Teicoplanin Pharmacokinetics in Healthy Volunteers after Administration of Intravenous Loading and Maintenance Doses

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Teicoplanin is an investigational glycopeptide antibiotic that is structurally and microbiologically similar to vancomycin. Since teicoplanin possesses a very long elimination half-life, the manufacturer suggests that the drug be administered every 12 h for the first day of therapy and once daily thereafter. We studied the multiple-dose (6 mg/kg per dose) pharmacokinetics of teicoplanin in volunteers following intravenous administration every 12 h for 5 days and then every 24 h for 9 days in an attempt to identify the optimal duration of the every-12-h loading-dose regimen. Multiple serum samples were obtained throughout the study, including intensive sampling after the first and last doses; urine was collected during the entire study. A three-exponential equation was fitted to the serum concentration data. The mean terminal-phase half-life was 157 ± 93 h. Concentrations of teicoplanin in serum similar to those observed after the administration of the last dose (day 14) were observed following the fourth or fifth dose given every 12 h. Therefore, it is suggested that for clinical dosing regimens for teicoplanin, dosing every 12 h for approximately 48 h should be used, followed by once-daily dosing thereafter.

Teicoplanin is a glycopeptide antibiotic that is structurally and microbiologically related to vancomycin (2). It is a complex consisting of six major components with different acylglucosamine units. The acyl units are believed to account for the increased lipophilicity and longer half-life of teicoplanin compared with those of vancomycin (1, 12). Teicoplanin possesses bactericidal activity against gram-positive aerobic and anaerobic bacteria, including Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus (Streptococcus) faecalis, and Clostridium difficile (8, 15, 17).

Wide variation exists regarding the pharmacokinetic parameters reported for teicoplanin, especially with regard to the terminal elimination half-life. In early studies, in which samples were obtained for relatively few days after dosing, half-lives of approximately 32 to 47 h were reported (16, 18). More recent work has indicated substantially longer terminal elimination half-lives as the duration of sampling was increased (4; G. Buniva, L. Cavenagh, F. Parenti, and G. M. Frigo, Proc. Int. Symp. Control Hosp. Infect., abstr. no. 122, p. 144, 1987). Our previous study, which involved sampling for 25 days following a single 3-mg/kg intravenous dose, demonstrated the longest terminal half-life of 130 h (4). For clinical purposes, however, the "effective" half-life of teicoplanin (which describes rising trough concentrations during multiple dosing) is approximately 60 h (4).

Based on an effective half-life of 60 h, approximately 10 days of once-daily administration would be necessary to achieve steady-state concentrations. As a result, in most clinical studies a loading-dose regimen is used, such as administration every 12 h for the first few doses (9–11). While administration of a single larger initial dose (such as 9 mg/kg) would be an alternative approach, the every-12-h approach would avoid transiently high peak levels and would rapidly achieve therapeutic trough concentrations. The optimal duration of every-12-h dosing, however, has not yet been determined. The purpose of the present study was to define the multiple-dose pharmacokinetics of teicoplanin in normal volunteers following the administration of a loading-and maintenance-dose regimen and to determine the appropriate number of loading doses needed every 12 h before changing to a once-daily maintenance regimen.

MATERIALS AND METHODS

Antibiotic. Teicoplanin was provided by Merrell-Dow Research Institute, Cincinnati, Ohio (lot C-39678), as a dry, sterile lyophilized powder (200 mg per vial) for reconstitution and intravenous administration.

Volunteers. The study protocol was approved by the Institutional Review Board of Hartford Hospital. Six healthy volunteers (three males, three females) were selected for inclusion in the study on the basis of a normal physical examination and laboratory parameters (Table 1). Except for subject 6, the volunteers were not the same as those in our previous study (4). Written informed consent was obtained from all subjects prior to the study. Volunteers abstained from ingesting caffeine, alcohol, or antibiotics from 72 h before the study. No volunteer had a history of hypersensitivity to vancomycin; female volunteers were not pregnant.

Study design. Teicoplanin (6 mg/kg per dose) was administered in 100 ml of normal saline as a 30-min infusion into a forearm vein. Subjects were dosed every 12 h for 5 days and then every 24 h for 9 days.

