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Comparison of Steady-State Pharmacokinetics of Two Dosage Regimens of Vancomycin in Normal Volunteers

DANIEL P. HEALY, RON E. POLK,* MICHELLE L. GARSON, DAVID T. ROCK, AND THOMAS J. COMSTOCK

Department of Pharmacy and Pharmaceutics, School of Pharmacy, Medical College of Virginia-Virginia Commonwealth University, Richmond, Virginia 23298-0001

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A pharmacokinetic comparison of the two recommended dosages of vancomycin given as multiple doses has not been previously performed. Eleven adult subjects with normal renal function randomly received 500 mg every 6 h (five doses) and, later, 1,000 mg every 12 h (three doses). Each dose was infused over 1 h, and regimens were separated by 1 week. Compared with the two-compartment fit, a three-compartment fit significantly reduced the residual weighted sums of squares. Accumulation occurred for both regimens after repeated dosing and was independent of dose. At steady state, concentrations in serum at 1 h showed little variation for the 1,000- or the 500-mg dose regimen (33.7 ± 3.8 versus 22.6 ± 3.2 μg/ml); trough concentrations were 7.9 ± 1.7 versus 11.2 ± 2.2 μg/ml, respectively. With the 1,000-mg dose, the terminal half-life was 7.7 ± 1.8 h, steady-state area under the curve for the dose interval was 227 ± 28.3 μg · h/ml, and total body clearance was 86.1 ± 8.9 ml/min per 1.73 m^2. The red-man syndrome occurred in 9 of 11 volunteers who received 1,000-mg doses and in none of those who received 500-mg doses. We concluded that (i) vancomycin disposition in healthy adults with normal renal function is best described by a three-compartment model, (ii) there is relatively little variation in vancomycin disposition in normal volunteers, (iii) significant accumulation occurs with multiple dosing, (iv) it is inappropriate to use the same therapeutic window for both regimens, and (v) the pharmacokinetics of vancomycin justify a 12-h dose interval; however, a 1-g dose is associated with a significantly greater incidence of the red-man syndrome.

Vancomycin is a potent antistaphylococcal antibiotic which is currently finding widespread clinical use, in part because of the emergence of methicillin-resistant strains of both *Staphylococcus aureus* and *Staphylococcus epidermidis*. Other factors contributing to the popularity of vancomycin include the increased incidence of hemodialysis-associated and central nervous system shunt infections, antibiotic-associated colitis due to *Clostridium difficile*, and multiply antibiotic-resistant organisms associated with prosthetic implant devices (10).

The renewal of interest in the use of vancomycin has also led to a reexamination of its pharmacokinetic characteristics. Several investigators have examined the disposition of vancomycin in patients with various degrees of renal function (16, 19), while pharmacokinetic data for normal volunteers have been presented only in three studies of single-dose regimens, with a total of 14 subjects (1, 5, 14). Uncertainty about the disposition of vancomycin has created confusion regarding its use in two important areas, namely, the timing of blood sample collections for therapeutic drug monitoring and the optimal dose regimen for patients with normal renal function.

In this investigation, the steady-state pharmacokinetics of the two commonly prescribed dose regimens for vancomycin were compared in volunteer subjects with normal renal function.

MATERIALS AND METHODS

Eleven healthy volunteers (seven males and four females) with normal renal function participated in this randomized crossover investigation. Subjects were admitted to the Clinical Research Center, Medical College of Virginia hospitals, after informed written consent was obtained. The age, weight, and creatinine clearance (mean ± standard deviation) of the subjects were 24.7 ± 2.1 years, 66.5 ± 11.2 kg, and 110 ± 19.3 ml/min per 1.73 m^2, respectively. Test subject exclusion criteria included pregnancy, hypersensitivity to vancomycin, medication for chronic illness, and consumption of antihistamine-containing product within 7 days before study participation. The regimens consisted of vancomycin hydrochloride (Vancocin, lot 9PJO8A; Eli Lilly &Co., Indianapolis, Ind.) at dosages of 500 mg every 6 h for 5 doses or 1 g every 12 h for three doses.

