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Pharmacokinetics of Vancomycin in Patients with Various Degrees of Renal Function

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The pharmacokinetics of vancomycin were characterized in 56 patients with different degrees of renal function after an intravenous dose of 18.4 ± 4.7 mg kg^{-1} (mean ± standard deviation). Seven subjects had a creatinine clearance (CL_{CR}) of >60 ml min^{-1} (group I), 13 had a CL_{CR} of 10 to 60 ml min^{-1} (group II), and 36 had a CL_{CR} of <10 ml min^{-1} (group III). Serial serum samples (range, 3 to 8) were collected during the 168 h after drug administration. The serum concentration-time profile in all patients demonstrated monoexponential decay. The mean half-lives were 9.1, 32.3, and 146.7 h in groups I, II, and III, respectively. A significant decline in serum clearance (CL_S) was also noted (62.7 to 28.3 to 4.87 ml min^{-1} in groups I, II, and III, respectively). The steady-state volume of distribution varied from 0.72 to 0.90 liter kg^{-1}. There was no significant relationship between the steady-state volume of distribution and CL_{CR}. The observed relationship between CL_S and CL_{CR} (CL_S = 3.66 + 0.689 CL_{CR}; r = 0.8807) can be utilized to devise dosage schedules for patients with any degree of renal impairment. This relationship was utilized to develop a nomogram for initial and maintenance dosing of vancomycin.

The pharmacokinetics of vancomycin have been extensively evaluated in patients with end-stage renal disease (2, 3, 5, 7; F. Y. Lam, A. Lidner, J. Plorde, A. Blair, and R. E. Cutler, Abstr. Am. Soc. Nephrol., 45A, 1980). However, only limited information is available regarding the pharmacokinetics of vancomycin in patients with mild to moderate renal insufficiency (6, 8, 10). This study was designed to assess the relationship between renal function and vancomycin pharmacokinetics and develop a nomogram for vancomycin dosage in patients with various degrees of renal function.

MATERIALS AND METHODS

Patients. Fifty-six patients (27 males, 29 females) ranging in age from 17 to 85 years were studied. None of the patients had known hypersensitivity to vancomycin, and all patients had been started on vancomycin by their attending physicians for treatment of serious systemic infections. Patients were retrospectively divided into three groups on the basis of their calculated creatinine clearances (CL_{CR}s), which were determined by the method of Cockroft and Gault (1). Groups I, II, and III had CL_{CR}s of >60, 10 to 60, and <10 ml min^{-1}, respectively. Of the 36 group III patients, 34 received chronic hemodialysis therapy.

The initial doses of vancomycin prescribed by the attending physicians ranged from 8.8 to 30.0 mg kg of body weight^{-1} (18.4 ± 4.7 mg kg^{-1} [mean ± strandard deviation]) and were infused over a minimum period of 1 h. The kinetic study described below was carried out after the initial dose of vancomycin in ca. 70% of the patients, providing data utilized to assess further dosing requirements. Kinetic studies were done twice in 10 patients, three times in 3 patients, and four times in 1 patient.

Serial blood samples (range, 3 to 8) were obtained from a forearm vein in the arm opposite to that used for drug administration during the 24 h (group I), 96 h (group II), and 168 h (group III) after infusion. The sampling times were 3, 6, 9, 12, 24, 48, 72, 96, 120, 144, and 168 h after infusion. Collection times for individuals could vary from the described pattern. A preinfusion sample was obtained from patients who had received a prior dose of vancomycin. The initial postinfusion blood sample was drawn at least 3 h after the end of the intravenous infusion. Blood samples were allowed to clot; serum was separated by centrifugation and, if not immediately assayed for vancomycin, stored at −20°C. Previous studies have shown no loss of vancomycin activity in samples stored under these conditions for more than 1 year (6).

Vancomycin concentrations in serum were determined in duplicate by radioimmunoassay (American Diagnostics, Newport Beach, Calif.). The minimum quantifiable vancomycin concentration was 1 mg $liter^{-1}$. The interassay coefficients of variation for this procedure were 9, 6.5, and 9.8% at 4, 17, and 32 mg $liter^{-1}$, respectively.

