Cefazolin and linezolid penetration into sternal cancellous bone during coronary artery bypass grafting

Martin Andreas, Markus Zeitlinger, Wilfried Wisser, Walter Jaeger, Alexandra Maier-Salamon, Florian Thalhammer, Alfred Kocher, Joerg-Michael Hiesmayr, Guenther Laufer and Doris Hutschala

Abstract

OBJECTIVES: Deep sternal wound infection is a severe complication after cardiac surgery. Insufficient antibiotic target site concentrations may account for variable success of perioperative prophylaxis. Therefore, we measured perioperative penetration of cefazolin and of linezolid into sternal cancellous bone after sternotomy in coronary artery bypass grafting (CABG) patients by in vivo microdialysis.

METHODS: Nine patients underwent CABG using a skeletonized left internal mammary artery. Standard antibiotic prophylaxis consisted of 4 g cefazolin prior to skin incision and additional 2 g during skin closure. In addition, 600 mg of linezolid were administered prior to skin incision and after 12 h for study purposes. Two microdialysis probes were inserted into the sternal cancellous bone (left and right side) after sternotomy.

RESULTS: First mean peak cefazolin and linezolid plasma concentrations were 273 ± 92 µg/ml and 22.1 ± 8.9 µg/ml, respectively. Mean peak concentrations of antibiotics in sternal cancellous bone on the left and right sternal side were 112 ± 59 µg/ml and 159 ± 118 µg/ml for cefazolin and 10.9 ± 4.0 µg/ml and 12.6 ± 6.1 µg/ml for linezolid, respectively. Cefazolin exceeded the required tissue concentrations for relevant pathogens by far, but linezolid did not gain effective tissue concentrations in all patients for some relevant pathogens. Mammary artery harvesting had no significant effect on antibiotic tissue penetration.

CONCLUSIONS: Direct measurement of antibiotic concentration in sternal cancellous bone with in vivo microdialysis is technically demanding but safe and feasible. We could demonstrate sufficient antibiotic coverage with our standard cefazolin-dosing regimen in the sternal cancellous bone during cardiac surgery. Mammary artery harvesting had no clinically relevant effect on tissue penetration. Linezolid concentrations were not sufficient for some relevant pathogens.

Keywords: Coronary artery bypass grafting • Deep sternal wound infection • Mediastinal infection • Perioperative antibiotics • Wound infection

INTRODUCTION

Surgical site infections are a severe burden on patients undergoing cardiac surgery [1–4]. In general, surgical site infections involving the sternum [deep sternal wound infections (DSWI)] are more threatening compared with other surgical incisions. Although superficial infections may be handled without relevant adverse events, DSWI are associated with an increased intensive care unit (ICU)-morbidity and ICU-mortality up to 46% [2]. Treatment of DSWI prolongs hospitalization, represents a high psychological burden for patients and is very expensive [2].

Perioperative antibiotic prophylaxis with cephalosporins is the state of the art during cardiac surgery to avoid wound infections [5–7]. In our previous study, we assessed the current recommendations regarding antibiotic prophylaxis with cefazolin [8]. Concentrations of cefazolin in plasma exceeded the minimal inhibitory concentrations (MIC90) of most of the susceptible pathogens, such as Staphylococcus aureus or Staphylococcus epidermidis. Although we applied a higher dose of cefazolin (4 g) prior to cardiac surgery in our institution and further administered a second dose of cefazolin (2 g) prior to skin closure, subcutaneous antibiotic penetration in the presternal area was impaired.
compared with unaffected tissue on the thigh. Furthermore, left internal mammary artery (LIMA) harvesting additionally decreased antibiotic penetration. Therefore, subcutaneous tissue concentrations of cefazolin failed to gain sufficient coverage against relevant pathogens in a significant number of cardiac surgery patients.

Clinical trials evaluating the antibiotic tissue concentration in the sternal bone are rare [9–11]. In addition, prior study groups measured the antibiotic concentration in tissue biopsies. This method of evaluation has distinct drawbacks, namely the punctual measurement obscuring the pharmacokinetic course and the measurement of the total antibiotic concentration, not differentiating between bound and unbound antibiotics, which therefore does not reflect the concentration of the active substance. In vivo microbiological activity is an appropriate method to measure the unbound, microbiologically active concentration of antibiotics in various tissues [6, 12, 13]. Reliable results have already been obtained in cardiac surgery [6, 8].

