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Teicoplanin in Cardiac Surgery: Intraoperative Pharmacokinetics and Concentrations in Cardiac and Mediastinal Tissues

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The concentrations of teicoplanin in the sera and mediastinal and heart tissues of 23 patients undergoing cardiac surgery were measured after two regimens of teicoplanin administration. Intraoperative pharmacokinetic parameters were also obtained. Patients were randomized into two groups. Those in group 1 were given teicoplanin at 6 mg · kg^{-1} intravenously at the time of induction of anesthesia. Patients in group 2 were given teicoplanin at 12 mg · kg^{-1} during the same period. The maximum concentration in serum (71 ± 20 and 131 ± 44 mg · 1^{-1}), the minimum concentration in serum (3.6 ± 1.3 and 6.8 ± 2.1 mg · 1^{-1}), the area under the concentration-time curve (AUC) from 0 to 12 h (108 ± 20 and 217 ± 38 μg · h · ml^{-1}), and the AUC from 0 h to infinity (154 ± 36 and 292 ± 77 μg · h · ml^{-1}) were twice as high after 12-mg · kg^{-1} injections as after 6-mg · kg^{-1} injections. No differences in mean residence time (9.7 ± 4.9 and 8.4 ± 2.7 h) or terminal half-life (8.5 ± 3.8 and 7.5 ± 2.3 h) were observed. Teicoplanin penetrated mediastinal and heart tissues but not sternal bone, where the antibiotic was detectable in only 1 of 13 patients in group 1 and 2 of 10 patients in group 2. In group 1, 7 of 13 patients had teicoplanin concentrations in tissue that were lower than the MIC for 90% of the strains of potential pathogens tested (MIC_{90}) that cause infection after cardiac surgery. All of the patients in group 2 but one had teicoplanin concentrations in tissue (other than in sternal bone) far in excess of the MIC_{90} for the potential pathogens. In conclusion, the 12-mg · kg^{-1} regimen of teicoplanin is followed by a significant increase in teicoplanin concentrations in heart and mediastinal tissues and should be preferred to the 6-mg · kg^{-1} regimen if teicoplanin is selected for antimicrobial prophylaxis in open heart surgery.

Although cardiac surgery is clean surgery, potential infectious complications have led to widespread prophylaxis with perioperative antibiotics (19). While cephalosporins are widely prescribed, the increasing prevalence of methicillin-resistant *Staphylococcus aureus* and methicillin-resistant, coagulase-negative staphylococci as potential pathogens has prompted a search for alternative prophylactic regimens (20). Teicoplanin, a glycopeptide antibiotic that is chemically related to the vancomycin-ristocetin group, has in vitro activities against a wide spectrum of gram-positive bacteria, including methicillin-susceptible and methicillin-resistant staphylococci (6) and seems to be less toxic. Teicoplanin is characterized by a slow bacterial killing rate, and there is evidence that the killing rate is concentration independent (7). Given this time dependency of bacterial killing, exposure of bacteria to antibiotic concentrations higher than the MIC for long period of time seems desirable. For prophylaxis of postoperative infections, such antibiotic concentrations should probably be achieved at all potential sites of infection from the beginning to the end of surgery (3, 19).

The present study was designed to compare two different dose regimens on teicoplanin concentrations achieved and maintained in mediastinal and heart tissues. Drug levels in tissue greater than or equal to the MICs for 90% (MIC_{90}) of the methicillin-susceptible or -resistant *S. aureus* (1 μg · ml^{-1}) strains and coagulase-negative staphylococci (3 μg · ml^{-1}) tested were considered desirable goals (1).

Subjects and study design. This study received the approval of the Ethics Committee of our institution (Hôpital Nord), and all patients gave their informed consent. The study was prospective and randomized and was designed to compare the intraoperative pharmacokinetics and tissue penetration of teicoplanin after two dose regimens in patients undergoing mitral or aortic valve replacement. Twenty-three patients divided into two groups were included in the study. Criteria for inclusion were an age of 18 years or older, absence of a prior history of hepatic or renal disease, elective surgery, and no clinical or laboratory signs of infection. Patients with a prior history of a hypersensitivity reaction to glycopeptide antibiotics were excluded from the study.

