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Published in:
APMIS - Journal of Pathology, Microbiology and Immunology

DOI (link to publication from Publisher):
10.1111/apm.13198

Publication date:
2022

Document Version
Accepted author manuscript, peer reviewed version

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/APM.13198

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Summary

Tøstesen SK, Hanberg P, Bue M, Thillemann TM, Falstie-Jensen T, Tøttrup M, Knudsen MB, Schmedes AV, Stilling M. **Weight-based cefuroxime dosing provides comparable orthopedic target tissue concentrations between weight groups - A microdialysis porcine study.**

Antibiotic prophylaxis is a key element in prevention of surgical site infections. For the majority of orthopedic procedures, antibiotic administration follows fixed dosing regimens irrespective of weight. However, this may result in insufficient antibiotic target tissue concentrations and higher risk of surgical site infections in obese individuals.

Aim: To investigate the effect of weight-based cefuroxime dosing on plasma and target tissue concentrations.

Eighteen female pigs were allocated into three groups differentiated by weight: 53-57kg, 73-77kg, and 93-97kg. Microdialysis catheters were placed for continuous sampling in bone, muscle and subcutaneous tissue during an 8-hour sampling interval. Blood samples were collected as reference. Cefuroxime was administered intravenously as a bolus according to weight (20 mg/kg). The primary endpoint was time above the cefuroxime minimal inhibitory concentration for *Staphylococcus aureus* (T>MIC (4 μg/mL)).

Comparable target tissue T>MICs (4 μg/mL) were found between weight groups. Mean T>MIC ranged between 116-137 min for plasma, 118-154 min for bone, 109-146 min for skeletal muscle, and 117-165 min for subcutaneous tissue across the groups.

Weight-based cefuroxime (20 mg/kg) dosing approach provide comparable perioperative plasma and target tissue T>MIC (4 μg/mL) in animals between 50 – 100 kg body weight, and thus a comparable prophylaxis of surgical site infections.

Keywords: Microdialysis; Weight-based cefuroxime dosing; Antibiotic prophylaxis; Surgical site infection; Orthopedic surgery.

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1. Introduction

Preoperative antibiotic prophylaxis is a key element in the prevention of surgical site infections following orthopedic surgery. Optimal antibiotic prophylaxis relies on two essential factors: 1) selection of a suitable agent active against relevant bacteria, and 2) achievement of adequate antibiotic target tissue concentrations for a sufficient time interval at the sites where infection is to be prevented [1, 2]. Current perioperative antibiotic prophylaxis regimens often comprise a fixed dose independent of patient individual factors, which is mainly based on tradition and experience from plasma concentration measurements, rather than specific target tissue concentrations [3, 4].

Within orthopedic surgery, the cephalosporin, cefuroxime, is commonly employed as perioperative antibiotic prophylaxis due to its broad-spectrum effect against both Gram-positive and Gram-negative bacteria [5]. The bactericidal effect of cefuroxime is time-dependent i.e., time above relevant minimal inhibitory concentration (T>MIC) is considered the best predictor of therapeutic efficacy [5, 6]. The most frequent causative orthopedic bacteria are *Staphylococcus aureus* (*S. aureus*) and coagulase-negative staphylococci (CoNS) [7, 8], exhibiting planktonic epidemiological cut-off MIC values (ECOFFs) in the range of 1-4 μg/mL for cefuroxime [9].

Using the pharmacological tool, microdialysis, multiple experimental and clinical studies have dynamically investigated the free tissue concentrations of cefuroxime simultaneously from various compartments [10-15]. The majority of these studies have demonstrated a heterogenous cefuroxime tissue distribution, which may be attributed to various physiological factors affecting cefuroxime pharmacokinetics e.g., subject weight. In retrospective observational cohort studies, obese patients with BMI ≥30 kg/m^2 exhibit higher risk of antibiotic treatment failure and surgical site infection (SSI) after orthopedic surgeries [16, 17]. Furthermore, studies investigating standard cephalosporin dosing in obese patients, have demonstrated a negative correlation between tissue concentrations and patient weight [18, 19]. Weight-based cefuroxime dosing and its effect on target tissue concentrations relevant to orthopedic surgery, have not previously been evaluated, but recent studies suggest that a weight-based dosing approach may ensure a more homogeneous target tissue distribution for multiple antibiotics, theoretically optimizing the antibiotic prophylactic treatment [20-22].

