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ORIGINAL ARTICLE

Cefuroxime plasma and tissue concentrations in patients undergoing elective cardiac surgery: Continuous *vs* bolus application. A pilot study

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Aims: Surgical site infections contribute to morbidity and mortality after surgery. The authors hypothesized that higher antibiotic tissue concentrations can be reached for a prolonged time span by continuous administration of prophylactic cefuroxime compared to bolus administration.

Methods: Twelve patients undergoing elective cardiac surgery were investigated. Group A received 1.5 g cefuroxime as bolus infusions before surgery, and 12 and 24 hours thereafter. In group B, a continuous infusion of 3.0 g cefuroxime was started after a bolus of 1.5 g. Cefuroxim levels were determined in blood and tissue (microdialysis). *T*-test, Wilcoxon signed rank test and χ^2 test were used for statistical analysis.

Results: The area under the curve (AUC) of plasma cefuroxime concentrations was greater in group B (399 [333–518]) as compared to group A (257 [177–297] h mg L^{-1}, [median and interquartile range], P = .026). Furthermore, a significantly longer percentage of time > minimal inhibitory concentrations of 2 mg L^{-1} (100% *vs* 50%), 4 mg L^{-1} (100% *vs* 42%), 8 mg L^{-1} (100% *vs* 17%) and 16 mg L^{-1} (83% *vs* 8%) was found for free plasma cefuroxime in group B. In group B, area under the curve in subcutaneous tissue (78 [61–113] h mg L^{-1}) and median peak concentration (33 [26–38] mg L^{-1}) were markedly higher compared to group A (P = 0.041 and P = .026, respectively).

Conclusions: Higher cefuroxime concentrations were measured in plasma and subcutaneously over a prolonged period of time when cefuroxime was administered continuously. The clinical implication of this finding still has to be elucidated.

KEYWORDS

antibiotic prophylaxis, cardiac surgery, microdialysis, surgical site infection, tissue cefuroxime concentration

The authors confirm that the PI for this paper is Edda M. Tschernko and that she had direct clinical responsibility for patients.

1 | INTRODUCTION

Despite routine antibiotic prophylaxis, surgical site infections (SSI) remain a feared complication after cardiac surgery. They are associated with significant morbidity and mortality, prolonged hospital stay, and exorbitant healthcare costs.[1] The reported total incidence of sternal wound infections after cardiac surgery ranges from 1 to 8% accounting for an in-hospital mortality of up to 25%.[1-3]

Antibiotic prophylaxis is efficient if antibiotic plasma and tissue concentrations reach effective levels during surgery and in the immediate postoperative period. The same dose of an antibiotic might be administered as bolus injection or as continuous infusion possibly leading to different pharmacokinetic profiles. For cephalosporins, like other β-lactam antibiotics, the most important pharmacokinetic/pharmacodynamic parameter is the percentage of time that the target site concentration (%T) exceeds the minimal inhibitory concentration (MIC: %T > MIC) after a single dose of the antibiotic.[4] For β-lactam, we usually target at least 50% (50%T > MIC).

Cefuroxime (CXM), a second-generation cephalosporin has been successfully used for SSI prophylaxis in cardiac surgery.[5] Traditionally, cephalosporin antibiotics have been administered as separate single bolus infusions, which provide cyclical peaks and troughs in plasma concentration. However, for maximized bactericidal potency the duration during which concentrations exceed the MIC of the underlying pathogen 4–8 times appears to require optimization.[6] In this context, it can be speculated that the mode of administration could play an important role, assuming that continuous infusion may lead to prolonged target site concentrations above the corresponding MIC. Recently, Roberts et al[7] and Abdul-Aziz et al[8] showed decreased hospital mortality and higher success rates after continuous infusion compared to bolus infusion of β-lactam antibiotics in severely septic patients. However, no data of tissue concentrations of CXM are available to date comparing the 2 modes of CXM administration in patients undergoing cardiac surgery.

We tested the hypothesis that higher surgical site concentration will be reached over time by continuous administration of CXM during heart surgery that might improve infection prophylaxis without increasing the cephalosporin dose. We therefore compared 2 different regimens (bolus *vs* continuous infusion) of prophylactic administration of CXM in patients undergoing elective cardiac surgery. To support our hypothesis, we assessed the treatment effect by describing the corresponding medians with the dispersion of the data as well as the interquartile ranges (IQRs), a measure of uncertainty.

What is already known about this subject

- First or second generation cephalosporines are successfully used to prevent surgical site infection after heart surgery.
- Continuous administration of antibiotics provides higher plasma concentrations.
- No data on tissue concentrations during continuously administered cefuroxime are available yet.