Antibiotic administration. Group 1 (13 patients) was given teicoplanin at 6 mg · kg^{-1} (body weight) intravenously by bolus injection (10 min) at the time of induction of anesthesia. Group 2 (10 patients) was given 12 mg · kg^{-1} (body weight) under the same protocol. A second dose of teicoplanin (6 mg · kg^{-1}) was given to both groups 12 h after the first administration.

Blood and tissue sampling. Blood samples (10 ml each) were collected from an arterial catheter and were carefully centrifuged (800 × *g* for 20 min). Tissue samples were immediately rinsed in normal saline and were pressed in sterile gauze to eliminate, as much as possible, contaminating blood. Serum and tissue samples were stored at −80°C until assay. Simultaneous blood and tissue samples were obtained from the thorax opening (thoracic wall fat, sternal bone [a mixture of cancellous and cortical bone], and pericardium), during cardiopulmonary bypass (CPB) (ventricular myocardium [cardiac

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apex or papillary muscle] and a fragment of the resected valve), and at the time of thorax closure (pericardium, sternal bone, and thoracic wall fat). Additional blood samples were obtained before teicoplanin (control); 5 (peak level), 15, 30, 45, and 60 min after teicoplanin injection; before initiation of a CPB; 10, 20, and 30 min after initiation of a CPB; at the end of aortic cross-clamping; at the end of the CPB; and at hours 8 and 12 (prior to postoperative teicoplanin administration).

Teicoplanin assay. Component $A2^{-2}$ (i.e., the 8-methylnonanoic acid derivative present in the complex) was kindly provided by Marion-Merrell-Dow Laboratories. All other reagents were of analytical grade and obtained from commercial sources. Concentrations of teicoplanin were determined by reversed-phase high-performance liquid chromatography combined with UV spectrophotometric detection at 214 nm. The technique used complied, for the most part, with the analytical recommendations of Jehl et al. (9). The equipment used was a Shimadzu LC6A pump high-performance liquid chromatograph (Touzard & Matignon, Courtaboeuf, France), coupled with an ISS-100 autosampler (Perkin Elmer Instruments, Saint-Quentin en Yvelines, France) combined with a Shimadzu SPD 10A spectrophotometer detector. Response signals (height integrations, calculations, and plotting of the chromatograms) were evaluated by a data processor fitted with I.C.S PIC3 analytical software (Instrumentation Consommable Service, Toulouse, France). The pH of the different eluents investigated was measured with a Metrohm pH meter (Roucaire, Courtaboeuf, France) equipped with a standard glass electrode and a standard calomel electrode and calibrated against aqueous buffers. Samples were eluted at room temperature at a constant flow rate of 1.0 ml/min. The mobile phase used was acetonitrile, sodium phosphate (1.0 M), and water (120:9:871, vol/vol). Before use, the mobile phase was filtered at room temperature with an HV 0.45-μm-pore-size filter (Millipore, Saint-Quentin en Yvelines, France); its final pH was 2.0 (the pH was adjusted with orthophosphoric acid). Separation was carried out on a Lichrospher RP C_{18} 5 μm column (125 by 4.0 mm; Merck-Clevenot, Nogent sur Marne, France). The method used consists of solid-liquid extraction on Bond Elut C_{18} columns with pretreatment (Varian, Saint-Quentin en Yvelines, France) with 1 ml of acetonitrile and 1 ml of water.

The method used a 150-μl test specimen (i.e., calibrators, controls, or sera) which was added to 350 μl of water and placed on a Bond Elut column. This solution was eluted by 0.5 ml of a solution consisting in acetonitrile and water (50:50 vol/vol). A 70-μl volume of the filtrate was injected.

Two calibration curves were prepared in pooled human serum (from 12 drug-free volunteers) spiked with teicoplanin at 0, 2.5, 5, 10, 16, and 25 μg/ml for the low concentrations and 0, 25, 50, 100, 150, and 200 μg/ml for the upper concentrations. Controls (4, 12, 25, 80, and 160 μg/ml) were prepared by using the same procedure. All calibration and control samples were processed as described above. Results were compared with standard curves obtained after analysis of the calibration samples.

