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Pharmacokinetics of Vancomycin in Adult Cystic Fibrosis Patients

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Although the dispositions of many antibiotics are altered in cystic fibrosis patients, that of vancomycin has not been studied. To assess vancomycin pharmacokinetics, 10 adult cystic fibrosis patients were given a parenteral dose of vancomycin (15 mg/kg) during the first 72 h of hospitalization for acute bronchopulmonary exacerbation. Blood samples were obtained at 0, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 15, and 24 h. The mean (standard deviation) weight, measured creatinine clearance, and Taussig clinical score were 51 (13) kg, 130 (39) ml/min/1.73 m^2, and 64 (13), respectively. Multicompartmental pharmacokinetic parameters were best described by a two-compartment model. The mean (standard deviation) volume of distribution, total body clearance, and terminal elimination rate constant were 0.58 (0.15) liter/kg, 91 (19) ml/min/1.73 m^2, and 0.123 (0.05) h^{-1}, respectively. These values were consistent with vancomycin pharmacokinetic parameters obtained in previous studies of healthy adult volunteers. Vancomycin dosages predicted by using a two-compartment Bayesian model were approximately 15 mg/kg every 8 to 12 h. There were poor correlations between clinical score or creatinine clearance and any pharmacokinetic parameter (r values of <0.32). The coefficient of correlation between urine flow rate and total body clearance was 0.7 ($P < 0.05$). Adult cystic fibrosis patients exhibit a disposition of vancomycin similar to that exhibited by healthy adults, and thus cystic fibrosis does not alter vancomycin pharmacokinetics.

Antibiotic pharmacokinetics in patients with cystic fibrosis (CF) have been extensively studied, because of the frequent use of antibiotics to manage acute bronchopulmonary exacerbations and because of the altered drug disposition in these patients (6). CF patients often require higher dosages of many antibiotics to achieve concentrations in serum similar to those in non-CF patients; however, it is uncertain whether this is a function of the disease itself, i.e., because CF patients are typically younger with normal renal function and have enhanced hepatic metabolism of drugs (11), or is because of the more aggressive dosing required with the antibiotics typically used to treat gram-negative respiratory infections. Although there are conflicting studies, the pharmacokinetics of some antibiotics, such as ciprofloxacin, trimethoprim-sulfamethoxazole, ceftazidime, and aminoglycosides, appear to be altered in CF patients, whereas the pharmacokinetics of certain other antibiotics, such as imipenem-cilastatin, do not appear to be altered (6). Consequently, it should not be assumed that the pharmacokinetics of all antibiotics are altered in CF patients.

Although pseudomonal species are the predominant bacteria in the respiratory tracts of CF patients, *Staphylococcus aureus* may be present. In CF patients, *S. aureus* strains cultured from the respiratory tract are usually susceptible to methicillin, with a reported incidence of methicillin resistance of approximately 3% (1, 3). Treatment of methicillin-susceptible staphylococcal infections in CF patients has been traditionally accomplished with beta-lactams such as nafcillin or cephalosporins.

Vancomycin is a glycopeptide antibiotic typically used for the treatment of moderate to severe infections due to methicillin-resistant staphylococci and for the treatment or prophylaxis of gram-positive aerobic infections in patients allergic to beta-lactams. For CF patients, the most likely clinical situations in which vancomycin may be used are (i) the treatment of staphylococcal infections of the respiratory tract in penicillin-allergic patients, (ii) the treatment of infections involving indwelling central intravenous catheters, in which *Staphylococcus epidermidis*, often resistant to beta-lactams, is a common cause, and (iii) for patients receiving home intravenous (i.v.) therapy for staphylococcal infections, in which frequently administered drugs such as nafcillin (every 4 h), are not practical and the longer dosing interval of vancomycin would be desirable. To our knowledge, the pharmacokinetics of vancomycin in CF patients has not been previously studied. Because of the altered drug disposition often encountered in CF patients and the potential benefits of vancomycin, we examined the pharmacokinetics of vancomycin in a group of adult CF patients experiencing acute bronchopulmonary exacerbations.