What this study adds

- We report plasma and tissue concentrations of cefuroxime after bolus and continuous infusion in patients undergoing elective cardiac surgery.
- Tissue concentrations were measured by the microdialysis technique.
- Continuous cefuroxime infusion provides higher tissue levels over a prolonged period.

2 | METHODS

The study was carried out at the Division of Cardiothoracic and Vascular Anaesthesia and Intensive Care Medicine of the Medical University of Vienna, Austria. The open, randomized, single-centre trial 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 surgery. The study was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines of the European Commission.

2.1 | Patients

Twelve male and female patients aged >19 years scheduled for elective cardiac surgery on cardiopulmonary bypass (CPB), were randomly allocated either to bolus (group A, $n = 6$) or to continuous (group B, $n = 6$) CXM administration. Exclusion criteria were: coexisting renal, hepatic or infectious diseases treated with β-lactam antibiotics or erythromycin prior to the start of the trial as well as prior medication with phenylbutazone, probenecid, acetazolamide or sodium bicarbonate, history of pseudomembranous colitis, haemodialysis or haemofiltration, previous cardiac surgery, combined procedures such as valve repair and coronary artery bypass graft (CABG) surgery or aortic aneurysm repair and known allergy or hypersensitivity against CXM. As use of the internal mammary artery as a bypass vessel during the CABG surgery impairs antibiotic penetration into the presternal tissue we primarily focused on patients scheduled for valve surgery.[9] The recruitment profile is depicted as a CONSORT flow diagram in Figure 1.

2.2 | Anaesthesia, cardiopulmonary bypass and surgical procedure

Anaesthetic management, surgical procedure and CPB were carried out as previously described.[10] Further details on the demographic data, surgical procedure, duration of surgery, aortic cross-clamp time, duration of CPB, total fluid balance and intensive care treatment of both study groups are given in Table 1.

2.3 | Experimental design

Microdialysis is an established technique at our department to measure antibiotic concentrations in the interstitial fluid (ISF). The detailed

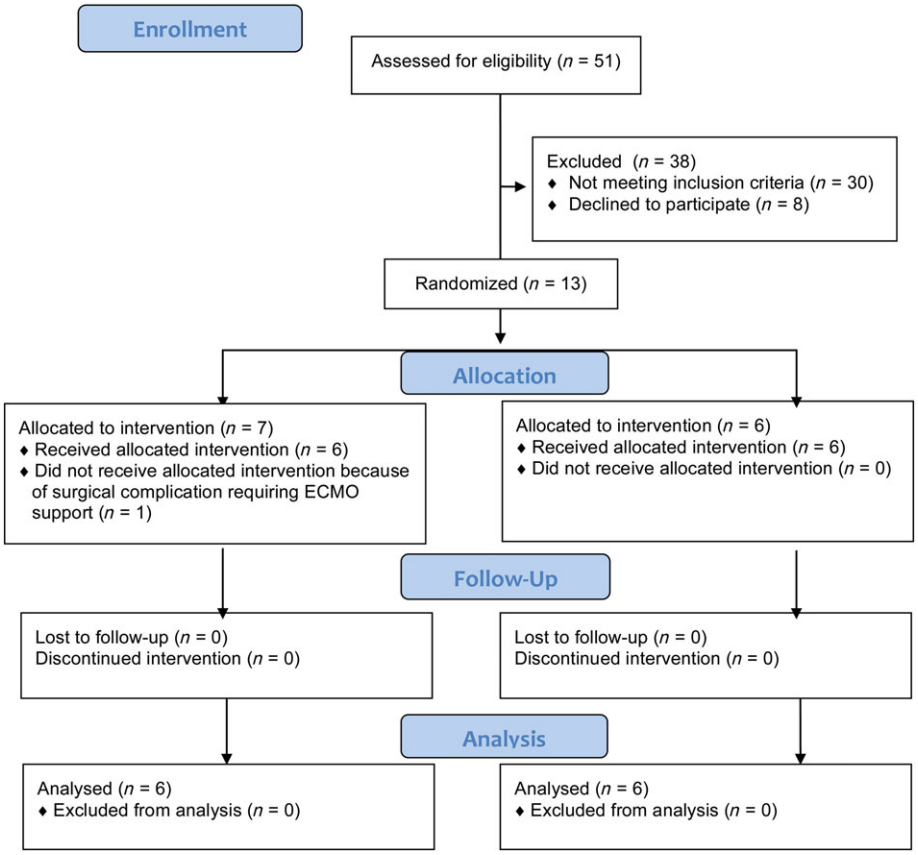

FIGURE 1 CONSORT 2010 flow diagram

methodology has been previously described.[11] In short, for this study we used a flexible microdialysis probe (CMA 70, Microdialysis AB, Stockholm, Sweden) with a membrane length of 20 mm and a molecular mass cut-off of 20 000 Dalton. All probes were inserted and calibrated after induction of anaesthesia.