Doses were reconstituted with sterile water for injection as described in the package insert and filtered with a 0.5-μm-pore-size filter (6). The vials were then rinsed three times to remove drug residue. The resultant volume was diluted with sufficient 5% glucose (D_5W) to produce final volumes of 100 and 200 ml for the 500-mg and 1-g doses. respectively. All doses were administered as 1-h continuous intravenous infusions with a volumetric infusion device (Travenol 8000 volumetric pump; Travenol Laboratories, Morton Grove, Ill.). Lot potency for vancomycin was 597 ± 5 mg/500-mg vial, as determined from multiple assays of three vials. There was a 1-week washout interval between the two regimens.

Blood samples were serially collected before infusion, at the end of infusion, and at 0.08, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, and 5 h after the end of the first dose of the 500-mg regimen. The sampling scheme was similar with the first 1-gram dose, with additional samples being collected at 6, 8, and 11 h after completion of the infusion. Samples were collected before infusion, at the end of infusion, and at 0.5 and 1 h after the second 1-g and the third 500-mg doses. For the last dose of each regimen, blood was collected before infusion, at the end of infusion, and at 0.08, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 30, and 36 h after completion of the infusion. The exact sampling times were recorded and used in the

* Corresponding author.

TABLE 1. Steady-state concentrations in serum and pharmacokinetic parameters of vancomycin at a dosage of 500 mg every 6 h[a]

Subject	C_{max} (μg/ml)	$C_{1\ h}$ (μg/ml)	C_{min} (μg/ml)	$t_{1/2\gamma}$ (h)	$AUC_{0-\tau}$ (μg · h/ml)	V_1 (liter/kg)	V_{ss} (liter/kg)	TBC (ml/min per 1.73 m^2)
1	41.8	23.5	11.4	8.0	115	0.167	0.580	91.0
2	37.1	25.6	12.4	13.3	118	0.212	0.539	77.4
3	46.1	24.1	11.4	5.8	123	0.019	0.515	85.5
4	47.7	27.2	15.2	7.9	140	0.162	0.572	78.2
5	37.7	20.9	10.6	8.1	105	0.135	0.571	81.8
6	34.5	19.8	9.4	6.5	117	0.076	0.359	70.0
7	53.7	25.4	12.3	5.3	132	0.045	0.524	84.2
8	30.9	14.9	5.9	8.8	76.5	0.130	0.925	117
9	38.0	23.1	11.6	9.8	118	0.218	0.618	83.7
10	38.3	23.2	12.8	9.7	122	0.184	0.663	77.8
11	37.0	20.8	9.7	5.8	108	0.165	0.600	85.9
Mean	40.3	22.6	11.2	8.1	116	0.138	0.588	84.8
SD	6.2	3.2	2.2	2.2	15.6	0.063	0.130	11.5

[a] C_{max}, Maximum drug concentration in serum; $C_{1\ h}$, 1-h concentration in serum; C_{min}, minimum drug concentration in serum; $t_{1/2\gamma}$, half-life at gamma phase; $AUC_{0-\tau}$, area under the curve from 0 h to τ; V_1, volume of distribution in the central compartment; V_{ss}, volume of distribution at steady state; and TBC, total body clearance.

analysis of data. Specimens were allowed to clot for approximately 45 min before centrifugation. Serum samples were stored at −70°C until the time they were analyzed for drug concentration.

All samples were assayed for vancomycin concentrations within 2 weeks of collection by a fluorescence polarization immunoassay procedure (TDx; Abbott Laboratories, Diagnostics Division, Irving, Tex.). The assay has a sensitivity limit of 0.6 μg/ml, with reported intrarun and interrun coefficients of variation of less than 5% in the concentration range of 0.6 to 100 μg/ml (1). Low (7.0 μg/ml), medium (35.0 μg/ml), and high (75.0 μg/ml) serum control standards were run with each carousel of subject specimens. This assay has been previously found to be equivalent to bioassay and other chemical methods (20).