This experimental study aimed to investigate the effect of weight-based cefuroxime dosing on plasma and target tissue concentrations, relevant for orthopedic surgery; cancellous bone, skeletal muscle and subcutaneous tissue.

2. Materials and Methods

This study was conducted at the Institute of Clinical Medicine, Aarhus University Hospital, Denmark. Chemical analyses were performed at the Department of Clinical Biochemistry, Lillebaelt Hospital, Vejle, Denmark. The study was approved by the Danish Animal Experiments Inspectorate (License No. 2017/ 15-0201-01184) and complied with the existing Danish laws regulating experimental animal research.

2.1 Study design, anesthetic and surgical procedures.

Eighteen female pigs (Danish Landrace Breed) were included and allocated to three study groups of six pigs differentiated by weight: Group A: 53-57 kg, Group B: 73-77 kg, and Group C: 93-97 kg. The weight of the pigs was measured on the day of the experiment. During the surgical procedure and sampling period, the pigs were anesthetized using a combination of propofol (450-750 mg/hour, continuous infusion) and fentanyl (0.6-0.85 mg/hour, continuous infusion). Arterial blood pH was monitored and regulated through ventilation and kept within the range of 7.40 to 7.50. Core temperature was kept within the range of 36.9°C to 39.2°C, regulated with blankets or ice bags throughout the study. Glucose was substituted when needed and 0.9% NaCl was administered continuously (150 ml/hour) to maintain normohydration. The pigs were euthanized with an intravenous injection of pentobarbital at the end of the sampling period.

The surgical intervention intended to imitate the shoulder arthroplasty approach, but without insertion of a prosthesis. With the pigs positioned in left lateral recumbency, the right shoulder was exposed through a lateral skin incision followed by dissection in the interval between the deltoid muscle and the cranial part of the infraspinatus muscle. To reach the glenohumeral joint, the caudal part of the infraspinatus muscle was released from the humeral attachment and the humeral head was excised using an oscillating saw. In total 3 microdialysis catheters were placed in shoulder related compartments as illustrated in figure 1; scapular cancellous bone, deltoid skeletal muscle and surgical site subcutaneous tissue. The bone catheter (membrane length: 10 mm) was placed in a drill hole (ø: 2 mm, depth 20-25 mm) in the scapular neck, approximately 10 mm above the superior part of the glenoid labrum. The muscle catheter (membrane length: 30 mm) was placed in the deltoid muscle using a splitable introducer, approximately 20 mm lateral to and parallel with the skin incision. The subcutaneous tissue catheter (membrane length: 30 mm) was placed just above the deltoid muscle. All microdialysis catheters were fixed to the skin with a single suture to avoid displacement. Hereafter, microdialysis catheters were perfused with 0.9% NaCl containing 5 mg/mL meropenem, allowing for individual calibration of all catheters using the internal standard method [23]. Following catheter placement, 30 min of tissue equilibration was allowed.

At time 0, cefuroxime (Fresenius Kabi AB, Sweden) was administered and dosed according to weight (20 mg/kg), and injected intravenously during 10 min. The overall sampling time was 8 hours. From time 0-240 min dialysates were sampled with 30 min intervals, and from time 240-480 min with 60 min intervals. Venous blood samples were collected from a central venous catheter in the middle of every dialysate sampling interval.

2.2 Microdialysis

Microdialysis is a catheter-based technique allowing continuous sampling of small, unbound and water-soluble molecules in the interstitial spaces of virtually all tissues [24-26]. Diffusion of solutes takes place across a semipermeable membrane, at the tip of the catheter, along the concentration gradient. Since the catheter is continuously perfused, equilibrium will never occur. Correspondingly, the concentration in the dialysate will only represent a fraction of the actual concentration in the tissue. This fraction is referred to as the relative recovery [26]. Consequently, calibration is imperative to determine total tissue concentration, and relative recovery can be calculated during several calibration methods [27]. In this study meropenem was used as an internal calibrator [23].