The postinfusion log vancomycin concentration in serum-time profiles were analyzed by the linear least-squares regression technique to estimate the elimination rate constant (k) and the serum concentration (C_{max}) at the end of the infusion period. The elimination half-life ($t_{1/2\beta}$), volume of distribution (V), and total body clearance (CL_S) were calculated as $t_{1/2\beta} = 0.693/k$, $V = k_0 (1 - e^{-kt})/k (C_{max} - C_0 e^{-kt})$, and $CL_S = k \times V$, respectively, where C_0 is the preinfusion concentration, k_0 is the infusion rate (milligrams per hour), and t is the infusion duration (hours).

The $t_{1/2\beta}$, V, k, and CL_S of the three groups were compared by analysis of variance. Differences between groups were subsequently analyzed by the unpaired Student t test. The relationship between CL_{CR} and $t_{1/2\beta}$, V, k, and CL_S were assessed by orthogonal regression analysis. The 0.05 level was chosen as the level of statistical significance.

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TABLE 1. Demographic and pharmacokinetic data for group I patients

Patient no.	Age (yr)	Sex	Wt (kg)	CL_{CR} (ml min^{-1})	SC[a]	CL_S (ml min^{-1})	$t_{1/2\beta}$ (h)	V (liters kg^{-1})	C_{max}[b]	Dose (mg kg^{-1})
1	23	M	65.9	144	3	74.7	5.2	0.51	1.70	15.2
2	48	M	79.9	104	3	99.0	7.7	0.83	1.79	18.8
3a	57	F	60.9	92	3	57.4	6.8	0.56	0.85	16.4
3b	57	F	60.9	92	4	61.8	15.2	1.33	1.30	19.7
4a	30	F	69.4	88	3	44.4	8.3	0.46	1.26	11.5
4b	30	F	69.1	82	3	80.8	7.3	0.74	1.18	14.5
4c	30	F	70.6	76	3	59.7	10.6	0.77	2.17	14.2
5	40	M	66.0	83	4	104.0	10.3	1.40	0.66	15.2
6a	68	M	66.3	76	3	52.0	7.1	0.48	1.54	22.6
6b	68	M	66.3	64	4	27.4	11.4	0.43	2.82	15.1
7	61	M	70.4	63	4	28.7	10.6	0.37	1.16	14.2
Mean ± SD	46.5 ± 16.6		67.8 ± 5.2	87.6 ± 22.3	3.4 ± 0.5	62.7 ± 25.3	9.1 ± 2.8	0.72 ± 0.35	1.49 ± 0.61	16.1 ± 3.1

[a] Number of determinations of drug concentration in serum.
[b] C_{max} is given in milligrams per liter per milligrams of drug administered per kilogram of body weight.

RESULTS

The demographic characteristics, CL_{CR}s, and pharmacokinetic parameters of the three patient groups are shown in Tables 1, 2, and 3, respectively. The profile of vancomycin concentration in serum over time in all patients demonstrated monoexponential decay (Fig. 1). The mean correlation coefficient of the log serum concentration-time linear regression analyses was 0.984 ± 0.018 (range, 0.940 to 1.000). The effect of renal functional impairment on the rate of vancomycin elimination from the body is indicated by the significant changes in the values of k, $t_{1/2\beta}$, and CL_S. The mean $t_{1/2\beta}$ of vancomycin increased from 9.1 to 32.3 to 146.7 h in groups I, II, and III, respectively, whereas the mean CL_S decreased from 62.7 to 28.3 to 4.87 ml min^{-1} in groups I, II, and III, respectively. No significant differences in V were observed among the three groups. On the basis of the observed relationship between the pharmacokinetic parameters and CL_{CR}, orthogonal regression analysis was used to obtain equations to estimate expected values of these parameters given values of CL_{CR}. The parameters associated with vancomycin elimination, k and CL_S, correlated well with CL_{CR} (Fig. 2 and 3). However, no significant relationship was observed between V and CL_{CR}.

DISCUSSION

Although vancomycin has been clinically utilized for over 20 years, its pharmacokinetic properties have not been rigorously evaluated. This reflects the fact that accurate and specific assay methodologies and sophisticated pharmacokinetic methods to assess the serum concentration-time data have only recently become available. Additionally, the renewed clinical interest in vancomycin has necessitated more precise guidelines for the use of vancomycin in patients with impaired renal function.

