, 2, 3, 4, 6, 9, 12, 24, 36, and 48 h after dosing and then at 24-h intervals for a total of 25 days. Blood samples were allowed to clot at room temperature and centrifuged for 10 to 12 min, and the serum was immediately decanted and frozen at −80°C until analysis.

Urine was collected before drug administration (blank) and for the following time intervals: 0 to 2, 2 to 4, 4 to 6, 6 to 9, 9 to 12, 12 to 24, 24 to 36, and 36 to 48 h and then in 24-h intervals for a total of 35 days. After each collection period, the total volume of urine was measured, and a 10-ml sample stored at −80°C pending microbiological analysis. Urine collections were stored in the refrigerator (4°C) during the longer (>4-h) collection periods. Concentrations in serum and urine were monitored during phase 1 until concentrations were undetectable (<0.1 μg/ml).

(ii) Phase 2: multiple-dose pharmacokinetics. Beginning 2 weeks after the completion of phase 1, the six volunteers were given a daily 3-mg/kg dose of teicoplanin (as a 5-min constant infusion) for 21 days.

For the first 12 h after the initial daily dose of teicoplanin, blood samples were collected as per the phase 1 sampling schedule. Subsequent samples (C_{min}) were collected at 24-h intervals, just before the administration of the daily teicoplanin dose. After the last dose of teicoplanin (day 21), blood was collected as in phase 1 for the first 48 h and then at 24-h intervals for a total of 72 days.

During day 1 of teicoplanin multiple-dose administration,

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TABLE 1. Volunteer demographics

Subject	Sex[a]	Age (yr)	W (kg)	Creatinine clearance (ml/min)[b]		
				Before	After SD	After MD
1	F	24	52.3	88	70	77
2	M	26	72.7	127	127	123
3	F	28	70.9	105	104	124
4	F	27	53.2	86	88	98
5	M	27	73.6	130	124	140
6	M	27	63.6	121	147	166

[a] M, Male; F, female.
[b] SD, Single dose; MD, multiple dose.

urine samples were collected as in the first 12 h of phase 1. During days 2 through 21, urine was collected in 24-h intervals, with collection ending just before the administration of the daily teicoplanin dose. Urine collection on the last day of multiple-dose teicoplanin administration followed the same schedule as on day 1 and then in 24-h increments for a total of 72 days after the last dose.

Laboratory evaluation. Each subject received a thorough physical examination (including laboratory tests) before and upon completion of phases 1 and 2 and at weekly intervals during phase 2 of the study. Laboratory tests included electrocardiogram, audiogram (with high-frequency testing), serum chemistry and biochemical profile, complete blood count with differential and platelet count, urinalysis, and 24-h urine collection for determination of creatinine clearance.

Antibiotic assay. Teicoplanin concentrations in serum and urine were determined by an agar diffusion microbiological assay utilizing *Bacillus subtilis* ATCC 6633 (Difco Laboratories, Detroit, Mich.) as the test organism. A modification of previously published teicoplanin assays provided an increase in assay sensitivity from 0.8 to 0.1 μg/ml (P. Carver, C. H. Nightingale, and R. Quintiliani, Program Abstr. 26th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 1131, 1986). Standards were prepared in pooled human serum or urine, and samples were run in quadruplicate. Recovery of spiked teicoplanin samples was within 10% of label. The correlation coefficient for the regression line of six standard concentrations was not less than 0.99.

Quality-control samples were assayed over the time of freezer storage to provide validation of the standard curve and an assessment of inter-day assay variability. There was no statistical difference in assayed values ($P > 0.24$). Over this time period, serum samples spiked with 20 or 0.25 μg of teicoplanin per ml had mean coefficient of variation (CV%) assay values of 19.76 (7.34%, $n = 43$) and 0.25 (8.00%, $n = 65$) μg/ml, respectively. Urine samples spiked with 10 or 0.25 μg of teicoplanin per ml had mean CV% assay values of 10.69 (10.57%, $n = 30$) and 0.25 (4.0%, $n = 30$) μg/ml, respectively.

Pharmacokinetic analysis. A triexponential equation was fitted to the single-dose concentration-versus-time data (5). This equation included a zero-order input function and was mathematically manipulated such that variables in the equation represented those obtained for an intravenous bolus equation. Variables included three pre-exponential constants and three first-order rate constants. The existing equation was modified to include an accumulation factor for each exponential and fitted to multiple-dose concentration-versus-time data. Additionally, an equation of the form $C_{min} = C_{min_{ss}}[1 - \exp(-K \cdot t)]$ was fitted to the observed C_{min} data, where K represents a curve shape factor, $C_{min_{ss}}$ is the C_{min} at steady state (SS), and t is time.

