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Pharmacokinetics of Vancomycin: Observations in 28 Patients and Dosage Recommendations

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Studies of the pharmacokinetics of vancomycin were conducted in a group of 28 patients with serious staphylococcal infection. Serum specimens were collected before and on 11 occasions after vancomycin administration. Serum concentration time data were fitted to a biexponential equation, using nonlinear regression analysis. A prolonged distribution phase with a half-life of 0.5 ± 0.3 h (standard deviation) and a central component volume of 9.0 ± 4.0 liters were demonstrated. Wide interpatient variation was observed in the terminal half-life which ranged from 3 to 13 h (mean, 6 h) and in the distribution volume which ranged from 14 to 111 liters (mean, 39 liters). A correlation of 0.45 (Pearson product moment correlation coefficient) was found between vancomycin clearance and creatinine clearance. Multiple regression analyses demonstrated that 50% of the variance (R^2) in the terminal half-life and vancomycin clearance could be explained on the basis of renal function, volume of distribution, age, weight, and sex. These observations suggest that adults with normal renal function should receive an initial dosage of 6.5 to 8 mg of vancomycin per kg intravenously over 1 h every 6 to 12 h. After 24 h, and through the period of therapy, trough and peak serum vancomycin concentrations should be monitored, and the dose and dosage interval should be changed to produce the desired peak (30 to 40 μg/ml) and trough (5 to 10 μg/ml) levels.

Until recently, vancomycin, a bactericidal antibiotic introduced in 1956, had not been used extensively because of reports of nephrotoxicity and ototoxicity (2, 5). At present, this antibiotic is being used to treat infections with antibiotic-resistant strains of *Staphylococcus aureus* and *Staphylococcus epidermidis* (3, 6).

There are few published reports on the pharmacokinetics of vancomycin (7, 10–12). Recently, two-compartment techniques of pharmacokinetic analysis, improved assay techniques, and a further refined formulation of this antibiotic have been introduced (4, 12). This investigation used contemporary methods to characterize vancomycin pharmacokinetics and to develop dosage guidelines.

MATERIALS AND METHODS

Twenty-eight patients (20 men and 8 women) ranging in age from 18 to 80 years were studied. Of these, 21 had severe thermal burns and were treated for presumed or documented infections caused by methicillin-resistant *S. aureus*. The seven other patients had a history of an anaphylactic reaction to penicillin (five patients) or were treated with methicillin-resistant *S. epidermidis* bacteremia (two patients). Of the 28 patients, 23 had a normal serum creatinine (≤1.5 mg/dl), and 5 patients had abnormal values (1.9, 2.3, 3.2, 4.6, and 5.4 mg/dl).

After giving informed consent, the patients received either 250 or 500 mg of vancomycin intravenously over 1 h, using a mechanical infusion pump. A 24-h urine collection for creatinine clearance determination was begun at the time of the vancomycin infusion. Serum samples for measuring vancomycin concentrations were obtained before the vancomycin infusion and at 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, and 10 h after drug administration. The exact sampling time was recorded and used in the data analysis. The serum was separated by centrifugation and frozen at −70°C until concentrations of vancomycin were measured. Serum vancomycin concentrations were determined by an agar diffusion method (24 patients) or, because of the presence of other antibiotics, by radioimmunoassay (4 patients). Vancomycin concentrations of 4, 8, 16, and 32 μg/ml were used to construct the standard curve for both assay techniques. Two control concentrations of 3 and 42 μg/ml were used in the assay procedure. The coefficient of variation for both assays, including day-to-day variation, was less than 10% and independent of vancomycin concentration (4).

By using conventional least-squares nonlinear regression analysis, serum vancomycin concentration time data were fitted to monoexponential ($C_{p_t} = C_{p_0} e^{-kdt}$) and biexponential ($C_{p_t} = Ae^{-\alpha t} + Be^{-\beta t}$) equations, which describe the standard one- and two-compartment open models (8, 13). The difference (residual) between measured and computer-fitted concentrations of vancomycin were determined for each time point. These values for each specific sampling time were summed for all patients, and the mean (± standard deviation) residual concentrations were calculated. This method of model analysis compared the ability of the one- and two-compartment models to describe the serum concentration time curve.

