

## Vancomycin Pharmacokinetics in Normal and Morbidly Obese Subjects

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In an uncontrolled study, vancomycin pharmacokinetics were determined in four normal (total body weight [TBW], 65.9 to 89.1 kg) and six morbidly obese (TBW, 111.4 to 226.4 kg) subjects. The morbidly obese subjects were investigated 3 to 4 h after gastric bypass surgery. Mean terminal half-lives, volumes of distribution, and total body clearances for the normal controls and the morbidly obese subjects were 4.8 h, 0.39 liter/kg, and 1.085 ml/min per kg versus 3.2 h, 0.26 liter/kg TBW, and 1.112 ml/min per kg TBW. The mean terminal half-life and volume of distribution values were significantly different between the two groups. Strong correlations were found between TBW and both volume of distribution (correlation coefficient, 0.943) and total body clearance (correlation coefficient, 0.981). These results implied that TBW should be used to calculate vancomycin doses for morbidly obese patients. This was supported by the finding that there was no significant difference in the daily dose (in milligrams per kilogram per day) required to produce an average steady-state concentration of 15  $\mu\text{g/ml}$  in the two groups ( $23.4 \pm 1.5$  mg/kg per day for normal weight subjects and  $24.0 \pm 3.4$  mg/kg per day TBW for the postsurgery morbidly obese subjects). Therefore, the morbidly obese required higher total doses (in milligrams per day) than did normal weight subjects to achieve the same mean steady-state concentrations. In addition, normal weight and morbidly obese subjects had similar volumes of the central compartment (7.7 and 6.4 liters, respectively). To avoid high transient peak concentrations which could occur when obese patients are given larger total doses (in milligrams per day), maintenance doses may be given at more frequent intervals. The shorter mean terminal half-lives observed in morbidly obese patients allows more frequent dosing without excessive accumulation.

Vancomycin is a narrow-spectrum, bactericidal antibiotic primarily used for the treatment of penicillinase-producing staphylococci (12). Ototoxicity and nephrotoxicity remain the most important side effects associated with vancomycin therapy. Ototoxicity has occurred at serum concentrations between 80 and 100  $\mu\text{g/ml}$  (11) but rarely occurs when serum concentrations are below 30  $\mu\text{g/ml}$  (17). The minimum inhibitory concentration and minimum bactericidal concentration ranges for *Staphylococcus aureus* are 1.56 to 3.12  $\mu\text{g/ml}$  and 1.56 to 6.25  $\mu\text{g/ml}$ , respectively (10). Moellering et al. (15) have developed a vancomycin dosage nomogram designed to give an average steady-state serum level of 15  $\mu\text{g/ml}$ , based on the patient's creatinine clearance ( $Cl_{cr}$ ) and body weight.

Severely obese individuals have significant changes in physiology (1, 16) which may alter the disposition of a drug (2, 4, 5, 9, 18) and the serum concentrations that are attained. It has

been previously shown with the aminoglycoside antibiotics that a fraction of the fat weight of an obese patient needs to be added to the ideal body weight (IBW) to normalize the volume of distribution ( $V_{area}$ ; 2, 5, 18). The effect of obesity on the disposition of vancomycin has not been elucidated. The purpose of this investigation was to determine the influence of morbid obesity on the pharmacokinetics of vancomycin.

### MATERIALS AND METHODS

Four normal (<15% overweight; 65.9 to 89.1 kg) healthy adult males and four female and two male morbidly obese subjects (>90% overweight; 111.4 to 226.4 kg total body weight [TBW]) were studied (Table 1). The study was approved by the human studies committee, and all patients gave informed consent before participating. Morbidly obese subjects (who were overweight for nutritional reasons) were all post-operative gastric bypass patients studied 3 to 4 h after surgery, had no clinical signs or symptoms of infection, were cardiovascularly stable, had no substantial

TABLE 1. Subject data

Subject	Sex	Age (yr)	TBW (kg)	IBW (kg)	% OW <sup>a</sup>	Ht (cm)	SA (m <sup>2</sup> ) <sup>b</sup>	Cl <sub>cr</sub> (ml/min)
Obese								
1	F	37	168.2	56.5	197.7	165.1	2.57	208
2	M	31	206.8	77.6	166.5	182.9	3.02	247
3	M	29	226.4	77.6	191.8	182.9	3.14	175
4	F	33	111.4	49.6	124.6	157.5	2.09	118
5	F	28	133.6	68.0	96.5	177.8	2.46	158
6	F	27	147.7	51.9	184.6	160.0	2.38	175
Normal								
1	M	28	70.5	70.7		175.3	1.86	120
2	M	25	65.9	70.7		175.3	1.80	113
3	M	30	72.7	70.7	3.0	175.3	1.88	145
4	M	25	89.1	78.8	13.0	184.2	2.13	175

<sup>a</sup> Percentage overweight.