Initial estimates of pharmacokinetic parameters were obtained by stripping the concentrations in serum with ESTRIP (2) after administration of the last doses of both regimens. These initial estimates were then used to generate a best fit of the data by using both two- and three-compartment open infusion models by nonlinear iterative least-squares regression with the aid of PCNONLIN (17). The amounts of the actual doses administered were used to calculate the dose-dependent parameters, such as the volumes of distribution (volume of distribution in the central compartment [V_1] and volume of distribution at steady state [V_{ss}]) and total body clearance. The three-compartment analysis required modification of the two compartment model found in PCNONLIN to the following standard equation: $C_t = Ae^{-\alpha t} + Be^{-\beta t} + De^{-\gamma t}$, where C is the computer-predicted concentration at time t; A, B, and D are the time zero intercepts; and α, β, and γ are the hybrid rate constants for the fast-distribution, slow-distribution, and elimination phases, respectively (11). The values for A, B, and D were corrected for infusion rate, infusion time, and predose vancomycin concentration in serum (11). The sum of weighted squared residuals for the three-compartment fit for each subject was significantly lower than that for the two-compartment prediction. The data were best described by using the reciprocal of the concentration in serum as a weighting factor. Area under the curve (AUC) was calculated at steady state by the trapezoidal rule from the beginning of the infusion to the end of the dose interval. V_1 was calculated as the acutal dose administered divided by the sum of the time zero intercepts. The noncompartmental determination of the V_{ss} during multiple dosing was calculated by the method described by Gibaldi and Perrier (12). Total body clearance was calculated as the actual dose administered divided by the AUC.

Differences in the pharmacokinetic parameters and vancomycin concentrations in serum between the two regimens

TABLE 2. Steady-state concentrations in serum and pharmacokinetic parameters of vancomycin at a dosage of 1,000 mg every 12 h[a]

Subject	C_{max} (μg/ml)	$C_{1\ h}$ (μg/ml)	C_{min} (μg/ml)	$t_{1/2\gamma}$ (h)	$AUC_{0-\tau}$ (μg · h/ml)	V_1 (liter/kg)	V_{ss} (liter/kg)	TBC (ml/min per 1.73 m^2)
1	73.7	35.6	4.5	8.3	229	0.137	0.570	91.7
2	53.9	34.2	8.4	12.6	219	0.155	0.664	83.7
3	65.8	36.8	7.6	6.4	233	0.171	0.568	90.4
4	75.0	34.6	9.9	6.9	275	0.093	0.609	79.7
5	96.5	32.1	8.9	8.2	227	0.172	0.522	75.4
6	74.1	30.4	7.6	8.5	222	0.071	0.537	74.0
7	76.1	40.5	9.3	6.4	266	0.160	0.587	83.4
8	57.6	26.5	5.1	6.2	171	0.038	0.556	105
9	68.6	37.9	10.3	6.9	249	0.044	0.605	79.3
10	60.7	31.8	7.6	8.4	216	0.160	0.631	88.0
11	60.4	30.8	8.1	5.9	194	0.042	0.609	96.0
Mean	65.7	33.7	7.9	7.7	227	0.113	0.587	86.1
SD	7.9	3.8	1.7	1.8	28.3	0.053	0.040	8.9

[a] See Table 1, footnote *a*.

were statistically compared by Student's paired t test. Prediction intervals were calculated by standard methods (4). Differences were considered significant if P was <0.05.

RESULTS

The individual and mean values for the steady state concentrations in serum and the pharmacokinetic parameters derived from the three-compartment model are shown in Tables 1 and 2. Mean vancomycin concentrations in serum for the two dosage regimens are shown in Fig. 1 and 2.