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MATERIALS AND METHODS

Adult (18 years or older) CF patients admitted for acute bronchopulmonary exacerbation to either Duke University Medical Center or the University of North Carolina at Chapel Hill Hospitals were eligible for entry into the study. The patients had been previously diagnosed with CF on the basis of positive sweat chloride tests and clinical history. The study was approved by both institutions' investigational review boards, and written informed consent was obtained from each subject prior to entry into the study. Acute bronchopulmonary exacerbation was defined as the presence of at least 5 of the following 10 clinical, laboratory, or radiologic findings, according to published criteria (24): (i) change in volume, appearance, or color of sputum; (ii) increased respiratory rate; (iii) progressive findings on chest ascultation; (iv) increased cough; (v) new infiltrates on chest roentgenogram; (vi) decreased appetite or recent weight loss; (vii) fever, defined as an oral temperature of greater than 38.3°C; (viii) leukocytosis with a left shift; (ix) decreased exercise tolerance and fatigue; and (x) deterioration in pulmonary function tests from baseline levels.

Patients were excluded if they were pregnant as determined by a urine pregnancy test, had a known hypersensitivity to vancomycin, were admitted to an intensive care unit, had received parenteral vancomycin or aminoglycosides within 3 weeks prior to admission, were participating in another drug study, had

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elevated liver function tests (transaminase or bilirubin test result greater than twice the normal level), or had a baseline serum creatinine level of greater than 1.4 mg/dl. Following entry into the study, each patient was evaluated by a pulmonologist and assigned a disease severity score based on two clinical prognostic scoring methods, the Shwachman score (23) and the Taussig score (25), and a chest radiographic scoring method (the Brasfield score) (4). Patients were recruited so that there was a range of disease severity, with one-half of the subjects having Taussig scores of less than 60 and the other subjects having scores above this value.

A single dose of i.v. vancomycin was administered to each study subject within 72 h after admission to the hospital. A manufacturer's single lot of vancomycin (Vancocin; Eli Lilly, Indianapolis, Ind.) was used for each patient at a dose of approximately (rounded to the nearest 50 mg) 15 mg/kg, on the basis of total body weight. The dose was reconstituted according to the guidelines of the manufacturer and diluted with 5% glucose in water in an evacuated glass bottle to yield a final concentration of 5 mg/ml. The total vancomycin dose prepared was in excess of the actual dose to allow for drug loss during priming of i.v. tubing and to account for drug remaining in the i.v. tubing at the end of the i.v. infusion. These steps were taken to ensure that the prescribed dose was the same as the actual dose administered to the patient. With the exception of one individual, the study patients did not receive vancomycin for therapeutic purposes; rather, they received it simply for study purposes. The patients received other antibiotics, such as aminoglycosides and antipseudomonal beta-lactams, as usually prescribed for acute exacerbations. Each dose of vancomycin was infused over 1 h with a single, calibrated volumetric infusion pump (Abbott Lifecare; Abbott Laboratories, Chicago, Ill.). The study patients were pretreated with hydroxyzine (50 mg orally) approximately 0.5 h prior to initiation of the vancomycin dose to prevent development of "red-man's syndrome."

Twelve blood samples were obtained, at around the time of the vancomycin dose (0 h) and at 1.0, 1.25, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 15.0, and 24.0 h after initiation of the vancomycin infusion. Blood samples were obtained from the arm contralateral to the arm used for drug administration. Previously placed indwelling central i.v. lines were used only when drug administration and blood sampling were not performed through the same lumen (e.g., drug administration through a central catheter and blood sampling through a peripheral i.v. access). The i.v. access was flushed with an amount of fluid adequate to ensure that no vancomycin remained in the catheter. A 24-h urine collection beginning with initiation of the vancomycin infusion was obtained to determine creatinine clearance (CL_{CR}). Each subject voided just prior to, during, and at the completion of the 24-h period. CL_{CR} was normalized to body surface area. Body surface area was calculated by the method of DuBois and DuBois (7).

Blood samples were harvested and frozen at −20°C within 2 h after collection and analyzed in duplicate within 72 h. The mean of the two analyses was used as the reported concentration. A fluorescence polarization immunoassay (TDx; Abbott Laboratories Diagnostics Div., Irving, Tex.) was used to determine vancomycin concentrations. The interday assay precisions were 4.9, 2.1, and 3.9% for the controls with low, medium, and high concentrations, respectively. The lower limit of detection for the assay is 1 μg/ml.