<sup>b</sup> Surface area calculated by the method of DuBois and DuBois (8).

blood loss during the bypass procedure, had not received vancomycin during the previous 30 days, and had normal renal function ( $Cl_{cr} > 90$  ml/min per 1.73 m<sup>2</sup>). Percentage overweight was calculated by the equation  $[(TBW - IBW)/IBW] \times 100$ . IBW was estimated by the method of Devine (6). Body surface area was determined by the equation derived by DuBois and DuBois (8); this method has been shown to produce accurate estimates for obese subjects (19). Actual body weight was used in all relationships for the control population.

Vancomycin (Vancocin, Eli Lilly & Co., 1 gm) was administered intravenously for 40 min into a peripheral line via a syringe infusion pump. Blood was collected at zero time, infusion midpoint, and the end of infusion, as well as 5, 10, 20, 30, 45 min, and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 h postinfusion from an arterial line or heparin lock. The serum was separated and frozen at -5°C until assayed. A 24-h  $Cl_{cr}$  determination was initiated at the time of vancomycin administration, with a serum creatinine concentration obtained at the midpoint of the urine collection.

**Assay.** A commercially available radioimmunoassay (Monitor Science) was used to determine serum concentrations of vancomycin. The lower limit of sensitivity was 0.5 µg/ml. The within-run coefficient of variation was determined on three different occasions with five observations of 4 and 32 µg/ml. The coefficient of variation values were 7.7, 4.3, and 3.0% for the lower concentration and 2.8, 2.7, and 4.1% for the higher concentration. A complete set of standards was used with each run. Serum and urine creatinine concentrations were performed by the clinical chemistry laboratory with the modified Jaffé reaction-kinetic method on a centrifugal analyzer.

**Pharmacokinetics.** The vancomycin serum concentration-time profile declined in a triexponential manner for both the normal and morbidly obese subjects. Individual postinfusion data sets were computer-fitted with the SAAM 23 nonlinear least-squares regression program (3) to the following equation:  $C = P'e^{-\pi t} + A'e^{-\alpha t} + B'e^{-\beta t}$ , where  $C$  is concentration and  $t$  is time. A weighting factor of  $1/(C_{observed})^2$  was used. The program calculated the postinfusion intercept constants  $P'$ ,  $A'$ , and  $B'$ , as well as their respective slopes  $\pi$ ,  $\alpha$ , and  $\beta$ , with  $\beta$  representing the terminal disposition constant. Corrected intravenous bolus

zero-time intercepts  $P$ ,  $A$ , and  $B$  were calculated from the postinfusion intercept constants by the method of Loo and Riegelman (14). The area under the serum concentration-time curve (AUC) was calculated by the trapezoidal rule plus the quotient of the last serum concentration and  $\beta$ . Total body clearance ( $Cl_T$ ) was derived by dividing the vancomycin dose by AUC. The volumes of distribution,  $V_{area}$  and  $V_{ss}$ , were calculated with the following equations:  $V_{area} = \text{dose}/(\beta \times \text{AUC})$  and  $V_{ss} = [\text{dose}(\text{AUMC})/\text{AUC}^2] - [t'(\text{dose})/(2\text{AUC})]$ , where  $t'$  is the infusion time and AUMC is the area under the moments curve ( $tC$  versus  $t$ ) measured with the trapezoidal rule. The volume of the central compartment,  $V_c$ , was calculated by dividing the dose by the sum of the corrected zero-time intercepts.

