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Bone, Subcutaneous Tissue and Plasma Pharmacokinetics of Cefuroxime in Total Knee Replacement Patients – a Randomized Controlled Trial Comparing Continuous and Short-Term Infusion

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Running title

Continuous versus Short-Term Infusion of Cefuroxime

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Summary

Authors

Tøttrup M, Søballe K, Bibby BM, Hardlei TF, Hansen P, Fuursted K, Birke-Sørensen H, Bue M

Title

Bone, Subcutaneous Tissue and Plasma Pharmacokinetics of Cefuroxime in Total Knee Replacement Patients – a Randomized Controlled Trial Comparing Continuous and Short-Term Infusion

Abstract

Cefuroxime is widely used as antibiotic prophylaxis for orthopaedic procedures. We evaluated bone, subcutaneous tissue (SCT) and plasma pharmacokinetics of cefuroxime in male patients undergoing total knee replacement (TKR) after both traditional short-term infusion (STI) and continuous infusion (CI). Eighteen male patients undergoing TKR were randomly assigned to STI or CI of 1.5 g of cefuroxime. Measurements were obtained in plasma, SCT, cancellous and cortical bone every 30 min for 8 h following surgery. For sampling in solid tissues, microdialysis was applied. Population pharmacokinetic modelling were performed in order to estimate pharmacokinetic parameters, and to assess the probability of attaining cefuroxime concentrations above clinically relevant minimal inhibitory concentrations (MICs) for 65% and 90% of the 8 h dosing interval. Low SCT and cortical bone penetration were found in both the STI and the CI group, but the findings were only significant in the STI group. Irrespective of MIC, tissue and target, CI leads to improved probability of attaining

relevant pharmacokinetic targets compared to STI. For the *Staphylococcus aureus* MIC breakpoint (4 μg/mL), STI leads to inadequate probability of target attainment. CI of 1.5 g of cefuroxime leads to improved probability of attaining relevant pharmacokinetic targets in male TKR patients compared to traditional STI. These findings suggest that application of CI may improve antibiotic prophylaxis for male TKR patients.

Keywords: Cefuroxime, population pharmacokinetics, microdialysis, bone concentrations, continuous infusion

Introduction

Prosthetic joint infections (PJI) is one of the most serious complications of joint replacement surgery. In addition to rigorous sterile measures, perioperative systemic antibiotic prophylaxis plays an important role in the prevention of postoperative infections. Although definite antibiotic target concentrations for this task are not established, it is advocated not only to achieve therapeutic concentrations in plasma but also in the relevant tissues throughout the surgical procedure (1). For most antibiotics, local perioperative tissue concentrations are currently unknown.

Cefuroxime is widely used as antibiotic prophylaxis for orthopaedic procedures because it provides coverage against a broad spectrum of both gram-positive and gram-negative bacteria including those most frequently responsible for PJIs (2). Cefuroxime is a second-generation cephalosporin, and like other beta lactams, the bactericidal activity is time-dependent. This means that its efficacy is best related to the time that the free concentration is sustained above the minimal inhibitory concentration of the invading pathogen (MIC) ($fT_{>MIC}$) (3, 4). Traditionally, $fT_{>MIC}$ targets in plasma of approximately 40-70% of a dosing interval have been associated with clinical success (3, 5). However, recent clinical studies have suggested that more aggressive targets of 100% $fT_{>1-5\times MIC}$ are more predictive of a successful outcome (6, 7). While definite targets for prevention of postoperative infection is lacking, the time-dependent activity of cefuroxime suggests that continuous infusion (CI) may provide favorable tissue exposure compared to standard short-term infusion (STI).

In recent years, a number of studies have demonstrated that a homogeneous plasma-tissue distribution of antibiotics cannot be taken for granted (8-10). Consequently, a number of attempts have been made towards determination of bone concentrations of antibiotics. The predominant and traditional bone biopsy method suffers from important methodological limitations, and may not be ideal for the task (11-13). Recently, the pharmacokinetic tool microdialysis (MD) has been successfully applied for sampling of various antibiotics in drill holes in bone (8, 14-16). This approach seems to reflect the true perioperative situation.

In the present study, we set out to evaluate bone, subcutaneous tissue (SCT) and plasma pharmacokinetics of cefuroxime in male patients undergoing total knee replacement (TKR) after both CI and traditional STI using MD.

Materials and methods

This study was conducted at the Department of Orthopaedic Surgery, Horsens Regional Hospital between September 2013 and July 2014. Quantification of cefuroxime was performed at the Department of Clinical Biochemistry, Aarhus University Hospital. The study was approved by the Ethics Committee of the Central Denmark Region (registration number 1-10-72-161-13) and the Danish Health and Medicines Authority (EudraCT number 2013-001138-17). The study was conducted in accordance with the Declaration of Helsinki and the ICH Harmonized Tripartite Guideline for Good Clinical Practice. The GCP unit at Aalborg and Aarhus University Hospitals conducted the mandatory monitoring procedures.

