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Application of a Modified Bioassay for Monitoring Serum Teicoplanin and Vancomycin in Febrile Neutropenic Patients

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Teicoplanin is a glycopeptide antibiotic with a mode of action and spectrum of activity similar to those of vancomycin. Its efficacy and tolerability as empiric therapy and its pharmacokinetic properties in neutropenic patients are being studied in a double-blinded, randomized trial in comparison with those of vancomycin. We report here a modified agar diffusion bioassay which is suitable for monitoring levels of either teicoplanin or vancomycin in serum during combination therapy with β-lactams, aminoglycosides, and amphotericin B. Serum samples spiked with either teicoplanin or vancomycin gave reproducible results (mean coefficient of variation, 8.8%) regardless of the presence of tobramycin, amikacin, piperacillin, ceftazidime, amphotericin B, or their combinations. Among 25 patients who received teicoplanin at a dosing schedule of 6 mg/kg every 24 h intravenously, steady state was reached after 14.2 ± 4.0 days, and 1-h peak and trough concentrations of teicoplanin in serum at steady state were 40.8 ± 15.0 and 12.5 ± 3.2 mg/liter, respectively. In contrast, among 25 patients who received vancomycin at a dosing schedule of 15 mg/kg every 12 h intravenously, steady state was reached by 24 h, and the 1-h peak and trough concentrations in serum were 37.5 ± 15.6 and 8.3 ± 3.8 mg/liter, respectively. The elimination half-lives for teicoplanin estimated by two separate approaches agreed closely with each other: 80.5 ± 21.5 h by an accumulation model (M. Gilbaldi and D. Perrier, *Pharmacokinetics*, 2nd ed., p. 121, 1982) and 87.3 ± 19.3 h as predicted from the degree of renal function (M. Rowland, Clin. Pharmacokinet. 18:184–209, 1990). These values were 14- to 15-fold higher than that for vancomycin (5.6 ± 1.8 h). Since considerable variability was noted in the pharmacokinetic parameters for both teicoplanin and vancomycin among the individual patients, our data further emphasized the need for frequent monitoring of these drugs during empiric therapy of the febrile neutropenic patient.

Teicoplanin is a glycopeptide antibiotic with a mode of action and spectrum of activity similar to that of vancomycin (2, 19, 25). It is two- to eightfold more active than vancomycin against staphylococci and streptococci, especially *Streptococcus faecalis* and other enterococci (3, 8). It offers the potential advantages of a longer half-life, less-frequent dosing, and lower nephrotoxicity compared with vancomycin (2, 19, 22, 25). Both teicoplanin (9) and vancomycin (13) have been reported in randomized, controlled trials to be useful as empiric therapy in combination with a β-lactam and an aminoglycoside in febrile neutropenic patients with acute leukemia. We are currently conducting a randomized clinical trial comparing teicoplanin with vancomycin in the empiric treatment of this patient population. Both experimental groups are also receiving tobramycin plus piperacillin. Since frequent monitoring of concentrations in serum is essential for both teicoplanin and vancomycin to optimize the dosing regimens and minimize toxicity, a bioassay was developed which permitted quantitation of both teicoplanin and vancomycin in the presence of concomitant β-lactams, aminoglycosides, and amphotericin B. The bioassay also enables continuation of a blinded protocol which includes the patient, clinical investigator, and laboratory personnel while allowing an unblinded observer to adjust the dosage on the basis of predetermined pharmacokinetic criteria. In this communication, we report the development of the bioassay and summarize the pharmacokinetic data from 50 febrile neutropenic patients who had received either teicoplanin or vancomycin by a randomized, double-blinded study design.