## RESULTS

The pharmacokinetic constants and selected vancomycin serum concentrations of individual patients are shown in Tables 2 and 3. Mean  $\beta$  values ( $\pm$  standard deviation) of  $0.220 \pm 0.040$  h<sup>-1</sup> and  $0.146 \pm 0.012$  h<sup>-1</sup> were observed for the morbidly obese and normal subjects, respectively; these values were significantly different (Student's  $t$  test,  $P < 0.02$ ). The half-lives  $t_{1/2\beta}$  calculated from these mean values were 3.2 and 4.8 h. A plot of  $\beta$  versus  $Cl_{cr}$  (in milliliters per minute) showed a correlation coefficient ( $r$ ) of 0.721, which is statistically significant ( $P < 0.05$ ).

Morbidly obese and normal subjects had average  $V_{ss}$  values of  $0.26 \pm 0.03$  liter/kg TBW or  $0.68 \pm 0.07$  liter/kg IBW and  $0.39 \pm 0.06$  liter/kg, respectively. Both morbidly obese  $V_{ss}$  values are significantly different from the  $V_{ss}$  value found in normal subjects. The mean  $V_{ss}$  values were significantly larger in morbidly obese subjects (43.0 liters) when compared with those of normal subjects (28.9 liters). A strong correlation ( $r = 0.943$ ,  $P < 0.005$ ) was observed between  $V_{ss}$  and TBW (Fig. 1). There is no significant difference between the  $V_c$  terms in

TABLE 2. Pharmacokinetic parameters<sup>a</sup>

Subject	P (μg/ml)	A (μg/ml)	B (μg/ml)	π (h <sup>-1</sup> )	α (h <sup>-1</sup> )	β (h <sup>-1</sup> )	V <sub>c</sub> (liters)	V <sub>area</sub> (liters)	V <sub>ss</sub> (liters)	Cl <sub>T</sub> (ml/min)	Cl <sub>T</sub> (ml/min per kg TBW)	Cl <sub>T</sub> (ml/min per kg IBW)
<b>Obese</b>												
1	46.57	17.64	14.86	5.03	0.950	0.230	12.6	47.5	38.8	181.9	1.081	3.220
2	152.30	16.77	10.29	20.00	0.926	0.240	5.6	63.6	53.8	254.2	1.229	3.276
3	140.80	10.27	10.41	11.84	0.835	0.252	6.2	63.4	57.3	266.3	1.176	3.432
4	149.50	24.03	22.71	4.48	1.240	0.148	5.1	37.0	34.9	91.3	0.820	1.841
5	255.20	23.65	10.18	15.31	0.675	0.202	3.5	50.3	37.4	169.2	1.266	2.488
6	125.70	37.55	22.05	17.02	3.010	0.248	5.4	39.2	35.9	162.1	1.097	3.123
Mean	145.01	21.65	15.08	12.28	1.273	0.220	6.40	50.1	43.0	187.50	1.112	2.897
SD	66.78	9.29	5.93	6.40	0.871	0.040	3.17	11.4	9.9	64.69	0.160	0.611
<b>Normal</b>												
1	58.19	14.34	22.61	3.47	0.557	0.147	10.5	34.1	29.1	83.6	1.186	
2	151.90	14.79	26.34	11.79	0.711	0.128	5.2	32.8	31.1	70.1	1.064	
3	68.64	37.96	25.17	5.27	0.766	0.153	7.6	29.0	23.8	74.0	1.018	
4	81.10	30.96	20.75	12.45	0.911	0.154	7.5	37.2	31.6	95.4	1.071	
Mean	89.96	24.51	23.72	8.25	0.736	0.146	7.70	33.2	28.9	80.78	1.085	
SD	42.34	11.84	2.52	4.54	0.146	0.012	2.17	3.4	3.6	11.28	0.071	

<sup>a</sup> Symbols: P, corrected, extrapolated zero-time intercept of the π slope; A, corrected, extrapolated zero-time intercept of the α slope; B, corrected, extrapolated zero-time intercept of the β slope; π, rate constant of the π slope; α, rate constant of the α slope; β, rate constant of the β slope. Corrected intravenous bolus zero-time intercepts P, A, and B were calculated from the postinfusion intercept constants by the method of Loo and Riegelman (14).

morbidly obese subjects (6.4 ± 3.2 liters) and normal subjects (7.7 ± 2.2 liters).

