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Impaired Target Site Penetration of Vancomycin in Diabetic Patients following Cardiac Surgery

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Soft tissue infections constitute a serious complication following surgery in diabetic patients and frequently require the administration of vancomycin. However, despite antibiotic treatment, mortality of patients with postoperative infections remains high and might be related to an impaired penetration of anti-infective agents to target tissues. Therefore, the present study was designed to measure vancomycin tissue concentrations in six diabetic and six nondiabetic patients after cardiac surgery. Vancomycin was administered as a continuous intravenous infusion at an infusion rate of 80 to 120 mg/h. Vancomycin concentrations in soft tissues and plasma were measured in all patients during steady state as "therapeutic window" concentrations in plasma by microdialysis on day 8 ± 4 after initiation of vancomycin treatment. Vancomycin tissue concentrations in diabetic patients were significantly lower than in nondiabetics (3.7 mg/liter versus 11.9 mg/liter; $P = 0.002$). The median $\text{vancomycin}_{\text{tissue}}/\text{vancomycin}_{\text{plasma}}$ concentration ratio was 0.1 in diabetic patients and 0.3 in nondiabetics ($P = 0.002$). Our study demonstrated that vancomycin penetration into target tissues is substantially impaired in diabetic patients versus nondiabetics. Insufficient tissue concentrations could therefore possibly contribute to failure of antibiotic treatment and the development of antimicrobial resistance in diabetic patients.

One of the most prevalent pathogens isolated from postoperative wound infections is *Staphylococcus aureus* (19, 24). Since methicillin resistance has been documented in 37.1% of 35 isolated *S. aureus* strains (19), there is a strong rationale for the administration of vancomycin, a glycopeptide antibiotic with favorable activity against gram-positive bacteria, including methicillin-resistant *S. aureus* with various degrees of resistance and coagulase-negative staphylococci (28, 29, 33).

However, despite initiation of antibiotic therapy, even with second-line antibiotics such as vancomycin (11, 24), postoperative wound infections remain a severe and potentially life-threatening complication after cardiac surgery (5, 19, 23). The incidence of postoperative wound infections is about 10% (11, 19, 24), with an associated mortality of up to 30% (5, 23). Patients with diabetes mellitus in particular have been shown to be at risk for the development of postoperative wound infections despite prophylactic antibiotic therapy (5, 11, 24).

Although the reasons for this particular situation in diabetic patients are manifold, it is conceivable that impaired penetration of antimicrobial agents into the interstitial space due to diabetes-associated changes in capillary density and permeability might be an important contributing factor. However, in vivo data on postoperative interstitial tissue concentrations in patients suffering from diabetes mellitus are not available.

To date, the penetration of vancomycin was addressed only in nondiabetic patients by means of total tissue biopsy samples, which yield methodologically questionable data (18).

In the present study we have therefore set out to address the question of interstitial penetration of the unbound, i.e., microbiologically active, concentration of vancomycin in patients suffering from diabetes mellitus. Vancomycin tissue concentrations were measured by means of microdialysis, an in vivo technique which allows the on-line measurement of unbound drug concentrations in the interstitial space fluid, the target site of most extracellular infections.

(This study was presented at the Annual Meeting of the European Association of Cardiothoracic Anaesthesiologists, 2004, London, United Kingdom.)

MATERIALS AND METHODS

The study was approved by the local ethics committee. All patients were given a detailed description of the study and their written informed consent was obtained prior to the study. The study was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines of the European Commission.

Patients. The investigation was performed on day 8 ± 4 (mean ± standard deviation [SD]) after the start of vancomycin treatment. Inclusion criteria for both groups were cardiac surgery, male or female, aged >19 years, body mass index ranging from 18 to 35, and prescription of vancomycin by a specialist from the Department of Infectious Diseases, who was not further involved in the study. Additionally, diabetic patients had to have been treated with insulin during the last 5 years or longer.