Relative recovery was calculated using the following equation:

$$Relative\ recovery\ (\%) = 100 \cdot \left(1 - \frac{C_{dialysate}}{C_{perfusate}}\right)$$

$C_{dialysate}$ is the mean concentration of meropenem in the dialysate and $C_{perfusate}$ is the meropenem concentration in the perfusate. When correcting for relative recovery, the total tissue concentrations of cefuroxime (C_{tissue}) were determined with the following equation:

$$\mathrm{C_{tissue}} = \frac{\mathrm{C_{dialysate}}}{\mathrm{Relative\ recovery}}$$

$C_{dialysate}$ is the cefuroxime concentration in the dialysate. All the catheters were individually calibrated. The obtained dialysate concentrations were attributed to the midpoint of the sampling intervals in the data analysis.

The microdialysis catheters included CMA 63 (M Dialysis AB, Stockholm, Sweden) with a length of 10 and 30 mm and a 20-kDa cut-off. CMA 107 precision pumps generated a flow rate of 2 μL/min.

2.3 Handling of Samples

Dialysates were stored at -80°C until analysis. Venous blood samples were stored at 5°C for a maximum of 10 hours before being centrifuged at 3,000 x g for 10 min. Plasma were then stored at -80°C until analysis.

2.4 Liquid chromatography tandem mass spectrometry (LC-MS/MS)

Cefuroxime and meropenem in dialysates and free concentrations in plasma were measured via a LC-MS/MS method. The analyses were conducted on a Waters Acquity 2-dimensional ultra-performance liquid chromatograph (2D-UPLC) with Xevo TQ-S tandem mass spectrometer operated in electrospray positive mode. The mobile phases consisted of 30 µmol/L NH_4F in water (A) and 30 µmol/L NH_4F in MeOH with 10% isopropanol (B).

Dialysates and plasma samples were prepared for analysis using a Hamilton STARlet workstation. For dialysates, 5 µL dialysate and calibrator or control was mixed for 15 min at 37°C with 45 µL internal standard (0.04 µg/mL Meropenem-d6 and 0.04 µg/mL Cefuroxim-d3 in ammonium acetate 5 mM in water, pH 7.0). Subsequently the samples were precipitated by adding 150 µL acetonitrile followed by 4 min mixing at room temperature. After centrifugation for 20 min at 1520 x g, 100 µL of the supernatant was transferred to a new microtiter plate and 200 µL ammonium acetate 5 mmol/L in water, pH 7.0, was added to each well. For plasma, samples were ultrafiltrated in Pall Corporation multi-well filter plates. 300 µL plasma was pipetted in the plate and placed on top of a 700 µL collection plate for 10 min centrifugation at 1520 x g. The lower plate with the filtrate was then sample prepared as described for dialysates.

Ten µL of the prepared samples were injected on a Waters XBridge C8, 3.5 µm column 2.1 x 50 mm (trap column) at 5% mobile phase B where the analytes were trapped on the column while unretained interferents eluted to waste. After one min, the trap column was switched into series with the analytical column, a Phenomenex Kinetex 2.6 µm Biphenyl, 150 x 3.0 mm, and the analytes were eluted from the trap column and refocused on the analytical column at 20% B. Gradient elution from the analytical column was as follows: Initially 20% B for 2.5 min, linear gradient to 100% B at 3.5 min, 100% B from 3.5-4.4 min and then re-equilibration at 20% B from 4.45 to 4.5 min. During the analytical gradient run, the trap column was switched back at 2.5 min and it was then washed with 100% B before being re-equilibrated at 5% B to be ready for the next sample.

For cefuroxime the intermediate precision for the internal controls at four levels determined over 43 runs were 14.2% (target 0.010 µg/mL), 9.6% (target 0.050 µg/mL), 2.6 % (target 5.00 µg/mL) and 3.9% (target 10.00 µg/mL). The lower limit of quantification (LOQ) was 0.010 µg/mL. For meropenem the intermediate precision for the internal controls at three levels determined over 36 runs were 16.6% (target 0.050 µg/mL), 3.9% (target 5.00 µg/mL) and 5.6 % (target 10.00 µg/mL). LOQ was 0.050 µg/mL.