The insertion of the probes was performed under sterile conditions. One microdialysis probe was introduced into skeletal muscle of the thigh and a second probe into the subcutaneous adipose layer of the thigh. Before insertion, the surface of the skin was punctured using a 20-gauge intravenous cannula. The steel stylet was then removed and inappropriate intravascular placement checked by negative aspiration after which the dialysis probe was advanced within the plastic cannula. Afterwards, the plastic cannula was removed, leaving the probe in the appropriate layer under the surface of the skin. The microdialysis system was connected and perfused with 0.9% saline solution at a flow rate of 1.5 μL min^{-1} using a microinfusion pump (Predicor, Infors-AG, Basel, Switzerland). After a 20-minute baseline perfusion period, in vivo probe calibration was performed for 40 minutes, followed by flushing the probe with Ringer's lactate until 20 gtt. had been evacuated. Then a 20-minute washout period began. Thereafter, 1.5 g CXM was administered intravenously (IV) within 10 minutes. This initial bolus dose was administered 30 minutes before skin incision in both groups. The following administration of CXM, however, differed between groups: patients of group A received a second and a third dose of 1.5 g CXM 12 and 24 hours after the initial administration, while group B patients received 3 g CXM as a continuous IV infusion over 24 hours that began immediately after the initial bolus infusion.

Microdialysis samples for determination of antibiotic concentrations were collected in both groups in a similar manner: the corresponding intervals were 20 minutes during the first 2 hours, 30 minutes during the following 2 hours, in 1-hour intervals during the 2 hours thereafter, and in 2-hour intervals during the final 6 hours. Microdialysis sampling was terminated 12 hours after the first IV CXM infusion.

Plasma samples were drawn in parallel to microdialysis samples. Sampling of plasma was terminated 32 hours after the first IV CXM administration in both groups. All samples were stored at −80°C until further analysis.

2.4 | In vitro experiment to determine the recovery rate of the microdialysis probes for cefuroxime

Three calibration solutions containing 5 μg mL^{-1}, 30 μg mL^{-1} and 60 μg mL^{-1} CXM were tested sequentially starting with the lowest concentration. These microdialysis probes were perfused with Ringer's lactate at a constant flow (1.5 μL min^{-1}). The dialysates were collected in 20 min intervals. The temperature of the calibration solution was measured during the whole procedure and was

TABLE 1 Demographic as well as perioperative data

Variable	Group A (bolus infusion; *n* = 6)	Group B (continuous infusion; *n* = 6)	*P* value
Age (y)	63 ± 10	69 ± 15	.442
Sex [male/female] (*n*)	2/4	3/3	>.999
BMI (kg m^{-2})	26 ± 2	26 ± 3	.877
LVEF >50% (*n*)	5	6	>.999
LVEF 30–50% (*n*)	1	0	>.999
Plasma protein level (g L^{-1})	77 ± 3	69 ± 11	.173
Plasma albumin level (g L^{-1})	45 ± 2	40 ± 7	.160
Serum creatinine (mg dL^{-1})	0.9 ± 0.2	1.1 ± 0.2	.076
Surgical procedure (*n*):			
AVR	4	5	
MVR + TVR	0	1	
ASD II	1	0	
MVR	1	0	
Duration of surgery (min)	165 ± 32	161 ± 38	.867
CPB time (min)	74 ± 24	73 ± 13	.919
ACC time (min)	51 ± 23	55 ± 9	.701
Fluid balance (mL)	2935 ± 1176	2897 ± 908	.952
Norepinephrine post-CPB (*n*)	4	4	>.999
Length of ICU stay (d)	1 ± 0	1 ± 0	>.999
Length of hospital stay (d)	11 ± 2	12 ± 3	.309

ACC, aortic cross clamping; ASD, closure of atrial septal defect; AVR, aortic valve replacement; BMI, body mass index; CABG, cardiac artery bypass grafting; CPB, cardio-pulmonary bypass; ICU, intensive care unit; LVEF, left ventricular ejection fraction; MVR, mitral valve reconstruction; TVR, tricuspid valve reconstruction. *T* test for numerical data and χ^2 test for categorical variables werer used for statistical analysis. Data are presented either as mean and standard deviation or numbers (*n*).

kept at 37°C, so that we could compare *in vivo* and *in vitro* results to each other. We found that mean recovery for all 3 concentrations was 85–88% (86 ± 5% with 5 μg mL^{-1}, 87 ± 9% with 30 μg mL^{-1} and 88 ± 9% with 60 μg mL^{-1}). Thus, we showed prior to the study that: (1) CXM does not adhere to the probes; and (2) CXM diffusion via the membrane of the probe is almost optimal.