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MATERIALS AND METHODS

Antibiotic regimens and serum sampling. Patients hospitalized in the Acute Leukemia and Bone Marrow Transplant Unit at the Vancouver General Hospital, Vancouver, British Columbia, Canada, were eligible for this study if they had absolute granulocyte counts below 500/mm^3 and oral temperatures of 38°C or more. Patients with a history of hypersensitivity to penicillins, aminoglycosides, or glycopeptides or who had received prior antibiotics within 72 h were excluded from the study. Also excluded were patients with a serum creatinine level above 2.5 mg/dl (220 mmol/liter). Eligible patients were randomized by a computer-generated program to receive either teicoplanin or vancomycin, each in combination with tobramycin plus piperacillin. Vancomycin was administered as a maintenance dose of 15 mg/kg every 12 h (q12h) intravenously (i.v.). Teicoplanin was administered with a loading dose of 6 mg/kg q12h i.v. for 3 doses followed by a maintenance dose of 6 mg/kg q24h i.v. A placebo dose of 5% glucose and water was interposed q24h in order to maintain blinding. The identity of the drug regimen of each patient was known only to the responsible pharmacy staff and to one of the investigators (P.J.J.), who adjusted the maintenance doses according to levels in serum and predetermined criteria. Serum samples were obtained prior to infusion and at 1 and 3 h postinfusion on a daily basis during the first 3 days of drug administration and every 3 to 7 days thereafter for quantitation of teicoplanin or vancomycin levels. Serum samples were stored at 4°C until assayed.

Maintenance doses were titrated to achieve 1-h peak concentrations in serum of 30 to 50 mg/liter and trough concentrations in serum of 5 to 15 mg/liter. Tobramycin was administered at the maintenance dose of 1.5 to 2 mg/kg q8h i.v. and subsequently adjusted to maintain 1-h peak concentrations in serum of 5 to 10 mg/liter and trough concentrations in serum of <2 mg/liter. Piperacillin was administered at the dose of 3 g q4h i.v. Patients requiring addition of amphotericin B were administered a dose of 0.5 to 1 mg/kg i.v. per day.

Bioassay for teicoplanin and vancomycin. The bioassay for both teicoplanin and vancomycin was adapted from that of Erickson et al. (11). Briefly, *Bacillus subtilis* ATCC 6633 was plated on AK2 agar (BBL Microbiology Systems, Div. Becton Dickinson and Co., Cockeysville, Md.), incubated at 37°C for 1 week, and pasteurized at 65°C for 30 min to prepare a stock spore suspension (4.5×10^9/ml). The bioassay agar consisted of Mueller-Hinton II medium (BBL) (50 g) containing NaCl (30 g), $CaCl_2$ (anhydrous) (8 g), and citric acid (monohydrate) (1 g/liter), final pH 5.0. This low pH antagonized the action of aminoglycosides by virtue of changing the proton motive force. The bioassay plates were prepared by pouring 196 ml of agar medium admixed with 4 ml of the stock spore suspension into 22.5-cm^2 plates (Nunc, Intermed, Roskilde, Denmark) and allowing it to harden on a level surface. These were stored for up to 1 to 2 weeks at 4°C until use. For the bioassay, 64 wells measuring 6.25 mm wide and 5.0 mm deep were cut in the agar to accommodate serum samples or antibiotic standards.

Teicoplanin or vancomycin standards were prepared from stock solutions (teicoplanin, 960 mg/liter, Merrell Dow Laboratories, Cincinnati, Ohio; vancomycin, 960 mg/liter, Sigma Chemicals Co., St. Louis, Mo.) and diluted in pooled human serum (Flow Laboratories, Inc., McLean, Va.) to achieve final concentrations of 3, 6, 12, 24, 48, and 96 mg/liter. Dilutions were incubated at room temperature for 2 h to allow optimal protein binding before storage at −70°C until use. As a further control for reproducibility of results, internal standards of teicoplanin (10, 30, and 50 mg/liter) and vancomycin (50 mg/liter) were separately prepared in human serum (Flow Laboratories) and added to each run. To assess the influence of concurrent antimicrobial agents, tobramycin (12 mg/liter), amikacin (25 mg/liter), piperacillin (128 mg/liter), and amphotericin B (5 mg/liter) were added in various combinations to each of the teicoplanin internal standards and assayed multiple times. Test serum samples (150 μl) were first incubated at room temperature for 30 min with 30 μl of penicillinase type I (Sigma; 20,000 mg/liter in phosphate buffer, pH 6.0, diluted in pooled human serum to give 1,000-mg/liter stock). Samples (50 μl) of the test serum or standards were then added to each well in triplicate. Plates were then incubated at 37°C for 18 h. Zone diameters were measured with calipers, and standard curves for either teicoplanin or vancomycin were constructed by using a log-linear regression program based on 10-fold concentrations of the studied antibiotics represented on the ordinate and the resultant zone diameters of inhibition represented on the abscissa. Predicted teicoplanin or vancomycin levels in the test serum were then obtained from the respective standard curves and reported in a blinded fashion to the unblinded investigator.