2.5 Pharmacokinetic Analysis and Statistical Considerations

Data processing

Standard pharmacokinetic parameters were determined separately for each compartment for each pig, using non-compartmental analysis. Pharmacokinetic parameters, descriptive statistics and analyses were performed in STATA (v. 16, StataCorpLLC, College Station, TX, USA). Half-life ($T_{1/2}$) was calculated as ln(2)/λeq, where λeq is the constant of terminal elimination rate, estimated by linear regression of the log concentration on time. Peak drug concentration (C_{max}) was the maximum of all the recorded concentrations, and T_{max} was the time to reach C_{max}. The area under the concentration−time curves from zero to the last measured value (AUC) was calculated by the linear up-log down trapezoidal method. Tissue penetration was described by the ratio of tissue AUC to free plasma AUC ($AUC_{tissue}/AUC_{plasma}$). T>MIC was determined by linear interpolation for the *S. aureus* ECOFF with a MIC of 4 µg/mL for cefuroxime. Microsoft Excel (v. 16.49, Microsoft corp. Redmont, WA, USA) was used to estimate the cefuroxime T>MIC 4 µg/mL, for each target tissue and for each pig. In addition, the pharmacokinetic parameters and T>MIC of the various tissues were compared using one-way analysis of variance (ANOVA) with subsequent pairwise comparison of relevant target tissues. A correction for degrees of freedom by the Kenward-Roger approximation method was used due to small sample size. The model assumptions were tested by visual assessment of residuals, fitted values, and estimates of random effects. A p-value less than 0.05 was considered statistically significant.

3. Results

18 pigs completed the study and data from all catheters were collected. Mean relative recovery (SD) were 33% (9) in bone, 53% (14) in skeletal muscle and 56% (9) in subcutaneous tissue. For one bone catheter, relative recovery could not be determined. Since the dialysate concentrations from this catheter resembled those of the other bone catheters, the mean value of the remaining bone relative recovery was applied for this catheter.

Concentration-time profiles are presented in Figure 2 demonstrating mean cefuroxime concentration as a function of time, for the three groups separately, in plasma, bone, muscle and subcutaneous tissue. Corresponding T>MIC (4 μg/mL) and pharmacokinetic parameters can be found in Table 1 and Table 2.

For the *S. aureus* ECOFF MIC (4 μg/mL), comparable T>MIC in all target tissues were found between groups and target tissues. Mean T>MIC (4 μg/mL) ranged between 116-137 min for plasma, 118-154 min for bone, 109-146 min for skeletal muscle, and 117-165 min for subcutaneous tissue across the three groups (Table 1). A cefuroxime concentration of 4 μg/mL was reached within a mean time of 19 min in all the investigated target tissues and groups. For all target tissues, there were no inter-groups differences for AUC, C_{max} $T_{1/2}$, T_{max}, and tissue penetration ($AUC_{tissue}/AUC_{plasma}$) (Table 2).

4. Discussion

This is the first study to evaluate the effect of weight-based cefuroxime dosing on plasma and orthopedic target tissue concentrations in cancellous bone, skeletal muscle and subcutaneous tissue. The main finding was comparable T>MIC for *S. aureus* ECOFF MIC (4 μg/mL), between three weight groups (mean weight: 55, 75 and 95 kg). The T>MIC (4 μg/mL) ranged from 109-165 min across all investigated tissues corresponding to 24-37% of an 8-hour dosing interval. A mean cefuroxime concentration of 4 μg/mL was reached within 19 min in all compartments and groups.

Optimal perioperative antibiotic prophylaxis is important to lower the risk of acquiring SSIs. In an orthopedic setting, sufficient antibiotic exposure to the surgical field, including bone, skeletal muscle and subcutaneous tissue, is the key as the extracellular space of these target tissues is a common nidus for SSIs [1-4]. Obese patients (BMI ≥30 kg/m^2) have proven to possess a higher risk of acquiring SSIs compared to nonobese patients (BMI <25 kg/m^2) [16, 17]. Obesity-related physiological changes, such as volume of distribution, changes in fat/water-ratio and renal function may alter the antibiotic tissue distribution [22, 28], potentially entailing subtherapeutic antibiotic target tissue concentrations, increasing the risk of SSIs and antibiotic resistance development if administered inadequately [29-31]. For glycopeptides e.g., vancomycin, a weight-based dosing approach has been shown to level out interindividual pharmacokinetic differences, kidney clearance, volume of distribution and half-life [32-34]. For cephalosporins, morbidly obese patients (BMI ≥40 kg/m^2) reached higher T>MIC in both plasma and tissues when receiving weight-based dosing compared to standard [19, 35]. In the present study,