The $t_{1/2\beta}$, CL_S, and V of vancomycin in patients with CL_{CR}s of <10 ml min^{-1} are similar to those in previous

TABLE 2. Demographic and pharmacokinetic data for group II patients

Patient no.	Age (yr)	Sex	Wt (kg)	CL_{CR} (ml min^{-1})	SC[a]	CL_S (ml min^{-1})	$t_{1/2\beta}$ (h)	V (liters kg^{-1})	C_{max}[b]	Dose (mg kg^{-1})
8	75	M	90.7	60	5	21.9	20.6	0.87	1.10	22.1
9	85	M	74.5	57	3	48.9	12.9	0.74	1.29	24.2
10a	82	M	75.0	57	4	36.4	21.0	0.89	1.12	17.3
10b	82	M	74.9	57	4	26.1	23.5	0.71	1.39	20.0
11	57	F	69.1	53	3	23.5	16.7	0.49	1.93	21.7
12	17	F	57.0	51	6	14.5	30.1	0.66	1.52	21.0
13	69	F	66.5	50	3	18.0	40.7	0.95	0.76	12.0
14	83	M	54.5	40	3	49.0	10.1	0.79	1.18	23.9
15a	72	M	69.1	36	4	63.2	10.6	0.84	1.18	14.5
15b	72	M	69.6	31	4	41.9	35.8	1.87	0.53	20.1
15c	72	M	69.1	31	4	43.2	20.5	1.11	0.87	20.3
16	53	F	66.6	31	3	22.6	21.2	0.62	1.48	22.5
17a	74	M	75.5	22	5	17.6	47.6	0.96	0.67	18.5
17b	74	M	70.0	17	4	16.0	53.2	1.06	0.94	20.0
18	47	F	60.9	17	4	8.8	64.2	0.81	1.25	14.8
19	55	F	60.5	15	4	6.3	75.1	0.68	1.47	16.5
20	66	M	81.8	10	3	23.3	45.4	1.12	0.87	24.4
Mean ± SD	66.8 ± 17.0		69.7 ± 8.9	37.4 ± 17.1	3.9 ± 0.9	28.3 ± 16.0	32.3 ± 19.3	0.89 ± 0.31	1.15 ± 0.36	19.6 ± 3.6

[a] Number of determinations of drug concentration in serum.
[b] C_{max} is given in milligrams per liter per milligram of drug administered per kilogram of body weight.

reports (2, 6; Lam et al., Abstr. Am. Soc. Nephrol.). The CL_S and $t_{1/2\beta}$ of the group I and II subjects are also similar to those reported by Nielsen et al. (8) and Rotschafer et al. (10), respectively. No comparison was made with the findings of Moellering et al. (6), since they did not report pharmacokinetic parameters for individual patients. Although vancomycin clearance is highly correlated with CL_{CR} (6, 8), Rothschafer et al. (10), in an evaluation of 28 patients, reported that CL_{CR} was poorly correlated with vancomycin clearance ($r = 0.45$). They suggested that prediction of vancomycin clearance from estimates of renal function, i.e., CL_{CR}, would be associated with significant error. The results of this study indicate that, although there is marked variability in the kinetic parameters of vancomycin within a defined range of renal function, the relationship between vancomycin clearance and CL_{CR} is highly significant.

Declining renal function was associated with a marked reduction in the elimination of vancomycin, and dosage adjustment will therefore be required. Marked variability exists in the dosage recommendations which have been proposed for vancomycin. Doses have ranged form 13 to 32 mg kg^{-1} day^{-1} (10) in subjects with normal renal function and from 15 mg kg^{-1} after each hemodialysis (11) to 500 mg every 8 days (2) in patients with end-stage renal disease. The variability in these recommendations may be related to the relatively small number of patients evaluated by each inves-