After the data were fitted to the biexponential equation, standard hybrid coefficients (A, B, and α, and β) for the two-compartment model were determined. The values for A and B were corrected for the infusion rate, infusion time, and predose serum concentration. Values for distribution half-life ($t_{1/2\alpha}$), elimination half-life ($t_{1/2\beta}$), central compartment volume (V_c), total distribution volume ($V_{d\beta}$), and vancomycin clearance were calculated in the standard way, using the hybrid parameters (8). Volume of the central compartment, α, and terminal half-life for patient 6 were not included in the statistical analysis because the serum sampling scheme used failed to describe the distributive phase. The terminal half-life for patient 24 was not included in the statistical analysis because it was three standard deviations beyond the mean value for the rest of the patient population.

Pearson correlations were determined for all variable pairs, including weight, lean body weight (men, 50 + 2.3 kg [height in inches − 60]; women, 45 + 2.3 kg [height in inches − 60]), height, percentage of body surface area burn, serum creatinine, calculated creatinine clearance, measured creatinine clearance, A, B, α, β, $t_{1/2\alpha}$, $t_{1/2\beta}$, V_c, $V_{d\beta}$, and total body clearance. Calculated creatinine clearance was determined by the method of Cockroft and Gault (1). Daily dose, V_c, $V_{d\beta}$, and vancomycin clearance were analyzed as the absolute values and as values standardized to lean and whole body weight. By using Student's t test, patients with burn injuries were compared with patients without burn injury for differences in pharmacokinetic parameters.

Patient variables significantly ($P < 0.05$) related to terminal half-life ($t_{1/2\beta}$) and vancomycin clearance were added to the multiple regression model in a forward stepwise manner. These statistical models were designed to explain the maximal amount of variance (r^2) from the variable set used in the data analysis. Equations generated from multiple regression analysis were then used to predict values for β, terminal half-life, and vancomycin clearance.

RESULTS

The serum concentration time data fitted biexponentially resulted in a lower range of residual concentration (−0.32 to 0.41 μg/ml) than when fitted monoexponentially (−2.21 to 3.42 μg/ml). Thus, the disposition of vancomycin demonstrated a lengthy distribution phase, and the fit of the data was improved with use of the biexponential model.

A summary of the demographic, clinical laboratory, and pharmacokinetic parameters for the 28 patients is presented in Table 1. A wide range occurred among the patients' drug half-life, rate of elimination, distribution volume, and vancomycin clearance. In 23 patients with serum creatinine levels of less than 1.5 mg/dl, the range in the terminal half-life was from 2.7 to 13.3 h. In 14 of the 23 patients who had a creatinine clearance of 100 ml/min or more, the terminal half-life ranged from 2.9 to 8.5 h. The volume of distribution was similar for the two patient groups. Vancomycin clearance ranged from 41 to 170 ml/min for both patient groups. The interpatient variation in half-life, volume of distribution, and vancomycin clearance was thus similar in the patients with normal renal function, whether this was defined by serum creatinine or creatinine clearance.

The variable burn-nonburn or percentage of body surface area burn was not significantly related to any of the pharmacokinetic variables. Similarly, the pharmacokinetic parameters from burn patients and nonburn patients were not significantly different ($P < 0.05$). The disposition of vancomycin was thus similar in burn and nonburn patients.

Glomerular filtration rate as estimated by creatinine clearance was correlated with vancomycin clearance but only explained 20% (r^2) of the variance. The correlation between vancomycin clearance and creatinine clearance was 0.45 (Fig. 1). A weak correlation was observed between serum creatinine and terminal half-life ($r = 0.04$). Predicting vancomycin clearance with estimates only of renal function would thus be associated with error in this patient group.

The elimination rate was also correlated with the distribution volume of the drug ($r = 0.56$). In general, the elimination rate decreased when the volume increased. These relationships were similar when the volume was standardized to total body weight ($r = 0.59$) or lean body weight ($r = 0.61$). There was a positive correlation between $t_{1/2\beta}$ and distribution volume ($r = 0.68$). Thus, patient variables which altered the distribution volume of the drug also influenced the elimination rate. In addition to creatinine clearance and distribution volume, vancomycin clearance varied with estimates of renal function, age, and weight. Vancomycin clearance decreased with increasing age and weight and with decreasing renal function. Women had a lower mean vancomycin clearance than did men.