Study patients and design

Competent male patients were offered enrolment in the study if they were scheduled for a TKR. The patients were identified in the outpatient clinic by the two operating surgeons. Written informed consent was obtained from all patients. Exclusion criteria included the following: allergy to cefuroxime or vancomycin, on-going treatment with cefuroxime, and clinically reduced renal function.

Eighteen patients were included in the study. The study was designed as an open-labelled randomized controlled trial. Block randomization was applied with blocks of 6 patients, and an allocation ratio of 1:1. The random allocation sequence was implemented using numbered envelopes (provided by the pharmacy at Aarhus University Hospital). According to the randomization, the patients were given 1.5 g of cefuroxime (Fresenius Kabi AB, Sweden) intravenously in a peripheral catheter as STI (over 15 min) or CI (0.5 g as loading dose over 5 min followed by CI of the remaining 1 g over 7 h and 55 min). Cefuroxime was administered after the surgical procedures and calibration of the MD catheters. As preoperative antibiotic prophylaxis, all patients were given 1 g of vancomycin prior to surgery.

The primary outcome was the probability of attaining a traditional pharmacokinetic target of 65% *f*T > MIC and a more aggressive 90% *f*T > MIC target in the different tissues over an 8 h dosing interval. Area under the concentration-time curves (AUC) and tissue penetration ratios were secondary outcomes.

Surgery

At the end of TKR surgery, but before closing, MD catheters were placed in drill holes in cancellous bone in the medial tibial condyle and in cortical bone in the anterior margin of the tibial diaphysis as previously described (14). In addition to the bone catheters, a SCT catheter was placed in the medial part of the thigh. At the end of surgery, a mixture of 150 mL ropivacaine (2mg/mL), 1.5 mL toradol (30 mg/mL) and 0.75 mL adrenaline (1 mg/mL) was injected locally in the soft tissues surrounding the knee, intraarticularly and in the posterior joint capsule of the knee.

Microdialysis and sampling procedures

MD is a catheter-based method, which allows for continuous sampling of water-soluble molecules, like the majority of antibiotics, in the interstitial space of most tissues (8, 9, 17). The diffusion of molecules follows the concentration gradient across a semipermeable membrane at the tip of the catheter. As the catheter is continuously perfused, equilibrium will never occur. Consequently, the concentration of solutes in the dialysate (i.e. the perfusate leaving the catheter) only represents a

fraction of the actual concentration in the tissue. This fraction is referred to as relative recovery (RR). Accordingly, determination of RR for each separate catheter is imperative if absolute tissue concentrations are to be determined. In this study, all catheters were calibrated using the retrodialysis method (18, 19). A more detailed description of MD can be found elsewhere (20).

In the present study, the MD system consisted of CMA 107 precision pumps (μ-Dialysis AB, Stockholm, Sweden) and CMA 63 catheters (membrane length 10 mm, molecular cut-off 20 kilo Daltons). When surgery was completed, the MD catheters were perfused with 0.9% NaCl containing cefuroxime at a concentration of 5 μg/mL (provided by the pharmacy at Aarhus University Hospital) at a perfusion rate of 2 μL/min. After a 30-min tissue equilibration period, all catheters were individually calibrated by collecting a sample over a 30-min interval. RR was calculated using the following equation:

$$RR\ (\%) = 100 \times (1 - \frac{C_{dialysate}}{C_{perfusate}})$$

where $C_{dialysate}$ is the cefuroxime concentration (μg/mL) in the dialysate and $C_{perfusate}$ is the concentration (μg/mL) in the perfusate. Following calibration, the perfusate was changed to blank 0.9% NaCl, and a 110-min washout period was allowed for. During the last 40 min of this period, two 20-min dialysates were collected in order to evaluate and quantify the effectiveness of washout. Cefuroxime was then administered according to the randomization, which took place during the washout period. Regardless of group, dialysates were collected with 30-min intervals for 8 h starting at the initiation of cefuroxime infusion. Dialysate concentrations of cefuroxime were considered to represent the concentration at the midpoint of the sampling interval. For the subsequent data analysis, the absolute tissue concentrations (μg/mL), C_{tissue}, were calculated by correcting the dialysates for RR using the following equation:

$$C_{tissue} = \frac{C_{dialysate}}{RR}$$

In the middle of every dialysate sampling interval, a blood sample was drawn from a venous catheter in the cubital vein. Dialysates were immediately frozen and stored on dry ice for a maximum of 10 h, after which they were stored at -80°C until analysis. Venous blood samples were stored at 2-8°C for a

maximum of 20 h before being centrifuged at 3,000 *g* for 10 min. Plasma aliquots were then frozen and stored at -80°C until analysis.

Before removal of the catheters, a CT scan of the cortical drill hole in the anterior aspect of the tibia was conducted in order to verify that the drill hole had not penetrated to the bone marrow, and that the catheter had not been displaced.