cefuroxime dosing (20 mg/kg) provided comparable inter-group T>MIC (4 μg/mL), C_{max}, $T_{1/2}$, T_{max}, and $AUC_{tissue}/AUC_{plasma}$, suggesting a proportional increase in volume of distribution with increasing weight. Employing standard cefuroxime administration (1500 mg) to all patients may consequently result in subtherapeutic antibiotic target tissue concentrations. A recent single-center before-and-after study (Hasler et al., 2021) found that a double-dose (3000 mg) cefuroxime perioperative prophylaxis to patients >80 kg had no influence on SSI incidence. However, the patients developing SSI in that study had a higher BMI than the baseline demographics and were exposed to a longer surgery duration [36]. An experimental porcine study (Jørgensen et al., 2021), found that two doses of 1500 mg cefuroxime administered 4 h apart resulted in longer T>MIC (4 μg/mL) in an 8 h dosing interval as compared to a single bolus of 3000 mg [37]. Thus, successful perioperative antibiotic prophylaxis does not only rely on the dose, but on several factors, e.g. dosing frequency, timing of administration, choice of drug, etc. The higher SSI risk associated with obesity in general is likely not overcome with the single intervention of optimizing perioperative antibiotic prophylaxis. However, especially for obese patients and heterogeneous populations, an individualized weight-based cefuroxime dosing approach is a simple, inexpensive and practical procedure optimization to ensure homogeneous antibiotic target tissue distribution in patients undergoing surgery.

For perioperative antibiotic prophylaxis, it is recommended that tissue concentrations, as a minimum, exceed MIC values of relevant bacteria from incision and until wound closure [2, 5]. In the present study, a mean cefuroxime target tissue concentration of 4 μg/mL was reached within 19 min across groups and compartments, complying with the general recommendations of administering cefuroxime as close to incision time as possible and within 60 min before incision [38]. The mean target tissue concentration of 4 μg/mL was maintained for 109 to 165 min across groups and target tissues, corresponding to most acute and elective orthopedic surgical procedures. For surgeries of longer duration or need of even higher MIC targets, alternative dosing regimens should be considered. In particular, continuous cefuroxime infusion has been shown to improve and control target tissue T>MIC significantly [10]. Since cefuroxime has few side effects and low toxicity for perioperative prophylactic use, sufficient weight-based dosing, repeated dosing or continuous infusion seems safe and may be relevant for most patients [37, 39].

This study has some appreciable limitations. The physiology and anatomy of pigs and humans resemble each other to a great extent. However, as the pig present different obesity-related physiological changes and fat distribution, the porcine model may not necessarily translate to a clinical setting for obese (BMI ≥30 kg/m^2) and nonobese (BMI <25 kg/m^2) individuals. Furthermore, as this study was performed on

healthy juvenile pigs (aged 5 months), important interspecies differences regarding comorbidity or age-related changes could not be evaluated. Moreover, pigs have been shown to have faster cefuroxime elimination (shorter T>MIC and $T_{1/2}$) in comparison to humans in comparable experimental and clinical studies [40, 41]. Due to these elimination differences, it can be speculated that our findings of sufficient target tissue concentration for most short orthopedic surgical procedures would be even more convincing in clinical practice. Finally, the correction for the relative recovery when determining the absolute tissue concentration is associated with an evident limitation as this correction will magnify the variations correlated with sample handling and analysis. A relative recovery of minimum 20% is recognized as acceptable [42]. In our study, the mean relative recovery ranged from 33% to 56%.

5. Conclusion

We found that weight-based (20 mg/kg) cefuroxime dosing approach provided comparable plasma and target tissue T>MIC (4 μg/mL) values in cancellous bone, skeletal muscle and subcutaneous tissue in animals between 50-100kg body weight. A weight-based cefuroxime dosing approach may optimize the perioperative target tissue exposure and potentially reduce the risk of surgical site infections. Validation of these findings in a clinical setting is warranted.

Declarations of interest

None to declare

Authorship contribution

Study design: SKT, PH, MB, TMT, TFJ, MT, MS

Surgery and data acquisition: SKT, PH, TMT, TFJ, MT, MB

Data analysis: AVS

Formal analysis: SKT, PH, MB, MS

Writing - Original draft: SKT

Writing - Review & editing: All authors

Supervision: PH, MB, TMT, TFJ, MT, MS

Funding acquisition: TMT, MS

All authors have approved the final article to be submitted.