TABLE 3. Demographic and pharmacokinetic data for group III patients

Patient no.	Age (yr)	Sex	Wt (kg)	SC[a]	CL_S (ml min^{-1})	$t_{1/2\beta}$ (h)	V (liters kg^{-1})	C_{max}[b]	Dose (mg kg^{-1})
21a	65	M	68.9	3	5.17	124.4	0.81	0.82	21.8
21b	65	M	68.9	5	6.01	100.5	0.76	0.88	21.8
22	67	F	63.5	5	6.31	84.1	0.72	1.38	15.7
23	56	F	70.8	4	3.32	180.8	0.74	1.36	24.0
24a	77	M	51.5	5	4.77	139.7	1.12	0.89	19.4
24b	77	M	50.9	5	4.51	166.2	1.28	0.79	27.5
25	70	F	43.3	4	2.63	137.2	0.72	1.39	23.0
26	65	F	55.4	3	1.05	406.4	0.67	1.50	25.3
27	52	M	69.6	6	3.55	179.5	0.79	1.27	17.2
28	77	F	40.6	3	2.94	204.6	1.22	0.78	24.6
29a	70	M	61.5	4	3.65	193.0	0.92	1.00	16.3
29b	70	M	63.7	6	5.26	163.2	1.17	0.85	9.4
29c	70	M	59.0	5	4.88	106.9	0.77	1.18	17.0
29d	70	M	64.0	7	2.11	255.7	0.74	1.38	10.0
30	52	F	55.6	3	2.77	191.3	0.84	1.21	18.0
31a	60	F	46.2	8	3.20	132.2	0.81	1.28	21.6
31b	60	F	45.5	4	2.83	91.2	0.49	0.95	13.0
32	68	M	63.0	3	4.56	166.2	1.04	0.96	22.2
33	68	F	56.8	3	3.80	161.2	0.92	1.06	8.8
34	28	M	41.8	4	3.03	106.6	0.67	1.49	23.9
35	69	M	85.0	4	5.09	134.9	0.70	1.42	11.8
36	72	F	55.5	3	4.61	143.9	1.04	0.96	25.2
37	60	M	68.4	3	5.58	141.5	1.05	1.00	14.6
38	76	F	74.6	5	4.27	260.7	1.29	0.78	13.4
39	69	F	62.3	5	2.72	227.4	0.86	1.16	24.1
40	68	M	49.1	3	4.21	161.5	1.20	0.83	20.4
41	55	F	44.0	3	2.68	165.8	0.88	1.14	22.7
42	49	M	49.1	5	2.81	169.0	0.84	1.19	25.5
43	70	F	82.5	4	6.66	150.7	1.09	0.91	12.0
44	64	F	58.0	4	7.12	74.3	0.79	1.26	14.7
45	68	F	57.5	4	3.39	157.5	0.80	1.26	12.0
46a	52	F	45.8	4	10.48	70.1	1.39	0.72	13.1
46b	52	F	49.5	4	9.46	44.1	0.73	1.37	30.0
47	40	F	56.0	3	7.00	67.9	0.73	1.35	17.9
48	62	M	85.2	3	9.96	70.0	0.71	1.41	16.4
49a	68	M	60.4	5	4.56	133.7	0.87	1.14	19.0
49b	68	M	60.0	3	2.76	250.0	0.98	1.00	16.7
50	71	M	86.4	4	15.67	40.1	0.63	2.16	11.6
51a	54	F	50.8	4	4.65	126.9	1.01	0.99	19.7
51b	54	F	54.8	6	5.97	67.9	0.64	1.55	18.2
51c	54	F	50.1	5	4.38	98.1	0.74	1.34	20.0
52	36	M	82.9	4	8.45	138.5	1.22	0.82	12.1
53	53	M	46.0	5	3.83	119.2	0.86	1.16	17.4
54a	77	M	50.9	5	4.51	166.2	1.28	0.78	27.5
54b	77	M	51.5	5	4.77	139.7	1.12	0.89	19.4
55	68	F	64.5	7	3.94	200.3	1.06	0.97	15.0
56	78	F	74.5	4	7.68	83.3	0.75	1.56	20.1
Mean ± SD	62.6 ± 11.8		59.6 ± 12.2	4.3 ± 1.2	4.87 ± 2.60	146.7 ± 65.5	0.90 ± 0.21	1.16 ± 0.31	18.5 ± 5.3

[a] Number of determinations of drug concentration in serum.
[b] $C_{máx}$ is given in milligrams per liter per milligram of drug administered per kilogram of body weight.