The type of cardiac procedure influences the risk of surgical site infection. Subjects undergoing coronary artery bypass grafting (CABG) including one or both internal mammary arteries are prone to developing surgical site infections due to impaired sternal perfusion after mammary artery harvesting [14]. Several strategies have been developed in the past to reduce the risk of surgical site infections. In addition to meticulous surgical technique regarding perfusion (skeletonized mammary artery harvesting, reduced application of electric cauterization and increased number of sternal wires), local antibiotic sponges and advanced dressing methods including postoperative sternal stabilization were developed [15, 16]. Furthermore, new antibiotics for prophylaxis may reduce DSWI.

Linezolid may be a candidate for perioperative antibiotic prophylaxis. It is frequently administered in cardiac surgery patients suffering from DSWI with susceptible pathogens, which are either methicillin-resistant or vancomycin-resistant [17]. Only one recent trial measured concentrations of unbound linezolid in the human bone [18]. Stolle et al. [19] postulated a decreased linezolid concentration measured by microdialysis compared with biopsy samples in cancellous pig bone. However, tissue concentrations of linezolid in the sternal cancellous bone were not yet measured in patients undergoing cardiac surgery with extracorporeal circulation.

In this clinical trial we measured perioperative concentrations of two different antibiotics, cefazolin and linezolid, in sternal cancellous bone of patients undergoing cardiac surgery. We aimed to demonstrate the penetration characteristics of these antibiotics into sternal cancellous bone in the specific setting of cardiac surgery. Our results may determine tissue penetration after mammary artery harvesting and could help to re-evaluate common clinical antibiotic dosing schemes of cefazolin and linezolid in CABG-patients.

MATERIALS AND METHODS

Nine patients undergoing isolated CABG with LIMA harvesting were asked to participate in this trial. Exclusion criteria were preoperative administration of antibiotic therapy or preoperative clinical signs of infection, allergy to penicillin, cephalosporins or linezolid, left ventricular ejection fraction <40%, chronic severe renal or liver impairment, osteoporosis requiring medical therapy, a body mass index >40 kg/m², previous cardiac surgery and longstanding diabetes (non-insulin dependent and insulin-dependent diabetes; >7 years). Written informed consent was obtained prior to the study from all patients. The study was approved by an independent ethics committee and performed in accordance with the Declaration of Helsinki.

Experimental design

On-pump CABG was performed through a median sternotomy. Routine monitoring and general anaesthesia were used in all patients. Four grams of cefazolin were administered 60 min prior to skin incision continuously over 30 min with an infusion pump. A second dose of 2 g cefazolin was administered according to our routine protocol during skin closure. In addition, 600 mg linezolid was administered continuously over 30 min, starting 60 min prior to skin incision. Twelve hours after the first antibiotic administration of linezolid, a second dose of 600 mg was infused.

Two boreholes with a diameter of 3 mm were drilled into the outer layer of the compact bone tissue of the sternal bone’s corpus after sternotomy. The boreholes were located in the area corresponding to the second intercostal space and drilled in an oblique caudal direction (Fig. 1A). Thereafter, the introducer guidance cannula was inserted through the borehole into the sternal cancellous bone parallel to the sternotomy. The correct placement of the probes was controlled by direct vision of the lower sternal plate (Fig. 1B). We used a custom flexible microdialysis probe (CMA63® microdialysis probe, M Dialysis AB, Stockholm, Sweden). The tip of the probe consisted of a 0.6 × 10 mm polyether sulfone semipermeable membrane with a molecular weight

Figure 1: Positioning of sternal microdialysis probes. (A) Boreholes were drilled in an oblique direction in the area of the sternal bone corresponding to the second intercostal space. (B) The introducer guidance cannula was inserted through the skin and the borehole into the sternal cancellous bone parallel to the sternotomy. (C) Final placement of the microdialysis probes.
cutoff of 20000 Da. No bone wax or glue was applied to the sternum. The microdialysis probes were continuously perfused with Ringer’s solution (1.5 µl/min) using a microinfusion pump (M Dialysis AB, Stockholm, Sweden). Samples were collected to determine concentrations of cefazolin and linezolid at 30 min intervals for 2 h. The sampling interval was increased to 60 min for the following 10 h. Blood and microdialysis samples were again taken every 30 min for 2 h after the second linezolid dose and then again every 60 min for 10 h. In vivo probe calibration was performed after sampling for 30 min. The probes were removed immediately after probe calibration.