Concerning tissue penetration by teicoplanin, a total of 225 samples were weighed and then frozen at −80°C until teicoplanin extraction was performed. In brief, each sample was frozen in liquid nitrogen (−192°C) and reduced in powder with an electric crusher (Spex 6700 Freezer-Mill; Bioblock Scientific, Illkirch, France). Each tissue powder was then exactly weighed and extracted as described above. Ratios of drug concentrations in cardiac and mediastinal tissues to those in patient sera were calculated to study teicoplanin distribution in cardiac tissues.

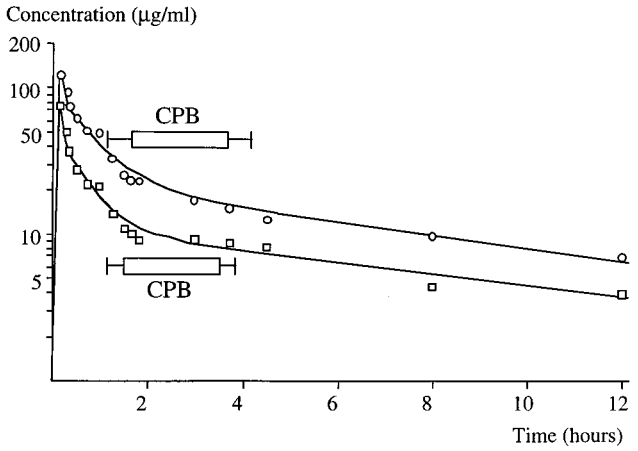

FIG. 1. Comparison of mean concentration profiles (semilogarithmic coordinates) for teicoplanin in serum obtained from two groups of patients after a first preoperative infusion of either 6 mg/kg (squares, group 1 [n = 13]) or 12 mg/kg (circles, group 2 [n = 10]). CPB periods are shown for both groups.

Pharmacokinetic analysis. Data were analyzed by a noncompartmental method (17). The terminal-phase rate constant (β; per hour) was determined as the slope of the terminal monoexponential decline in the drug concentration in serum with time by the least-squares method. The terminal half-life ($t_{1/2\beta}$; hours) was calculated by the equation $t_{1/2\beta} = 0.693/\beta$. The area under the concentration-time curve from time zero to time t of the last sample ($AUC_{0\rightarrow t}$) was calculated by the trapezoidal rule and was extrapolated to infinity by the equation $AUC_{t\rightarrow\infty} = C_t/\beta$, where C_t is the concentration of the drug in serum for the last sample withdrawn at time t. The mean residence time (MRT; hours) after intravenous infusion was calculated by the formula $MRT = \int_0^\infty tCdt/Cdt - T/2$, where T represents the time over which the drug was infused. Total clearance from serum (CL; milliliters per minute) was calculated by the equation $CL = dose/AUC_{0\rightarrow\infty}$. The apparent volume of distribution (V; liters) was determined as follows: $V = CL/\beta$. The apparent V at steady state (V_{ss}; liters) was calculated by the following equation: $V_{ss} = MRT(dose/AUC_{0\rightarrow\infty})$. The maximum concentration in serum (C_{max}; milligrams per liter) and the time to the maximum concentration in serum (T_{max}; hours) were experimental values.

The method of superimposition was used to predict the concentrations in serum after repeated administrations; concentrations in serum from the first dose of teicoplanin were summed, and the concentrations from subsequent doses over time were predicted. The predicted levels were compared with the concentrations measured in serum after the repeated doses. Thus, a predicted or theoretical accumulation ratio was estimated with the equation $R_{th} = AUC1_{0\rightarrow\infty}/AUC1_{0\rightarrow12}$, where $AUC1_{0\rightarrow12}$ and $AUC1_{0\rightarrow\infty}$ are the AUCs during a 12-h dosing interval and from time zero to infinity following the single dose, respectively.

Tissue penetration by teicoplanin. Tissue penetration by teicoplanin was evaluated by calculation of the ratio of the antibiotic concentration in tissue to that in serum. For each individual patient, in each tissue, and at the different stages of the surgical procedure (opening of the thorax, CPB, and closure of the thorax), individual ratios were calculated. Mean ratios were then calculated for each group and used as an estimation of tissue penetration by teicoplanin.