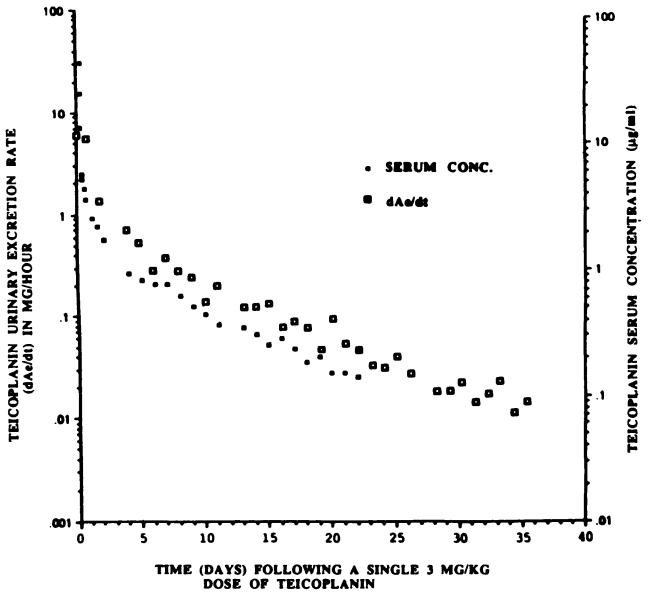

FIG. 1. Serum concentration (■) and urinary excretion data (□) for a representative subject (no. 5) after a single 3-mg/kg intravenous dose of teicoplanin.

Pharmacokinetic disposition parameters were calculated from output variables of least-squares fitting by usual methods (5). The area under the concentration-time curve (AUC) was calculated as the sum of the ratios of the pre-exponential constants and rate constants. The area under the moment curve (AUMC) was calculated as the sum of the ratios of the pre-exponential constants and the square of the rate constants. The AUC of the SS interval was calculated from the observed data by using the trapezoidal rule method (5). Total clearance (CL_T) and renal clearance (CL_R) were calculated by the ratio of the administered dose and AUC and the cumulative amount of drug excreted into the urine and AUC, respectively. The volume of the central compartment (V_1) was calculated as the ratio of the administered dose and the sum of the pre-exponential constants; the volume of distribution at SS (V_{ss}) was calculated as the ratio of administered dose times AUMC and AUC squared.

Final estimates of pharmacokinetic parameters were obtained by use of the nonlinear, least-squares regression program NLIN (11), with a weighting factor of $1/y$ or $1/y^2$. Goodness of fit was evaluated by visual examination of the residuals and plots of residuals versus time.

Statistics. Statistical differences between single- and multiple-dose pharmacokinetic parameters were determined by analysis of variance. A P value of <0.05 was considered significant.

RESULTS

Pharmacokinetics. (i) Single-dose phase. A semilogarithmic plot of serum concentration-time data and urinary excretion-time data after single-dose administration of teicoplanin in a representative study subject (subject 1) is shown in Fig. 1. This curve shape was consistent among all subjects. Pharmacokinetic parameters calculated from the three-exponential fit of the serum data are presented in Table 2. Low

TABLE 2. Single-dose pharmacokinetic parameters

Subject	AUC[a] (μg · h/ml)	CL_T (ml/min per kg)	V_1 (liter/kg)	V_{ss} (liter/kg)	Terminal $t_{1/2}$ (h)
1	346	0.145	0.069	1.09	130
2	374	0.134	0.075	1.06	129
3	365	0.137	0.070	1.08	130
4	349	0.143	0.069	1.12	125
5	436	0.115	0.080	1.13	157
6	281	0.178	0.092	1.12	111
Mean	359	0.142	0.076	1.10	130
SD	50.1	0.0206	0.009	0.028	14.9
CV%	14.0	14.5	11.8	2.51	11.5

[a] AUC from 0 h to 25 days.

intersubject variability was observed, as evidenced by the low coefficients of variation calculated for the disposition parameters.

(ii) Multiple-dose phase. An equation describing C_{min} as a function of $C_{min_{ss}}$ and K was simultaneously fitted to the observed C_{min} data. The observed $C_{min_{ss}}$ was determined as that value which fell within the 95% confidence interval of the regression output; the time to SS was the time corresponding to the observed $C_{min_{ss}}$. The average C_{min} (CV%) required to achieve SS was 10 days (19.0%) with a range of 7 to 13 days. The mean half-time (CV%) required to reach SS calculated from the C_{min} data was 61.0 h (16.3%). This half-time predicted a mean $C_{min_{ss}}$ of 8.45 μg/ml, which was very close to the observed value of 8.33 μg/ml.