Quantification of cefuroxime concentrations

Dialysate and plasma concentrations of cefuroxime were quantified using a validated ultra high performance liquid chromatography assay. Briefly, intra- and interrun imprecisions were below 6.8% and 6.5% for dialysate (assessed at concentrations of 0.2, 2.5 and 10 μg/mL), and free plasma concentrations (assessed at concentrations of 9.2 and 37.7 μg/mL), respectively. The lower limit of quantification was 0.06 μg/mL in dialysates. A detailed description of the assay can be found elsewhere (15, 19).

Population pharmacokinetic modelling

One- and two-compartment models with zero'th and first order kinetics were explored in order to obtain the best description of the drug concentration in each tissue. An ordinary two-compartment model with first order kinetics, elimination from the second compartment only, and measurement in the first compartment was found to provide the best description of the free plasma concentrations. For the solid tissues, a two-compartment model with zeroth order appearance, first order clearance, no flow back into the first compartment, elimination from the second compartment only, and measurement in the second compartment provided the best description. For CI, the drug concentration in the solid tissues is given by the following equation:

$$C_{tissue}(t) = \begin{cases} \frac{k_1}{k_3}\left(1 - e^{-k_3 t}\right) & , \; t \leq \frac{x_0}{k_1 - I} \\ \frac{I}{k_3} + \left(\frac{k_1 - I}{k_3} e^{k_3 \frac{x_0}{k_1 - I}} - \frac{k_1}{k_3}\right) e^{-k_3 t} & , \; t > \frac{x_0}{k_1 - I} \end{cases}$$

where k_1 is the appearance rate, k_3 is the clearance rate, t is the time, I is the continuous infusion rate, and x_0 is the plasma concentration at time 0. The restriction $k_1 > I$ was made in order to exclude the scenario of a steady drug concentration increase in the first compartment. For free plasma, the drug concentration is given by:

$$C_{plasma}(t) = \frac{(k_1 + \beta)(\alpha x_0 + I)}{\alpha(\beta - \alpha)} e^{\alpha t} - \frac{(k_1 + \alpha)(\beta x_0 + I)}{\beta(\beta - \alpha)} e^{\beta t} + \frac{(k_2 + k_3)I}{k_1 k_3}$$

where

$$\alpha = \frac{-(k_1 + k_2 + k_3) + \sqrt{(k_1 + k_2 + k_3)^2 - 4k_1 k_3}}{2}, \qquad \beta = \frac{-(k_1 + k_2 + k_3) - \sqrt{(k_1 + k_2 + k_3)^2 - 4k_1 k_3}}{2}$$

and k_2 is the rate constant associated with the flow from the second to the first compartment. In the case of STI, the drug concentration is obtained from the expressions above by putting I equal to zero.

Based on these expressions, $AUC_{0-\infty}$ and target attainment for any given target could be determined.

Statistical analysis

Using a non-linear mixed effects regression model with a random patient effect for each of the model parameters (x_0, k_1, k_3 - k_2 in case of plasma - and I in connection with continuous infusion) the two-compartment models were fitted to the drug concentration data separately for the different tissues. The concentrations in the washout samples were low, and therefore neglected in the analysis. For a range of relevant MICs, Monte Carlo simulation was used to determine the probability of target attainment (PTA) for 65% (low target) and 90% fT > MIC (high target) for the observation period of 8 h and 95% confidence intervals for $AUC_{0-\infty}$ and the ratio between $AUCs_{0-\infty}$ (21). More specifically, 50000 curves were simulated from the asymptotic multivariate normal distribution of the parameter estimates, and the relevant quantities were calculated for each simulation. Tests for no difference between STI and CI with respect to $AUC_{0-\infty}$ and the ratio between $AUCs_{0-\infty}$ were based on the simulated 95%-confidence intervals and the normal distribution. The acceptable level of PTA is

debatable, but 90% is generally considered as adequate and thus applied in this study (22). The data were analyzed using R (R v 3.0.2, R core team, Vienna, Austria) with the package nlme.

Results

No MD or cefuroxime adverse related events were encountered. The flow of patients through the study is shown in figure 1. Reasons for exclusion from analysis of all dialysates from a microdialysis catheter were: blood in all dialysates, displacement of the catheter from the drill hole, bone marrow penetration of the cortical drill hole, and no flow through the catheter after connection to the pump. Patient characteristics can be found in table 1.

Mean (SD) *in vivo* RRs were 11 (5) %, 22 (10) % and 14 (6) %, for SCT, cancellous and cortical bone respectively. The mean (SD) concentrations in the first and second washout samples were 0.15 (0.28) µg/mL and 0.11 (0.16) µg/mL, 0.09 (0.19) µg/mL and 0.06 (0.12) µg/mL and 0.24 (0.26) µg/mL and 0.17 (0.17) µg/mL for the corresponding anatomical sites, respectively.