The diabetic group comprised two female and four male patients, with a mean age of 69 ± 7 years and a mean body mass index of 26 ± 1 kg/m^2 (mean ± SD). Three patients were in a stepdown unit and two patients required catecholamine treatment. The following mean hemodynamic variables were determined: heart rate of 97 ± 16 beats/min and mean arterial blood pressure of 79 ± 13 mm Hg. The following mean arterial plasma values were observed: saturation of oxygen, 99 ± 1%; creatinine, 1.8 ± 1.4 mg/dl; creatinine clearance, 52 ± 21 liters/h; total

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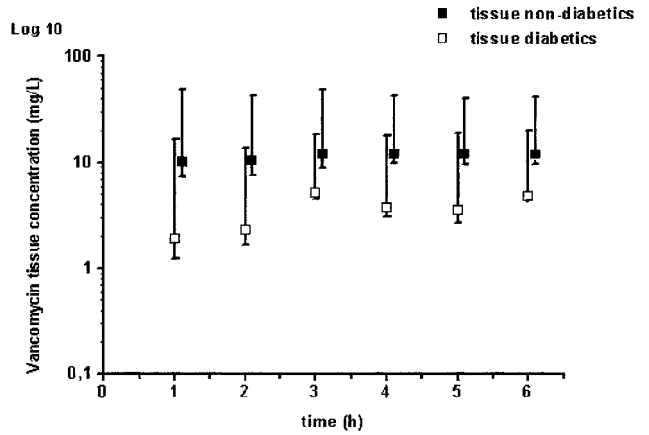

FIG. 1. Time versus vancomycin concentration profiles for soft tissue after determination of steady-state vancomycin plasma concentrations in diabetic (open squares, $n = 6$) and nondiabetic (solid squares, $n = 6$) patients. Values are presented as medians and ranges. The tissue and plasma concentrations were measured at the same time point. For better discrimination, the values for nondiabetics have been shifted.

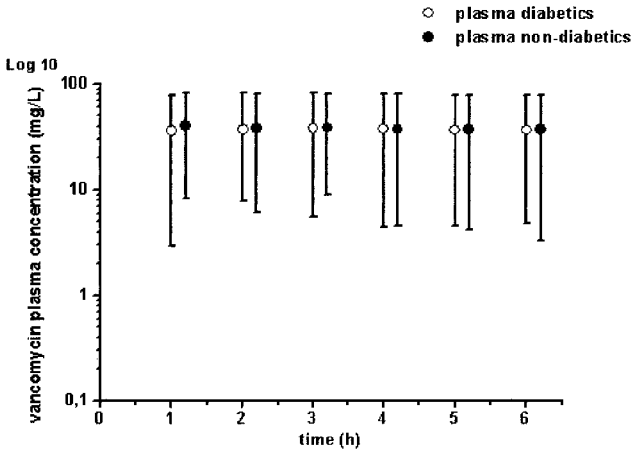

FIG. 2. Time versus vancomycin concentration profiles for plasma after determination of steady-state vancomycin plasma concentrations in diabetic (open circles, $n = 6$) and nondiabetic (solid circles, $n = 6$) patients. Values are presented as medians and ranges. The tissue and plasma concentrations were measured at the same time point. For better discrimination, the values for nondiabetics have been shifted.

plasma protein, 44 ± 5 g/liter; C-reactive protein, 11 ± 11 mg/dl; leukocytes, $12 \times 10^9 \pm 3 \times 10^9$G/liter; hemoglobin, 9 ± 2 g/dl; activated partial thromboplastin time, 47 ± 7 seconds; and blood glucose, 138 ± 2 mg/dl.

The nondiabetic group comprised six male patients, with a mean age of 56 ± 11 years and a mean body mass index of 26 ± 5 kg/m^2. All nondiabetic patients were in the intensive care unit and five patients were treated continuously with catecholamines. The following mean hemodynamic and laboratory variables were determined: heart rate, 119 ± 9 beats/min; mean arterial blood pressure, 80 ± 18 mm Hg; saturation of oxygen, 95 ± 5%; creatinine, 1.6 ± 0.7 mg/dl; creatinine clearance, 70 ± 32 liters/h; total plasma protein, 48 ± 8 g/liter; C-reactive protein, 22 ± 14 mg/dl; leukocytes, $19 \times 10^9 \pm 3 \times 10^9$/liter; hemoglobin, 10 ± 2 g/dl; activated partial tromboplastin time, 52 ± 13 seconds; and blood glucose, 138 ± 5 mg/dl.