The mean steady-state drug concentration in serum at the completion of the infusion was significantly higher for the 1-g dose than for the 500-mg dose (65.7 ± 7.9 versus 40.3 ± 6.2 μg/ml, respectively). After 15 min these concentrations had declined to 41.0 ± 4.8 and 27.4 ± 3.8 μg/ml, respectively. The intersubject variations of these concentrations in serum at each time of measurement were small. For example, the mean ± standard deviation of drug concentration in serum at steady state 1 h after completion of the infusion (1,000 mg) was 33.7 ± 3.8 μg/ml (range, 26.5 to 40.5 μg/ml). There was a significant correlation between the 1-h concentration in serum and the dose normalized for weight (1-h concentration in micrograms per milliliter = 1.18 multiplied by the dose in milligrams per kilogram + 15.6; $r = 0.76$; $P < 0.05$). Thus, 58% of the variation in drug concentration in serum at this time can be accounted for by differences in the weight of the volunteers. The steady-state 95% prediction interval at 1 h for a 70-kg subject receiving a 1,000-mg dose every 12 h is 26 to 39 μg/ml. The mean 1-h concentration in serum for the 500-mg dose was 22.6 ± 3.2 μg/ml (range, 14.9 to 27.2 μg/ml). The 95% prediction interval for a subject weighing 70 kg is 15 to 28 μg/ml. Thus, the prediction intervals for the two doses do not appreciably overlap, and subjects receiving 500 mg of vancomycin every 6 h achieve concentrations in serum at 1 h significantly lower than those achieved with the 1-g dose given every 12 h.

Accumulation was significant for both regimens, with trough values increasing from 5.4 ± 0.9 μg/ml with the 6-h interval and 4.9 ± 1.5 μg/ml with the 12-h interval after the first dose to 11.2 ± 2.2 and 7.9 ± 1.7 μg/ml after the final doses of the respective regimens. Inspection of Fig. 1 and 2 indicated that further accumulation would not occur.

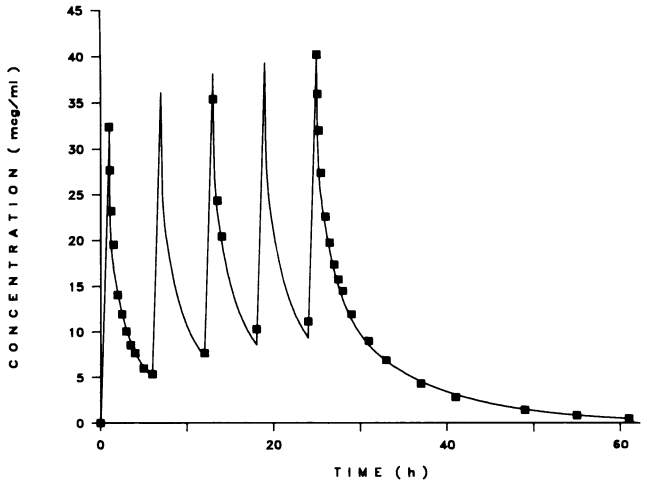

FIG. 1. Mean observed (■) and three-compartment computer-predicted (———) concentrations of vancomycin in serum at a dosage of 500 mg every 6 h.

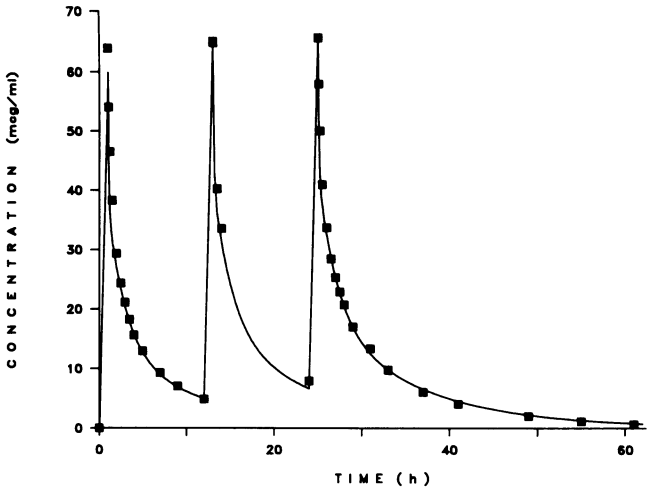

FIG. 2. Mean observed (■) and three-compartment computer-predicted (———) concentrations of vancomycin in serum at a dosage of 1,000 mg every 12 h.