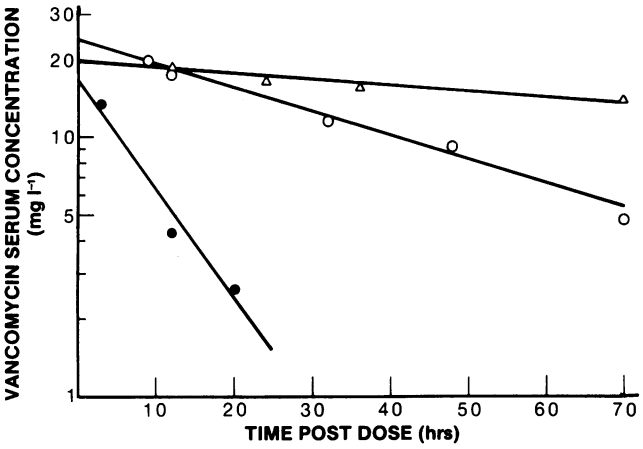

FIG. 1. Profiles of vancomycin concentration in serum over time for patients 4C (●), 12 (○), and 27 (△). The profiles are representative of the subjects in groups I, II, and III, respectively.

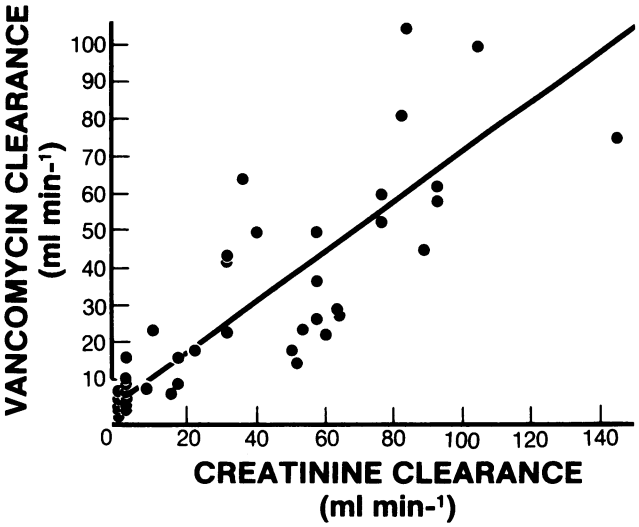

FIG. 3. Vancomycin clearance versus CL_{CR} (r = 0.8807; y = 0.689 x + 3.66; n = 75).

tigator, variability in the sampling schemes, or differences in the techniques utilized to determine and evaluate the pharmacokinetics of vancomycin. Vancomycin pharmacokinetics have been described in terms of one-, two-, and three-compartment models (2, 6, 6, 10; R. D. Blevins, C. E. Halstenson, N. G. Salem, and G. R. Matzke, submitted for publication; Lam et al., Abstr. Am. Soc. Nephrol.). The number of samples required to characterize the distributional phase of the disappearance of vancomycin from serum is, however, clinically prohibitive. Therefore, a one-compartment model analysis was selected, and sampling during the distributional phase was avoided.

There are several approaches to modified drug dosage schedules in patients with impaired renal function. The prolongation of the maintenance dosing interval (τ) may be preferred because of its simplicity and combined benefits of less-frequent drug administration with the assurance of obtaining high peak drug concentrations. Since the V of vancomycin was not related to alterations in CL_{CR}, a loading dose of 25 mg kg^{-1} followed by a maintenance dose of 19 mg kg^{-1} can be utilized in all patients to attain postdistribution-phase peak and trough concentrations of 30 and 7.5 mg $liters^{-1}$, respectively. Vancomycin concentrations in serum drawn immediately after the end of an intravenous infusion may be markedly higher (≥25 to 30 mg $liters^{-1}$) than the nomogram desired peak, owing to the distributional characteristics of vancomycin (2, 6, 6; Blevins et al., submitted for publication; Lam et al., Abstr. Am. Soc. Nephrol.). Transient peak concentrations in the range of 50 to 60 mg $liters^{-1}$ have not been associated with ototoxicity or nephrotoxicity (4, 6). To prevent the histamine-like reaction and hypotension which have been associated with rapid intravenous infusions (4), the administration rate should be no greater than 15 mg min^{-1}.