Mean Cl<sub>T</sub> values for the morbidly obese were 1.112 ± 0.160 ml/min per kg TBW or 2.897 ± 0.611 ml/min per kg IBW, whereas normal patients had a Cl<sub>T</sub> of 1.085 ± 0.071 ml/min per kg. No significant difference existed between Cl<sub>T</sub> in normal subjects and that of morbidly obese

subjects adjusted for TBW; there was a significant difference between the Cl<sub>T</sub> calculated in normal subjects and that found in morbidly obese patients adjusted for IBW. Morbidly obese subjects had a mean Cl<sub>T</sub> (187.50 ml/min) that was significantly larger than that found in normal subjects (80.78 ml/min). Figure 2 shows the strong correlation which exists between Cl<sub>T</sub>

TABLE 3. Selected postinfusion vancomycin serum concentrations

Subject	Serum concentration after:											
	0.08 h	0.17 h	0.5 h	0.75 h	1.0 h	1.5 h	2.0 h	4.0 h	6.0 h	10.0 h	16.0 h	24.0 h
<b>Obese</b>												
1	36.5	33.0	22.0	18.0	16.5	12.5	11.3	6.0	3.7	1.4		0
2	23.0	20.0	17.0		12.5	9.2	7.8	4.4	2.2	0.8	0	0
3	23.0	19.0	14.0	11.2		8.8	7.4	3.5	2.0	0.9		0
4	42.0		28.5	26.0	23.0	20.0	16.4	11.4	10.0	4.7	1.9	0.6
5	38.0	34.0	26.0	19.5	17.0	14.3	11.0	5.5	3.3	1.3	0.5	0
6	39.0	32.0	23.0	20.0	16.5	14.0	12.0	8.9	4.6	1.7	0.5	0
Mean	33.6	27.6	21.8	18.9	17.1	13.1	11.0	6.6	4.3	1.8	0.7	
SD	8.4	7.4	5.4	5.3	3.8	4.1	3.3	3.0	3.0	1.5	0.8	
<b>Normal</b>												
1	52.0	45.0		29.0		23.0	20.0	13.5	9.6	4.8	2.0	0.6
2	46.0	38.0	32.0	30.0		26.0	22.5	15.0	12.5	6.8	3.5	1.3
3	64.0	60.0	45.0		34.0	29.0	25.0	14.5	11.3	5.2	2.0	0.7
4	48.0	39.0		32.0	27.0	23.0	18.0	10.3	8.2	4.0	1.7	0.5
Mean	52.5	45.5	38.5	30.3	30.5	25.3	21.4	13.3	10.4	5.2	2.3	0.8
SD	8.1	10.1	9.2	1.5	4.9	2.9	3.0	2.1	1.9	1.2	0.8	0.4

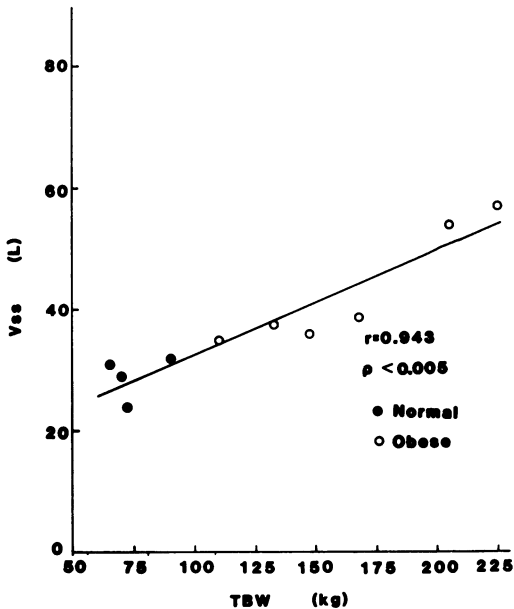


FIG. 1. Relationship between  $V_{ss}$  of vancomycin and TBW in morbidly obese and normal patients. The equation for the regression line is:  $V_{ss} = 0.173(TBW) + 15.1$ .

(in milliliters per minute) and TBW for all subjects ( $r = 0.981$ ,  $P < 0.001$ ). Vancomycin  $Cl_T$  (in milliliters per minute) and  $Cl_{Cr}$  also showed a good correlation when plotted against each other, i.e.,  $r = 0.783$  (Fig. 3,  $P < 0.025$ ).