Ethical Approval

The study was approved by the Danish Animal Experiments Inspectorate (License No. 2017/ 15-0201-01184) and complied with the existing Danish laws regulating experimental animal research.

Data availability statement

Data available on request from the authors.

Acknowledgments

We would like to thank Department of Clinical Medicine, the surgical research laboratories, Aarhus University Hospital for supporting this study.

This work was supported by the Novo Nordisk Foundation [NNF20OC0062032, 2020]. We are grateful for the financial support. The funding sources had no role in the study.

Figure 1 was created with BioRender.com.

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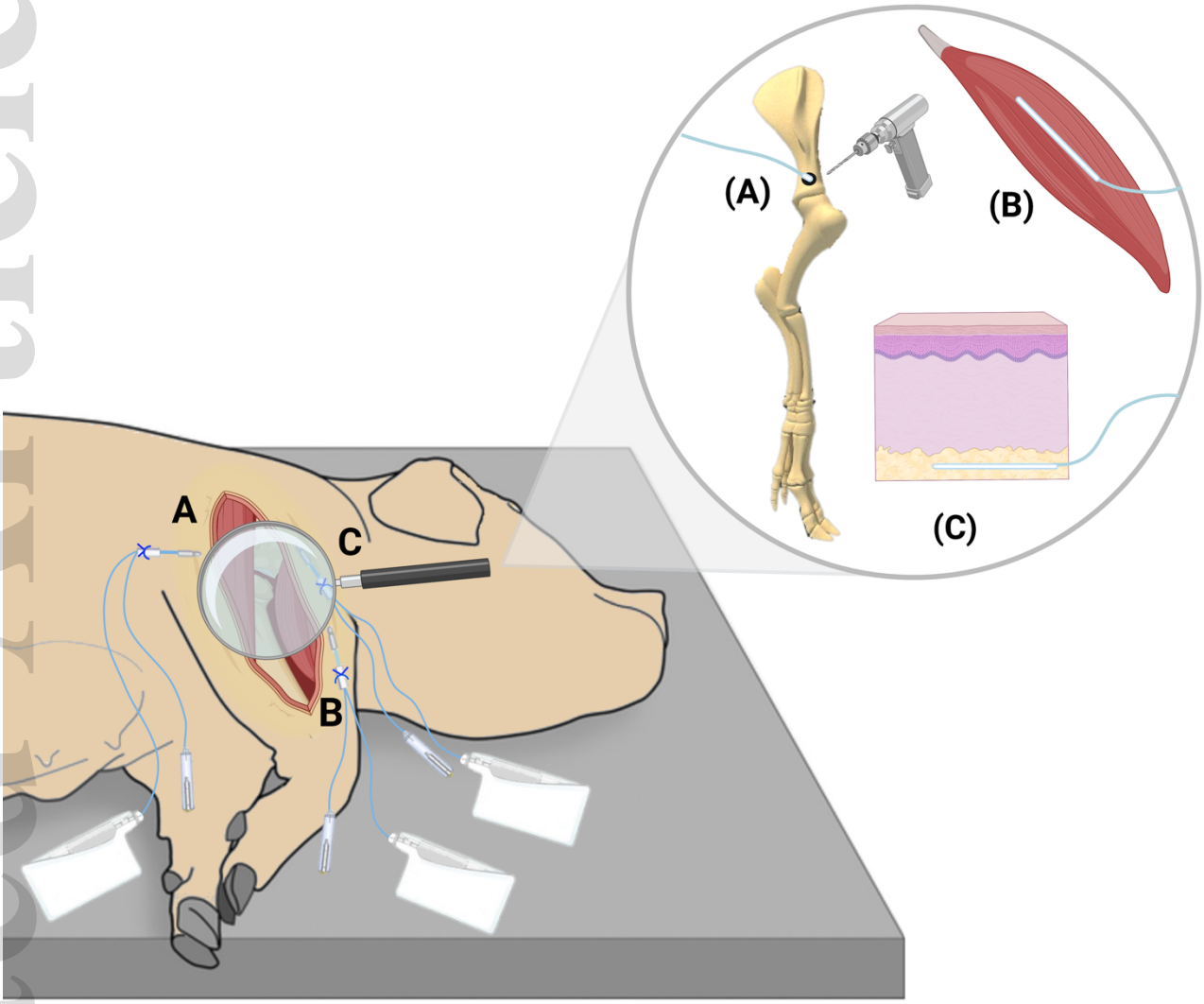

Figure 1:

Illustration of the location of microdialysis catheters. A (A) cancellous bone, B (B) skeletal muscle and C (C) subcutaneous tissue.