Blood samples (7 ml) were obtained from the contralateral arm before administration and at 15, 30, 35, 40, and 45 min and 1, 1.25, 1.5, 2, 4, 6, 8, 10, 12, 13.5, and 24 h after the start...
of the infusion of the first dose. Additional blood samples were obtained at 0.5, 1, and 12 h after the start of the infusion of doses 3, 5, 7, and 9 and 0.5, 1, and 24 h after the start of the infusion of doses 11 to 18 (days 6 to 13). Blood samples were also obtained at 0, 15, 30, 45 min and 1, 1.25, 1.5, 2, 4, 6, 8, 10, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, and 192 h after the start of the infusion of dose 19 (days 14 to 21). Blood samples were allowed to clot at room temperature and centrifuged; serum was decanted and frozen at -70°C until it was shipped, in dry ice, to the sponsor of the study for assay.

Urine was collected before drug administration and from 0 to 1 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, and 12 to 24 h after the start of the infusion of doses 1 and 19. Urine was also collected for the intervals 0 to 12 h after the start of the infusion for doses 3 to 10 and 0 to 24 h after the start of the infusion for doses 11 to 18. Additional collections were made for the intervals 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168, and 168 to 192 h after the start of the infusion of dose 19. Urine collections were refrigerated (4°C) during the longer (>2 h) collection periods. Urine volumes were recorded, and portions were frozen at -70°C until they were shipped, in dry ice, to the sponsor of the study for assay.

Laboratory evaluation. Each subject underwent a complete physical examination (including electrocardiogram) before and after the study. Serum chemistries, complete blood count with differential and platelet count, and urinalysis were obtained prior to the first dose and were repeated on days 7 and 14 and within 24 h of the last blood sampling (day 21). Creatinine clearances were measured prior to drug administration and were repeated on day 14 and within 24 h of the last blood sampling. Audiograms (with high-frequency testing) were performed prior to the study and on days 7 and 14.

Antibiotic assay. Teicoplanin concentrations in serum and urine were determined by an agar diffusion microbiological assay performed by Merrell-Dow Research Institute (6). The test organism was Bacillus subtilis ATCC 6633. Assay sensitivities were 0.3 mg/liter for serum and 1.5 mg/liter for urine. Standards were prepared in pooled human serum or urine, and the assays were linear over the ranges of 0.3 to 48 mg/liter and 1.5 to 48 mg/liter, respectively. Samples containing concentrations greater than 48 mg/liter were diluted in blank, pooled human serum or urine and reassayed. The within- and between-day coefficients of variation were <10%.

Pharmacokinetic analysis. A three-exponential equation with a zero-order input function was fitted to the serum concentration-versus-time data. The three preexponential constants were converted to those corresponding to the model with the intravenous bolus input function (7). The equation was then modified to include an accumulation factor for each exponential. All serum concentration-versus-time data were then fitted simultaneously in an effort to increase the precision of the final output parameters. This modeling approach has been used by our group previously (4).

Pharmacokinetic disposition parameters were calculated from output variables of least-squares fits by standard methods (7). The area under the concentration-time curve (AUC) for the steady-state dosing interval was calculated from the observed data by using the trapezoidal rule method (7). The area under the moment curve was calculated as the sum of the ratios of the preexponential constants and the square of the rate constants. Total clearance (CLR) and renal clearance (CLRr) were calculated from the ratio of the administered dose and AUC and the cumulative amount of drug excreted into the urine during the steady-state dosing interval and AUC, respectively.

The volume of distribution at steady state (Vss) was calculated as the ratio of administered dose times the area under the moment curve and the AUC squared. The volume of the central compartment was calculated as the ratio of the administered dose and the sum of the preexponential constants.

Final parameter estimates were obtained by use of the nonlinear, least-squares regression program NLIN (14). A weighting factor of 1/y2 with the three-exponential fit yielded the model with the fewest exponents that provided an adequate fit based on randomness of scatter of the residuals.

Statistics. The paired Student t test was used to check for a statistical difference between CLR and CLRr. A P value of <0.05 was considered significant.