2.5 | Calibration of the microdialysis system

For determination of relative recovery, the microdialysis probes were calibrated *in vivo* in each experiment according to the retrodialysis method.[12] The principle of this method is based on the fact that the diffusion process is quantitatively equal in both directions through the semipermeable membrane. Therefore, CXM was included in the perfusion medium for probe calibration at 30 μg mL^{-1}, and the disappearance rate (delivery) through the membrane was calculated subsequently for each individual microdialysis probe. The *in vivo* recovery value was calculated as follows:

$$\text{Recovery}\ (\%) = 100 - \left(\text{CXM}_{\text{dialysate}}/\text{CXM}_{\text{perfusate}}\right) \times 100$$

2.6 | Analysis of plasma and microdialysis samples

Concentrations of CXM in plasma and microdialysis samples were quantified using HPLC with detection at 274 nm according to the method of Signs et al.[13] Proteins in plasma samples were precipitated with an equal volume of an ice-cold mixture of methanol, containing the internal standard cefazoline and 0.1 M sodium acetate pH 5.2. After centrifugation at 1500 *g* for 10 minutes the clear supernatant was used for analysis. Microdialysis samples were injected directly. The lower limit of quantitation was 1 mg L^{-1} and the relative standard error (imprecision) was between 2.7% (100 mg L^{-1} plasma) and 8.5% (1 mg L^{-1} microdialysis sample). Protein binding was determined with a microcentrifugation system (Centrifree, Millpore, Austria) using the above method for the determination of CXM.

For microdialysis experiments, interstitial concentrations were calculated by the following equation:

$$\text{Interstitial concentration} = 100 \times \left(\text{concentration}_{\text{dialysate}}/\text{in vivo recovery value}\right)$$

2.7 | Calculation and statistical analysis

Demographic as well as perioperative data are presented as means ± standard deviation (SD). The following key pharmacokinetic parameters were determined: area under the concentration curve (AUC) over time, $AUC_{tissue}/AUC_{free\ plasma}$ ratio, maximum drug concentration (C_{max}) and time to maximum drug concentration (T_{max}). The corresponding values after 1 dose have been termed C_{1max} and T_{1max}, respectively. Percentage of time > minimum inhibitory concentrations (MIC) of 2, 4, 8 and 16 mg L^{-1} were also calculated. To provide a measure of precision of the reported estimates, medians and the respective IQR are given for these main pharmacologic variables in view of the fact that data were not normally distributed. Furthermore, the time *vs* CXM concentration profiles for plasma and ISF (subcutaneous and muscular) were determined and plotted.

Microcal Origin 5.0™ was used to calculate differences between pharmacokinetic parameters and also to create the corresponding figures. Further statistical analyses were done with the help of SigmaStat 2.03. Apart from the primarily intended more descriptive presentation of the data we additionally employed *t* test for normally distributed variables, the Wilcoxon signed rank test for non-normally distributed variables and the χ^2 test for categorical data. *P* values were not corrected for multiple comparisons, which is considered to be acceptable in exploratory pharmacological trials.[14]

3 | RESULTS

All patients underwent uncomplicated cardiac surgery. None of them experienced re-operation or SSI requiring prolonged hospital stay. Additionally, no complications associated with the microdialysis procedure were observed. Patient characteristics and preoperative data are depicted in Table 1, indicating that both groups were comparable.

Median recovery was 100% in group A *vs* 91% in group B for muscle tissue and 100% in group A *vs* 99% in group B for subcutaneous tissue (not significant). The individual median recovery was used for calculation of individual tissue concentrations.

Main pharmacokinetic parameters for plasma, free plasma, muscle and subcutaneous tissue for both groups are presented in Table 2. The median values of the total and free plasma concentration–time profiles are shown in Figures 2A and 2B, respectively. Protein binding was determined in the majority of patients and free plasma concentration calculation was based on a 24% plasma protein binding according to our measurements.

The medians of tissue concentrations over time for both groups are shown in Figures 3A and 3B, respectively (please note the different concentration scales on the y-axis).

In group A (Figure 2B), free plasma cefuroxime concentrations rose rapidly immediately after each bolus infusion and achieved the following 3 median free peak concentrations in plasma: 58 mg L^{-1} at 10 minutes (first peak), 65 mg L^{-1} at 5 minutes (second peak), and 65 mg L^{-1} again at 5 minutes (third peak) after each administration, respectively. After each bolus, free plasma concentrations decreased rapidly to their respective trough levels of 1.9 mg L^{-1} (first trough), 1.3 mg L^{-1} (second trough) and 2.3 mg L^{-1} (third trough) at 10 hours after start of the respective bolus infusion. In group B (Figure 2B), median free plasma CXM concentrations peaked at 68 mg L^{-1} 10 minutes after the initial bolus infusion. During the subsequent continuous infusion, free plasma concentrations decreased slowly but steadily, reaching the lowest median concentration of 2.7 mg L^{-1} 32 hours after the initial bolus infusion.