**In vivo measurements and probe calibration**

In vivo microdialysis is a minimally invasive technique based on sampling of unbound (free), microbiologically active molecules from the interstitial space (extracellular space) by means of a semi-permeable membrane at the tip of the microdialysis probe [20]. The principle of the in vivo microdialysis method is similar to a dialysis technique. The probe is constantly perfused with Ringer's solution. Substances present in the extracellular fluid (C\text{tissue}), surrounding the microdialysis membrane, diffuse out of the extracellular fluid into the probe, resulting in a concentration in the perfusion solution (C\text{dialysate}). For many analytes, equilibrium between extracellular tissue fluid and the perfusion solution is incomplete; therefore, C\text{tissue} is higher than C\text{dialysate} (C\text{tissue} > C\text{dialysate}). The factor by which the concentrations are interrelated is termed ‘relative recovery’ (recovery in % = C\text{dialysate} × C\text{tissue} × 100).

To obtain the absolute extracellular concentrations from the dialysate concentrations, microdialysis probe calibration was performed in each patient according to the retrodialysis method [20]. The in vivo recovery value was calculated as follows: recovery (%) = 100 − [100 × cefazolin (dialysate)/cefazolin (perfusate)]. The in vivo recovery was assessed for each individual microdialysis probe by dialyzing the subcutaneous tissue with a perfusion medium containing 400 µg/ml of cefazolin and 200 µg/ml of linezolid for 30 min. Interstitial, extracellular concentrations were calculated according to the following equation: Interstitial concentration (µg/ml) = 100 × [sample concentration (µg/ml/in vivo recovery (%))].

Study blood samples were kept on ice for a maximum of 60 min and were centrifuged at 4°C and 4000 rpm for 10 min. Cells were then discharged, and plasma was obtained. Plasma samples and dialysate samples were snap frozen at −20°C and stored at −80°C until analysis.

**Determination of cefazolin and linezolid concentration**

The concentration of cefazolin and linezolid in plasma and microdialysate was determined by high-performance liquid chromatography (HPLC; Dionex Ultime 3000 system, Dionex Corp/Thermo Scientific, Sunnyvale, CA, USA). Frozen plasma samples were thawed at room temperature and then centrifuged at 13,000 g for 5 min. After the addition of 200 µl acetonitrile to 100 µl plasma, the samples were centrifuged (13,000 g for 5 min) and 80 µl of the supernatant was injected onto the HPLC column. Microdialysate samples (10 µl) were injected onto the column without any previous precipitation procedure. Separation of cefazolin was carried out using a Hypersil BDS C18 column (5 µm, 250 × 4.6 mm internal diameter; Thermo Fisher Scientific, Waltham, MA, USA) preceded by a Hypersil BDS-C18 precolumn (5 µm, 10 × 4.6 mm internal diameter) at a flow rate of 1 ml/min as previously described [8]. Briefly, the column oven was set at 35°C and the ultraviolet detector at 270 nm. The mobile phase consisted of a continuous gradient mixed from ion pair buffer, pH 3.0 (50 mM potassium phosphate with phosphoric acid and 5 mM heptane sulfonic acid (mobile phase A) and acetonitrile (mobile phase B)). The mobile phase was filtered through a 0.45-µM filter (HVL/P04700, Millipore, Billerica, MA, USA). Mobile phase B linearly increased from 10% (0 min) to 70% at 17 min, at which point it was kept constant until 22 min. The percentage of acetonitrile was then decreased within 1 min to 10% to equilibrate the column for 7 min before application of the next sample. Separation of linezolid was carried out again on a Hypersil BDS C18 column (5 µm, 250 × 4.6 mm internal diameter; Thermo Fisher Scientific, Waltham, MA, USA) preceded by a Hypersil BDS-C18 precolumn. The mobile phase consisted of a continuous gradient mixed from 10 mM ammonium acetate/acetic acid buffer, pH 5.0 (mobile phase A) and methanol (mobile phase B). The mobile phase was also filtered through a 0.45-µM filter (HVL/P04700, Millipore, Billerica, MA, USA). The gradient ranged from 10% B at 0 min to 95% at 15 min where it remained constant for 5 min. Subsequently, the percentage of methanol decreased within 2 min to 10% in order to equilibrate the column for 8 min. The column oven was set at 45°C and the ultraviolet detector at 254 nm. Quantification of cefazolin and linezolid was based on external calibration curves of spiked human drug-free plasma and microdialysate with cefazolin and linezolid concentrations ranging from 0.05 µg to 500 µg/ml (limit of quantification was 0.03 µg/ml for cefazolin and linezolid, respectively). Coefficients of accuracy and precision for this compound were <9%.