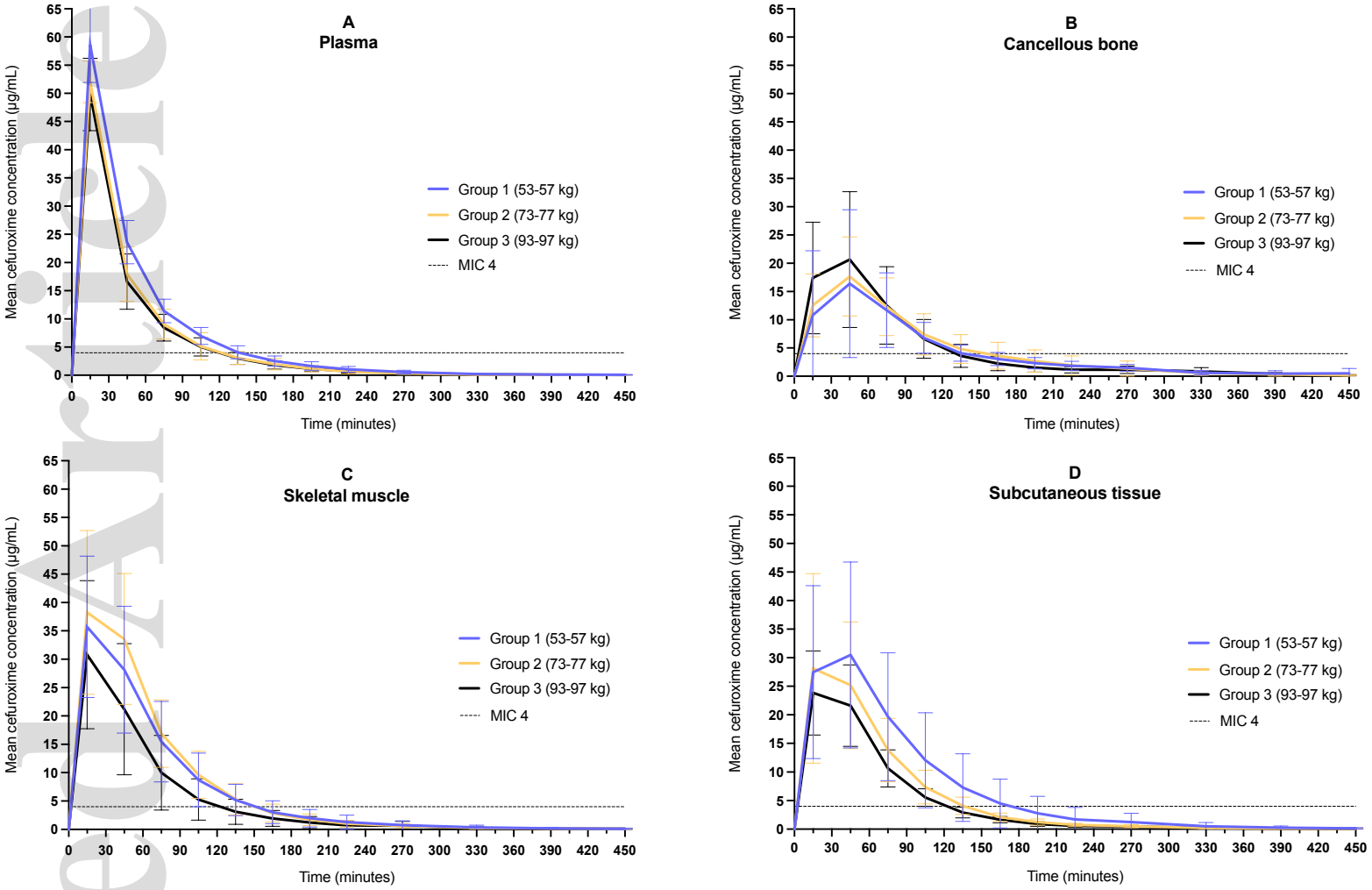

Figure 2:
Mean concentration-time profiles in plasma (A), bone (B), muscle (C) and subcutaneous tissue (D), for the three groups, separately. SD visualized with bars.