In group A (Figure 3A), median peak CXM concentrations of 21 mg L^{-1} in subcutaneous tissue and 26 mg L^{-1} in muscle tissue were reached at 65 minutes after the first bolus infusion in both group. In group B (Figure 3B), median peak CXM concentrations of 33 mg L^{-1} in subcutaneous tissue and 32 mg L^{-1} in muscle tissue were reached at 65 and 40 minutes, respectively. The discrepancy between tissue peak concentrations that are given in Table 2 and Figure 3 respectively can be explained as follows. C_{1max} was calculated for every individual patient as well as T_{1max} and AUC. While C_{1max} values given in Table 2 represent the median of the patients true C_{1max}, values in Figure 3 represent the actual median value that was calculated at the time of each predesigned measurement. Therefore, the differences result from the difference in the time to reach C_{1max} in each patient. Consequently, Figure 3 and Table 2 do not show identical numbers.

TABLE 2 Main pharmacokinetic parameters of cefuroxime in plasma and in the interstitial space fluid of muscle and subcutaneous tissue calculated for the study populations

Variable	Group A (bolus infusion; *n* = 6)	Group B (continuous infusion; *n* = 6)	*P* value
AUC (h mg L^{-1})			
$Plasma_{0\text{-}32h}$	338 (233–391)	542 (438–682)	.026*
Free $plasma_{0\text{-}32h}$	257 (177–297)	399 (333–518)	.026*
Muscle $tissue_{0-12h}$	49 (45–67)	81 (48–113)	.240
Subcutaneous $tissue_{0-12h}$	42 (39–47)	78 (61–113)	.041*
Muscle/$plasma_{free0-12h}$	0.49 (0.44–0.73)	0.28 (0.2–0.36)	.065
Subcutis/$plasma_{free0-12h}$	0.46 (0.39–0.49)	0.29 (0.22–0.46)	.180
C_{1max} (mg L^{-1})			
Plasma	77 (70–85)	90 (83–97)	.394
Free plasma	58 (53–79)	68 (63–73)	.394
Muscle	26 (23–28)	32 (22–43)	.589
Subcutaneous tissue	21 (19–29)	33 (26–38)	.026*
T_{1max} (h)			
Plasma	0.17 (0.17–0.17)	0.17 (0.08–0.17)	.065
Free plasma	0.17 (0.17–0.17)	0.17 (0.08–0.17)	.065
Muscle	1.1 (0.2–1.4)	0.7 (0.2–1.0)	.699
Subcutaneous tissue	1.1 (0.4–1.2)	1.1 (1–1.2)	.818

AUC, area under the concentration curve; C_{1max}, first maximum drug concentration; T_{1max}, time to reach first peak drug concentration (C_{1max}); muscle/plasma and subcutis/plasma, tissue penetration expressed as the ratio of free AUC tissue to free AUC plasma. Data are presented as median and interquartile range (IQR); Wilcoxon signed rank test was used for statistical analysis; *P < .05.