#### DISCUSSION

Despite the finding that  $V_{ss}$  values (in liters/kg TBW or IBW) were significantly different between normal and morbidly obese subjects, a strong correlation coefficient ( $r = 0.943$ ) was found when all  $V_{ss}$  values (in liters) were plotted against TBW (Fig. 1). A very strong correlation also exists between  $Cl_T$  (in milliliters per minute) and TBW (Fig. 2), with no significant difference between the mean  $Cl_T$  values (in milliliters per minute per kg TBW) calculated for morbidly obese and normal subjects. These results imply that vancomycin dosage should be based on TBW. This can be illustrated by calculating the mean steady-state serum concentration [ $\bar{C}_{ss} = \text{dose}/(\text{dosing interval} \times Cl_T)$ ] for normal subject number 1 and morbidly obese patient number 1 when each is given the standard dose of 500 mg every 6 h (subject selection was based on the fact that these patients were closest to the mean  $Cl_T$  for their respective groups). The normal subject's  $\bar{C}_{ss}$  would equal 16.6  $\mu\text{g}/\text{ml}$ , whereas the morbidly obese subject's  $\bar{C}_{ss}$  would be 7.6  $\mu\text{g}/\text{ml}$ . This 2.2-fold decrease in  $\bar{C}_{ss}$  could be of

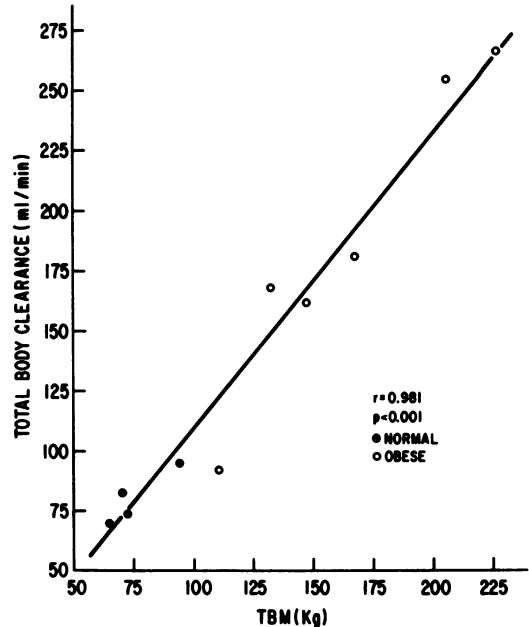


FIG. 2. Relationship between  $Cl_T$  of vancomycin and TBW in morbidly obese and normal patients. The equation for the regression line is:  $Cl_T = 1.251(TBW) - 16.84$ .

clinical significance when life-threatening infections are treated in morbidly obese patients. With Moellering's (15) recommendations, there is no significant difference in the mean daily vancomycin dose (in milligrams per kilogram per day) needed to produce a  $\bar{C}_{ss}$  of 15  $\mu\text{g}/\text{ml}$  in normal and morbidly obese subjects when TBW is used in the dosage calculation ( $23.4 \pm 1.5$  mg/kg per day for normal patients and  $24.0 \pm 3.4$  mg/kg per day TBW for the postsurgical morbidly obese). Therefore, larger total daily doses (in milligrams per day) are needed for morbidly obese subjects compared with those needed for normal subjects to maintain the same  $\bar{C}_{ss}$ .

However, both morbidly obese and normal subjects have similar  $V_c$  values of 6.4 and 7.7 liters. To avoid high peak concentrations in morbidly obese patients given larger doses, the daily dose could be given at more frequent intervals (every 4 h as opposed to the usual 6 h) or the infusion time could be prolonged. Serum concentrations greater than 80 to 100  $\mu\text{g}/\text{ml}$  have been suspected of causing ototoxicity (11); it is unknown whether transient high peak levels will cause this side effect. Since the mean  $t_{1/2\pi}$  is 3.4 min, peak serum levels will only be present for a short time. The shorter terminal half-life,  $t_{1/2\beta}$ , observed in morbidly obese patients allows more frequent dosing without excessive accumulation.