The initial distribution half-life was approximately 4 min, and it was highly variable (range, 1.5 to 23 min). The slower distribution half-life was 1.5 ± 0.9 h. The mean elimination half-life was 8.1 ± 2.2 h (range, 5.3 to 13.3 h) for the 6-h regimen and 7.7 ± 1.8 h (range, 5.9 to 12.6 h) for the 12-h regimen. These values were not statistically different.

Volume-of-distribution parameters were not significantly different between regimens. V_1 and V_{ss} (mean ± standard deviation) for the 6-h regimen were 0.14 ± 0.06 and 0.59 ± 0.13 liter/kg, respectively. Respective volume-of-distribution values for the 12-h regimen were 0.11 ± 0.05 and 0.59 ± 0.04 liter/kg.

The mean AUC from time zero to τ ($AUC_{0-\tau}$) at steady state as determined by the method of linear trapezoids for the 6- and 12-h dosing intervals were 116 ± 15.6 and 227 ± 28.3 μg · h/ml, respectively. Dose dependency was not observed for any of the subjects since a doubling of the dose resulted in a proportional increase in AUC.

Symptoms of the red-man syndrome were observed in 9 of 11 subjects receiving the 1,000-mg dose but in none of those receiving the 500-mg dose (R. Polk, D. Healy, M. Garson, and L. Schwartz, Program Abstr. 26th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 32, 1986).

DISCUSSION

Early studies of vancomycin disposition in normal volunteers were mainly descriptive and did not include pharmacokinetic analysis (9). The currently available information on the pharmacokinetics of vancomycin in adults with normal renal function is limited to studies of single-dose regimens with relatively few patients (8, 16, 21) and volunteers (1, 5, 14). Most of these studies have used dissimilar methods of analysis of data, a factor which has created confusion regarding the use of vancomycin in three important areas, including identification of the optimum pharmacokinetic model to describe the disposition of the drug after multiple-dose administration, timing of blood sample collection for therapeutic drug monitoring, and selection of the most appropriate dosage regimen from the two which are commonly recommended.

Our results with subjects having normal renal function are consistent with previous reports of results with healthy

adults (1, 5, 14). A three-compartment model best described our data since there was a significant lowering of the sum of weighted squared residuals over one- and two-compartment fits. Unlike other investigators (8, 18, 21), we found relatively little variability among our subjects with respect to elimination half-life, volume of distribution, and total body clearance. The coefficient of variation for the drug concentrations in serum obtained immediately on termination of the infusion (12.0%) is not appreciably different from those obtained 15 and 30 min later (11.7 and 11.2%, respectively). Additionally, the variability in the 1-h drug concentrations in serum was largely accounted for by differences in subject weight. This low variability is likely a result of the use of a homogeneous study population consisting of young, healthy subjects with good renal function.

Because some of the adverse effects of vancomycin appear to be related to high concentrations in serum, it is commonly recommended that concentrations in serum be monitored. However, there is disagreement on when blood samples should be obtained and the desired therapeutic concentrations. In part, these disagreements reflect the lack of reliable data which relate concentrations in serum to either efficacy or toxicity (24). A review of the literature reveals recommendations for obtaining peak levels at 15 min (3, 15), 1 h (22), and 3 or more h (16) after a 1-h infusion. Therapeutic peak concentrations of vancomycin in serum (in micrograms per milliliter) which have been proposed are <80 (3), <50 to 80 (19), 30 to 40 (9, 18), 15 to 50 (24), and 20 to 40 (15). These recommendations have been made without regard to which of the two dosage regimens is used. Since peak concentrations in serum from the 6-h regimen are lower than those achieved with the 12-h regimen, use of the same therapeutic range for both is inappropriate.