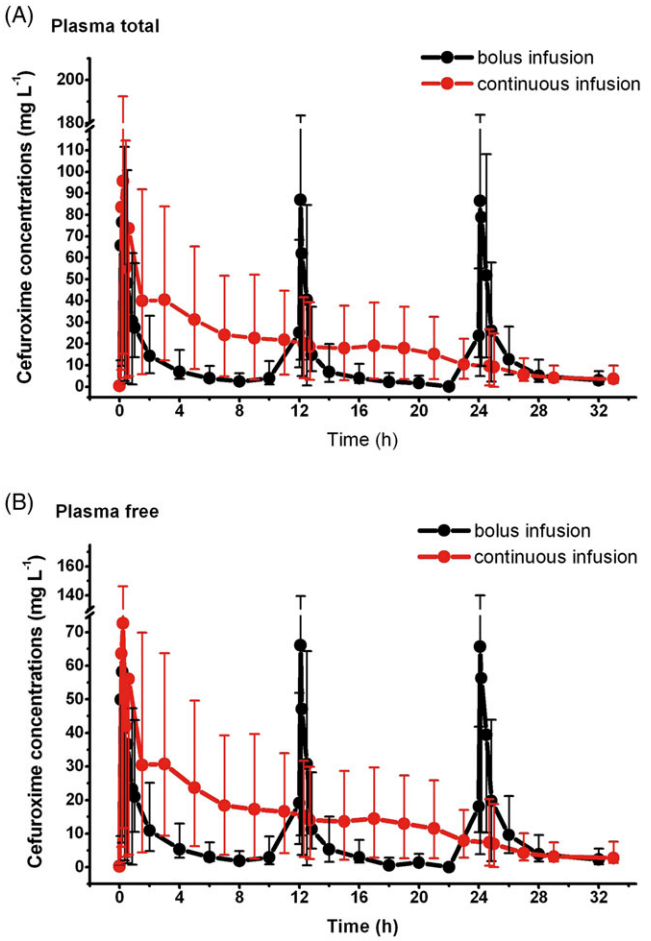

FIGURE 2 Median concentration – time profile for total (Panel A) and free (Panel B) plasma cefuroxime concentration for group A (bolus infusions) and group B (continuous infusion). The plasma concentrations in both groups were measured at the same time. For better discrimination, however, the values for group B have slightly been shifted to the right. The error bars represent interquartile range

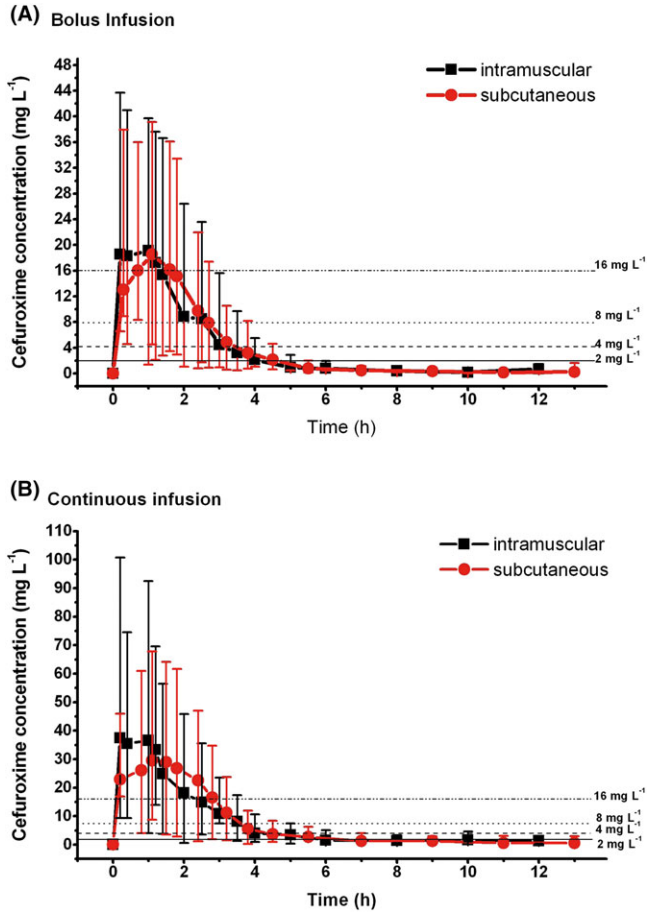

FIGURE 3 Median concentration-time profiles for bolus (Group A, Panel A) and continuous (Group B, Panel B) infusion of cefuroxime for muscle and subcutaneous tissues. Tissue concentrations have been determined at the same time. For better discrimination, however, values for subcutaneous concentrations have slightly been shifted to the right. The error bars represent interquartile range

Regarding pharmacokinetic parameters, AUC of the total plasma, free plasma as well as subcutaneous CXM concentrations, were significantly higher ($P < 0.05$) with continuous administration (Table 2). This was also the case for C_{max} of subcutaneous tissue, whereas no group difference was found for C_{max} of intramuscular tissues despite a numerically greater C_{max} in group B. In contrast, the mode of administration (bolus *vs* continuous) did not affect tissue/plasma AUC ratio, which indicates similar penetration of CXM into muscular and subcutaneous tissue. Accordingly, the ratio $AUC_{tissue/plasma}$ was comparable between groups. CXM was able to penetrate quickly into both tissues with a T_{1max} being reached within 65 minutes for both intermittent and continuous application (Table 2).

Another important pharmacokinetic parameter is the T > MIC, particularly for β-lactam antibiotics and especially for such a short-acting drug as CXM. The corresponding relationship between the T > MIC for free plasma, subcutaneous and muscular tissues are depicted in Table 3. Graphical evaluation of the respective cefuroxime concentrations over time for each patient has been used to determine the percentage of time > MIC. As shown in Table 3, a significantly longer

TABLE 3 Comparison of time in minutes (T_{min}) above minimal inhibitory concentration (MIC) by concentrations in mg L^{-1} and % of T > MIC for plasma and tissue in a 1 dosing interval i.e. from 0 to 12 hours