Patient variables significantly related to pharmacokinetic parameters of vancomycin were examined by using multiple regression analysis in an attempt to explain the variance (R^2) in these parameters. The largest amount of variance in beta was explained by the reciprocal of

TABLE 1. Demographic and pharmacokinetic data

Creatinine clearance (ml/min)	Patient no.	Age (yr)	Sex	Wt (kg)	Serum creatinine (mg/dl)	Creatinine clearance (ml/min)	Vancomycin clearance (ml/min)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	V_c (liters)	$V_{d\beta}$ (liters)
<10	10[a]	80	M	65.9	4.6	5.0	32.9	0.9	5.0	8.5	14.1
	21[a]	71	F	61.5	5.4	9.0	13.3	0.5	35.2	12.6	39.7
10–50	1	34	M	55.5	1.9	43.0[b]	95.3	0.9	8.5	12.2	69.7
	16	17	M	69.1	3.2	17.0	24.2	0.3	8.9	1.2	18.5
50–100	5	54	F	54.5	0.7	79.0[b]	53.6	1.0	4.1	10.5	19.0
	7	68	M	93.6	1.3	95.0	51.5	1.0	5.3	12.2	24.1
	8	39	M	83.6	1.2	98.0[b]	48.7	0.4	3.6	5.3	15.6
	9	29	M	63.6	1.2	82.0[b]	68.9	0.3	2.7	7.0	16.0
	11	29	M	65.0	1.1	91.0[b]	81.2	0.9	13.3	10.1	93.2
	12	30	M	59.5	2.3	81.0	42.6	0.3	5.8	3.9	21.1
	14	48	M	78.2	0.9	95.0	58.6	0.4	4.6	4.6	23.5
	15[a]	61	M	66.8	0.8	92.0[b]	51.2	0.3	7.0	2.2	30.9
	25[a]	63	M	78.3	1.4	56.0[b]	109.6	0.3	3.5	8.5	33.2
	26[a]	41	F	58.3	1.1	85.0	53.4	0.3	9.0	5.1	41.9
	28	21	M	66.4	1.0	83.0[b]	105.0	0.3	8.4	9.4	76.7
>100	2[a]	48	F	100.0	0.7	155.0[b]	41.7	1.2	7.1	10.3	25.3
	3	30	M	63.2	1.1	199.0	94.7	1.1	5.0	16.0	40.5
	4	39	F	69.1	1.5	126.0	50.6	0.4	4.3	9.2	19.2
	6	28	F	75.4	0.4	247.0	57.8	0.6	6.9	9.6	34.7
	13	18	M	73.6	1.1	168.0	183.9	0.4	7.5	11.3	110.7
	17	69	M	90.9	1.0	124.0	77.2	0.1	4.4	1.6	29.8
	18	38	F	107.3	0.8	239.0	69.7	0.3	3.6	6.2	21.6
	19[a]	18	M	65.0	0.6	193.0[b]	122.4	0.3	3.2	11.4	33.8
	20	64	M	65.9	1.1	101.0	81.2	0.3	6.2	8.9	43.8
	22	41	M	70.5	0.6	282.0	108.0	0.5	8.0	19.7	75.4
	23	27	F	71.1	0.7	213.0	71.1	0.4	2.9	7.4	17.7
	24	45	M	60.0	0.8	185.0	91.0	0.2	5.9	5.2	46.3
	27	57	M	60.0	0.8	161.0	104.0	0.7	7.2	14.4	64.7

[a] Patient without thermal injury.
[b] Calculated.

the volume of distribution ($V_{d\beta}$), creatinine clearance, age, and sex. This statistical model was predictive of beta at a level of $R = 0.70$. This coefficient was statistically significant ($P < 0.003$). The multiple regression model for terminal half-life included volume of distribution ($V_{d\beta}$), serum creatinine, age, and sex. The model represented a predictive capacity of $R = 0.74$, which was statistically significant. The statistical model for total body clearance included creatinine clearance, age, weight, and sex. The model was significant ($P < 0.03$) with a moderate association ($R = 0.61$). The unexplained variance in each of the pharmacokinetic parameters suggested that additional factors need to be identified to accurately predict the distribution and elimination characteristics of vancomycin.