RESULTS

A semilogarithmic plot of serum concentration-versus-time data in a representative subject (subject 3) is shown in Fig. 1. The pharmacokinetic disposition parameters generated from the three-exponential fit of all of the serum concentration data are given in Table 2. Intersubject variability was low (i.e., low coefficients of variation were observed) for all parameters except Vss, for which subject 4 was a clear outlier. Although numerically very close, CLR was significantly lower than CLR (P = 0.002). The serum half-life in the terminal phase was 157 h (coefficient of variation, 59%). Parameter estimates from least-squares fits are provided in Table 3.

Safety and tolerance. Teicoplanin was generally well tolerated. There was no evidence of phlebitis or renal, hepatic, or ototoxicity. One subject did experience transient lighthead-
edness during the infusion of some, but not all, doses. The total leukocyte count on the last day of teicoplanin dosing (day 14) was lower than the pretreatment value for all subjects (mean decrease, 25%). Although this change was statistically significant, it is unlikely to be clinically important. The reason for this small, yet consistent, decrease in leukocyte counts is unclear. A recent review has concluded that the incidence of leukopenia and neutropenia in patients treated with teicoplanin is low (5).

**DISCUSSION**

Perhaps the greatest source of disagreement relative to teicoplanin pharmacokinetics has been the issue of the terminal-phase half-life. Values for this parameter have ranged from approximately 32 to as high as 176 h; the latter value was from a multiple-dose (3 mg/kg per dose) study conducted at our institution (4, 16). The terminal-phase half-life in the present study, 157 h, was consistent with our previous value (4). However, as was noted in the earlier study (4), a more clinically useful value for teicoplanin half-life, determined from the time needed to reach steady state, is approximately 60 h. This apparent discrepancy is explained by the fact that when a drug exhibits a polyexponential disposition, the time required to reach steady state is determined by all the exponential terms, not simply the terminal-phase half-life (13). In clinical trials with teicoplanin, several different dosage regimens have been used against a variety of infections in different patient populations. Once-daily dosing was used initially; however, at one point the dose of teicoplanin for seriously ill patients was increased to 400 mg every 12 h for 1 day followed by 400 mg once daily (9). The intent of this regimen was to reach therapeutic concentrations more rapidly than those achieved with once-daily dosing and to maintain trough levels between 5 and 15 mg/liter (a range similar to that used for vancomycin). However, with a working terminal-phase half-life of roughly 60 h, it would seem that dosing every 12 h for longer than 24 h might be necessary to function as a proper loading dose. In the present study, the mean (percent coefficient of variation) concentrations of teicoplanin in serum at 0.5, 1, and 12 h after the start of the infusion of the last dose (day 14) were 62.5 (11.1%), 45.3 (16.4%), and 17.6 (13.6%) mg/liter, respectively. From Fig. 1, it is apparent that levels similar to these were reached following approximately the fourth or fifth dose given every 12 h; mean (percent coefficient of variation) concentrations in serum at 0.5, 1 and 12 h after the fifth dose were 72.8 (13.7%), 48.4 (17.0%), and 18.1 (13.5%) mg/liter, respectively. Based on this information, it is suggested that for clinical dosage regimens for teicoplanin, dosing every 12 h for approximately 48 h should be used, followed by once-daily dosing thereafter.

Results of previous pharmacokinetic studies, including studies with [14C]teicoplanin, indicated that teicoplanin is predominantly renally eliminated (3, 4). The finding of a lower CLR than CLT in early studies probably reflects the failure to collect urine for a sufficiently long period of time. Our previous study, which involved collection of urine for 25 days after administration of a single dose, indicated that there was no difference between CLR and CLT (4). The fact that CLR (0.19 ± 0.015 ml/min/kg) was slightly lower than CLT (0.21 ± 0.018 ml/min/kg) in the present study was not an unexpected finding given the duration of urine collection (7 days postdosing). Although statistically significant (P < 0.05), the magnitude of this difference was quite small and probably negligible. The CLT obtained in this study was similar to, but slightly greater than, the CLT of 0.175