CPB. Anticoagulation was induced with heparin (300 IU · kg^{-1}), and the activated clotting time was monitored (over 400

TABLE 1. Individual and mean intraoperative pharmacokinetic parameters of teicoplanin after a 6-mg · kg^{-1} infusion into the patients in group 1[a]

Patient no.	C_{max} (mg/liter)	C_{CPB1} (mg/liter)	C_{CPB2} (mg/liter)	C_{min} (mg/liter)	$AUC_{0\rightarrow12}$ (mg/h/liter)	$AUC_{0\rightarrow\infty}$ (mg/h/liter)	CL (ml/min)	V (liters)	V (liters/kg)	V_{ss} (liters/kg)	MRT (h)	$t_{1/2\lambda}$ (h)
1	55.7	20.9	8.5	2.5	105.0	120.3	45.7	16.8	0.31	0.30	6.0	4.2
2	86.1	9.0	5.4	2.2	87.9	126.1	42.0	37.5	0.71	0.49	10.3	10.3
3	33.6	7.1	5.0	5.2	77.9	178.3	35.9	36.3	0.57	0.75	22.4	16.9
4	71.2	7.0	10.3	4.0	117.7	153.6	40.4	22.2	0.36	0.31	8.0	6.4
5	65.5	7.7	7.3	2.5	119.3	150.1	46.6	18.4	0.26	0.30	7.6	6.6
6	86.7	24.2	16.7	5.1	145.5	206.5	26.7	17.8	0.32	0.28	9.7	7.7
7	78.6	20.4	2.7	2.9	112.1	150.2	46.6	25.2	0.36	0.34	8.6	9.0
8	74.7	5.8		4.5	118.6	160.7	44.8	30.0	0.42	0.32	8.5	7.7
9	57.5	17.0	10.1	4.0	117.0	161.7	30.9	14.2	0.28	0.34	9.2	7.7
10	93.8	12.2		2.5	106.7	110.0	40.0	9.7	0.22	0.13	2.5	2.8
11	46.3	13.4	3.5	1.9	70.3	92.9	74.2	38.8	0.56	0.53	8.2	8.7
12	70.4	13.1	5.1	5.4	105.0	218.8	34.7	43.4	0.57	0.44	16.2	14.4
13	106.9	17.1	18.7	4.5	127.1	173.2	51.4	22.7	0.26	0.30	8.7	7.4
Mean	71.3	13.5	8.5	3.6	108.5	154.0	43.0	25.6	0.4	0.4	9.7	8.4
SEM	5.5	1.7	1.4	0.3	5.6	10.0	3.2	2.9	0.04	0.04	1.3	1.0

[a] C_{CPB1}, drug concentration in serum at the beginning of bypass; C_{CPB2}, drug concentration in serum at the end of bypass.

s during the CPB). The CPB pump (SARNS 9000; 3M Santé Laboratory, Malakoff, France) was primed with 500 ml of lactated Ringer solution, 500 ml of 14‰ bicarbonate, and 500 ml of dextran (molecular weight, 60,000). The pump flow rate was 2 liters · min^{-1} · m^{-2}, and blood was oxygenated with a membrane oxygenator (William Harvey, Bard College, Annandale-on-Hudson, N.Y.). The mean blood pressure was maintained at about 80 mmHg during CPB, and the core body temperature was decreased to approximately 28°C. Cardiac arrest was instituted by infusion of cold cardioplegia solution (hyperpotassic blood) into the aorta. A core body temperature of ≥34°C was required to achieve a CPB. After the CPB, heparin was neutralized with protamine (1.5 doses of protamine per dose of heparin).

Statistical analysis. All results are expressed as a mean ± the standard error of the mean (SEM). The Wilcoxon *t* test and linear regression by the method of least squares were used when appropriate. A P value of ≤0.05 was considered statistically significant.

The two groups were matched for the parameters studied. In group 1 (13 patients), the mean age was 42 ± 16 years, the CPB duration was 120 ± 34 min, and the duration of aortic cross-clamping was 70 ± 17 min. In group 2 (10 patients), the mean age was 47 ± 13 years, the CPB duration was 125 ± 31 min, and the duration of aortic cross-clamping was 65 ± 15 min.