A semilogarithmic plot of concentration in serum-time data and urinary excretion-time data during the washout period after the last dose of teicoplanin is presented in Fig. 2. For a drug such as teicoplanin that is virtually totally renally eliminated, the slopes of these two curves should be parallel. The observation of nonparallel slopes in our study is not clearly understood but is consistent with in vivo formation of microbiologically active hydrolysis products (HP) of teicoplanin (1, 2, 6, 8). As a result of the decreased renal clearance of the more lipophilic HP as compared with teicoplanin, one would predict that the apparent half-life should be greater in serum than in urine, which would result in the observed nonparallel character of these curves.

To utilize the most appropriate data for the estimation of teicoplanin pharmacokinetic disposition parameters, for each subject only serum data that exhibited a parallel decline over time in relation to the urinary excretion data were used. It was apparent from inspection of these curves that there was a trend toward convergence, which we attributed to

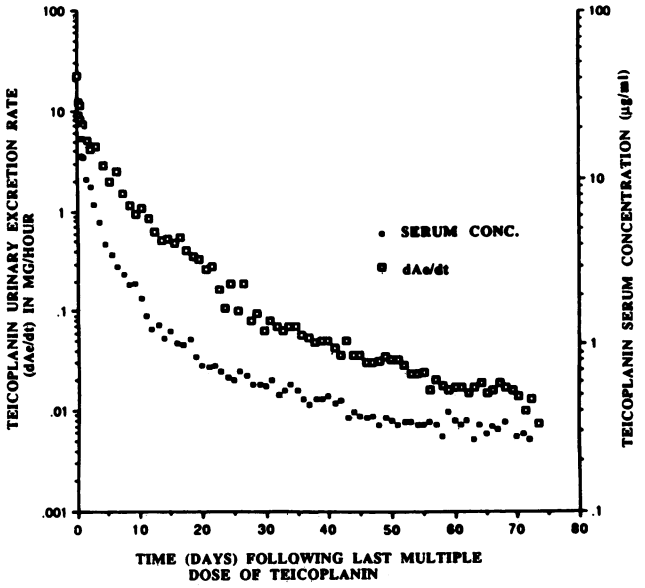

FIG. 2. Concentration in serum (■) and urinary excretion data (□) for a representative subject (no. 5) during the 72-day washout phase after the multiple-dose (3 mg/kg per day for 21 days) intravenous administration of teicoplanin.

contamination of total serum activity by HP. The intent of this truncation at 240 h was to minimize the impact of HP on teicoplanin disposition parameters. This was accomplished in all subjects by visual inspection of the data. The remainder of this report describes this truncated data.

Table 3 contains the pharmacokinetic parameters generated from a three-exponent fit of the truncated multiple-dose serum data. A representative subject (subject 1) is presented in Fig. 3. As was observed in the single-dose disposition parameters, there was low intersubject variability observed after multiple dosing.

The pharmacokinetic disposition parameters between the single- and multiple-dose phases were compared. All $t_{1/2}$ data were logarithmically transformed prior to statistical analysis. The volume terms, V_1 ($P = 0.1331$) and V_{ss} ($P = 0.6543$), did not differ statistically. A statistically significant difference was detected between AUC ($P = 0.0002$), CL_T ($P = 0.0002$), and terminal $t_{1/2}$ ($P = 0.0075$). At steady state, the mean $CL_{R_{ss}}$ of 0.170 ml/min per kg was not significantly different from the mean $CL_{T_{ss}}$ of 0.174 ml/min per kg ($P = 0.4555$).

TABLE 3. Multiple-dose pharmacokinetic parameters

Subject	AUC[a] (μg · h/ml)	CL_T (ml/min per kg)	V_1 (liter/kg)	V_{ss} (liter/kg)	Terminal $t_{1/2}$ (h)	$C_{min_{ss}}$ (μg/ml)	Time to SS (days)
1	279	0.179	0.096	1.06	144	7.49	10
2	328	0.153	0.085	1.08	220	9.96	10
3	281	0.178	0.064	1.04	149	7.66	7
4	288	0.174	0.076	1.25	185	8.44	10
5	346	0.145	0.088	1.00	193	9.84	13
6	229	0.218	0.094	1.26	156	6.59	11
Mean	292	0.175	0.084	1.12	176	8.33	10.2
SD	41.2	0.0255	0.012	0.112	29.8	1.35	1.94
CV%	14.1	14.6	14.3	10.0	16.9	16.2	19

[a] AUC from 0 to 72 days after the day 21 dose (3 mg/kg) of teicoplanin.