The volume of the central component and the rate of drug distribution (α) varied widely among the study patients (Table 1). The volume of the central compartment was substantially lower than the peripheral volume. The average half-life for tissue distribution was 0.5 h. The correlation between volume of the central compartment and rate of distribution was 0.58. Patient variables which influence or determine the volume of the central compartment would appear to indirectly affect the rate of distribution to the tissues. The relatively small volume of the central compartment and prolonged rate of tissue distribution explains the high initial concentrations observed and the prolonged distribution phase of vancomycin.

DISCUSSION

Since 1956, only a few studies of the pharmacokinetics of vancomycin have been published (7, 9, 10). Moellering et al. recently published a nomogram for the determination of the vancomycin dose based on the relationship between vancomycin clearance and creatinine clearance (11, 12). From this investigation it would appear that factors other than renal function may have important influences on vancomycin elimination. This is supported by the results of our

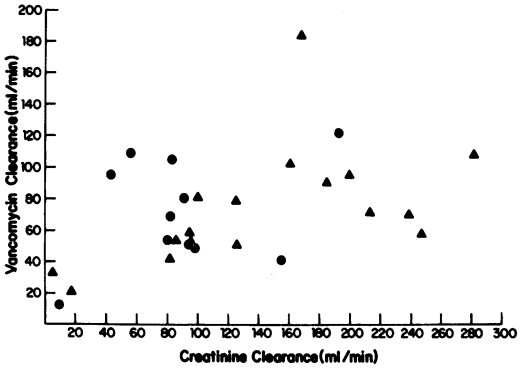

FIG. 1. Vancomycin clearance versus creatinine clearance. Symbols: ●, calculated; ▲, measured. $r = 0.45$; $y = 0.21x + 47.00$.

multivariant analysis in which creatinine clearance and the distribution volume were found to explain only 50% of the variance (r^2) in beta or vancomycin clearance. Age, weight, and sex were weakly associated with vancomycin clearance and explained additional variance.

The existence of a nonrenal mechanism for vancomycin elimination may explain the relatively high vancomycin clearances observed in patients with compromised renal function. This is supported by the positive intercept observed in the relationship between vancomycin clearance and creatinine clearance (Fig. 1).

Hepatic conjugation of vancomycin would seem the most likely nonrenal route of excretion. The molecule is of proper molecular weight (1,450) and has the necessary functional groups for conjugation (14). Geraci et al. reported measurable vancomycin concentrations in the bile and stool after intravenous administration, which also supports the concept of an extrarenal route of elimination (7).

The current vancomycin dosage regimen suggested by the manufacturer for adult patients with normal renal function is 500 mg every 6 h or 1 g every 12 h. It is recommended that the dose be infused over 20 to 30 min.

From the pharmacokinetic data obtained in this study, we suggest that initial dosage recommendations be based on body weight. In adult patients with normal renal function initial maintenance regimens of 6.5 to 8 mg of vancomycin per kg administered every 6 to 12 h will provide therapeutic serum concentrations (peak concentrations, 30 to 40 μg/ml; and trough concentrations, 5 to 10 μg/ml). Lean body weight should probably be used in very obese patients. Longer dosage intervals may be required in older patients or in patients with compromised renal function. To prevent potentially toxic vancomycin serum concentrations after intravenous infusion, a 1-h infusion time is suggested.

Measuring serum concentrations and adjusting dosage regimens are essential to optimize vancomycin therapy. Adjustments in dose and dosage interval should be guided by trough and peak serum vancomycin concentrations obtained 24 h after starting therapy and periodically during the treatment course. The prolonged distribution phase of vancomycin adds a degree of complexity and potential source of error when dosages are adjusted. The time at which peak serum levels are obtained must be carefully controlled to avoid error in adjusting the patient's dosage regimen.

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