The degree of alteration in the dosing interval required to maintain peak and trough concentrations of 30 and 7.5 mg $liters^{-1}$, respectively, may then be calculated by utilizing the relationship between CL_S and CL_{CR}. From this relationship,

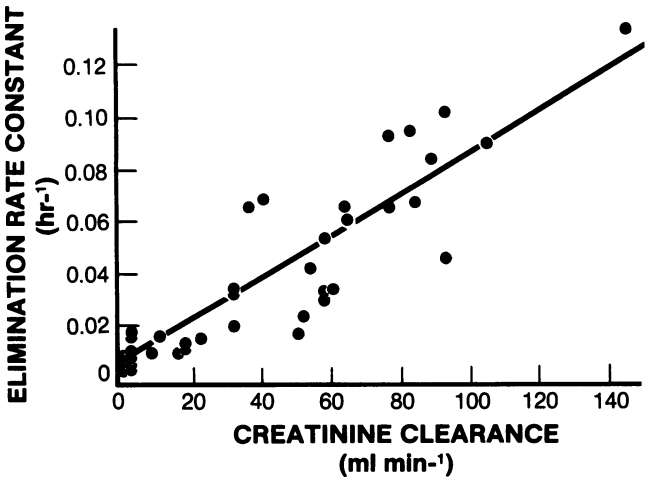

FIG. 2. Vancomycin elimination rate constant versus CL_{CR} (r = 0.9324; y = 0.00083 x + 0.0044; n = 75).

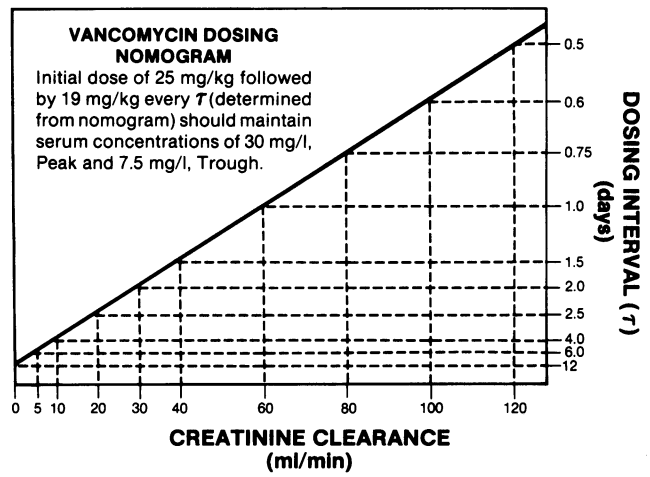

FIG. 4. Dosage nomogram for vancomycin in patients with various degrees of renal function. The nomogram is not valid for peritoneal dialysis patients.

a CL_S of 86 ml min^{-1} can be calculated for a "normal" CL_{CR} of 120 ml min^{-1}. The maintenance dosing interval can then be estimated from the following equation or interpolated from the nomogram (Fig. 4) which was derived from the equation: $\tau_{failure} = \tau_{normal}[86 \text{ ml min}^{-1}/(0.689\ CL_{CR} + 3.66 \text{ ml min}^{-1})]$.

To use the nomogram, one must ascertain the CL_{CR} of the patient. If CL_{CR} cannot be measured directly, it should be estimated by using the patient age, body weight, and serum creatinine (1). The interval (τ) at which to administer the maintenance dose of 19 mg of vancomycin kg^{-1} is then determined by passing a line perpendicular to the CL_{CR} of the patient to the point at which it intercepts the sloping line of the nomogram. At the point of intercept, a horizontal line is drawn, intersecting the appropriate dosage interval on the right side of the nomogram. The dosing interval is given in fractions of days.

The nomogram may be utilized to aid in the initiation of vancomycin therapy for functionally anephric patients on hemodialysis, but not for patients treated with intermittent or continuous ambulatory peritoneal dialysis. Although intermittent peritoneal dialysis (9) and continuous ambulatory peritoneal dialysis therapy (Blevins et al., submitted for publication) may markedly alter the vancomycin dosing requirements of a patient, hemodialysis therapy has not been reported to require dosage adjustment (4, 5). Adjustments in subsequent maintenance doses and the dosing interval should be guided by serial determinations of vancomycin concentrations in serum when they are available.

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