Pharmacokinetic parameters were determined by standard methods. Serum vancomycin concentrations were fit to a multicompartment model, initially by using RSTRIP (8) to obtain initial estimates of parameters and then by using a computerized nonlinear regression analysis program (PCNONLIN) (14). The area under the serum concentration-time curve (AUC) was determined by the log trapezoidal rule and extrapolated to infinity ($AUC_{0-\infty}$) by dividing the last measurable serum concentration by the terminal elimination rate constant estimated from PCNONLIN. The volume of distribution at steady state (V_{ss}) was determined by the equation $V_{ss} = [(\text{dose})(\text{AUMC})]/(\text{AUC})^2$, where AUMC is the area under the first moment of the serum concentration-time curve. A correction was made for the infusion by subtracting $[(t/2) \times (\text{dose/AUC})]$ from the V_{ss} values, where t is the duration of the infusion. Total body clearance (CL) was calculated by the formula $CL = \text{dose}/AUC_{0-\infty}$.

A Bayesian pharmacokinetic computer program (Abbott Pharmacokinetics System; Abbott Diagnostics Division) was used to estimate vancomycin dosing requirements. Pharmacokinetic values derived from PCNONLIN (V_c, K12, and K21) were used to determine predicted dosages by the Bayesian program with a two-compartment model. Target steady-state concentrations were 1-h-postinfusion peaks of 30 to 40 μg/ml and troughs of 5 to 10 μg/ml. For purposes of comparison, a one-compartment model utilizing the method of Sawchuk et al. (22), a commonly used method in clinical practice, was also used to predict dosage requirements, targeting similar steady-state peak and trough concentrations. For this method, the volume of distribution and elimination rate constant were calculated by using the 1-h-postinfusion peak and the lowest detectable concentration in serum (usually that of the 15-h sample) and were then used to predict doses.

Statistical analysis involved analysis of the correlations between severity of disease and pharmacokinetic parameters (V_{ss}, CL, and terminal elimination rate constant), between CL_{CR} and CL, and between urine flow rate and CL. The Mann-Whitney nonparametric t test was used to compare the values for noncompartmental parameters (V_{ss} and CL) obtained for the CF study subjects with those obtained for normal volunteers in studies by Healy et al. (10) and Golper et al. (9).

TABLE 1. Patient characteristics[a]

Characteristic	Value
No. male/no. female	4/6
Age (yr)	27.1 ± 6.7 (21–38)
Wt (kg)	51.2 ± 12.8 (32–76)
Body surface area (m^2)	1.51 ± 0.21 (1.19–1.91)
Taussig score	63.6 ± 12.9 (44–85)
Shwachman score	61.5 ± 17.0 (35–90)
Brasfield score	14.2 ± 5.1 (5–22)
FEV1 (liters)	1.19 ± 0.44 (0.65–1.90)
Albumin (g/100 ml)	3.6 ± 0.3 (3.1–4.1)
Measured CL_{CR} (ml/min/1.73 m^2)	130 ± 39 (88–187)
Vancomycin dose (mg)	723 ± 129 (450–900)
Concurrent antibiotics (no. of subjects)	
Aminoglycosides	10
Ceftazidime	4
Imipenem-cilastatin	3
Piperacillin	1
Aztreonam	2

[a] Unless otherwise indicated, values are expressed as means ± standard deviations, with the range given in parentheses.

RESULTS

The demographic characteristics of the 10 patients who participated in this study are shown in Table 1. Upon enrollment into the study, 90% of the patients had sputum changes, 50% had an increased respiratory rate, 40% had progressive findings on chest ascultation, 100% had increased cough, 30% had new infiltrates on chest roentgenogram, 70% had leukocytosis with a shift to the left, 80% had weight loss and decreased appetite, 70% had decreased exercise tolerance and fatigue, 50% had a deterioration in pulmonary function tests, and 40% had fever. One subject (patient 4) initially received vancomycin therapeutically (1 g i.v. every 12 h) for sepsis due to *S. aureus*, which probably was associated with an indwelling central venous catheter. The other nine patients received vancomycin solely for study purposes to determine vancomycin pharmacokinetics.