Comparison of vancomycin concentrations in serum measured by an immunoassay. Vancomycin concentrations in some serum samples were also measured by the fluorescence polarization immunoassay method (17, 18) according to instructions of the manufacturer (TDX; Abbott Laboratories, North Chicago, Ill.) as described by Schwenzer et al. (21). This system utilizes fluorescein-labeled vancomycin, which competes with the unlabeled vancomycin in the sample for antibody-binding sites. Since the polarization of fluorescent light emitted by fluorescein-labeled vancomycin increases as the vancomycin is bound to the antibody, the concentration of unlabeled vancomycin could be derived from a standard curve following competitive binding with labeled vancomycin. This assay is highly sensitive (lower limit, 0.60 mg/liter with 95% confidence) and reproducible (coefficient of variation, typically less than 5%).

Pharmacokinetic parameters. Pharmacokinetic parameters for both teicoplanin and vancomycin were estimated at steady state after multiple dosing according to standard procedures (12). The time to steady state for each patient was estimated from the sequential trough concentration in serum data. The area under the serum concentration-time curve was obtained by the trapezoidal rule. The apparent volume of distribution was calculated by the method of Gibaldi and Perrier (12) by using teicoplanin concentration in serum data obtained under steady-state conditions at 10 to 14 days of therapy. The elimination half-life for teicoplanin was estimated by two separate methods (i) by determining the accumulation factor A according to the method of Gibaldi and Perrier (12) in which $A = (C_{ss})_{min}/(C_1)_{min} = 1/(1 - e^{-kr})$ where $(C_{ss})_{min}$ is the trough concentration in serum at steady state, $(C_1)_{min}$ is the trough concentration in serum after the first daily maintenance dose (a correction factor of 3 was used to take into account the three loading doses administered within the preceding 24 h), k is the terminal disposition rate constant equal to $\ln 2/(t_{1/2})$ ($t_{1/2}$, elimination half-life), and r is the dose interval (i.e., 24 h for teicoplanin); and (ii) by calculation from the formula of Rowland (20) in which terminal half-life (in hours) = $87/[1 - 0.75(1 - RF)]$ where RF is the degree of renal function (ratio of creatinine clearance in the patient to that in a young adult with normal renal function, both normalized to 70 kg of body weight).

The elimination half-life for vancomycin was determined based on pre- and postinfusion (3 h) concentrations in serum at steady state.

RESULTS

Sensitivity and reproducibility of the bioassay. Representative standard curves for the bioassay of teicoplanin and vancomycin are shown in Fig. 1A and 1B, respectively. The regression coefficients (r) of standard curves calculated by the method of least squares were 0.998 ± 0.001 (99% confidence limits, $n = 100$) for teicoplanin and 0.997 ± 0.001 for vancomycin, respectively. The interday coefficients of variation were 10.1% at 10 mg/liter, 5.5% at 30 mg/liter, and 10.0% at 50 mg/liter (Table 1) for the teicoplanin assay and 10.9% at 50 mg/liter for the vancomycin assay. Ten coded serum samples containing teicoplanin at clinical concentrations (5 to 40 mg/liter) were assayed in triplicate (Table 2). The mean recovery of teicoplanin was 101% ± 6.8%. In separate experiments, vancomycin concentrations in 34 serum samples from 8 patients were assayed both by the bioassay and by the fluorescence polarization immunoassay. Excellent correlation was demonstrated between the two methods ($r = 0.96$, $P < 0.001$, Fig. 2). However, results of the bioassay were 19% higher than corresponding values obtained by the fluorescence polarization immunoassay method.

Influence of aminoglycosides, β-lactams, and amphotericin B. The bioassay for teicoplanin was further evaluated in the