Table 1: Mean time above MIC 4 μg/ml (T>MIC 4) for plasma, bone, skeletal muscle and subcutaneous tissue in the three groups.

Pharmacokinetic parameter	Plasma	Bone	Muscle	Subcutaneous tissue
Grp 1: T>MIC 4, min (95% CI)	137 (55 - 219)	118 (36 - 200)	146 (64 - 228)	165 (83 - 245)
%T>MIC 4, min (95% CI)	30 (12 - 49)	26 (8 - 44)	32 (14 - 51)	37 (18 - 54)
Grp 2: T>MIC 4, min (95% CI)	119 (37 - 201)	154 (72 - 235)	145 (64 - 227)	110 (28 - 191)
%T>MIC 4, min (95% CI)	26 (8 - 45)	34 (16 - 52)	32 (14 - 50)	24 (6 - 42)
Grp 3: T>MIC 4, min (95% CI)	116 (34 - 198)	124 (42 - 205)	109 (27 - 191)	117 (35 - 199)
%T>MIC 4, min (95% CI)	26 (8 - 44)	28 (9 - 46)	24 (6 - 42)	26 (8 - 44)

T>MIC 4, mean time above minimal inhibitory concentration of 4 μg/ml for *S. aureus*

%T>MIC 4, mean %time (of an 8-hour dosing interval) above minimal inhibitory concentration of 4 μg/ml for *S. aureus*

Table 2: Key pharmacokinetic parameters for plasma, cancellous bone, skeletal muscle and subcutaneous tissue in the three groups.

Pharmacokinetic parameter	Plasma	Bone	Muscle	Subcutaneous tissue

Grp 1: $AUC_{0\text{-}last}$, min µg/mL (95% CI)	2918 (1760 - 4075)	1801 (644 - 2958)	2799 (1642 - 3956)	3096 (1939 - 4254)
Grp 2: $AUC_{0\text{-}last}$, min µg/mL (95% CI)	2378 (1221 - 3535)	1911 (753 - 3068)	3057 (1900 - 4215)	2021 (864 - 3179)
Grp 3: $AUC_{0\text{-}last}$, min µg/mL (95% CI)	2270 (1112 - 3427)	1965 (808 - 3122)	1940 (782 - 3097)	1879 (721 - 3036)
Grp 1: C_{max}, µg/mL (95% CI)	59 (49 - 68)	17 (7 - 27)	36 (26 - 46)	32 (22 - 41)
Grp 2: C_{max}, µg/mL (95% CI)	52 (42 - 62)	18 (8 - 28)	39 (29 - 49)	26 (16 - 36)
Grp 3: C_{max}, µg/mL (95% CI)	50 (40 - 60)	21 (11 - 30)	27 (17 - 37)	26 (16 - 36)
Grp 1: T_{max}, min (SD)	15 (0)	55 (15)	15 (0)	35 (15)
Grp 2: T_{max}, min (SD)	15 (0)	45 (19)	20 (12)	27 (16)
Grp 3: T_{max}, min (SD)	15 (0)	45 (0)	20 (12)	25 (15)
Grp 1: $T_{½}$, min (SD)	46 (2)	87 (39)	44 (8)	48 (7)
Grp 2: $T_{½}$, min (SD)	44 (3)	72 (22)	46 (3)	47 (4)
Grp 3: $T_{½}$, min (SD)	46 (3)	63 (25)	44 (7)	45 (6)
Grp 1: $AUC_{tissue}/AUC_{plasma}$ (95% CI)	-	0.63 (0.20 - 1.06)	0.95 (0.52 - 1.37)	1.03 (0.60 - 1.46)
Grp 2: $AUC_{tissue}/AUC_{plasma}$ (95% CI)	-	0.79 (0.36 - 1.22)	1.26 (0.83 - 1.69)	0.89 (0.46 - 1.32)
Grp 3: $AUC_{tissue}/AUC_{plasma}$ (95% CI)	-	0.84 (0.41 - 1.27)	1.27 (0.85 - 1.70)	0.83 (0.40 - 1.26)