Teicoplanin concentrations in serum, pericardium, pericardial fluid and thoracic wall fat in patients undergoing cardio-pulmonary bypass surgery

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Introduction

The prophylaxis of bacterial infections during cardiac surgery is widely used in clinical practice and its value has been documented in controlled studies. 1 Staphylococcus aureus and Staphylococcus epidermidis are the pathogens most frequently involved in infective complications of cardio-pulmonary bypass (CPB) surgery. 2-4 It is generally agreed that the success of prophylaxis is dependent on the ability to reach and maintain free antibiotic concentrations in tissues higher than the MICs for the most common pathogens. There is also evidence that effective antimicrobial prophylaxis is mainly due to an exposure to antibiotics during the operation period, as continuation of therapy after surgery does not achieve better clinical results than single day administration. 1 This implies that an adequate single dose should be used and that possible changes in drug distribution and elimination induced by CPB 5 should be taken into account. Glycopeptide antibiotics, such as vancomycin and teicoplanin, may be effective in the prophylaxis of staphylococcal infections especially in the presence of methicillin-resistant strains. Long duration of action and good tolerability are possible therapeutic advantages of teicoplanin 6,7 over vancomycin. Although various authors 4,8-11 have described the disposition and tissue uptake of teicoplanin during cardiac surgery, no information is available on drug levels attained in pericardial fluid, which should closely reflect free drug concentration in cardiac tissue. 12 The aim of the present study was two-fold: to evaluate teicoplanin serum level changes induced by CPB after the administration of a single high dose (12 mg/kg) and to evaluate teicoplanin penetration into pericardium, pericardial fluid and thoracic wall fat.

The concentrations of teicoplanin in serum, pericardium, pericardial fluid and thoracic wall fat were measured in patients undergoing cardio-pulmonary bypass (CPB) after the administration of a single iv 12 mg/kg dose. Five minutes after the start of CPB, teicoplanin serum concentrations decreased by, on average, 35% (95% confidence interval (CI): 28–42%) and remained significantly lower than the expected values over the subsequent 60 min period. After aortic unclamping drug concentrations rebounded but remained significantly lower than the expected values in the next 60 min. Immediately before CPB, penetration of teicoplanin in pericardium and thoracic wall fat was 0.44 (95% CI: 0.23–0.65) and 0.05 (95% CI: 0.03–0.7), respectively, and increased at the end of CPB to 0.90 (95% CI: 0.55–1.25) and 0.17 (95% CI: 0.05–0.29), respectively. MICs for most staphylococcal strains were attained during CPB procedure in pericardium but not in thoracic wall fat. However, since staphylococcal infections involve the interstitial space it is likely that penetration into fat cells is not important for antimicrobial prophylaxis. In this respect, it is worth noting that drug concentration in pericardial fluid, which should reflect the interstitial concentration, was higher than the MIC for most staphylococcal strains. Although no infective complications were observed in our limited series of patients, larger clinical trials are needed to assess whether the dose regimen employed is effective in preventing post-CPB surgery infections.
Materials and methods

Patients

Sixteen cardiac patients, six females and ten males, aged between 52 and 69 years (mean 62 years) and weighing between 60 and 91 kg (mean 72 kg) took part in the study after giving oral informed consent. The study protocol was approved by the local Ethics Committee. The patients underwent coronary-aortic bypass grafting (CABG) or valve replacement. None of them had a prior history of hepatic or renal disease. All patients were premedicated with oral flunitrazepam the evening before surgery and 1 h before anaesthesia. Before induction of anaesthesia all patients were monitored with 5-lead ECG, arterial catheter and peripheral venous line. Teicoplanin was infused intravenously over 3–5 min at a dose of 15 mg/kg, immediately before the induction of anaesthesia. Induction and maintenance of anaesthesia were accomplished with intravenous diazepam and fentanyl, and paralyis induced with pancuronium. A fter oral tracheal intubation, a central venous line and a Foley catheter were inserted. CPB was conducted in the standard fashion with a Stockert (Munich, Germany) pump and a Mono I yth (Sorin, Saluggie, Ver celli, Italy) oxygenator with integral heat exchanger. The CPB pump was primed with a Ringer solution (1500 mL) of the following composition: 20% mannitol (250 mL), 5% sodium bicarbonate (50 mL), Na heparin (50 mg) and aprotinin (2×10^6 IU). Before insertion of the aortic and vena caval/atrial cannulae, heparin was infused at a dose of 300 IU/kg body weight. Following aortic cross-clamping, a St Thomas cardioplegic solution was infused. The initial pump flow rate was 2.2–2.4 L/min/m^2 and was adjusted to maintain mean arterial pressure between 50 and 70 mm Hg. CPB was associated with moderate hypothermia (27–28°C) and a decrease in the haematocrit value (to about 25%), due to haemodilution. At t he end of CABG or cardiac valve replacement, re-warming was started and the aortic cross-clamp removed. CPB was started 119 min (95% CI: 104–134 min) after drug administration and lasted 89 min (95% CI: 75–103 min).