Observed concentrations and modelled concentration-time profiles are depicted in figure 2. Observed vs. fitted cefuroxime concentrations are shown in figure 3. These plots demonstrate that the model provides a satisfactory description of the cefuroxime concentration data.

Comparisons of $AUCs_{0-\infty}$ and tissue penetration ratios can be found in table 2. Tissue penetration was incomplete for SCT and cortical bone in the STI group. In the CI group, low SCT and cortical bone penetration were also found, but in this group, the findings were not statistically significant. No significant differences in AUCs and tissue penetration ratios were found between the two groups.

The probability of attaining the selected targets in the different tissues is shown in figure 4 for a range of relevant MICs. Irrespective of MIC, tissue and target, CI leads to higher PTA compared to STI. Except for cancellous bone, the differences in PTA between the high and low target are negligeable for CI, whereas for STI, a substantial reduction is found. For the European Committee on

Antimicrobial Susceptibility Testing (EUCAST) clinical *Staphylococcus aureus* breakpoint MIC of 4 μg/mL, STI leads to inadequate PTA in all tissues but cancellous bone (23).

Discussion

This is the first clinical study to assess concurrent cefuroxime pharmacokinetics in plasma, SCT and bone administered as STI and CI in male TKR patients. The study has a number of interesting findings. Using the clinical breakpoint MIC of 4 μg/mL for *Staphylococcus aureus*, traditional STI of 1.5 g cefuroxime only leads to acceptable PTA in cancellous bone, but not in the remaining tissues. Even for the low target and a MIC of 2 μg/mL, STI does not lead to adequate PTA in plasma and SCT. When looking at figure 4, it appears that CI leads to improved PTA compared to STI irrespective of MIC and tissue. Also, except for cancellous bone, the difference in PTA is negliceable between the high and the low target for CI which is not the case for STI. Specifically, for the *Staphylococcus aureus* breakpoint, CI leads to adequate PTA for free plasma, SCT and cancellous bone even for the high target, while for cortical bone, a PTA of approximately 80% is achieved. Finally, it should be noted that both STI and CI leads to low PTAs for high organism MICs of ≥ 8 μg/mL. From a pharmacokinetic point of view, this study therefore suggests that CI of a standard dose of 1.5 g of cefuroxime may provide superior antibiotic prophylaxis in male TKR patients compared to traditional STI infusion.

While the time-dependency and plasma targets for treatment of infection are well-established for cefuroxime, specific tissue targets for prevention of postoperative orthopaedic infections remain somewhat unknown (1, 7). For time-dependent drugs, which are commonly used for antibiotic surgical prophylaxis, it is, however, recommended that not only plasma but also tissue concentrations exceed planktonic MIC values of relevant pathogens throughout the surgical procedure (1). In relation to total hip replacement, a practice of administering time-dependent antibiotics four times within the first 24 h of surgery has, retrospectively, been shown to lower postoperative infection rates compared to a single preoperative dose (24). The latter suggests that a single preoperative dose may be insufficient to eradicate the entire surgical site bacterial inoculum, and that the time with concentrations above MIC during the first 24 h may play a role in antibiotic prophylaxis in joint

replacement surgery. These speculations are somewhat supported by our findings of rather low PTA with STI for MICs ≤ 4 μg/mL. Furthermore, the severity of PJIs in itself calls for adoption of validated treatment targets instead of only sustaining antibiotic concentrations above the MIC during surgery. Finally, it could be speculated that antibiotics are ineffective against bacterial dormancy that may occur instantly following perioperative inoculation. In that case, prolonged time with concentrations above relevant MICs may have a positive effect in lowering postoperative infections rates. Based on these considerations, our application of a traditional 65% $fT_{>MIC}$ target and a more aggressive 90% $fT_{>MIC}$ target for evaluation of postoperative tissue pharmacokinetics in TKR patients and concurrent comparison of CI and STI therefore seems reasonable. Though a target of 100% $fT_{>MIC}$ appears fundamental for a CI approach, this would not be possible to obtain with the present setup due to time delays associated with the 5 min bolus infusion and the distribution from plasma to tissue.

Incomplete and uneven tissue distribution of antibiotics has been demonstrated for various combinations of drug and tissue and under different conditions, including infection (8, 16, 17, 25). In this study, low SCT and cortical bone penetration were found in both the STI and the CI group, but the findings were only significant in the STI group. Nonetheless, our findings support that a homogeneous tissue distribution of antibiotics cannot be taken for granted, particularly in special situations like surgery. This emphasize the importance of antibiotic pharmacokinetic studies evaluating specific drug and tissue concentrations under different conditions.

Males undergoing TKR surgery is a rather selected group that does not reflect the average population. Consequently, the results can only safely be regarded as representative for this specific population and the actual situation of TKR surgery. The tissue pharmacokinetics may have been affected by the local injection of adrenaline and ropivacaine at the end of surgery as both drugs induces vasoconstriction. Also, MD sampling of antibiotics in bone has to await surgical creation of drill holes. Consequently, measurements could not be obtained during the TKR surgery. Nonetheless, the present data obtained in drill holes shortly following the end of surgery seems to be reflective of the true postoperative situation.