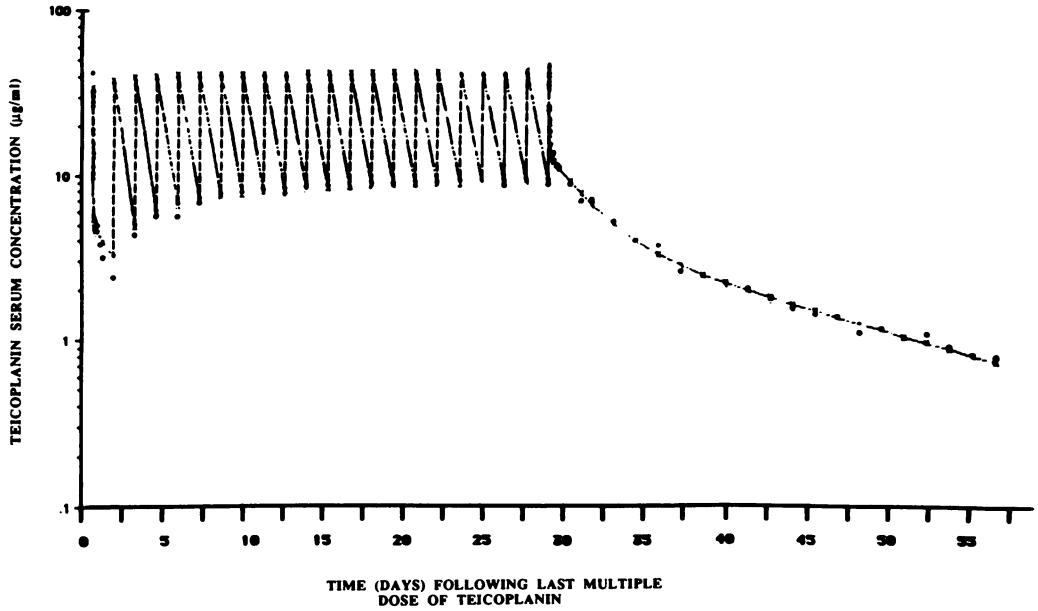

FIG. 3. Concentration in serum-versus-time data for a representative subject (no. 5) during the entire multiple-dose phase of the study.

Safety and tolerance. Teicoplanin was well tolerated in all volunteers. Specifically, there was no evidence of phlebitis, renal, hepatic, or hematologic toxicity, or ototoxicity either during the study or during follow-up evaluation.

DISCUSSION

The pharmacokinetics of teicoplanin have been reported by several investigators. Traina et al. described the pharmacokinetic profile of teicoplanin after a single 2- or 3-mg/kg intravenous dose. They reported a terminal elimination $t_{1/2}$ of 40.5 h in the serum and 45.9 h in the urine by using a three-compartment model. Urinary recovery of teicoplanin from 0 to 96 h was 52% (12). Similar findings were reported by Verbist et al. after administration of 3- or 6-mg/kg intravenous doses with terminal $t_{1/2}$s of 47.3 and 44.1 h in serum and urine, respectively. Urinary recovery from 0 to 102 h was approximately 44% for each dose (13). Both studies examined only single-dose data, and, due to limitations in assay sensitivity, serum sampling was limited to 96 to 102 h postdose. In the Verbist et al. study, concentrations of 0.2 to 0.8 μg of teicoplanin per ml were present in urine 3 weeks after the study. These short sampling times resulted in an apparent recovery in urine of 50% of the administered dose. Recoveries in urine in the present study accounted for 103 and 98% for the administered dose for the single-dose and SS phases, respectively. Our study demonstrates that total and renal clearances at SS are the same; therefore the drug is virtually all eliminated by the renal route.

The single-dose phase results in our study (Table 2) show a mean terminal elimination $t_{1/2}$ of 130 h in serum. This $t_{1/2}$ is not in good agreement with previous reports. This discrepancy may be due to the marked difference in sampling time postdose. Discontinuation of sampling before 11 days postdose will include distributional-phase data in the terminal phase, and therefore the apparent terminal $t_{1/2}$ will appear shortened.

After the last dose in the multiple-dose phase, the mean serum $t_{1/2}$ was statistically different from the single-dose data (176 versus 130 h). A possible explanation for the apparent increase in the terminal $t_{1/2}$ after multiple-dose administration could be the in vivo presence of microbiologically active HP of teicoplanin. Loss of the *N*-acetylglucosamine and mannose side chains of teicoplanin results in more lipophilic aglycone moieties that retain some in vitro activity (1, 2, 6, 8). In the aridicins, a novel series of glycopeptide antibiotics chemically related to teicoplanin, aglycone hydrolysis products exhibit more potent antistaphylococcal activity and prolonged serum $t_{1/2}$s relative to the parent drug (10).