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**TABLE 2. Pharmacokinetic disposition parameters**

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>CL_T (ml/min/kg)</th>
<th>CL_R (ml/min/kg)</th>
<th>V_1 (liter/kg)</th>
<th>V_ss (liter/kg)</th>
<th>t_1/2 (h)</th>
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<tr>
<td>1</td>
<td>0.20</td>
<td>0.20</td>
<td>0.074</td>
<td>1.07</td>
<td>172</td>
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<tr>
<td>2</td>
<td>0.19</td>
<td>0.17</td>
<td>0.085</td>
<td>0.94</td>
<td>170</td>
</tr>
<tr>
<td>3</td>
<td>0.22</td>
<td>0.19</td>
<td>0.082</td>
<td>0.86</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>0.20</td>
<td>0.18</td>
<td>0.098</td>
<td>2.34</td>
<td>327</td>
</tr>
<tr>
<td>5</td>
<td>0.22</td>
<td>0.18</td>
<td>0.089</td>
<td>0.98</td>
<td>107</td>
</tr>
<tr>
<td>6</td>
<td>0.24</td>
<td>0.21</td>
<td>0.100</td>
<td>1.07</td>
<td>98</td>
</tr>
</tbody>
</table>

Mean ± SD: 0.21 ± 0.018, 0.19 ± 0.015, 0.088 ± 0.010, 1.21 ± 0.56, 157 ± 92.8

CV%: 8.57, 7.89, 11.2, 46.3, 59.1

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**TABLE 3. Parameter estimates from least-squares fits**

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>C_1 (mg/liter)</th>
<th>λ_1 (1/h)</th>
<th>C_2 (mg/liter)</th>
<th>λ_2 (1/h)</th>
<th>C_3 (mg/liter)</th>
<th>λ_3 (1/h)</th>
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<td>0.00402</td>
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<td>2</td>
<td>60.9</td>
<td>1.15</td>
<td>9.45</td>
<td>0.0268</td>
<td>0.533</td>
<td>0.00408</td>
</tr>
<tr>
<td>3</td>
<td>60.0</td>
<td>1.34</td>
<td>10.1</td>
<td>0.0806</td>
<td>2.88</td>
<td>0.0101</td>
</tr>
<tr>
<td>4</td>
<td>54.3</td>
<td>1.13</td>
<td>6.70</td>
<td>0.0249</td>
<td>0.394</td>
<td>0.00212</td>
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<tr>
<td>5</td>
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<td>7.93</td>
<td>0.0326</td>
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<td>1.22</td>
<td>0.00704</td>
</tr>
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</table>

Mean ± SD: 59.8 ± 7.53, 1.23 ± 0.140, 8.17 ± 1.33, 0.0378 ± 0.0214, 1.12 ± 0.930, 0.00564 ± 0.00283

CV%: 12.6, 11.4, 16.3, 56.6, 83.0, 50.2

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*Abbreviations: CL_T, total clearance; CL_R, renal clearance; V_1, volume of the central compartment; V_ss, volume of distribution at steady state; t_1/2, terminal-phase half-life; CV%, percent coefficient of variation.

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* C_1, C_2, and C_3 are preexponential constants and λ_1, λ_2, and λ_3 are exponents from the three-exponential equation fitted to concentration-time data. CV%, Percent coefficient of variation.
ml/min/kg determined previously by our group (4). Because the value of CLT in the present study was larger, this difference is not consistent with dose-dependent nonlinear elimination and in all likelihood represents variability between the subject groups.

The Vss determined in the present study (1.21 liters/kg) was not significantly different from the value reported previously (1.12 liters/kg) (4). If the Vss for subject 4 (an obvious outlier) is excluded, the mean value is 0.98 liter/kg. These values are consistent with the values for teicoplanin reported previously (16).

In summary, the pharmacokinetics of teicoplanin presented here are consistent with those reported previously (4). Because teicoplanin has such a long terminal-phase half-life, dosage regimens used clinically should be administered every 12 h for approximately 48 h before changing to once-daily dosing.

ACKNOWLEDGMENTS

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LITERATURE CITED