**Determination of cefazolin and linezolid-protein binding**

Plasma samples (n = 4) were thawed to room temperature and centrifuged at 13,000 g for 5 min. A 300 µl aliquot was transferred to a Vivaspin 500 ultrafiltration device (Sartorius Stedim Biotech GmbH, Goettingen, Germany) and centrifuged at 13,000 g for 10 min at room temperature. The recovered ultrafiltrate was analysed directly by HPLC without extraction, as described, to determine the concentration of free (unbound) drug in the plasma. Samples that did not undergo ultrafiltration were assayed to determine total (bound and unbound) drug concentration. Protein binding was then determined according to the following formula: protein binding (%) = total drug–unbound (free) drug/total drug × 100.

**Statistical analysis**

We performed the pharmacokinetic analysis with a commercially available computer programme (Kinetica® 2.0.2, Innaphase, Philadelphia, PA, USA). The time versus cefazolin/linezolid concentration profiles for plasma and sternal cancellous bone were measured, and the following pharmacokinetic parameters were determined: maximum drug concentration after the first and second dose (C\text{max} 1, II), time to maximum drug concentration (t\text{max} 1, II), the area under the concentration curve for different time periods and the tissue penetration [ratio of tissue area under
the curve \((AUC)_{2.5-24}\) to plasma \((AUC)_{2.5-24}\). The AUC/MIC ratio for relevant pathogens was calculated in the linezolid group \([7]\).

Calculations and data analysis were performed using commercially available computer programmes (Statistica®, StatSoft, Inc., Tulsa, OK, USA and SPSS 20.0, IBM, Armonk, New York, NY, USA). Data are presented as the mean and standard deviation (±SD). A paired Student’s t-test was applied after logarithmic transformation as appropriate to compare pharmacokinetic parameters between the sternal sides. A P-value of <0.05 was considered significant.

**RESULTS**

Nine patients undergoing isolated CABG surgery with a skeletonized LIMA harvested with electric cautery were included in this analysis. Patients’ characteristics are depicted in Table 1. Insertion of microdialysis probes into sternal cancellous bone was technically demanding but could be performed without adverse events in all patients. Two microdialysis probes were damaged during implantation and were replaced immediately. Another two microdialysis probes (one on the left and one on the right side in two different patients) were damaged during the sampling period and therefore excluded from further calculation. In addition, results of 18 single measurement time points (6% of all samples) could not be analysed due to low sample volume and therefore were also excluded from the analysis. No deep or superficial sternal wound infection occurred in the postoperative period.

Mean peak cefazolin plasma concentration was \(273 ± 92 \mu g/ml\) after administration of 4 g cefazolin. After the second dose of 2 g cefazolin during skin closure, the mean peak plasma concentration was \(135 ± 63 \mu g/ml\) (Table 2, Fig. 2A). Mean peak linezolid plasma concentration after 600 mg linezolid was \(22.1 ± 8.9 \mu g/ml\) after the first and \(17.4 ± 6.1 \mu g/ml\) after the second dose (Table 2, Fig. 2B).

**Table 1:** Demographic, laboratory, haemodynamic and intraoperative treatment data (n = 9)

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Sex (male/female)</th>
<th>Age (years)</th>
<th>Size (cm)</th>
<th>BMI (kg/m²)</th>
<th>Number of grafts</th>
<th>Creatinine (mg/dl)</th>
<th>BUN (mg/dl)</th>
<th>Lactate max (mmol/l)</th>
<th>SaO₂ (%)</th>
<th>ECC time (min)</th>
<th>ACC time (min)</th>
<th>Norepinephrin intraoperative (μg/kg/min)</th>
<th>Norepinephrin postoperative (μg/kg/min)</th>
<th>Dobutamine (μg/kg/min) (n = 3)</th>
<th>Albumin (g/dl)</th>
<th>Total protein (g/dl)</th>
<th>Protein binding of cefazolin (%)</th>
<th>Protein binding of linezolid (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5/4</td>
<td>67 ± 16</td>
<td>168 ± 9</td>
<td>26.9 ± 6.2</td>
<td>2.4 ± 0.9</td>
<td>1.05 ± 0.27</td>
<td>19.8 ± 5.9</td>
<td>2.5 ± 1.1</td>
<td>97 ± 2</td>
<td>106 ± 56</td>
<td>58 ± 27</td>
<td>0.07 ± 0.05</td>
<td>0.02 ± 0.03</td>
<td>3.6 ± 0.7</td>
<td>41.9 ± 3.3</td>
<td>72.2 ± 4.0</td>
<td>57.0 ± 17.9</td>
<td>15.6 ± 5.5</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± standard deviation or as total number (gender).