In pharmacokinetic MD studies, a correction for RR is required in order to obtain absolute concentrations. This leads to a magnification of the variations associated with the preanalytical sample handling and the chemical assay. We have previously found comparable variations between plasma and tissue pharmacokinetic parameters, but in this study, the variations in tissue pharmacokinetic parameters were higher than those found in plasma. This is in accordance with findings in other clinical studies (9, 26). Given the RR-related magnification of the variations, the surgical trauma, local injection of adrenalin and the well-known biological variation, the sizes of the tissue variations illustrated in figure 2 and by the 95%-CIs of the AUCs in table 2 are not surprising, and supposedly not an indication of inadequate precision of the methodological setup nor a poor model description of the data.

In summary, this pharmacokinetic study shows that CI of 1.5 g of cefuroxime leads to improved probability of attaining relevant pharmacokinetic targets in male TKR patients compared to traditional STI. In fact, standard STI results in considerably inadequate PTA when applying the clinical *Staphylococcus aureus* MIC breakpoint. These findings suggest that application of CI may improve antibiotic prophylaxis for TKR patients.

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References

1. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. Am J Infect Control. 1999;27(2):97-132; quiz 3-4; discussion 96.

2. Illingworth KD, Mihalko WM, Parvizi J, Sculco T, McArthur B, el Bitar Y, et al. How to minimize infection and thereby maximize patient outcomes in total joint arthroplasty: a multicenter approach: AAOS exhibit selection. The Journal of bone and joint surgery American volume. 2013;95(8):e50.

3. Nielsen EI, Cars O, Friberg LE. Pharmacokinetic/pharmacodynamic (PK/PD) indices of antibiotics predicted by a semimechanistic PKPD model: a step toward model-based dose optimization. Antimicrob Agents Chemother. 2011;55(10):4619-30.

4. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 1998;26(1):1-10; quiz 1-2.

5. Drusano GL. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nature reviews Microbiology. 2004;2(4):289-300.

6. Li C, Du X, Kuti JL, Nicolau DP. Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. Antimicrob Agents Chemother. 2007;51(5):1725-30.

7. McKinnon PS, Paladino JA, Schentag JJ. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. International journal of antimicrobial agents. 2008;31(4):345-51.

8. Schintler MV, Traunmuller F, Metzler J, Kreuzwirt G, Spendel S, Mauric O, et al. High fosfomycin concentrations in bone and peripheral soft tissue in diabetic patients presenting with bacterial foot infection. The Journal of antimicrobial chemotherapy. 2009;64(3):574-8.

9. Wiskirchen DE, Shepard A, Kuti JL, Nicolau DP. Determination of tissue penetration and pharmacokinetics of linezolid in patients with diabetic foot infections using in vivo microdialysis. Antimicrobial agents and chemotherapy. 2011;55(9):4170-5.

10. Bue M, Hanberg P, Tottrup M, Thomassen MB, Birke-Sorensen H, Thillemann TM, et al. Vancomycin concentrations in the cervical spine after intravenous administration: results from an experimental pig study. Acta Orthop. 2018:1-6.

11. Landersdorfer CB, Bulitta JB, Kinzig M, Holzgrabe U, Sorgel F. Penetration of antibacterials into bone: pharmacokinetic, pharmacodynamic and bioanalytical considerations. Clinical pharmacokinetics. 2009;48(2):89-124.

12. Mouton JW, Theuretzbacher U, Craig WA, Tulkens PM, Derendorf H, Cars O. Tissue concentrations: do we ever learn? The Journal of antimicrobial chemotherapy. 2008;61(2):235-7.

13. Pea F. Penetration of antibacterials into bone: what do we really need to know for optimal prophylaxis and treatment of bone and joint infections? Clinical pharmacokinetics. 2009;48(2):125-7.

14. Bue M, Tottrup M, Hanberg P, Langhoff O, Birke-Sorensen H, Thillemann TM, et al. Bone and subcutaneous adipose tissue pharmacokinetics of vancomycin in total knee replacement patients. Acta Orthop. 2017:1-6.

15. Tottrup M, Hardlei TF, Bendtsen M, Bue M, Brock B, Fuursted K, et al. Pharmacokinetics of cefuroxime in porcine cortical and cancellous bone determined by microdialysis. Antimicrobial agents and chemotherapy. 2014;58(6):3200-5.

16. Bue M, Hanberg P, Koch J, Jensen LK, Lundorff M, Aalbaek B, et al. Single-Dose Bone Pharmacokinetics of Vancomycin in a Porcine Implant-Associated Osteomyelitis Model. J Orthop Res. 2017.

17. Joukhadar C, Frossard M, Mayer BX, Brunner M, Klein N, Siostrzonek P, et al. Impaired target site penetration of beta-lactams may account for therapeutic failure in patients with septic shock. Critical care medicine. 2001;29(2):385-91.