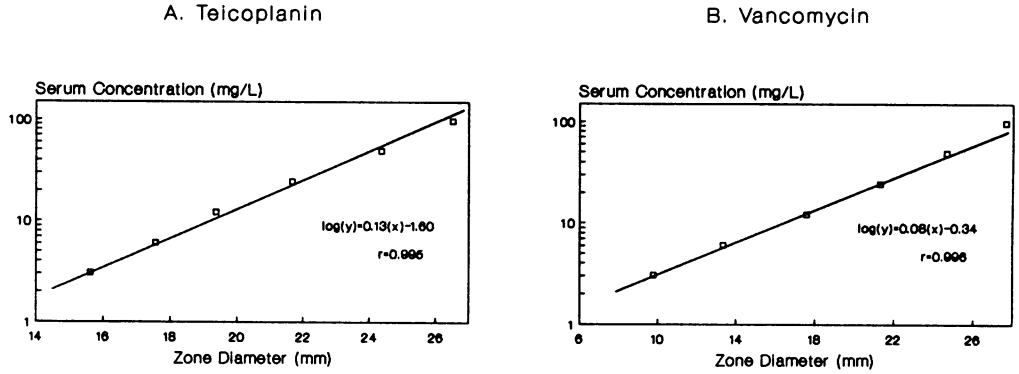

FIG. 1. Typical standard curves used for determining concentrations of teicoplanin (A) and vancomycin (B) in serum in the bioassay. L, Liter.

presence or absence of various antimicrobial agents in combination, including tobramycin (12 mg/liter), amikacin (25 mg/liter), piperacillin (128 mg/liter), and amphotericin B (5 mg/liter) (Table 1). The results indicate that the accuracy of the bioassay for teicoplanin was not influenced by the presence of these antimicrobial agents even at relatively high concentrations. Teicoplanin concentrations assayed in the presence of other antimicrobial agents were within 97% ± 4.1% (95% confidence limits) relative to concurrent control samples assayed in the absence of these agents (mean coefficient of variation, 8.8%) (Table 1). The presence of ceftazidime also did not interfere with the bioassay for teicoplanin or vancomycin (data not shown).

Concentrations of teicoplanin and vancomycin in serum from febrile neutropenic patients. Fifty febrile neutropenic patients undergoing cytotoxic chemotherapy for hematologic malignancies (primarily acute and chronic myelogenous leukemia) were randomized to receive either teicoplanin (25 patients) or vancomycin (25 patients), each in combination with tobramycin and piperacillin. The mean ± standard deviation age was 38.9 ± 11.7 years; 26 were male, and 24 were female. Seventeen patients in the teicoplanin group and 12 in the vancomycin group also received amphotericin B concurrently. Among the patients who received teicoplanin, steady state was not achieved until 14.2 ± 4.0 days (Table 3). At 24 h after the initiation of therapy, the mean ± standard deviation 1-h peak and trough teicoplanin levels in serum were 38.8 ± 22.7 and 7.9 ± 2.6 mg/liter, respectively, but rose to 40.8 ± 15.0 and 12.5 ± 3.2 mg/liter, respectively, at steady state. In contrast, patients receiving vancomycin reached steady state by 24 h, and the 1-h peak and trough vancomycin levels in serum at this time were 37.5 ± 15.6 and 8.3 ± 3.8 mg/liter, respectively (Fig. 3). Thus, trough concentrations in serum of both teicoplanin and vancomycin exceeded the MIC for 90% of the susceptible organisms tested (≤4 mg/liter) during the entire dosing interval within 24 h after the initiation of therapy. The elimination half-life of teicoplanin estimated by the accumulation model (80.5 ± 21.5 h) agreed closely with estimates based on renal function (87.3 ± 19.3 h) (Table 3). These values were 14- to 15-fold higher than that for vancomycin (5.6 ± 1.8 h). The estimated volume of distribution of teicoplanin was 1.41 ± 0.82 liter/kg (Table 3). The estimated volume of distribution for vancomycin was 0.61 ± 0.21 liter/kg (data not shown).

TABLE 1. Assay of teicoplanin in the presence of aminoglycosides, β-lactams, or amphotericin B