Teicoplanin levels in serum. Figure 1 and Tables 1 and 2 show the evolution of teicoplanin levels in the sera of both groups at different periods. In groups 1 and 2, the peak levels of teicoplanin in serum were 71 ± 5.5 and 131 ± 13.9 mg · $liter^{-1}$, respectively ($P < 0.01$). Statistically significant differences in teicoplanin levels in serum were observed between the two groups ($P < 0.01$). At hour 12, the trough teicoplanin levels were 3.6 ± 0.3 and 6.8 ± 0.7 mg · $liter^{-1}$ in groups 1 and 2, respectively ($P < 0.01$).

Pharmacokinetics. Tables 1 and 2 present the pharmacokinetic parameters calculated for the two groups. Patients in group 2, who received a 12-mg · kg^{-1} dose of teicoplanin, had significantly higher C_{max}, C_{min}, $AUC_{0\rightarrow12}$, and $AUC_{0\rightarrow\infty}$ than patients in group 1, who received a teicoplanin dose of 6 mg · kg^{-1} (Table 3). No significant difference in MRT, V_{ss}, CL, or $t_{1/2\beta}$ was observed between the two groups. The method of superimposition was used to predict the drug concentration in serum after repeated administrations. Some degree of accumulation was predicted after injection every 6 h (R_{th} at 6 h, 1.774) and after injection every 8 h (R_{th} at 8 h, 1.491) (Fig. 2).

TABLE 2. Individual and mean intraoperative pharmacokinetic parameters of teicoplanin after a 12-mg · kg^{-1} infusion into the patients in group 2[a]

Patient no.	C_{max} (mg/liter)	C_{CPB1} (mg/liter)	C_{CPB2} (mg/liter)	C_{min} (mg/liter)	$AUC_{0\rightarrow12}$ (mg/h/liter)	$AUC_{0\rightarrow\infty}$ (mg/h/liter)	CL (ml/min)	V (liters)	V (liters/kg)	V_{ss} (liters/kg)	MRT (h)	$t_{1/2\lambda}$ (h)
1	87.3	28.6	13.3	8.0	177.1	254.2	55.9	27.3	0.38	0.47	9.9	8.1
2	109.0	24.8	14.6	6.4	185.4	241.4	70.4	40.0	0.47	0.39	7.8	6.6
3	108.1	38.4		4.6	189.5	234.9	35.0	11.3	0.23	0.26	6.7	6.5
4	121.4	22.5	14.5	9.5	238.6	329.5	58.9	39.1	0.40	0.33	9.0	7.7
5	244.6	38.5	15.5	3.2	178.8	198.8	47.8	22.1	0.40	0.39	4.2	4.6
6	132.2	37.4	21.1	4.9	211.5	258.3	58.1	30.0	0.40	0.30	6.5	6.0
7	102.0	26.8	13.0	7.0	197.9	271.7	55.3	15.2	0.23	0.25	8.9	7.7
8	114.4	28.3	11.1	7.4	244.9	296.9	41.7	16.3	0.31	0.34	6.4	5.4
9	148.5	32.9	7.9	10.1	279.7	454.6	32.1	23.6	0.32	0.36	13.8	12.2
10	142.1	38.8	20.8	7.1	265.6	381.5	39.3	34.9	0.46	0.33	10.4	10.2
Mean	131.0	31.7	14.6	6.8	216.9	292.2	49.4	26.0	0.36	0.34	8.4	7.5
SEM	13.9	1.9	1.3	0.7	11.9	24.3	3.9	3.2	0.03	0.02	0.8	0.7

[a] C_{CPB1}, concentration before bypass; C_{CPB2}, concentration at the end of bypass.

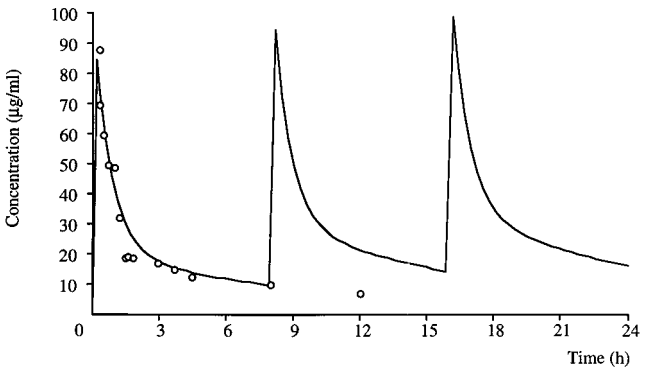

FIG. 2. Estimation of teicoplanin concentrations in serum after repeated administration (every 8 h). The R_{th} was 1.491.