18. Stahle L, Arner P, Ungerstedt U. Drug distribution studies with microdialysis. III: Extracellular concentration of caffeine in adipose tissue in man. Life Sci. 1991;49(24):1853-8.

19. Tottrup M, Bibby BM, Hardlei TF, Bue M, Kerrn-Jespersen S, Fuursted K, et al. Continuous versus short-term infusion of cefuroxime: assessment of concept based on plasma, subcutaneous tissue, and bone pharmacokinetics in an animal model. Antimicrobial agents and chemotherapy. 2015;59(1):67-75.

20. Chaurasia CS, Muller M, Bashaw ED, Benfeldt E, Bolinder J, Bullock R, et al. AAPS-FDA Workshop White Paper: Microdialysis Principles, Application, and Regulatory Perspectives Report From the Joint AAPS-FDA Workshop, November 4-5, 2005, Nashville, TN. The AAPS Journal. 2007;9(1):47-59.

21. Drusano GL. Pharmacokinetics and pharmacodynamics of antimicrobials. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2007;45 Suppl 1:S89-95.

22. Mouton JW, Brown DF, Apfalter P, Canton R, Giske CG, Ivanova M, et al. The role of pharmacokinetics/pharmacodynamics in setting clinical MIC breakpoints: the EUCAST approach. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2012;18(3):E37-45.

23. EUCAST. European Committee on Antimicrobail Susceptibility Testing 2019 [Data from the EUCAST MIC distribution website]. Available from: https://mic.eucast.org/Eucast2/SearchController/search.jsp?action=performSearch&BeginIndex=0&Micdif=mic&NumberIndex=50&Antib=179&Specium=-1.

24. Engesaeter LB, Lie SA, Espehaug B, Furnes O, Vollset SE, Havelin LI. Antibiotic prophylaxis in total hip arthroplasty: effects of antibiotic prophylaxis systemically and in bone cement on the revision rate of 22,170 primary hip replacements followed 0-14 years in the Norwegian Arthroplasty Register. Acta orthopaedica Scandinavica. 2003;74(6):644-51.

25. Tottrup M, Bue M, Koch J, Jensen LK, Hanberg P, Aalbaek B, et al. Effects of Implant-Associated Osteomyelitis on Cefuroxime Bone Pharmacokinetics: Assessment in a Porcine Model. The Journal of bone and joint surgery American volume. 2016;98(5):363-9.

26. Bulik CC, Wiskirchen DE, Shepard A, Sutherland CA, Kuti JL, Nicolau DP. Tissue penetration and pharmacokinetics of tigecycline in diabetic patients with chronic wound infections described by using in vivo microdialysis. Antimicrob Agents Chemother. 2010;54(12):5209-13.