There were no statistically significant differences between the groups.

Experimental design. Patients received a 1,000-mg intravenous loading dose of vancomycin (Eli Lilly Ges. m.b.H., Vienna, Austria) administered over 60 min, followed by a continuous infusion of vancomycin, 80 to 120 mg/h. The target plateau vancomycin serum concentration was achieved by either increasing or decreasing the pump speed. This concentration was chosen based on the MIC of vancomycin against *Staphylococcus* species (3, 33).

For the measurement of unbound interstitial vancomycin concentrations, in vivo microdialysis was employed as described previously in detail (22, 25, 27). For both groups of patients, the insertion of the microdialysis probes and sampling of dialysates and plasma were performed identically. For the study, we employed a flexible microdialysis probe (CMA 70 brain microdialysis catheter; Solna, Sweden) with a membrane length of 20 mm and molecular weight cutoff of 20,000. The microdialysis probe was inserted under sterile conditions into the interstitium of soft tissue at the thigh. The surface of the skin was punctured using a 20-gauge intravenous plastic cannula. The steel mandrin was removed, the appropriate site of the probe was checked by aspiration, and the dialysis probe was inserted via the plastic cannula. The microdialysis system was connected and perfused by means of a microinfusion pump (Predictor; Infors-AG, Basel, Switzerland) with Ringer's solution at a flow rate of 1.5 μl/min. After a 30-min baseline sampling period, microdialysis samples for determination of antibiotic concentration in the soft tissue were taken at 60-min intervals for 6 h. Simultaneously, blood samples were collected.

After determining steady-state concentrations for 6 h, in vivo probe calibration was performed for 40 min according to a modified non-net flux/retrodialysis method (22). The principle of this method relies on the assumption that the diffusion process is quantitatively equal in both directions through the semipermeable membrane. For the purpose of calibration, vancomycin at a concentration of 1 mg/ml was included in the perfusion medium and the disappearance rate (delivery) was calculated subsequently. The in vivo recovery was calculated as % recovery = $100 - (100 \times \text{vancomycin}_{out}/\text{vancomycin}_{in})$.

All samples were stored at −80°C until analysis.

Analysis. Vancomycin samples were analyzed by a fluorescence polarization immunoassay on a TDX analyzer (Abbott). The sample size has to be >50 μl. Samples included standards, controls, and patient specimens. These samples were placed in the sample slide of a dual-chamber sample cup and then automatically diluted in the generally used agents (8) and read for background fluorescence. Antibodies to vancomycin (25 μl) and fluorescein-labeled vancomycin (25 μl) were automatically dispensed into each cuvette containing the sample. After a 3-min incubation, a final polarization measurement is made. After blank correction, the concentrations of the specimens were determined by reference to a standard curve. The day-to-day coefficient of variation of the standards used by our laboratory was <8%.

Calculations for microdialysis experiment. For microdialysis experiments the interstitial concentrations were calculated by the following equation (22): interstitial concentration = 100 × (sample concentration/% in vivo recovery).

When individual recovery data could not be obtained, a mean tissue value from all other experiments was employed. Data were calculated by a commercially available computer program (Microcal Origin, version 5.0, Microcal, Northampton, Mass.) and the maximum concentration and the area under the concentration curve (AUC) were determined. The ratio $AUC_{tissue}/AUC_{plasma}$ was calculated as a measure for drug penetration into the peripheral compartment.

Statistical calculation. For data showing no normal distribution the values are presented as medians and ranges. For these data the Mann-Whitney rank sum test was used for analysis. A P of <0.05 was considered significant. For statistical calculations we used SigmaStat for Windows, version 2.03 (SPSS Inc. Build 2.03.0).

RESULTS

The results of in vivo microdialysis experiments and vancomycin plasma concentration measurements are shown in Fig. 1 and 2.