The pharmacokinetic data obtained from PCNONLIN for each subject are shown in Table 2. A two-compartment model provided the best computer fit on the basis of the Aikake

TABLE 2. Pharmacokinetic data[a]

Subject	Alpha (h^{-1})[b]	Beta (h^{-1})[c]	V_{ss} (liters/kg)	CL (ml/min/1.73 m^2)
1	1.3	0.1196	0.506	107.0
2	1.47	0.1352	0.345	67.0
3	2.12	0.1891	0.516	80.4
4	1.73	0.0782	0.631	73.5
5	0.92	0.1475	0.463	91.2
6	2.14	0.1224	0.669	81.3
7	2.0	0.1364	0.707	103.8
8	2.15	0.1510	0.513	78.1
9	1.71	0.2377	0.530	131.0
10	0.41	0.0525	0.857	100.0
Mean (SD)	1.60 (0.6)	0.123 (0.05)	0.58 (0.15)	91.0 (19)
Coefficient of variation (%)	37.5	40.7	25.8	20.8

[a] Pharmacokinetic data derived from PCNONLIN by using all vancomycin concentration values and a two-compartment model.
[b] Distribution rate constant.
[c] Terminal elimination rate constant.

TABLE 3. Pharmacokinetic and dosing data based on a Bayesian two-compartment model

Subject	V_{ss} (liters/kg)	Terminal elimination rates constant (h^{-1})	Dosage (dose [mg/kg] and interval)[a]
1	0.580	0.1510	16.6, every 12 h
2	0.500	0.1278	14.0, every 12 h
3	0.480	0.2090	21.0, every 8 h
4	0.450	0.0770	13.9, every 12 h
5	0.440	0.1280	15.0, every 12 h
6	0.500	0.1870	20.1, every 12 h
7	0.510	0.2010	16.4, every 12 h
8	0.410	0.3140	19.2, every 8 h
9	0.450	0.1640	15.4, every 8 h
10	0.580	0.1500	17.9, every 12 h
Mean (SD)	0.490 (0.057)	0.171 (0.06)	16.9 (2.5)

[a] Doses were calculated so as to achieve peaks of 30 to 40 μg/ml and troughs of 5 to 10 μg/ml by using a computerized Bayesian program (Abbott Pharmacokinetics System).

criterion (8), although a three-compartment model was best for three subjects. Two-compartment data were subsequently reported for all subjects. The results of dosing predictions obtained by using the Bayesian pharmacokinetic computer program for each subject are shown in Table 3. When the method of Sawchuk et al. (22) was used to calculate vancomycin pharmacokinetic parameters and dosages, the mean volume of distribution, terminal elimination rate constant, and doses were 0.6 liter/kg, 0.177 h^{-1}, and 15.9 mg/kg (with dosing intervals of every 8 h for four subjects and every 12 h for six subjects), respectively. Serum vancomycin concentration data (means and standard deviations) for all subjects are shown in Fig. 1.

The results of analysis of correlations between pharmacokinetic parameters and patient parameters showed weak correlations between CL and CL_{CR} ($r = 0.34$), CL and Taussig score ($r = -0.28$), and CL and Shwachman score ($r = -0.26$). There was a stronger relationship between CL and urine flow rate ($r = 0.70$; $P < 0.05$). All r values from analysis of the correlation between V_{ss} and CL_{CR} or prognostic scores were less than 0.3.

Adverse effects due to vancomycin were observed in three patients. Two patients received hydroxyzine approximately 30 min prior to vancomycin, and the third patient refused the hydroxyzine. One patient experienced marked erythema and pruritis approximately 10 min into the infusion. The symptoms began to resolve over the next 30 min despite continuation of the vancomycin, but it was 24 h before the erythema disappeared. The second and third patients experienced a milder erythema and pruritis of the scalp. The second patient, who was pretreated with hydroxyzine, had resolution of symptoms after 20 min, whereas the patient who had refused pretreatment required several hours before the pruritis abated. None of the three subjects had decreases in blood pressure associated with the apparent red-man's syndrome. None of the symptoms were judged severe enough to necessitate discontinuation of the vancomycin infusion.