Figures and tables

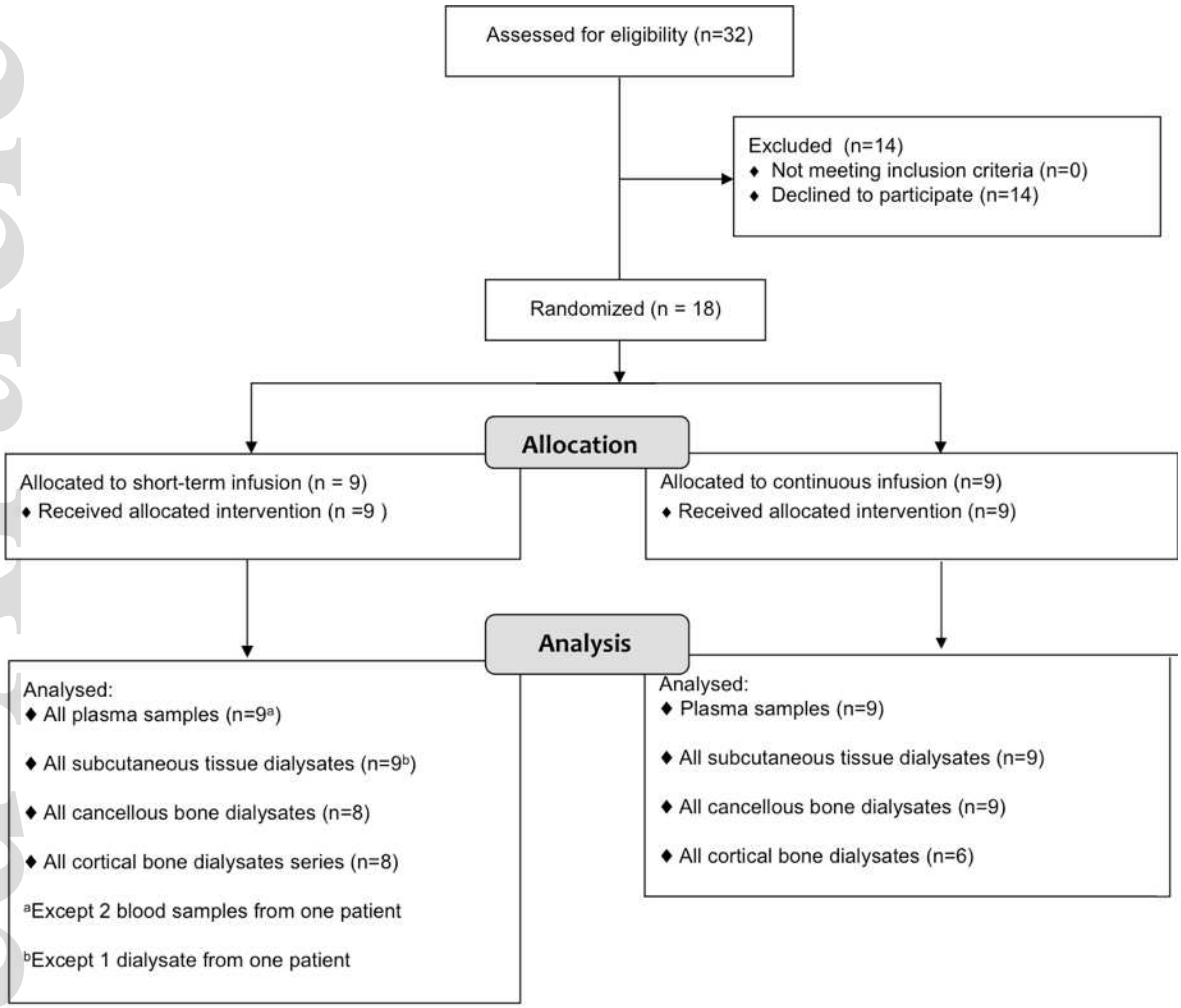

Figure 1. Patient flow.