%T > MIC T_{min} > MIC	Group A (bolus infusion; *n* = 6)	Group B (continuous infusion; *n* = 6)	*P* value
2 mg L^{-1}			
Free $plasma_{0-12\ h}$	50% 360 (120–480)	100% 720 (720–720)	.004*
Muscle $tissue_{0-12\ h}$	31% 225 (210–300)	46% 330 (300–360)	.015*
Subcutaneous $tissue_{0-12\ h}$	33% 240 (210–240)	46% 330 (240–720	.132
4 mg L^{-1}			
Free $plasma_{0-12\ h}$	42% 300 (150–360)	100% 720 (720–720)	.002*
Muscle $tissue_{0-12\ h}$	23% 165 (150–210)	33% 240 (233–345)	.017*
Subcutaneous $tissue_{0-12\ h}$	25% 180 (180–210)	31% 225 (210–300)	.132
8 mg L^{-1}			
Free $plasma_{0-12\ h}$	17% 120 (50–240)	100% 720 (690–720)	.004*
Muscle $tissue_{0-12\ h}$	19% 135 (120–180)	25% 180 (150–233)	.177
Subcutaneous $tissue_{0-12\ h}$	19% 135 (120–150)	25% 180 (120–180)	.394
16 mg L^{-1}			
Free $plasma_{0-12\ h}$	8% 60 (50–60)	83% 600 (120–720)	.004*
Muscle $tissue_{0-12\ h}$	11% 80 (60–150)	17% 120 (115–172)	.177
Subcutaneous $tissue_{0-12\ h}$	14% 100 (60–100)	17% 120 (105–150)	.082

Data are presented as % of T above MIC and as median and IQR; *Wilcoxon Signed Rank* Test was used for statistical analysis;

*$P < 0.05$ Group A *vs* B.

%T > MIC was found in group B for MICs of 16, 8, 4 and 2 mg L^{-1} for plasma as well as for muscle tissue but only for an MIC of 4 and 2 mg L^{-1}. The clinical relevance can probably be better appreciated in Figures 2 and 3.

4 | DISCUSSION

The current exploratory study is the first to compare plasma and tissue concentrations of prophylactically administered CXM in patients undergoing elective cardiac surgery with CPB. We tried to determine whether continuous administration of CXM might be superior to intermittent dosing.

Antibiotic prophylaxis aims to achieve MICs exceeding those recommended for the suspected pathogens in all body compartments, i.e. in the intravascular, intracellular and interstitial space. Since the primary infection mostly affects the interstitial compartment, high interstitial antibiotic concentrations should to be provided.

Our trial revealed that despite administration of an equal cumulative dose over 24 hours (i.e. 4.5 g CXM) %T > MIC in plasma and tissue is shorter when CXM is given as 1.5 g bolus 3 times a day instead of a bolus of 1.5 g followed by 3 g CXM via continuous infusion. Statistically significant differences between the AUC of total and free plasma CXM concentrations could be demonstrated between groups (P = .026). In subcutaneous tissue AUC was higher (P = .041) when CXM was administered continuously. We also found significantly higher values (P = .026) for C_{max} in subcutaneous tissue.

The observed differences between the AUC of the respective plasma concentrations is not unexpected as continuous administration achieves constantly higher AUC_{plasma} values compared to an intermittent infusion (Figure 2).[10,11] Free concentrations of CXM in the ISF were lower than free plasma concentrations for the entire length of our experiment, which also was as expected.[10,11] Due to the technically highly demanding microdialysis technique intraoperative data are extremely rare. Pojar et al[15] reported an in vitro recovery rate of 89% and protein binding rate of 16–29%, which is comparable to our findings. In contrast, the recovery rate determined by Mandak et al[16] was merely 30% and protein binding ranged between 8 and 27%. These 2 trials reported much higher CXM plasma and tissue concentrations than ours. Muscular tissue concentrations of CXM even exceeded total and free plasma concentrations of CXM during surgery with CPB. However, it should be mentioned that baseline CXM dosage used in these trials were twice as high as those used in our investigation. Barbour et al[17] administered a single dose of 1.5 g CXM as prophylaxis in 6 obese patients undergoing abdominal surgery. Concentrations of CXM in muscle and subcutaneous tissue were also determined by microdialysis. In relation to the CXM tissue concentrations they obtained, ours were higher throughout the trial. Barbour et al[17] reported free plasma concentrations of CXM (based on a 33% protein binding) being less in relation to muscle concentrations (P > .05) but greater than the subcutaneous concentrations (P > .05). Furthermore, recovery rate in their trial was extremely low, i.e. 20% for subcutaneous adipose tissue and 10% for skeletal muscle tissue. In contrast, Naschimento et al[18] compared CXM tissue (subcutaneous tissue of the chest wall) and plasma concentrations in patients undergoing cardiac surgery. Their findings were comparable to our results despite different analytical and sampling methods.

