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Penetration of Vancomycin in Uninfected Sternal Bone

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Concentrations of vancomycin in sternal bones of 10 patients undergoing cardiac surgery were studied at steady state, 48 h after starting intravenous prophylaxis. A sample of sternal bone was taken before (group I) or after (group II) cardiopulmonary bypass. The mean vancomycin concentrations in sternal bones were not significantly different between the groups and were 9.3 ± 3.0 μg/g. The concentrations of vancomycin in sternal bones were always above the MICs for staphylococci, streptococci, and enterococci.

Antibiotic prophylaxis is widely used in cardiac surgery. Methicillin-resistant coagulase-negative staphylococci are among the most common pathogens in this setting, and vancomycin is increasingly being used in patients with infections due to both coagulase-negative and coagulase-positive strains, indwelling devices, and immunosuppression. Vancomycin could be an alternative to cephalosporins (cefazolin and cefamandole) for prophylaxis during cardiac operations in allergic patients or when there are significant numbers of methicillin-resistant coagulase-negative staphylococci. Generally, vancomycin is given intravenously just before surgery (15 mg/kg of body weight) and then at 10 mg/kg every 8 h for 48 h (1, 3). Information on the ability of vancomycin to penetrate the sternum is limited. To evaluate the range of diffusion, we determined vancomycin concentrations in sternal bone at steady state during a dosage regimen ensuring trough levels in serum higher than those required for a bactericidal effect against most *Staphylococcus epidermidis* strains. Vancomycin (10 mg/kg) was administered prophylactically every 8 h over a 48-h period before surgery in 1-h perfusions.

The study design was approved by the local ethics review committee, and all of the subjects gave their written informed consent. Ten patients (eight males and two females) with a mean age of 50 ± 11 years undergoing myocardial revascularization (six patients) or valve replacement (four patients) with cardiopulmonary bypass (CPB) were enrolled. Renal and hepatic functions were normal (Table 1). None of the subjects had had an infectious disease in the 6 months prior to surgery.

The last preoperative administration of vancomycin (Vancocin; Eli Lilly & Co.) was started 3 h before surgery; vancomycin was not given during the operation but was administered every 8 h for 24 h postsurgery.

CPB is known to reduce plasma drug levels. The most likely explanation is the rapid increase in the volume of distribution because of the additional volume in the priming pump, which leads to a rapid change in drug concentration in plasma. This phenomenon has been observed with vancomycin (2, 6). To detect such an effect, patients were divided into two groups. A sample (250 mg) of sternal bone (a mixture of cancellous and cortical bone) was taken before (group I; five patients) or after (group II; five patients) CPB, which lasted 53.4 ± 26.9 min. The aortic clamp time was 35.2 ± 21.7 min; there was no significant difference between the two groups. Blood samples for plasma assays were drawn into heparinized tubes before the first perfusion (T_0), before (T_1) and at the end of (T_2) the penultimate perfusion, at the time of bone sampling (T_3), at the time of admission to the intensive care unit (T_4), just before the last postoperative perfusion (T_5), and at the end of the last perfusion (T_6).

Plasma was stored at −18°C until assay by fluorescence polarization immunoassay (TDX; Abbott Laboratories). Bone specimens were quickly washed with 0.9% NaCl, gently dried with a compress, and plunged into liquid nitrogen. They were then reduced to a fine powder with a SPEX 6700 crusher (SPEX Industries, Edison, N.J.). Vancomycin was extracted by 2 h of diffusion in a blank human plasma sample (250 mg of bone in 500 μl of plasma at 37°C). The mixture was then centrifuged before analysis of the supernatant. Vancomycin is known to be stable for 2 h under these conditions (2a). Calibration curves were prepared for the same conditions. Briefly, 500-μl aliquots of plasma containing 0, 2, 4, 6, 8 or 10 μg of vancomycin per ml were incubated for 2 h at 37°C with 250 mg of drug-free powdered bone. The mixture was then centrifuged, and the supernatant was analyzed for vancomycin by fluorescence polarization immunoassay. The measured net polarization values were used to establish the calibration curves. Net polarization was higher than that obtained with the same drug concentration in bone-free plasma, indicating the need to calibrate with bone-incubated standards. The concentration of vancomycin in the supernatant (C_s; in micrograms per milliliter) was converted to the concentration of vancomycin in bone (C_b; in micrograms per gram) by the equation $C_b = C_s \times V_s/W_b$ where V_s is the volume of supernatant (0.5 ml) and W_b is the weight of the bone sample in grams.