Teicoplanin penetration of mediastinal and cardiac tissues. Table 4 shows the teicoplanin concentrations in various tissues during surgery in both groups. During the beginning stages of surgery, significantly higher teicoplanin concentrations were obtained in thoracic wall fat and pericardium than in sternal bone ($P < 0.001$). Indeed, only one patient in each group had a detectable teicoplanin concentration in sternal bone. When the two groups were compared, significantly higher ($P < 0.01$) teicoplanin concentrations in tissue were obtained for patients in group 2 with regard to thoracic wall fat and pericardium. In group 2 patients, teicoplanin concentrations were two to three times those in group 1 patients.

During the CPB period, significantly higher teicoplanin concentrations were obtained in the myocardium than in the endocardium ($P < 0.01$). When the two groups were compared, significantly higher ($P < 0.01$) teicoplanin concentrations in tissue were obtained for patients in group 2. Once again, in this group of patients, teicoplanin concentrations in tissue were two- to threefold higher than those in the other group.

At the end of surgery, the pattern of tissue (sternal bone, pericardium, and thoracic wall fat) penetration by teicoplanin was similar to that observed at the beginning of surgery. No patient in group 1 and two in group 2 had detectable teicoplanin concentrations in sternal bone. In thoracic wall fat and pericardium, teicoplanin concentrations were twice as high in group 2 patients as in group 1 patients ($P < 0.01$).

Table 4 shows teicoplanin penetration of the tissues studied. High levels of penetration (one to four times the level in serum) were achieved in myocardium and resected valve tissues and, at time of thorax closure, in pericardium and thoracic wall fat. With the exception of three patients (one in group 1 and two in group 2), no penetration of sternal bone was obtained, either at the beginning of surgery or at thorax closure.

In both groups, the ratios of the concentrations in tissue to the MIC_{90}s for the staphylococci tested (*S. aureus*, 1 $\mu g \cdot g^{-1}$; *S. epidermidis*, 3 $\mu g \cdot g^{-1}$) were calculated to evaluate the potential clinical efficacy of the teicoplanin concentrations achieved with each regimen of administration (6 or 12 $mg \cdot kg^{-1}$). Ratios were between 0 and 75.2. For *S. aureus*, the ratios were between 0 and 75.2, and for *S. epidermidis*, the ratios were between 0 and 25.1. When the two regimens of teicoplanin administration were compared, significant differences ($P < 0.01$) were observed with higher ratios achieved in group 2.

The proportion of patients with teicoplanin concentrations in tissues (except sternal bone) that were greater than or equal to the MIC_{90}s for *S. aureus* and *S. epidermidis* were calculated for both groups during the different periods studied. In group

TABLE 3. Comparison of pharmacokinetic parameters measured after a first preoperative infusion of teicoplanin[a]

Group	C_{max} (mg/liter)	C_{CPB1} (mg/liter)	C_{CPB2} (mg/liter)	C_{min} (mg/liter)	$AUC_{0\rightarrow\infty}$ (mg/h/liter)	$AUC_{0\rightarrow12}$ (mg/h/liter)	CL (ml/min)	CL (ml/min/kg)	V (liters)	V (liter/kg)	V_{ss} (liters/kg)	MRT (h)	$t_{1/2\lambda}$ (h)
1	71.3 ± 5.5	13.5 ± 6.1	8.5 ± 5.2	3.6 ± 0.3	108.5 ± 5.6	154.0 ± 10.0	43.0 ± 3.2	0.67 ± 0.94	25.6 ± 2.9	0.4 ± 0.04	0.4 ± 0.04	9.7 ± 1.3	8.4 ± 1.0
2	131.0 ± 13.9[b]	29.7 ± 11.4[b]	13.2 ± 6.1[b]	6.8 ± 0.7[b]	216.9 ± 11.9[b]	292.2 ± 24.3[b]	49.4 ± 3.9	0.71 ± 0.82	26.0 ± 3.2	0.36 ± 0.03	0.34 ± 0.02	8.4 ± 0.8	7.5 ± 0.7

[a] Groups 1 ($n = 13$) and 2 ($n = 10$) received teicoplanin at 6 and 12 $mg \cdot kg^{-1}$, respectively. The data shown are mean ± SEM.
[b] $P < 0.05$ versus group 1.