Blood and tissue sampling

Blood samples (5 mL) were taken via arterial catheter at the end of drug administration and after 0.5, 1, 6, 8 and 12 h after drug administration were fitted to a two-compartment iv model:

\[ C(t) = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} \]  

Data obtained in the interval between the first and sixth hour, i.e. during the CPB procedure, were analysed separately. Experimentally determined drug concentrations were compared with those extrapolated at the same times using Equation 1. The area under the curve (AUC) of serum concentrations, during and immediately after CPB, was calculated by the trapezoidal rule for both experimental and extrapolated data.

Statistical analysis

Data are presented as arithmetic means and variability as 95% confidence intervals (95% CI). The expected and measured AUC were compared using the paired t-test. The significance level was considered as P < 0.05.

Results

Serum

The time courses of mean teicoplanin serum concentrations measured before and after CPB procedure are shown in Figure 1, while concentrations measured during CPB are depicted in Figures 2 and 3. Teicoplanin serum concentrations show a sharp decrease immediately after starting CPB (Figure 2, upper panel) and a gradual

Drug assay

Drug concentrations in serum were determined by means of a fluorescence polarization immunoassay (TDX; Abbott Laboratories; sensitivity: 1.7 mg/L). For drug measurements in pericardial fluid, pericardial tissue and thoracic wall fat, a microbiological assay set up in our laboratory was employed, using Bacillus subtilis ATCC 6633 as test microorganism on Antibiotic Medium No. 1 (Difco, Detroit, MI, USA). Tissue samples were weighed and homogenized in distilled water (1:10 w/w). A fter centrifugation, the supernatant was lyophilized and redissolved in distilled water before assay. The calibration curves were prepared using pooled tissue homogenates containing no antibiotics. The sensitivity of the microbiological assay was 0.8 mg/L. Within-day reproducibility was 6.5% at 5 mg/kg and 2.4% at 80 mg/kg; between-day reproducibility was 8.9% at 5 mg/kg and 5.1 at 80 mg/kg. The equivalence of the two methods was tested in preliminary experiments. Drug concentrations were measured in spiked sera (n = 15) with both methods and the results were correlated by linear regression analysis: the slope was close to unity and the correlation coefficient was 0.97.
Effect of CPB on teicoplanin disposition

Figure 1. Mean serum concentrations (95% CI) at selected sampling times after iv teicoplanin 12 mg/kg iv bolus (n = 16) administration. The open box indicates the mean CPB time.

Figure 2. Mean serum concentrations (95% CI) of teicoplanin after start of CPB (upper panel) and after aortic unclamping (lower panel). Open circles represent the measured values and the closed circles the extrapolated values (see text).

Discussion

Our data indicate that CPB can modify the time course of teicoplanin serum concentrations. A sharp decrease in drug concentrations occurred at the start of CPB and lasted until CPB ended. The initial decrease in serum concentrations (−35%) is comparable to that reported in other studies (about −40%).\textsuperscript{1,4,11} Teicoplanin serum concentrations at the end of CPB were, on average, 20.3 mg/L, a value similar to that found by Wilson et al.\textsuperscript{9} (15 mg/L) after administration of the same iv dose. As pointed out by Buylaert et al.\textsuperscript{5} the decrease in drug serum concentrations at the onset of CPB is mainly due to an increase in the volume of distribution. Many factors may underlie this pharmacokinetic alteration such as an increase in blood volume, plasma protein dilution, drug binding to CPB apparatus, and drug-protein displacement by heparin-induced free fatty acid increase. It is likely that, after the initial haemodilution phase, a redistribution of the drug from tissues to blood occurred, which may explain the dome-shaped time course of teicoplanin serum concentrations during the 60 min interval after the start of CPB. During the post-bypass period a slow and partial rebound phenomenon was observed in

increase after aortic unclamping (Figure 2, lower panel).