The sensitivity of the assay was 1 μg/g for a 250-mg sample. Within-run coefficients of variation for plasma controls of 7, 35, and 75 μg/ml were 10, 8, and 6%, respectively. The between-run coefficient of variation was 5.5% (samples were obtained from Interlaboratory Quality Control; United Kingdom External Quality Assessment Scheme, Department of Medical Microbiology, Southmead Hospital, Bristol, United Kingdom).

Blood contamination of bone samples was assessed by spectrophotometric determination of hemoglobin and was determined by the formula of Roncoroni et al. (9). As bone samples were generally insufficient, only five patients' sam-

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TABLE 1. Patient demographic information

Patient	Sex[a]	Age (yr)	Ht (cm)	Wt (kg)	TBPV[b] (min)	Serum creatinine (μmol/liter)	CPB[c] (min)	V_1[d] (liters/kg)	$t_{1/2\beta}$[e] (h)	Vancomycin concn in plasma (mg/liter)			
										Expected[f]		Measured	
										T_1	T_2	T_1	T_2
1	M	62	172	76.5	320	107	159	0.24 ± 0.04	13.11	17.57 ± 1.66	41.80 ± 5.05	20.1	35.9
2	M	58	164	63	330	96	70	0.21 ± 0.04	12.25	21.96 ± 3.95	44.60 ± 7.36	19.2	45.5
3	M	59	165	87	300	91	42	0.19 ± 0.03	8.46	13.39 ± 2.04	42.28 ± 4.80	11.8	44.2
4	F	64	153	78	240	93	35	0.21 ± 0.03	18.54	26.60 ± 4.85	55.06 ± 8.51	25.4	57.2
5	M	58	182	94	285	122	34	0.24 ± 0.04	17.38		43.20 ± 7.44		37.6
6	M	62	160	60	427	104	94	0.21 ± 0.04	10.78	15.64 ± 2.21	42.02 ± 5.19	15.0	41.7
7	M	50	179	66	320	88	63	0.20 ± 0.04	13.51	23.78 ± 3.45		27.1	
8	M	67	165	88	300	73	45	0.20 ± 0.04	8.31	12.11 ± 2.05		11.0	
9	M	54	159	66	360	139	36	0.21 ± 0.04	12.07	16.71 ± 2.56	42.74 ± 5.63	15.0	42.2
10	F	44	165	75	360	78	38	0.20 ± 0.03	8.79	13.80 ± 1.99	42.32 ± 4.81	12.9	44.5

[a] F, female; M, male.
[b] TBPV, time between preoperative vancomycin infusion and sternal sample.
[c] Duration of CPB surgery.
[d] V_1, volume of distribution in the central compartment (mean ± standard deviation).
[e] $t_{1/2\beta}$, half-life at β phase.
[f] Mean ± standard deviation.

ples were investigated. As contamination was always less than 7% and as it could not be evaluated for every sample, vancomycin concentrations were not corrected for hemoglobin levels.

Plasma and bone vancomycin concentrations for each patient are presented in Table 2 together with the doses given every 8 h.

Steady state was achieved in every case, and plasma vancomycin concentrations at T_1, T_3, and T_5 were always above the inhibitory concentration for staphylococci (MIC = 3.1 μg/ml) (10). Calculated volumes of distribution and half-lives (Abbottbase pharmacokinetic system; Abbott Laboratories) were in agreement with published data. The mean sternal bone vancomycin concentrations were not significantly different between the groups (Mann-Whitney test).

The mean vancomycin concentration in sternal bone (± standard deviation) for the patients in both groups was 9.3 ± 3.0 μg/g. Figure 1 shows the individual vancomycin concentration ratios (concentration in bone/concentration in plasma) at T_3; the mean value (± standard deviation) was 0.57 ± 0.20.

The only infectious complication of CPB was an abscess on the lower part of the sternotomy scar of one patient due to a *Klebsiella* sp. The patient responded well to piperacillin and amikacin.