DISCUSSION

Parenteral vancomycin is sometimes employed to manage bacterial infections due to gram-positive aerobes in CF patients (particularly with methicillin-resistant organisms), in penicillin-allergic patients, and in the home health care setting. When we examined the disposition of vancomycin in 10 adult CF patients, we found that the pharmacokinetics of vancomycin did not differ from those in healthy adults or other patient populations reported in the literature.

The principal question in pharmacokinetic studies with CF patients is often whether the dosage requirements for a particular antibiotic are different than those with non-CF patients. Table 4 summarizes the results of studies of vancomycin pharmacokinetics in healthy adult volunteers (2, 9, 10) as well as patients with various disease states (13, 18–20). The determination of pharmacokinetic parameters, assay methodology, and serum sampling strategies in these studies were similar to those in our study, and thus the studies should be comparable. The V_{ss} and CL were essentially the same in our study patients and the normal healthy volunteers. In fact, an examination of the data reported for each of 11 subjects by Healy et al. (10)

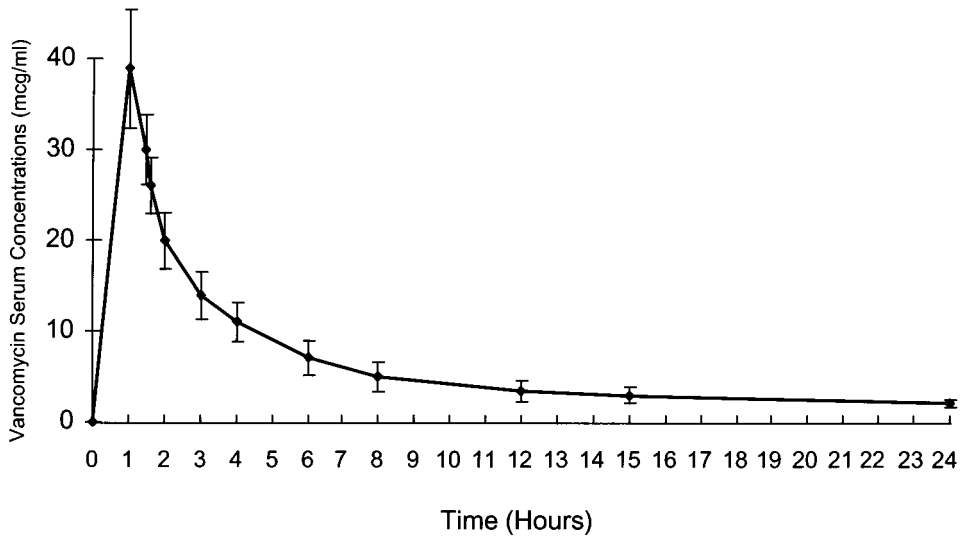

FIG. 1. Serum vancomycin concentration-versus-time curve for 10 adult CF patients. The vertical lines represent one standard deviation.

TABLE 4. Comparison of results of studies of vancomycin pharmacokinetics in young, healthy adults and adult patients with various diseases

Authors (reference)	Patient population (*n*)	Mean CL_{CR}	Mean V_{ss} (liters/kg)	Mean CL
Golper et al. (9)	Healthy adult volunteers (9)	115 ml/min/1.73 m^2	NA[a]	114 ml/min/1.73 m^2
Healy et al. (10)	Healthy adult volunteers (11)	110 ml/min	0.59	86 ml/min/1.73 m^2
Boeckh et al. (2)	Healthy adult volunteers (10)	93 ml/min/1.73 m^2	0.62	1.5 ml/min/kg
Ryback et al. (20)	i.v. drug abusers (14)	85.5 ml/min	0.56	98 ml/min
	Burn patients (10)	111.0 ml/min	0.59	143 ml/min
Rodvold et al. (18)	Medical or surgical patients (10)	93.4 ml/min/1.73 m^2	0.50	98 ml/min/1.73 m^2
Matzke et al. (13)	Medical or surgical patients (56)	87.6 ml/min	0.72	62.7 ml/min
Rotschafer et al. (19)	Primarily burn patients (28)	157 ml/min/70 kg	0.62	87.8 ml/min/70 kg
Pleasants et al. (this study)	Adult CF patients (10)	130 ml/min/1.73 m^2	0.57	91 ml/min/1.73 m^2