BMI: body mass index; BUN: blood urea nitrogen; ECC time: time of extracorporeal circulation; ACC time: time of aortic cross clamp; SaO₂: arterial blood oxygen saturation.

**Figure 2:** Cefazolin and linezolid pharmacokinetics in plasma and tissue. (A) Cefazolin; (B) linezolid; data are presented as the mean and standard deviation.

**Table 2:** Main pharmacokinetic parameters of cefazolin and linezolid in plasma

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Cefazolin</th>
<th>Linezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td>(t_{\text{max} \text{ I}}) plasma (h)</td>
<td>1.2 ± 0.3</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>(t_{\text{max} \text{ II}}) plasma (h)</td>
<td>6.0 ± 0.0</td>
<td>13.9 ± 0.2</td>
</tr>
<tr>
<td>(C_{\text{max} \text{ I}}) plasma (µg/ml)</td>
<td>273 ± 92</td>
<td>22.1 ± 8.9</td>
</tr>
<tr>
<td>(C_{\text{max} \text{ II}}) plasma (µg/ml)</td>
<td>135 ± 63</td>
<td>17.4 ± 6.1</td>
</tr>
<tr>
<td>(\text{AUC}_{0-24}) plasma (µg/h/ml)</td>
<td>1518 ± 808</td>
<td>169.8 ± 51.5</td>
</tr>
</tbody>
</table>

\(t_{\text{max} \text{ I}}\) and \(t_{\text{max} \text{ II}}\): time until maximum drug concentration after the first (I) and the second (II) dosage; \(C_{\text{max} \text{ I}}\) and \(C_{\text{max} \text{ II}}\): maximum drug concentration after the first (I) and the second (II) dosage; \(\text{AUC}_{0-24}\): area under the concentration curve (from 0 to 24 h).
of LIMA harvesting (81 ± 41 vs 112 ± 59 µg/ml; P = 0.03), which was not the case for the right side (134 ± 145 vs 159 ± 118 µg/ml; P = 0.06). Tissue concentrations for linezolid were not different between the sternum halves and the second mean peak tissue concentrations were comparable with the first mean peak concentrations (Table 3, Fig. 2).

The tissue penetration of cefazolin during the 21.5 h (ratio of tissue AUC<sub>2.5–24</sub> to plasma AUC<sub>2.5–24</sub>) was 0.99 ± 0.59 on the right side and 0.74 ± 0.36 on the left side. This difference did not gain statistical significance (P = 0.93).

Linezolid showed excellent penetration into the sternal cancellous bone (Table 3). The calculated mean tissue/plasma ratio was 1.02 ± 0.47 on the right side and 0.82 ± 0.28 on the side of LIMA harvesting (P = 0.33).

Mean cefazolin tissue concentrations were well above the MIC<sub>90</sub> for Staphylococcus epidermidis (MIC<sub>90</sub> 4.0 µg/ml) and for Staphylococcus aureus (MIC<sub>90</sub> 1.0 µg/ml) during the whole surgical procedure and thereafter until 18 h after first administration [21]. Mean linezolid concentrations were above the MIC<sub>90</sub> for Staphylococcus epidermidis (MIC<sub>90</sub> 2.0 µg/ml) in 94 and 83% of measurements on the right and left side, respectively. However, the MIC<sub>90</sub> for Staphylococcus aureus (MIC<sub>90</sub> 4.0 µg/ml) was only covered in 67 and 56% of measurements on the right and left side, respectively. The calculated AUC<sub>2.5–24</sub>/MIC<sub>90</sub> ratio for the right and left side was 35 and 27 for Staphylococcus aureus as well as 69 and 55 for Staphylococcus epidermidis, respectively.