Antimicrobial agent added (mg/liter)	Teicoplanin (mg/liter)		Teicoplanin recovered (% of control[a])	CV[b] (%)
	Added	Recovered [mean ± SD (n)]		
None	10	10.7 ± 1.08 (5)	100	10.1
	30	25.4 ± 1.42 (5)	100	5.5
	50	49.7 ± 4.98 (5)	100	10.0
Tobramycin (12)	10	9.7 ± 0.78 (4)	91	8.0
	30	25.7 ± 0.80 (4)	101	3.1
	50	52.1 ± 0.61 (4)	104	1.2
Amikacin (25)	10	11.8 ± 1.28 (10)	100	10.7
	30	34.6 ± 5.70 (10)	119	16.4
	50	51.6 ± 4.31 (10)	96	8.3
Piperacillin (128)	10	10.4 ± 1.21 (10)	88	11.6
	30	26.1 ± 1.96 (10)	90	7.5
	50	49.1 ± 7.43 (10)	91	15.1
Tobramycin (12) + piperacillin (128)	10	11.0 ± 1.34 (4)	102	12.1
	30	24.5 ± 1.30 (4)	96	5.3
	50	50.4 ± 5.10 (4)	101	10.1
Amikacin (25) + piperacillin (128)	10	11.5 ± 1.22 (10)	97	10.6
	30	25.0 ± 2.11 (10)	87	8.4
	50	51.1 ± 6.18 (10)	95	12.1
Amphotericin B (5)	5	5.1 ± 0.13 (2)	112	2.5
	15	11.4 ± 0.66 (2)	91	5.7
	25	21.8 ± 2.53 (3)	84	11.6

[a] Relative to control assays in the absence of added antimicrobial agents.
[b] CV, Coefficient of variation.

DISCUSSION

Teicoplanin is a fermentation product of *Actinoplanes teichomyceticus*. It is structurally related to vancomycin,

TABLE 2. Recovery of teicoplanin from coded unknown serum samples

Coded sample	Teicoplanin (mg/liter)		% Teicoplanin recovered
	Added	Recovered [mean (n)]	
1	5	5.6 (2)	112
2	5	5.0 (2)	100
3	5	5.1 (2)	102
4	10	10.4 (2)	104
5	10	11.1 (2)	111
6	20	18.7 (2)	94
7	20	20.3 (2)	101
8	40	36.9 (2)	92
9	40	37.6 (2)	94
10	40	41.8 (1)	104

TABLE 3. Patient characteristics, terminal half-lives, and volume of distribution at steady state among 22 patients receiving teicoplanin (6 mg/kg)

Patient no.	Age (yr)	Sex[a]	Wt (kg)	CL_{CRn}[b] (ml/min)	Terminal $t_{1/2}$ (h)[c] by:		AUC_{0-24}[d] (mg · h/liter)	V_β[e] (liter/kg)	$(C_{ss})_{min}$ (mg/liter)	$Time_{ss}$[f] (days)
					Method A	Method B				
1	57	F	60.0	73.4	80.7	108.6	693	1.18	21.4	18
2	41	F	58.3	88.6	139.5	95.1	516	2.94	16.1	18
3	41	M	87.3	99.5	82.6	87.3	407	1.95	12.4	11
4	31	F	55.2	93.0	89.2	91.8	397	1.88	10.4	18
5	24	M	70.5	97.6	66.6	88.5	395	1.52	9.6	8
6	31	F	72.2	97.5	68.1	88.6	472	1.33	12.7	12
7	21	F	61.0	154.0	75.6	61.9	442	1.70	12.6	16
8	39	M	64.3	135.0	57.6	68.9	234	2.20	6.3	19
9	25	M	88.4	94.1	92.6	91.0	504	1.74	14.7	15
10	40	M	80.5	122.8	82.7	74.3	402	1.84	12.1	11
11	21	M	70.0	126.7	54.0	72.4	326	1.36	9.6	10
12	49	F	61.0	106.6	113.5	82.9	ND[g]	ND	12.5	13
13	41	M	68.5	109.4	89.3	81.2	347	2.39	11.7	10
14	42	M	68.8	91.2	47.7	93.1	ND	ND	8.6	7
15	36	M	55.9	161.3	64.3	59.6	333	2.49	8.4	21
16	49	F	73.1	69.8	69.6	112.4	440	0.87	15.7	15
17	41	F	61.2	96.6	87.5	89.2	516	1.84	14.8	22
18	35	M	84.0	134.5	57.9	69.1	401	1.29	11.9	12
19	49	F	72.0	151.9	114.4	62.6	ND	ND	10.1	17
20	41	F	65.2	54.7	71.8	131.7	374	1.02	13.6	11
21	67	M	76.8	55.6	96.9	130.3	578	1.51	14.7	15
22	49	M	120.0	113.0	67.6	79.2	ND	ND	14.6	14
Mean	39.5		71.5	105.7	80.5	87.3	353.8	1.41	12.5	14.2
SD	11.4		14.1	29.0	21.5	19.4	190.5	0.82	3.2	4.0
CV[h]	28.8		19.7	27.4	26.7	22.2	53.8	57.86	25.5	28.2