The in vivo recovery was assessed for each individual microdialysis probe by dialyzing the soft tissue with a perfusion medium containing 1 mg/ml of vancomycin for 40 min after the end of each experiment. The recovery of the microdialysis procedure was high, 83% (median) for diabetic patients and 66% (median) for nondiabetics. The individual recoveries were used for calculation of tissue concentrations.

Median vancomycin plasma concentrations were 36.5 mg/liter (range, 29.0 to 44.8 mg/liter) in diabetic and 37.6 mg/liter (range, 29.5 to 42.1 mg/liter) in nondiabetic patients (not significant). Median vancomycin tissue concentration were sig-

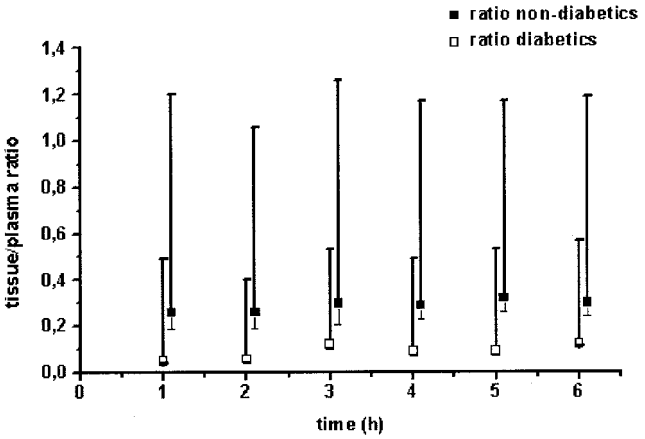

FIG. 3. Time course of $vancomycin_{tissue}/vancomycin_{plasma}$ concentration ratios as a measure of vancomycin penetration into soft tissue in diabetic patients (open squares, $n = 6$) and nondiabetics (solid squares, $n = 6$). Values are presented as medians and ranges. The tissue and plasma concentrations were measured at the same time point. For better discrimination, the values for nondiabetics have been shifted.

nificantly lower in diabetic patients, 3.7 mg/liter (range, 0.4 to 15.5 mg/liter), than in nondiabetic patients, 11.9 mg/liter (range, 2.2 to 38.4 mg/liter) ($P = 0.002$). The median $vancomycin_{tissue}/vancomycin_{plasma}$ concentration ratio in diabetics was 0.1 (range, 0.01 to 0.45), in contrast to that in the control group, which was 0.3 (range, 0.46 to 0.94) ($P = 0.002$) (Fig. 3).

We observed a median vancomycin concentration of <2 mg/liter in two diabetic patients and in none of the nondiabetic patients.

The main pharmacokinetic variables for plasma and interstitial tissue are given for both groups in Table 1.

DISCUSSION

Vancomycin is commonly employed for the treatment of systemic and local infections caused by *S. aureus* (17, 30) and is effective for methicillin-susceptible and methicillin-resistant strains. The reported MIC_{90} of vancomycin ranges from 0.5 to 2 mg/liter (28, 29, 30), and according to the definition of the National Committee for Clinical Laboratory Standards, staphylococci requiring a concentration of vancomycin of ≤4 mg/liter for growth inhibition are susceptible (33).

The study was done after achieving steady-state vancomycin plasma concentrations. Therefore, our results cannot discriminate differences in the times required to reach steady state between groups. The results demonstrated that the tissue concentrations and ratio of tissue/plasma concentrations were lower in patients suffering with diabetes mellitus than in controls. Two out of the six diabetic patients were observed to have vancomycin tissue concentrations of less than 2 mg/liter during the entire observation period, whereas all control patients had tissue levels of >2 mg/liter. This indicates that insufficient penetration of vancomycin in diabetics could be at least one of the reasons for frequent treatment failure in this patient subgroup.