**DISCUSSION**

We report herein the plasma and tissue concentrations of cefazolin and linezolid in CABG patients during and after cardiopulmonary bypass. This is, to the best of our knowledge, the first clinical trial assessing the sternal cancellous bone concentrations of the currently recommended antibiotic prophylaxis with cefazolin during cardiac surgery by applying in vivo microdialysis [7]. Previous results with direct antibiotic measurements were limited by a higher detection limit due to the drawbacks of antibiotic concentration measurement in bone biopsies [11, 22]. Therefore, our results regarding cefazolin cannot be compared directly to previous trials in the sternal bone.

The peak concentration was detected at the beginning of our sampling period. Therefore, the real peak may be even higher, indicating a very fast penetration of cefazolin into the sternal spongiosa. The second peak concentration of cefazolin was lower than the first peak, which reflects the reduced dose of cefazolin compared with the first dose applied during skin closure.

Plasma concentrations of cefazolin detected in this trial were similar to our previous results [8]. Tissue concentrations were well above the 4-fold MIC indicating clinical effectiveness. However, mean peak cefazolin concentrations in subcutaneous prestenral tissue observed in the previous study were 13.1 ± 5.8 µg/ml on the left and 24.1 ± 4.7 µg/ml on the right sternal side, which is strikingly lower compared with the concentrations in the cancellous sternal bone (112 ± 59 and 159 ± 118 µg/ml). Hence, cefazolin offers a very high tissue penetration into sternal cancellous bone compared with subcutaneous tissue. It is quite obvious during surgery that the blood support and the blood turnover in the cancellous bone are higher compared with subcutaneous tissue. In addition, we avoided closing of the sternal cancellous bone with bone wax or gluing during or at the end of surgery. Therefore, bleeding of the sternal cancellous bone may additionally increase the sternal cancellous blood turnover.

Furthermore, the subcutaneous antibiotic tissue concentration measured in our previous trial was significantly decreased on the side of mammary artery harvesting. Interestingly, these side-related differences were not as pronounced as in the subcutaneous tissue, probably due to the much higher tissue penetration. This suggests a clinically non-relevant effect of mammary artery harvesting on the antibiotic tissue penetration of cefazolin into the sternal cancellous bone. However, deep sternal wound infections may start in the subcutaneous tissue and include the sternal tissue in a later stage of infection. Therefore, both subcutaneous and sternal antibiotic coverage are required during CABG to prevent sternal infections. Isolated sternal antibiotic penetration may be of increased clinical relevance in patients with sternal osteomyelitis.

We administered a rather high dose of perioperative antibiotic prophylaxis of cefazolin with a repeated dose prior to skin closure (in total 6 g of cefazolin). This dosing regimen was introduced several years ago according to the recommendations of our infectious disease specialists. We could previously show effective tissue penetration with this dosing and kept the higher perioperative dose as a routine regimen at our department [6]. Although cefazolin concentrations were above the MIC<sub>90</sub> of relevant pathogens during cardiac surgery, no extrapolation can be provided for lower doses of cefazolin applied in other centres. Current guidelines regarding duration of antibiotic prophylaxis for cardiac surgery highlight the lack of evidence to provide a clear recommendation towards isolated intraoperative prophylaxis compared with prolonged prophylaxis during the first 48 h [23]. Our study may raise the question of higher dosing even when prolonged prophylaxis is applied. Tissue penetration into subcutaneous areas should also be studied during prolonged prophylaxis in future trials.

**Table 3: Main pharmacokinetic parameters of cefazolin and linezolid in tissue**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cefazolin Left sternum</th>
<th>Cefazolin Right sternum</th>
<th>Linezolid Left sternum</th>
<th>Linezolid Right sternum</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; I tissue (µg/ml)</td>
<td>112 ± 59</td>
<td>159 ± 118</td>
<td>10.9 ± 4.0</td>
<td>12.6 ± 6.1</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; II tissue (µg/ml)</td>
<td>81 ± 41</td>
<td>134 ± 145</td>
<td>13.4 ± 6.9</td>
<td>14.0 ± 4.8</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;2.5–24&lt;/sub&gt; tissue (µg/h/ml)</td>
<td>700 ± 276</td>
<td>1157 ± 925</td>
<td>109.7 ± 20.7</td>
<td>138.2 ± 60.1</td>
</tr>
<tr>
<td>Tissue penetration</td>
<td>0.74 ± 0.36</td>
<td>0.99 ± 0.59</td>
<td>0.82 ± 0.28</td>
<td>1.02 ± 0.47</td>
</tr>
</tbody>
</table>