[a] F, Female; M, male.
[b] CL_{CRn}, Creatinine clearance, normalized to 70 kg of body weight.
[c] $t_{1/2}$, Half-life; method A by accumulation model, method B by renal function (see text).
[d] AUC_{0-24}, Area under the concentration-time curve from 0 to 24 h.
[e] V_β, Apparent volume of distribution.
[f] $Time_{ss}$, Time to steady state.
[g] ND, Not determined.
[h] CV, Coefficient of variation (in percent).

with a spectrum of activity that includes gram-positive aerobic and anaerobic bacteria such as methicillin-susceptible and -resistant staphylococci, streptococci, enterococci, *Clostridium difficile*, and JK corynebacteria (8, 16). When compared with vancomycin, teicoplanin is two- to eightfold more active in vitro and appears to be less nephrotoxic and ototoxic. In addition, teicoplanin provides a much longer half-life in serum than vancomycin (approximately 15-fold), requiring administration only once daily. In this communication, we have reported a modified bioassay for the determination of both teicoplanin and vancomycin levels in serum. This assay is applicable in the clinical setting where

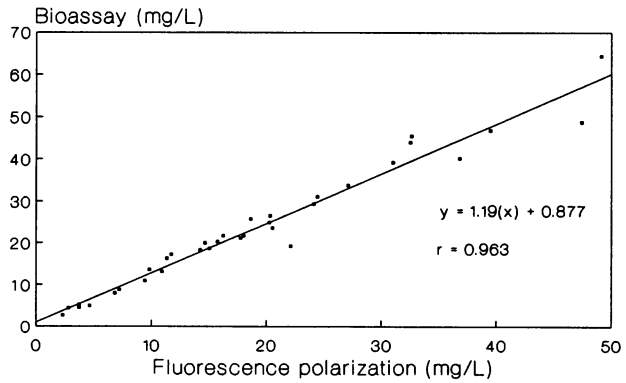

FIG. 2. Correlation of the bioassay and fluorescence polarization immunoassay methods for the quantitation of vancomycin concentrations in 34 serum specimens. L, Liter.

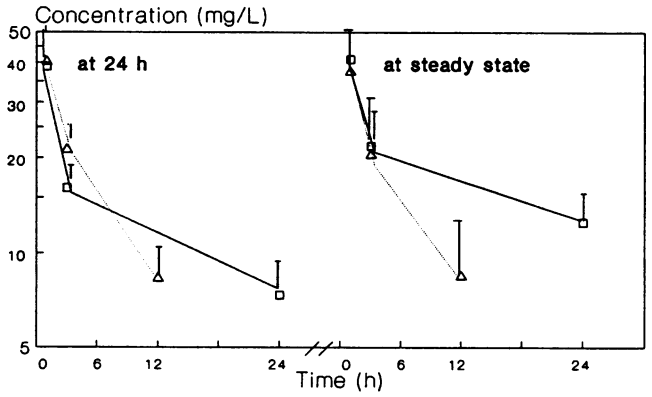

FIG. 3. Concentration in serum (mean ± standard deviation) versus time determinations at 24 h after initiation of therapy and at steady state for 25 patients receiving teicoplanin (6 mg/kg q24h i.v.) (□) and 25 patients receiving vancomycin (15 mg/kg q12h i.v.) (△). Both drugs showed multiexponential decay. Steady-state conditions were achieved by 14 days for teicoplanin and by 24 h for vancomycin. L, Liter.

blinding is desired and has acceptable interrun reproducibility. Furthermore, the assay is not affected by the concomitant administration of β-lactams, aminoglycosides, or amphotericin B. This assay does not require sophisticated equipment such as high-pressure liquid chromatography or fluorescence polarization, and the turnaround time for the assay was only 24 h. Another advantage is that the assayed drugs were stable in refrigerated serum for at least 72 h. A disadvantage of the bioassay, however, is that it measures total drug but does not distinguish between free versus protein-bound fractions. This may be particularly important for a drug such as teicoplanin which is highly protein bound (88 to 91%, irrespective of drug concentration over the range of 4 to 60 mg/liter) (1, 20). Underdosing could result if the total rather than free-drug concentrations were relied upon for the selection of therapeutic dose regimens (7).