TABLE 4. Intraoperative penetration by teicoplanin of mediastinal and cardiac tissues[a]

Period and group	Mean concn (mg/g) ± SEM, range, tissue/serum concn ratio in:					
	Thoracic wall fat	Sternal bone	Pericardium	Myocardium 1	Myocardium 2	Resected valve
Opening of thorax						
1	10.5 ± 3.6, <LOQ–37.6, 0.41 ± 0.15	0.8 ± 0.8, <LOQ–10.9, 0.0 ± 0.0	12.1 ± 3.3, <LOQ–21.8, 0.54 ± 0.17			
2	18.5 ± 7.5,[b] <LOQ–43.4, 0.37 ± 0.13	1.1 ± 1.1, <LOQ–12.3, 0.0 ± 0.0	37.9 ± 5.7,[b] <LOQ–69.8, 0.37 ± 0.13			
CPB						
1				46.9 ± 4.2, 23.3–64.9, 5.1 ± 1.7	47.1 ± 7.5, 14.4–103.9, 5.1 ± 1.7	10.8 ± 1.6, <LOQ–19.8, 1.2 ± 0.6
2				80.3 ± 12.2,[b] 11.5–142.5, 4.2 ± 1.9	69.5 ± 14.2, 14.5–129.3, 4.2 ± 1.9	24.8 ± 4.8,[b] <LOQ–55.9, 1.3 ± 0.7
Closure of thorax						
1	7.6 ± 2.2, <LOQ–33.6, 0.93 ± 1.1	<LOQ; 0.0 ± 0.0	35.7 ± 9.4, 11.8–83.2, 4.1 ± 4.2			
2	16.2 ± 4.4,[b] <LOQ–55.2, 1.3 ± 1.1	1.9 ± 1.3, <LOQ–14.5, 0.0 ± 0.0	47.4 ± 5.4, 18.2–87.9, 3.9 ± 2.1			

[a] The 13 patients in group 1 received an infusion of 6 mg of teicoplanin per kg, and the 10 in group 2 received a 12-mg/kg infusion. LOQ, limit of quantification.
[b] $P < 0.05$ versus group 1.

1, 7 patients (of 13) had inadequate teicoplanin concentrations in tissue, compared with only 1 patient in group 2 ($P < 0.05$).

The present study confirms the effective penetration of human mediastinal and heart tissues by teicoplanin. Concentrations in the heart valves and myocardium were high and, in most cases, greater than or equal to the MIC_{90}s for usually susceptible pathogens. Furthermore, very satisfactory levels were also achieved in the pericardium and thoracic wall fat. In most cases, these levels in tissues were also greater than the MIC_{90}s for pathogens usually responsible for infections following cardiac surgery. Similar results were obtained with vancomycin in a prior study in which in 70 to 100% of the patients antibiotic concentrations greater than or equal to the MIC for usually susceptible pathogens were achieved (12). Interestingly, high levels of penetration by teicoplanin were achieved in the thoracic wall fat (a poorly vascularized tissue) at times of thoracic opening and closure as well. Similar high vancomycin concentrations were observed in cardiac surgery patients who received the drug at 15 mg/kg before induction of anesthesia (12). This is of great clinical interest, since mediastinal infections are among the most severe complications after cardiac surgery. This finding is true even when the usual modalities of surgical antibiotic prophylaxis, which call for immediate (less than 2 h) preoperative administration of the chosen drug, are used (3). Unlike that of other tissues, penetration of sternal bone was poor at times of thorax opening and closure. Most patients (12 in group 1 and 8 in group 2) had no detectable teicoplanin concentration in sternal bone samples. This is at variance with the 20 to 30% penetration reported for cefazolin (15) and cefamandole (8) and the 30 to 60% penetration reported for vancomycin (12). In patients who underwent total knee replacement, de Lalla and colleagues, using a microbiological assay with *Bacillus subtilis*, found that teicoplanin readily penetrated bone, with concentrations ranging from 1.3 to 2.5 mg/kg in bone samples (4). Thus, there might be some methodological problems with the interpretation of penetration of bone by teicoplanin and other studies are needed to clarify this important point.