C<sub>max</sub> I and C<sub>max</sub> II: maximum drug concentration after the first (I) and the second (II) dosage; AUC<sub>2.5–24</sub> area under the concentration curve (from first measurement to 24 h); Tissue penetration: AUC<sub>2.5–24</sub> tissue (µg/h/ml)/AUC<sub>2.5–24</sub> plasma (µg/h/ml).
In addition to the standard antibiotic prophylaxis with cefazolin, we aimed to investigate the pharmacokinetic profile and tissue penetration of linezolid during and after CABG. The dosage of linezolid administered routinely for the therapy of sternal infections (2 x 600 mg in 24 h) showed a fast concentration peak of comparable concentrations in plasma as well as in both sides of the sternal cancellous bone after each dose (Tables 2 and 3, Fig. 2). Our data demonstrate excellent penetration of linezolid into sternal cancellous bone [24]. However, the recommended 24-h AUC/MIC target ratio for bacteriostatic effects of 50–80 was only achieved for *Staphylococcus epidermidis*, but not for *Staphylococcus aureus* [25]. The reported AUC/MIC ratio herein cannot be directly compared with the recommendations in the literature because the AUC could only be calculated after probe placement between 2.5 h and 24 h, therefore our values will slightly underestimate the true value for AUC/MIC0–24. However, it seems unlikely that a full 24-h measurement could improve the results for *Staphylococcus aureus* to fulfill the required threshold. Furthermore, tissue concentrations of linezolid exceeded the MIC90 of *Staphylococcus aureus* only in 56% of measurement time points on the left side. Therefore, linezolid tissue concentration may not be sufficient to protect from *Staphylococcus aureus* infections in this setting [25]. A higher dose of linezolid may be required to achieve tissue concentrations, which exceed the MIC90 of *Staphylococcus aureus*.

Our results regarding tissue concentration of linezolid are in line with previous publications. Traummüller et al. [18] detected comparable mean peak tissue concentrations in cancellous bone of diabetic patients with bacterial foot infections (15.1 ± 4.1 μg/ml). Furthermore, the results were also comparable with microdialysis measurements in the pig cancellous bone [19]. Microdialysis results obtained in bone tissue of the pig were reduced compared with simultaneously harvested biopsy samples. We did not take biopsies in our trial, however, we suppose that the microdialysis measurements are clinically more relevant compared with the biopsy samples as our results reflect the unbound and microbiological active antibiotic concentrations. Furthermore, Stolle et al. [19] discussed methodological problems as concentrations obtained in biopsies cannot be readily transferred to antibiotic concentrations and pharmacokinetics of linezolid in pigs at an age of 4 years may not reflect the adult patient. The comparability of our results with previously investigated populations that were not subject to intensive care indicate that special circulatory conditions due to cardiopulmonary bypass and catecholamine support at the intensive care unit are not a limiting factor for tissue penetration of linezolid. We cannot support the role of linezolid as a last-resort antibiotic drug for the treatment of sternal infections unconditionally. Infections with *Staphylococcus aureus* may require a higher dose of linezolid.

**LIMITATIONS**

A small sample size was chosen for this trial due to the invasive nature of the measurement technique. Several parameters including age, body size, body mass index, renal function, catecholamine dose and other parameters may influence antibiotic concentration and tissue penetration. These effects could not be evaluated in the current analysis. Further, no correction for multiple testing could be performed due to the small sample size.

The patient population was limited to patients with a left ventricular ejection fraction >40% and patients with LIMA harvesting. Therefore, antibiotic tissue concentration may differ in patients with severely impaired ventricular function or bilateral mammary artery harvesting.

Furthermore, two microdialysis probes (one on the left and the other on the right side) of two different patients were damaged during the sampling period. This was probably due to thoracic movements associated with sternal closure or cuffing during the awakening from anaesthesia. Single measurements (n = 18) could not be included into analysis as the sampling volume was too small.

**CONCLUSIONS**

Direct antibiotic measurement in sternal cancellous bone with in vivo microdialysis is technically demanding but safe and feasible in a difficult surgical setting such as in cardiac surgery. Cefazolin proved sufficient coverage with our advanced dosing regimen in the sternal cancellous bone. Linezolid did not gain effective plasma and tissue concentrations in all on-pump CABG patients for some relevant pathogens.

**Conflict of interest:** none declared.

**REFERENCES**