Similar to previous studies of normal hosts, both teicoplanin and vancomycin in our neutropenic patients demonstrated a multicompartmental distribution phase (14, 15, 23, 24). The elimination half-life and other pharmacokinetic parameters of both agents in the febrile neutropenic patient population appear similar to those previously reported for nonneutropenic individuals with comparable renal functions. We estimated the elimination half-life of teicoplanin by two separate approaches, and the results closely agreed with each other. In the accumulation model, the elimination half-life was determined from a fit of the trough concentration in serum data, since the time to achieve steady state is a function of the half-life. Our results of 80.4 ± 21.4 h in our patients with variable renal function was similar to that of 61 h among healthy subjects following multiple dosing reported by Carver et al. (6). These investigators suggested that teicoplanin half-life values obtained from trough concentration in serum data may be more accurate than those obtained from multiple-dose concentration-time curves in which higher values were obtained, perhaps because of the presence of active metabolites of teicoplanin.

Because of the markedly prolonged half-life of teicoplanin, steady state for trough teicoplanin levels in serum was not reached until approximately 10 to 15 days in our patients with adequate renal function. However, a loading dose of 6 mg/kg q12h for three doses resulted in the targeted 1-h peak (30 to 50 mg/liter) and trough (5 to 15 mg/liter) concentrations in serum being achieved within 24 h of the initiation of therapy. In this regard, it is important to note that the optimal dose regimen and desired concentrations in serum during teicoplanin therapy remain controversial. This is in part due to the high protein binding of teicoplanin. Thus, therapeutic failures despite adequate total drug levels of teicoplanin have been well documented (5). It appears that in some of these instances, treatment failure was related to suboptimal free-drug levels which were lower than the MIC for the infecting organism. For agents such as teicoplanin which have markedly prolonged half-lives and are administered on a once-daily basis, the trough concentration in serum may be more important than the 1-h peak level in predicting therapeutic efficacy (7). Frequent monitoring of concentrations in serum during therapy of serious infections appears warranted, particularly since considerable variability was noted in the pharmacokinetic parameters for both teicoplanin and vancomycin among the individual patients (4, 10, 15). The bioassay we have described is particularly suited for this purpose in the clinical laboratory.