The corresponding expected teicoplanin serum concentrations, extrapolated from Equation 1, are shown in parallel. Five minutes after initiating CPB, teicoplanin serum concentrations decreased by, on average, 35% (95% CI: 28–42%) and remained significantly lower than the expected values over the subsequent 60 min. Accordingly, the mean AUC values during CPB were significantly lower than the mean expected AUC [1258 mg/L/min (95% CI: 1059–1457 mg/L/min) vs 1725 mg/L/min (95% CI: 1496–1954 mg/L/min); mean decrease: 28% (95% CI: 8–14%)]. In the 60-min period following CPB, teicoplanin serum concentrations rebounded, but remained significantly lower than the expected values [AUC: 1229 mg/L/min (95% CI: 1039–1419 mg/L/min) vs 1505 mg/L/min (95% CI: 1307–1703 mg/L/min)]; mean decrease: 19% (95% CI: 13–25%).

Pericardium, pericardial fluid and thoracic wall fat

Figure 3 shows the time course of teicoplanin mean concentrations in serum, pericardium, pericardial fluid and thoracic wall fat. It appears that they are above the MIC for most strains of staphylococci (4 mg/L) in all samples except in adipose tissue. Before CPB, penetration of teicoplanin into pericardium and thoracic wall fat, measured as tissue to serum concentration ratio (T/S), was 0.44 (95% CI: 0.23–0.65) and 0.05 (95% CI: 0.025–0.075), respectively. At the end of CPB the ratios were 0.90 (95% CI: 0.55–1.25) and 0.17 (95% CI: 0.05–0.29), respectively. The increase in T/S during CPB procedure was mainly due to the fall in serum drug levels, while tissue concentrations were relatively stable, especially in fat. Teicoplanin concentrations in pericardial fluid were lower than in pericardium but higher than in fat (Figure 3).
serum levels. Indeed, drug concentrations remained significantly lower than the expected values over the 60-min observation period. This finding may be partly explained by the slow reinfusion of the fluid contained in the pump and, possibly, by some degree of drug sequestration by apparatus. So far, only one controlled study has evaluated the effectiveness of teicoplanin in antimicrobial prophylaxis during CPB surgery. Two different teicoplanin dose regimens were compared with a broad-spectrum antibiotic association (flucloraxillin plus tobramycin) and the effectiveness of teicoplanin was reported to be lower, in terms of number of sternal wound infections, than that of the association. The authors ascribed this partial prophylactic failure to the low antibiotic concentrations attained in fat, which were below the breakpoint for staphylococci (4 mg/L). Two subsequent smaller studies, and the present one with a total of 42 cardiac patients, employed a higher teicoplanin dose (12 mg/kg) and no prophylaxis failure was referred to. Although the small number of patients involved does not entitle us to draw firm conclusions, the hypothesis that higher doses of teicoplanin may increase therapeutic effectiveness is worth testing in a wider trial.

In agreement with data from the literature we found that teicoplanin penetration into fat is minimal (mean T/S ratio at CPB end: 0.18) and MIC values for most staphylococcal strains (4 mg/L) are barely attained. A previous study by Wilson et al. reported that teicoplanin concentration in fat at the end of bypass was, on average, 6.1 mg/L (95% CI: 4.6–7.7), which is somewhat higher than that found by us (3.8 mg/L (95% CI: 3.33–7.27 mg/L)). This difference is probably not significant and may be ascribed to the small size of the population studied and to interpatient pharmacokinetic variability. However, it should be recognized that free antibiotic concentration in tissue fluids may be more relevant than total (bound plus unbound) tissue concentration. In this respect, it is noteworthy that drug concentration in pericardial fluid, which more closely approaches that present in the interstitial fluid, is slightly above the breakpoint of most pathogens responsible for post-CPB infections (6 mg/L vs 4 mg/L). Since pericardial fluid does not generally contain proteins, drug concentration should be entirely available for the pharmacological action and in equilibrium with the unbound concentration in plasma. In agreement with this view, the serum concentration-to-pericardial fluid concentration ratio we found (0.12) is practically coincident with the free fraction of teicoplanin (0.11) measured in plasma. In conclusion, despite the low overall fat concentrations, free teicoplanin tissue concentrations, after a 12 mg/kg dose, may be above the MIC for most staphylococcal strains. Whether this dose regimen could be a valuable alternative to conventional antibiotic prophylaxis during CPB surgery needs to be evaluated in a larger scale clinical trial.

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References


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