The significant group difference regarding C_{max} in subcutaneous tissue and $AUC_{sc(0-12h)}$ in our trial can easily be explained. As already alluded to, the time course of the administration was different between groups, which means that, within a maximum 65 minutes (i.e. the time to reach C_{1max}) group B had received a greater amount of CXM than group A. However, the difference of administered CXM between groups at that time was only 125 mg, which may explain why we did not see a similar difference in muscular tissue.

Another aspect of antibiotic prophylaxis, apart from the questions whether MIC is reached, is the duration the tissue concentration of the antibiotic exceeds the respective MIC. In general, the MIC_{90} for CXM for most causative Gram-positive bacteria lies between 1 and 4 mg L^{-1} (see Table 4).[19-21]

TABLE 4 Minimal inhibitory concentration (MIC) of cefuroxime against indicated organism[20]

	MIC (μg mL^{-1})	
Bacteria	**Ranges**	**MIC 90**
MSSA	0.25–2	2
MRSA	4–64	>128
MSSE	0.25–4	1
MRSE	0.5 - >128	> 128
MSSH	0.5–4	2
MRSH	8 - >128	>128
CoNS	0.25–8	4

CoNS, Coagulase-negative *Staphylococci*; MRSA, Methicillin-resistant *Staphylococcus aureus*; MRSE, Methicillin-resistant *Staphylococcus epidermidis*; MRSH, Methicillin-resistant *Staphylococcus haemoliticus*; MSSA, Methicillin-susceptible *Staphylococcus aureus*; MSSE, Methicillin-susceptible *Staphylococcus epidermidis*; MSSH, Methicillin-susceptible *Staphylococcus haemoliticus*.

As previously mentioned, the percentage of time tissue concentrations are above the corresponding MIC is an important determinant of the efficacy of all β-lactam antibiotics.[4] For clinical and microbiological efficacy against Gram-positive staphylococci, T > MIC of the serum level of the free drug should be al least 40–50% of the dosing interval. For Gram-negative bacteria and streptococci, T > MIC should be 70% of the dosing interval.[4,22] In addition, a trough level of 4–16 mg L^{-1} is recommended for improved prophylaxis, particularly since the drug has a large therapeutic index and adverse events have not been reported as a consequence of high plasma concentrations.[6,23-26]

In the present study, the free plasma steady-state concentration of CXM achieved with continuous infusion in 1 initial dose was 100%T > MIC 2 mg L^{-1}, 4 mg L^{-1}, 8 mg L^{-1} and 83%T > MIC 16 mg L^{-1} compared to bolus infusion, where %T > MIC achieved for 1 dosing interval were 50% for MIC 2 mg L^{-1}, 42% for 4 mg L^{-1}, 17% for 8 mg L^{-1}, and 8% for 16 mg L^{-1} (Table 3). This means that via continuous infusion of CXM free drug concentration achieves at least 83%T > MIC that should be sufficient for the treatment of most causative Gram-positive cocci.

There are some limitations of our study that should be mentioned. First, the group size is small, which is due to the difficulty to include matching patients undergoing similar procedures with a comparable duration on CPB. A further limitation was the slightly different time course in the administration of the antibiotic between groups. Nevertheless, both groups received the same amount of antibiotic within 24 hours. In addition, statistical significance alone, which either confirms or rejects the underlying hypothesis, does not necessarily indicate clinical relevance especially when small groups are studied. The degree of uncertainty of the estimates and thus the potential clinical impact may better be appreciated in Figures 2 and 3 that incorporate IQRs.[14] Nevertheless, larger studies need to be performed to test for clinical outcome.

In conclusion, our findings demonstrate that higher plasma concentrations and longer time periods above MIC in muscle and

subcutaneous tissue can be achieved by continuous infusion of CXM after an initial bolus. This mode should therefore guarantee better prophylaxis for patients undergoing cardiac surgery. If bolus administration with shorter dosing intervals (e.g. every 6 hours) will maintain MIC_{90} of 4 mg L^{-1} (necessary to treat most Gram-positive bacteria) still has to be determined. Independent of the chosen regimen it may be prudent to administer CXM 60 minutes prior to skin incision in order to guarantee adequate tissue concentrations at the beginning of surgery since maximum interstitial drug concentrations were frequently reached only after 60 minutes following the first infusion.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

K.S.-D. helped design the study, conduct the study, recruit the patients, collect the data, analyse the data, write the manuscript and approve the final version. D.H. helped conduct the study and recruit the patients. G.R. helped conduct the study and recruit the patients. P.D. helped analyse the plasma and microdialysis samples and the data. A.B. helped design the study, conduct the study, recruit the patients and collect the data. M.D. helped interpret the data and write the manuscript. E.T. helped design the study, conduct the study, analyse the data, write the manuscript and approve the final version.

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