LITERATURE CITED

1. **Assandri, A., and A. Bernareggi.** 1987. Binding of teicoplanin to human serum albumin. Eur. J. Clin. Pharmacol. **33**:191–195.
2. **Babul, N., and M. Pasko.** 1988. Teicoplanin: a new glycopeptide antibiotic complex. Drug Intell. Clin. Pharm. **22**:218–226.
3. **Barry, A. L., C. Thornsberry, and R. N. Jones.** 1986. Evaluation of teicoplanin and vancomycin disk susceptibility tests. J. Clin. Microbiol. **23**:100–101.
4. **Bibler, M. R., P. T. Frame, D. N. Hagler, R. B. Bode, J. L. Staneck, V. Thamlikitkul, J. E. Harris, A. Haregewoin, and W. E. Bullock, Jr.** 1987. Clinical evaluation of efficacy, pharmacokinetics, and safety of teicoplanin for serious gram-positive infections. Antimicrob. Agents Chemother. **31**:207–212.
5. **Calain, P., K. H. Krause, P. Vaudaux, R. Auckenthaler, D. Lew, F. Waldvogel, and B. Hirschel.** 1987. Early termination of a prospective, randomized trial comparing teicoplanin and flucloxacillin for treating severe straphylococcal infections. J. Infect. Dis. **155**:187–191.
6. **Carver, P. L., C. H. Nightingale, R. Quintiliani, K. Sweeney, R. C. Stevens, and E. Maderazo.** 1989. Pharmacokinetics of single- and multiple-dose teicoplanin in healthy volunteers. Antimicrob. Agents Chemother. **33**:82–86.
7. **Chambers, H. F., and S. Kennedy.** 1990. Effects of dosage, peak and trough concentrations in serum, protein binding, and bactericidal rate on efficacy of teicoplanin in a rabbit model of endocarditis. Antimicrob. Agents Chemother. **34**:510–514.
8. **Cynamon, M. H., and P. A. Granato.** 1982. Comparison of the in vitro activities of teichomycin A_2 and vancomycin against staphylococci and enterococci. Antimicrob. Agents Chemother. **21**:504–505.
9. **Del Favero, A., F. Menichetti, R. Guerciolini, G. Bucaneve, F. Baldelli, F. Aversa, A. Terenzi, S. Davis, and S. Pauluzzi.** 1987. Prospective randomized clinical trial of teicoplanin for empiric combined antibiotic therapy in febrile, granulocytopenic acute leukemia patients. Antimicrob. Agents Chemother. **31**:1126–1129.
10. **Domart, Y., C. Pierre, B. Clair, J. J. Garaud, B. Regnier, and C. Gibert.** 1987. Pharmacokinetics of teicoplanin in critically ill patients with various degrees of renal impairment. Antimicrob. Agents Chemother. **31**:1600–1604.
11. **Erickson, R. C., A. R. Hildebrand, P. F. Hoffman, and C. B. Gibson.** 1989. A sensitive bioassay for teicoplanin in serum in the presence or absence of other antibiotics. Diagn. Microbiol. Infect. Dis. **12**:235–241.
12. **Gibaldi, M., and D. Perrier.** 1982. Pharmacokinetics, 2nd ed., p. 121. Marcel Dekker, Inc., New York.
13. **Karp, J. E., J. D. Dick, C. Angelopulos, P. Charache, L. Green, P. J. Burke, and R. Saral.** 1986. Empiric use of vancomycin during prolonged treatment-induced granulocytopenia. Randomized, double-blind, placebo-controlled clinical trial in patients with acute leukemia. Am. J. Med. **81**:237–242.
14. **Krogstad, D. J., R. C. Moellering, and D. J. Greenblatt.** 1980. Single-dose kinetics of vancomycin. J. Clin. Pharmacol. **20**:197–201.
15. **Levy, J., B. L. Troung, H. Goignau, Y. Van Laethem, J. P. Butzler, and P. Bourdoux.** 1987. High-pressure liquid chromatographic quantitation of teicoplanin in human serum. J. Antimicrob. Chemother. **19**:533–539.
16. **Pallanza, R., M. Berti, B. P. Goldstein, E. Mapelli, E. Randisi, R. Scotti, and V. Arioli.** 1983. Teichomycin: *in vitro* evaluation in comparison with other antibiotics. J. Antimicrob. Chemother. **11**:419–425.
17. **Patton, K. R., A. Beg, D. Felmingham, G. L. Ridgeway, and R. N. Gruneberg.** 1987. Determination of teicoplanin concentration in serum using a bioassay technique. Drugs Exp. Clin. Res. **13**:547–550.
18. **Pfaller, M. A., D. J. Krogstad, G. G. Granich, and P. R. Murray.** 1984. Laboratory evaluation of five assay methods for vancomycin: bioassay, high-pressure liquid chromatography, fluorescence, polarization immunoassay, radioimmunoassay, and fluorescence immunoassay. J. Clin. Microbiol. **20**:311–316.
19. **Pryka, R. D., K. A. Rodvold, and J. C. Rotschafer.** 1988.

Teicoplanin: an investigational glycopeptide antibiotic. Clin. Pharm. 7:647–658.
20. **Rowland, M.** 1989. Clinical pharmacokinetics of teicoplanin. Clin. Pharmacokinet. 18:184–209.
21. **Schwenzer, K. S., C. H. J. Wang, and J. P. Anhalt.** 1983. Automated fluorescence polarization immunoassay for monitoring vancomycin. Ther. Drug Monit. 5:341–345.
22. **Smith, S. R., J. Cheesbrough, R. Spearing, and J. M. Davies.** 1989. Randomized prospective study comparing vancomycin with teicoplanin in the treatment of infections associated with Hickman catheters. Antimicrob. Agents Chemother. 33:1193–1197.
23. **Verbist, L., B. Tjandramaga, L. B. Hendrickx, A. Van Hecken, P. Van Melle, R. Verbesselt, J. Verhaegen, and P. De Schepper.** 1988. In vitro activity and human kinetics of teicoplanin. Antimicrob. Agents Chemother. 26:881–886.
24. **Walker, C. A., and B. Kopp.** 1978. Sensitive bioassay for vancomycin. Antimicrob. Agents Chemother. 13:30–33.
25. **Williams, A. H., and R. N. Gruneberg.** 1988. Teicoplanin. J. Antimicrob. Chemother. 22:397–401.