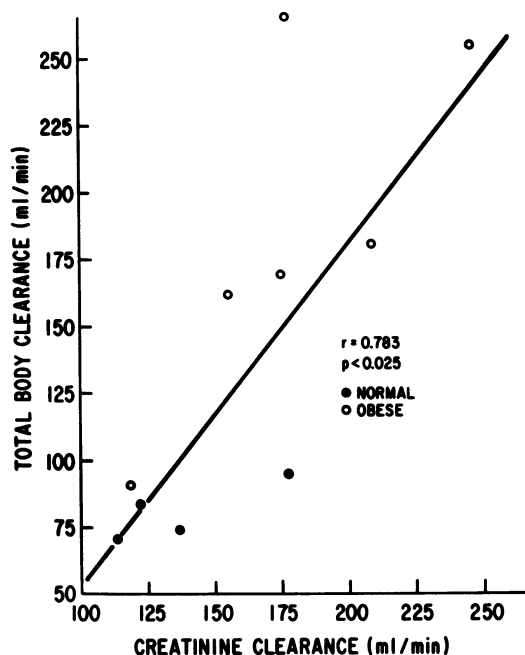


FIG. 3. Relationship between  $Cl_T$  of vancomycin and  $Cl_{cr}$  in morbidly obese and normal patients. The equation for the regression line is:  $Cl_T = 1.353(Cl_{cr}) - 76.23$ .

Since little is known about vancomycin pharmacokinetics in normal subjects, it is interesting to contrast our results to those previously reported. Krogstad et al. (13), using a microbiological assay, have reported that vancomycin kinetics conform to a three-compartment open model, with mean  $t_{1/2\beta}$ ,  $V_{area}$ , and  $Cl_T$  values of 7.88 h, 0.92 liter/kg, and 1.19 ml/min per kg, respectively. Although our mean  $Cl_T$  value for normal subjects was similar (1.085 ml/min per kg), the  $t_{1/2\beta}$  and  $V_{area}$  values were different, with mean values of 4.7 h and 0.45 liter/kg. The reasons for these differences are not entirely clear but may be related in part to the fact that different assay methods were used.

Alterations observed in the disposition of vancomycin in the morbidly obese subjects we studied can probably be explained by the pathophysiological changes which occur with obesity. Alexander et al. (1) have reported the blood volume to be approximately twice the volume predicted by IBW in patients who had a fat weight of 100 kg. Other tissues have also been shown to significantly increase with obesity (16). These differences may in part account for the increased  $V_{ss}$  found in the morbidly obese patients we treated.

Renal function (indicated by  $Cl_{cr}$ ) was significantly greater in the morbidly obese group com-

pared with controls and was strongly correlative with TBW and body surface area. Similar increases in  $Cl_{cr}$  have been noted in morbidly obese subjects with normal serum creatinine values (0.5 to 1 mg/dl) who were not postsurgery patients (7). The mean  $Cl_{cr}$  in these previously reported subjects was 160 ml/min (range, 132 to 264 ml/min) (7). Therefore, it is unlikely that surgery had a substantial influence on  $Cl_{cr}$ . Increases in  $Cl_{cr}$  could be attributed to increases in the number or size of functioning nephrons or to increases in blood flow to the organ. Although kidney mass has been shown to increase with obesity (16), a morphological evaluation was not performed.  $Cl_{cr}$  values for all subjects studied ranged from 113 to 247 ml/min. The six morbidly obese subjects had  $Cl_{cr}$  values of  $180 \pm 44$  ml/min, whereas four normal subjects had values of  $138 \pm 28$  ml/min. As would be expected with a drug predominantly eliminated by the kidney via glomerular filtration, a strong correlation was demonstrated between  $Cl_{cr}$  and  $Cl_T$ .

Caution should be exercised when our results are applied to patients. The morbidly obese subjects we investigated were in a postsurgical state, whereas the subjects did not undergo surgery. In this sense, the normal subjects may not be considered as a strict control group for the morbidly obese postsurgery subjects. We used IBW to normalize the morbidly obese subjects' pharmacokinetic parameters instead of lean body mass. Better correlations may exist between the subjects' kinetic parameters and lean body mass than were observed between the kinetic parameters and IBW. In addition, our results may not apply to patients who are slightly or moderately obese.

In summary, normal and morbidly obese subjects had similar  $V_{ss}$  (in liters per kilogram) and  $Cl_T$  (in milliliters per minute per kilogram) parameters when TBW was used to normalize the values. This suggests that similar doses (in milligrams per kilogram) should be given both normal and morbidly obese patients requiring vancomycin therapy and that the dose should be calculated by using TBW. This is confirmed by the fact that the same total daily dose (in milligrams per kilogram per day TBW) is needed to attain similar  $C_{ss}$  values in both groups. To avoid high transient peak concentrations, a shorter dosage interval may be desirable for morbidly obese subjects.

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