The main finding of the present study supports the hypothesis that the process of distribution of antimicrobial agents might be significantly impaired due to micro- and macroangiopathy associated with diabetes mellitus, but this is in contrast to previous reports showing a similar or only slightly altered penetration of moxifloxacin (15), fosfomycin (9, 20), and ciprofloxacin (26) into the inflamed and noninflamed soft tissues of diabetic patients. A potential explanation for these findings might be that besides the influence of diabetes per se, various factors such as age, the pathophysiology of the underlying disease, positive fluid balance, and protein binding, etc., can alter drug kinetics. It has been shown for beta-lactams, notably piperacillin (6), cefpirome (14), and imipenem (32), that drug kinetics and interstitial concentrations are substantially altered by postoperative trauma and by septicemia (6, 14). Surgical trauma is associated with the release of various endogenous mediators influencing microcirculation and, thus, antibiotic distribution to the peripheral tissues (16).

Besides capillary density and permeability, protein binding is another important factor affecting unbound-drug distribution (1, 31). Vancomycin protein binding has been reported to range from 10% to ~80% (mean, 55%) (1, 31). Aside from this enormously wide range in protein binding, it is unclear which protein(s) is the major binding protein for vancomycin in serum (31). Therefore, it remains speculative whether protein binding influenced our results. In our study, the tissue/plasma drug ratio of 0.3 in controls is compatible with the published range of protein binding for vancomycin, and therefore the tissue-to-plasma gap of 0.7 in nondiabetic patients even at steady state is best explained by protein binding. The threefold-lower tissue/plasma ratio of 0.1 in diabetic patients, however, cannot be explained by protein binding alone and indicates an additional process that hampers distribution in diabetic patients.

It is a generally accepted therapeutic aim to reach high tissue concentrations of vancomycin while keeping vancomycin plasma concentrations as low as possible. Vancomycin serum levels in excess of 40 mg/liter were reported to be toxic (2, 4), whereas serum concentrations of 5 to 10 mg/liter have been demonstrated to be ineffective (10, 21). James et al. (13) and Wysocki et al. (34) employed a dose of 2 g or 30 mg/kg of vancomycin administered continuously over 24 h, yielding a steady-state concentration of between 20 and 25 mg/liter. This range is manyfold higher than the typical MICs of susceptible organisms.

In the present study the steady-state median vancomycin plasma concentration of 36.5 mg/liter in diabetics provided only a low median tissue concentration of 3.7 mg/liter. In

TABLE 1. Main pharmacokinetic variables calculated for the study population[a]

Subjects and target site	$AUC_{tissue}/AUC_{plasma}$	$AUC_{60-360min}$ (mg/liter · h)	C_{max} (mg/liter)
Diabetic	0.44 (0.08–2.02)		
Plasma		184 (157–215)	37.7 (35–45)
Tissue		18 (3.4–68)	5.1 (0.87–15.5)
Nondiabetic	1.45 (0.35–3.72)		
Plasma		199 (160–206)	40 (33–42)
Tissue		57.3 (14–157)	12 (4–38)

[a] AUC, area under the concentration versus time curve; C_{max}, maximum concentration of vancomycin. The values are presented as medians and ranges.

contrast, the median tissue concentration was about three times as high in nondiabetic patients, despite comparable plasma concentrations.

Our results indicate that the increased incidence of postoperative wound infections in diabetic patients could be at least partly caused by insufficient distribution of the antibiotic to the interstitial tissue. Furthermore, these data clearly demonstrate that high steady-state plasma concentrations of vancomycin do not guarantee sufficient concentrations in the interstitial tissue, the target site of the antibiotic in diabetic patients. Therefore, we conclude that diabetes mellitus influences vancomycin distribution to the interstitium. We hypothesize that this is due to impaired microcirculation in diabetics (7). However, this study did not measure microcirculation due to the technical difficulties of in vivo measurements of microcirculation.

Vancomycin is commonly used in patients suffering with diabetes mellitus in a rather liberal manner. This clinical practice can clearly be doubted according to our present data showing insufficient tissue concentrations together with high plasma concentrations in patients suffering from diabetes. Our data indicate that vancomycin tissue concentrations can be insufficient. Liberal use of vancomycin in diabetics might even contribute to the development of antimicrobial resistance (11).

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