At the time of CPB initiation, many physiological changes occur in patients, and this technique is known to alter drug levels in plasma (18). At least two factors can explain this result: a rapid increase in V because of the additional volume in the priming pump and drug sequestration within the CPB circuit, which has been suspected for vancomycin (10). Whatever the mechanism, in the present study concentrations of teicoplanin in serum decreased when patient were placed on a CPB, from 13.5 ± 6.1 to 9.1 ± 2.8 $\mu g \cdot ml^{-1}$ in group 1 and from 29.7 ± 11 to 16.9 ± 6.4 $\mu g \cdot ml^{-1}$ in group 2. To prevent an alteration in tissue penetration, patients in group 2 received a higher dose of teicoplanin. With this dose regimen, significantly higher teicoplanin concentrations in tissue were achieved and significantly more patients had antibiotic levels in tissue that were equal to or greater than the MIC_{90}s for potential pathogens. Achieving and maintaining sufficient drug concentrations (equal to or greater than the MIC_{90}s for potential pathogens) in tissues to avoid the risk of postoperative infection are important goals when using antibiotics with time-dependent efficacy, such as teicoplanin. These concentrations should be maintained throughout the surgical procedures. This should be the case for total and unbound antibiotic concentrations as well. The present study was not designed to measure unbound teicoplanin concentrations, but other studies should be carried out to clarify this important point. With teicoplanin, efficacy is directly related to the time during which its concentration in target tissues exceeds the MIC for the offending organisms (7). Little gain in the rate or extent of killing is ob-

tained by increasing concentrations above that level. However, what constitutes an optimal antibiotic concentration in tissue is poorly understood (2). It is often described as a concentration above the MIC for the bacteria, but there are many examples of effective prophylaxis with antibiotic concentrations below the MIC and failures of prophylaxis with concentrations above the MIC (14, 16). Antibiotic concentrations below the MIC do produce morphological damage to bacteria, thus decreasing the growth rate and favorably influencing the outcome of an infection (11). It has also been shown that the efficacy of teicoplanin for the prophylaxis of endocarditis in rats is conferred in the absence of bacterial killing (5). It has been suggested that prophylaxis prevents endocarditis by inhibition of bacterial adherence, and another likely explanation is prolonged inhibition of bacterial growth (13). This may indicate that low levels of antibiotics allow the bacteria to be cleared from the valves by an undetermined mechanism.

Teicoplanin AUCs were significantly higher in group 2 than in group 1. Pharmacokinetic parameters related to teicoplanin behavior, such as $t_{1/2\beta}$ and MRT, were not significantly different between the two groups. The relatively short $t_{1/2\beta}$ is probably related to the short sampling time (12 h). However, this is not the only explanation, since in patients in group 1, C_{min} was as low as 3.6 mg · liter^{-1}. Actually, a dramatic increase (sixfold) in the apparent V compared with that of healthy volunteers was observed in the present study. This increase in V was also accompanied by a moderate decrease in CL, and both could account for the observed change in half-life. The method of superimposition was used to predict teicoplanin concentrations in serum after repeated administrations. The predicted accumulation ratios were 1.491 and 1.774 after injections given every 6 and 8 h, respectively. Since teicoplanin should be used for less than 48 h for antimicrobial prophylaxis, this degree of accumulation is probably negligible in clinical practice.

In conclusion, by comparison with a 6-mg · kg^{-1} injection, a teicoplanin dose of 12 mg · kg^{-1} results in significantly higher antibiotic concentrations in cardiac and mediastinal tissues in humans. The 12-mg · kg^{-1} dose regimen makes it possible to achieve and maintain, in most patients and throughout the operative procedure, antibiotic concentrations in tissues that equal or exceed the MIC_{90}s for potential pathogens that cause infection after open-heart surgery. HPLC determination showed that most patients had no detectable teicoplanin concentrations in sternal bone, whichever the teicoplanin dose administered.

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