In the absence of a nonlinear pharmacokinetic disposition, concentration in serum-versus-time curves and urinary excretion-versus-time curves should decline in parallel for any drug reported to be eliminated by primarily renal mechanisms. Parallel slopes were not observed for teicoplanin in this study (Fig. 2). It can be inferred that formation of HP is a slow process, since the time at which the curves diverge from a parallel decline is 240 h. Also, the percentage of teicoplanin converted to HP must be very small, since the concentration in serum-time curve during the SS washout period levels off at approximately 0.3 μg/ml. This is presumably due to the low clearance, large volume of distribution, and prolonged $t_{1/2}$ associated with lipophilic moieties. These facts suggest that contamination by HP provides the greatest percentage contribution to total microbiological activity at the low total activity levels present at prolonged periods postdose. After multiple doses of teicoplanin, the prolonged sampling time during the multiple-dose washout phase offer a greater potential for HP contamination than that after single-dose administration. Therefore, we assume that SS concentrations in serum are the most representative of true teicoplanin activity, due to the high total activity measured, with a mean maximal concentration at SS ($C_{max_{ss}}$) of 52.0 μg/ml (CV, 12.5%).

The prolonged $t_{1/2}$s observed in the present study can be explained by an apparent decrease in renal clearance, consistent with the more lipophilic nature of the HP. As a result of the decreased clearance of HP as compared with teicoplanin, one would predict a more prolonged $t_{1/2}$ in serum

TABLE 4. SS clearance determinations

Subject	Clearance (ml/min per kg)	
	CL_T	CL_R
1	0.170	0.173
2	0.169	0.160
3	0.190	0.167
4	0.168	0.154
5	0.156	0.163
6	0.190	0.204
Mean	0.174	0.170
SD	0.0135	0.0178
CV%	7.76	10.5

than in urine (4, 7). Our results support this contention. As stated above, accumulation of HP during the multiple-dose phase would affect the $t_{1/2}$ to a greater extent during the washout period than after a single dose.

The average time observed for the six subjects to achieve SS teicoplanin concentrations in serum was 10 days. This time is inconsistent with what one would predict from the $t_{1/2}$ obtained from the single-dose phase (130 h), which predicts that 27 days would be needed to achieve SS concentrations. A more clinically useful teicoplanin $t_{1/2}$ was obtained from C_{min} data, since the time to achieve SS is a function of $t_{1/2}$. The mean $t_{1/2}$ determined from a fit of the C_{min} data was 61 h. This value is probably a better indicator of teicoplanin $t_{1/2}$ than those obtained from the terminal elimination phases of single- or multiple-dose concentration-time curves.

Total clearance (CL_T) after single-dose administration and at SS (0 to 24 h after the last dose of teicoplanin) are listed in Tables 2 and 4, respectively. Although these values were statistically different, as $CL_{T_{ss}}$ was greater than the CL_T after a single dose, this difference is not consistent with nonlinear elimination. The smaller clearances after single-dose administration are most probably due to greater percentage contribution of HP (relative to simultaneous parent drug concentrations) during the single-dose sampling period as compared with that during the SS sampling period. Consequently, the clearance derived from SS data is more reflective of teicoplanin kinetics when microbiological assays are utilized.

At SS, CL_R was not significantly different than $CL_{T_{ss}}$. This comparison was performed at SS because intersubject variability decreases with multiple dosing and because the concentrations in serum are higher and therefore the SS data provide a better reflection of teicoplanin kinetics. A $CL_{R_{ss}}$ of 12 ml/min per 70 kg is consistent with a net elimination via filtration in a drug reported to be 90% protein bound (13). Since teicoplanin is a low-extraction drug, alterations in protein binding or renal function will be expected to affect its kinetics and subsequent concentration-time profiles.

In summary, the pharmacokinetic profile of teicoplanin can be described by a three-exponent equation with a terminal $t_{1/2}$ of 130 to 176 h. However, the clinically useful $t_{1/2}$ used for the prediction of time required to attain SS concentrations appears to be 61 h. This difference may be due to the potential accumulation of HP and the relative proportion of total AUC contributed by the terminal exponential. Multiple-dose regimens based upon terminal $t_{1/2}$s from single-dose studies will therefore result in an overestimation of $C_{min_{ss}}$. This may explain failures in early clinical trials of serious gram-positive infections, where relatively low doses (200 mg) were utilized (3). Further work is needed to determine the dosage adjustments necessary for patients with renal dysfunction and to further clarify the pharmacokinetics of hydrolysis products.

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