It is obvious from the preceding discussion that standardization of both timing of the blood sample collection and definition of the desired concentrations is needed. The most desirable method for the specification of clear guidelines is a prospective clinical study which establishes a concentration-response curve for drug in serum. Since it is unlikely that such a study will be done, we propose the following method of interpretation of drug concentrations in serum in adults. Long experience has indicated that a daily dose of 2 g for adults with normal renal function is effective and reasonably safe (10). Therefore, the concentrations of vancomycin in serum which are achieved when 2 g is administered to healthy adults can be regarded as the therapeutic levels, and patients who are receiving vançomycin should have the dose adjusted if necessary to conform to these concentrations. The concentration range to be regarded as therapeutic can be arbitrarily selected from any point along the entire concentration-time curve. However, it is usually recommended that the true peak (at the end of the infusion) be avoided, since concentrations at that time are normally the most variable and the slope of the curve is greatest. On the basis of this reasoning and our data, we recommend that blood for determinations of vancomycin concentration in serum be obtained 1 h after completion of a 1-h infusion. The concentration in serum at that time after a 1-g dose should be between 25 and 40 μg/ml, since this range represents the 95% prediction interval at steady state for adults of normal body weight and renal function. These concentrations are also similar to those recommended by the aforementioned authors and should confirm, rather than further confuse, existing recommendations. If the 6-h-interval regimen is selected, the range for peak drug concentrations in serum should be revised downward (i.e., to 15 to 30 μg/ml). The great change in drug concentrations in serum over a short time (during the distribution phase) requires that careful attention be paid to timing of the blood sample collection.

Since vancomycin has a long half-life relative to the usual dose interval, significant accumulation occurred. Traditionally, loading doses have been recommended to more rapidly produce therapeutic concentrations, especially in patients with renal impairment. However, we do not recommend that subjects with normal renal function receive an initial dose of more than 1 g, in part because of questions regarding safety (see below).

Since monitoring of vancomycin concentrations in patients with impaired renal function represents the most common clinical setting in which assays are useful, we attempted to confirm that the presence of renal failure would not change the concentrations in serum at 1 h postdose. Computer simulation of concentration curves for drug in serum after the terminal half-life was changed to approximate those reported for patients with renal failure (e.g., 4 to 10 days) did not change the predicted concentration at 1 h compared with that of normal volunteers. Data presented by Garaud et al. indicated that the distribution phase was unchanged for subjects with renal failure when compared with those with normal renal function (8). Additionally, we reviewed our own data for patients with renal impairment receiving 1-g doses of vancomycin (13). For five patients with peritonitis who were being treated with continuous ambulatory peritoneal dialysis, the mean concentration of vancomycin in serum after completion of a half-hour infusion of 1 g was 34.8 μg/ml (range, 30 to 41 μg/ml). Thus, the drug concentrations in serum appear to be within our proposed therapeutic range for adults with renal impairment who receive 1 g of vancomycin by intravenous infusion; however, this observation should receive additional study.

A retrospective study reported that elevated trough concentrations may be associated with nephrotoxicity (7), and it has been recommended that trough concentrations of vancomycin be kept at 5 to 10 μg/ml (10, 18). However, the mean trough concentration for the 6-h-interval regimen was 11.1 μg/ml and, consequently, most patients on this regimen will likely have trough concentrations in excess of 10 μg/ml. Therefore, adjustment of the dose to obtain trough concentrations of <10 μg/ml for all patients may be overly restrictive. Further study is also required to evaluate the significance of elevated trough concentrations.

The recommended daily dose of vancomycin for patients with normal renal function is 2 g divided into doses given at 6- or 12-h intervals (6), and authorities regard these two regimens as being equally effective (10). A fact supporting the equivalence of these two regimens is that the trough concentrations from the 1-g and 500-mg doses are, respectively, approximately two and three times the MBC for staphylococci (10). Since it is more convenient and less expensive to administer vancomycin at 12-h intervals, this regimen would be preferred if efficacy and toxicity were comparable. However, a surprising finding in this study was a high incidence of red-man syndrome in subjects receiving 1,000-mg doses compared with those receiving 500-mg doses. In many cases, these reactions consisted of pruritis and erythema, which are likely to go unnoticed with the routine clinical use of vancomycin. However, four of the subjects also had angioedema, and more serious reactions have been previously described (23). Despite this finding, extensive experience indicates that if vancomycin is infused over the span of at least 1 h, serious reactions are unusual. Further study is required to determine the optimal method of

vancomycin administration. Until such data are available, practitioners should closely monitor for this reaction, especially for patients receiving 1-g doses.

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