[a] NA, not available.

and 9 subjects by Golper et al. (9) showed that there was no statistical difference between our CF patients and the normal volunteers (Mann-Whitney test). In all of the studies of patients except that of Matzke et al. (13), the V_{ss} and CL are similar to those reported in our study. Thus, the pharmacokinetics of vancomycin in adult CF patients does not appear to be substantially different from that observed in other patient groups with relatively normal renal function or in normal healthy adults.

The correlation between pharmacokinetic parameters and patient characteristics (prognostic scores and CL_{CR}) was poor in most instances. However, there was a strong correlation between urine flow rate and CL for vancomycin in our study. An examination of the relationship between CL and urine flow rate was prompted by the extremely rapid drug elimination in one patient who ingested very large amounts of water during the study day. It has been reported that renal clearance does not account for all of the elimination of vancomycin from the body, indicating potentially significant nonrenal elimination (12). A good correlation between vancomycin clearance and urine flow rate suggests that vancomycin may be reabsorbed, and consequently, an increase in urine flow rate would result in a decrease in drug reabsorption and thus in increased elimination from the kidney via glomerular filtration. However, one study has indicated that vancomycin renal clearance is inversely related to urine flow rate (9). Further study would be necessary to more clearly determine if this relationship between urine flow and vancomycin clearance in CF patients exists.

The manufacturer recommends a vancomycin dose of 15 mg/kg every 12 h (or 7.5 mg/kg every 6 h) in patients with normal renal function. Dosage predictions obtained by using both a Bayesian two-compartment computer program and the more simplified one-compartment method of Sawchuk et al. (22) indicated that a vancomycin dosage of ~15 mg/kg every 8 to 12 h appears to be appropriate. After completion of this study, of the first 10 CF patients at Duke University Medical Center who received vancomycin therapeutically, 8 patients received vancomycin dosages of approximately 15 mg/kg every 12 h and 2 patients required every-8-h dosing to achieve therapeutic concentrations. One approach may be to use a 12-h dosing interval for mildly to moderately ill adult CF patients with normal renal function and an 8-h dosing interval for severely ill patients with normal renal function or those previously requiring every-8-h dosing and then to determine concentrations in serum to verify the appropriateness of the dosing.

There is controversy in the literature regarding the need to monitor blood vancomycin concentrations (5, 15). The manufacturer of vancomycin recommends monitoring concentrations in blood for patients with decreased renal function, the elderly, severely ill patients, and patients receiving nephrotoxins concurrently (17). The typical CF patient experiencing an acute bronchopulmonary exacerbation is treated with a 10- to 14-day course of an aminoglycoside plus another antipseudomonal antibiotic. Although aminoglycoside nephrotoxicity is rare in patients with CF, ototoxicity does occur (16). The effect of combining both agents on ototoxicity in CF patients is unknown but could justify the monitoring of blood vancomycin concentrations. Another potential reason to monitor blood vancomycin levels is because our study suggests that dosages higher than those recommended by the manufacturer are necessary for some CF patients, although these dosages are probably not different from those appropriate for other young adult patients with good renal function.

The adverse effects from vancomycin experienced by three CF patients in this study were consistent with red-man's syndrome. These reactions occurred in two patients despite pretreatment with an antihistamine. The incidence of red-man's syndrome from vancomycin has not been previously reported for CF patients. The incidence in this study may be relatively high because of red-man's syndrome being more likely to occur with the first dose (21). We did not evaluate the effect of vancomycin on hearing but no patient reported any symptoms of tinnitus or apparent hearing loss.

In summary, the results of this study indicate that adult CF patients appear to have a vancomycin disposition similar to that of healthy adult volunteers as well as adult patients with normal renal function who have various disease states. A dosage of 15 mg/kg every 8 to 12 h appears to be an appropriate initial vancomycin dosage in adult CF patients with normal renal function.

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