Although vancomycin has been in clinical use for over 35 years, limited information on its diffusion in infected and noninfected human bone is available in the literature (4, 11). Here we provide more data on noninfected subjects undergoing thoracic surgery. One of the main findings was the good penetration of vancomycin into the sternum at plasma steady state. With the proposed drug dosage regimen, the concentration in bone was always above 4.2 μg/g 3 h after the last perfusion and during CPB and was, surprisingly, 30 to 70% of the concentration in plasma. This is higher than the 20 to 30% reported for cefazolin (7, 8), cefamandole, and cefotiam in femoral (cancellous) bone (5). Several factors may explain these differences, including the nature of the antibiotic, the bone studied, and the drug dosage regimen. Indeed, the studies cited above generally concerned prophylaxis in patients undergoing arthroplasty and receiving a single intravenous dose of antibiotic.

TABLE 2. Vancomycin concentrations in plasma and sternal bone

Patient	Dose (mg/8 h)	Vancomycin concn[a] at indicated time						
		Plasma (T_1)	Plasma (T_2)	Plasma (T_3)	Sternum	Plasma (T_4)	Plasma (T_5)	Plasma (T_6)
Group I								
1	765	20.1	35.9	19.25	5.9	16.0		
2	630	19.2	45.5	16.0	10.6	13.7	16.5	47.3
3	870	11.8	44.2	8.25	4.2	8.3	16.0	47.25
4	780	25.4	57.2	16.0	7.1	20.0	32.8	61.2
5	940		37.6	19.2	14.4	21.0	24.5	46.65
Mean ± SD		19.1 ± 5.5	44.0 ± 8.4	12.8 ± 7.7	8.4 ± 4.0	15.8 ± 5.1	22.4 ± 7.9	50.5 ± 7.0
Group II								
6	600	15.0	41.7	11.6	11.0	9.6	13.1	50.9
7	660	27.1		15.1	7.2	11.9	8.2	22.8
8	880	11.0		19.8	6.9	16.6	12.9	33.0
9	660	15.0	42.2	24.9	11.4	23.7	24.7	86.9
10	750	12.9	44.5	18.1	14.1	21.0	8.95	
Mean ± SD		16.0 ± 6.3	42.8 ± 1.5	17.9 ± 5.0	10.1 ± 3.0	16.5 ± 5.9	13.5 ± 6.6	48.4 ± 28.1

[a] Units are micrograms per milliliter for plasma and micrograms per gram for sternal bone.

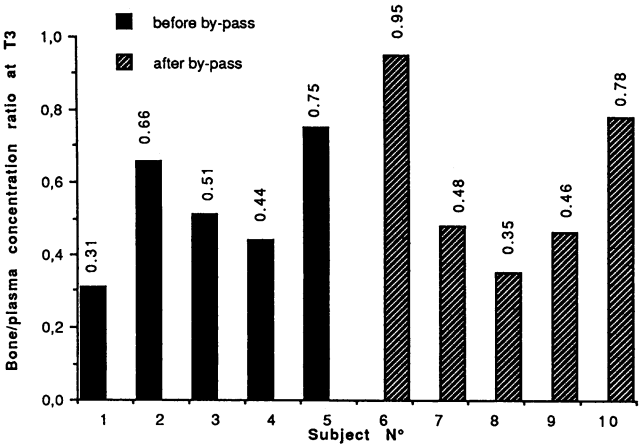

FIG. 1. Individual vancomycin concentration ratios (concentration in bone/concentration in plasma) at T_3.

Another interesting point is the interindividual variability of both the bone vancomycin concentration and the ratio of bone vancomycin concentration to plasma vancomycin concentration, which prevented us from determining a correlation between plasma and sternal bone drug concentrations. A similar phenomenon has been reported for cefazolin by Quentin et al. (8). It may be due to differences in vascularization and in the organization of bone tissue as well as to interpatient pharmacokinetic variability (4, 11). However, 5.4 ± 0.8 h after the last preoperative perfusion, plasma vancomycin concentrations were higher than 8 μg/ml, while bone vancomycin concentrations remained higher than 4.2 μg/g; these concentrations did not seem to be affected by CPB. Plasma and sternal bone vancomycin concentrations did not differ significantly between groups I and II.

In conclusion, the sternal bone vancomycin concentration was always above the MICs for *Staphylococcus aureus*, *S. epidermidis*, streptococci, and enterococci (usually 0.25 to 3.1 μg/ml) (10). These values do not certify the efficacy of vancomycin, but they suggest that further pharmacokinetic and clinical studies of vancomycin are warranted for the prophylaxis of patients undergoing chest surgery who are allergic to beta-lactams and for the treatment of osteomyelitis due to methicillin-resistant staphylococci.

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