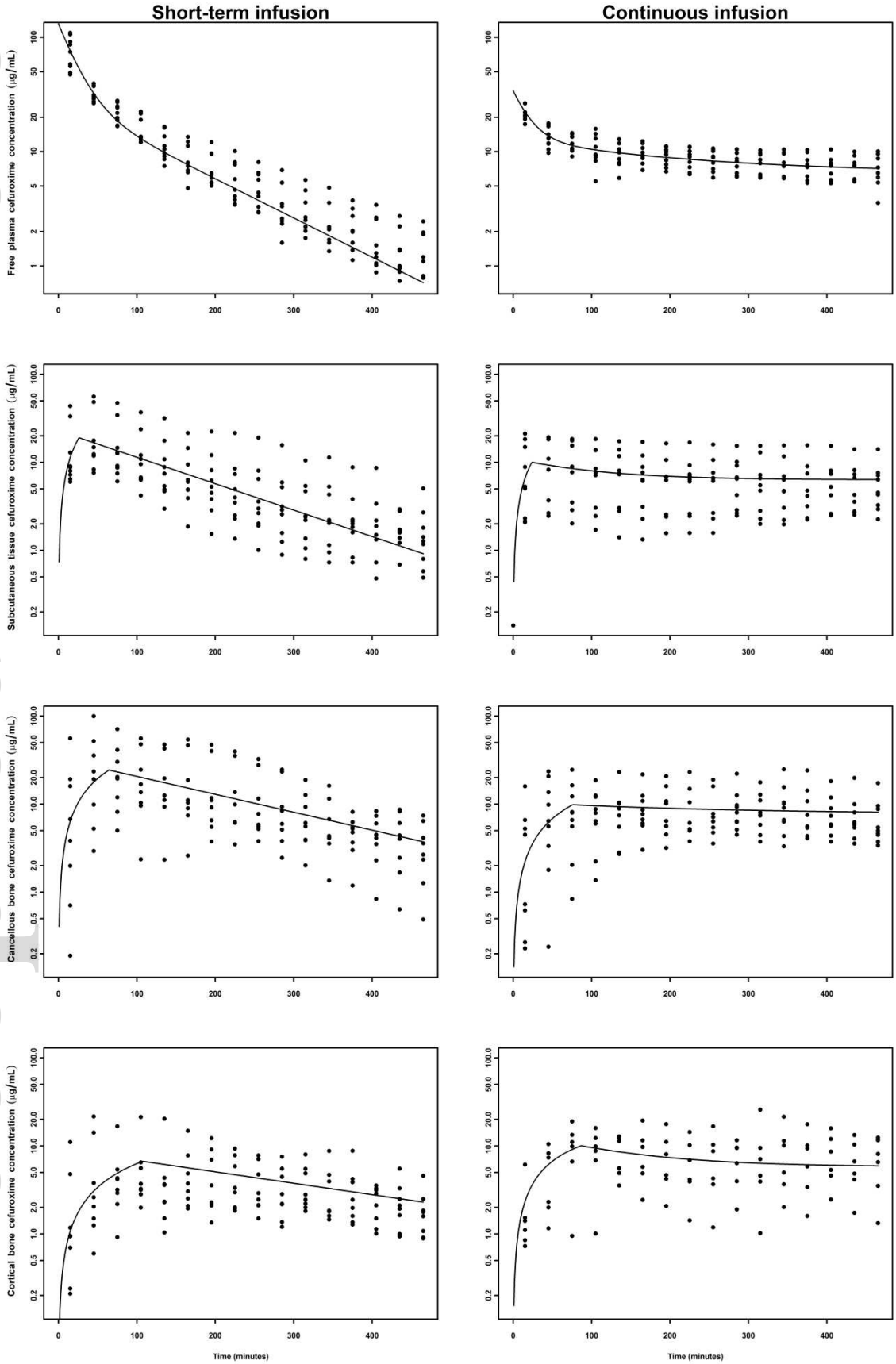

Figure 2. Observed concentrations (dots) and modelled concentration-time profiles (solid lines).

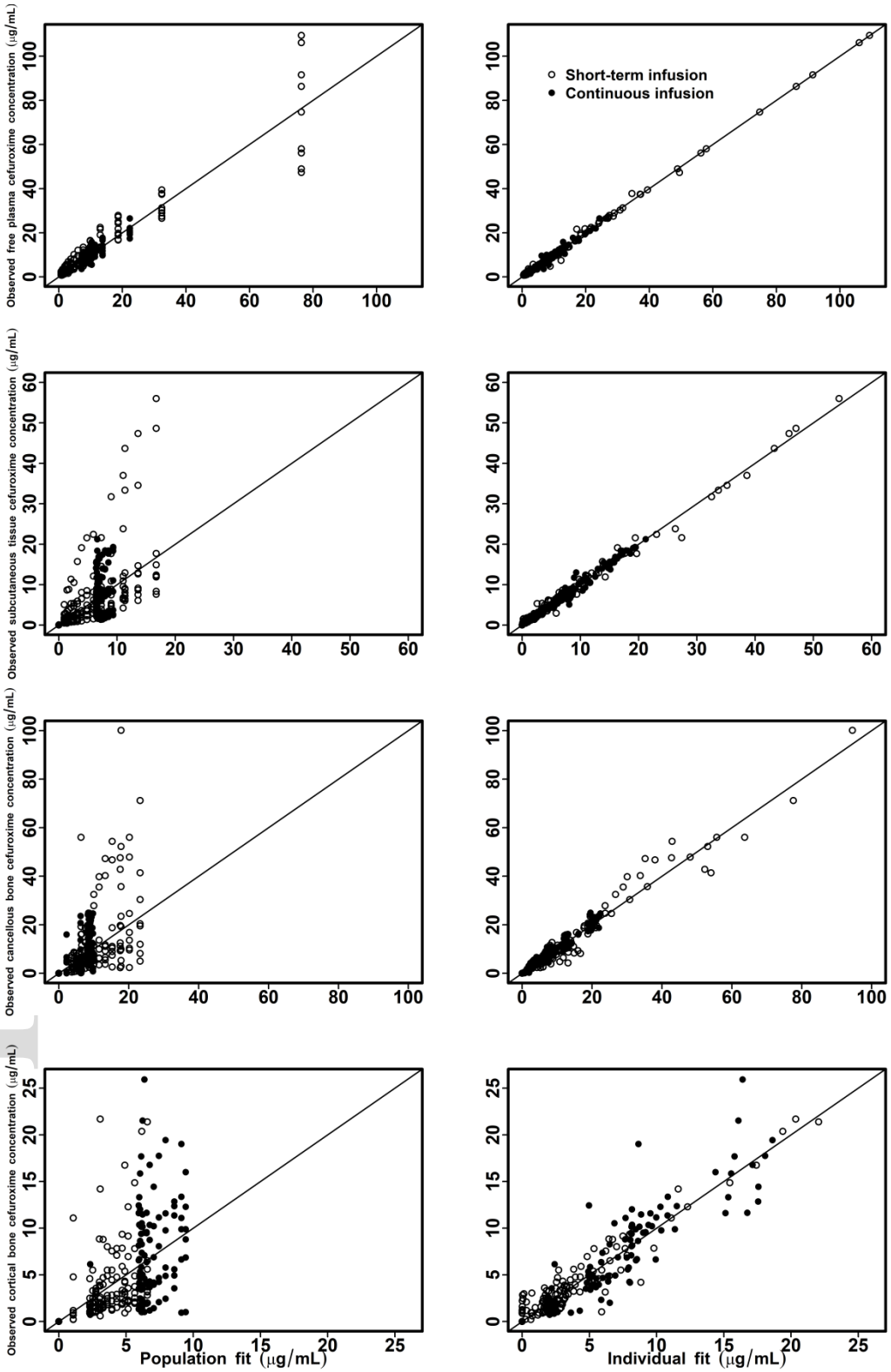

Figure 3. Observed versus fitted individual- and population cefuroxime concentrations for free plasma, SCT, cortical and cancellous bone.

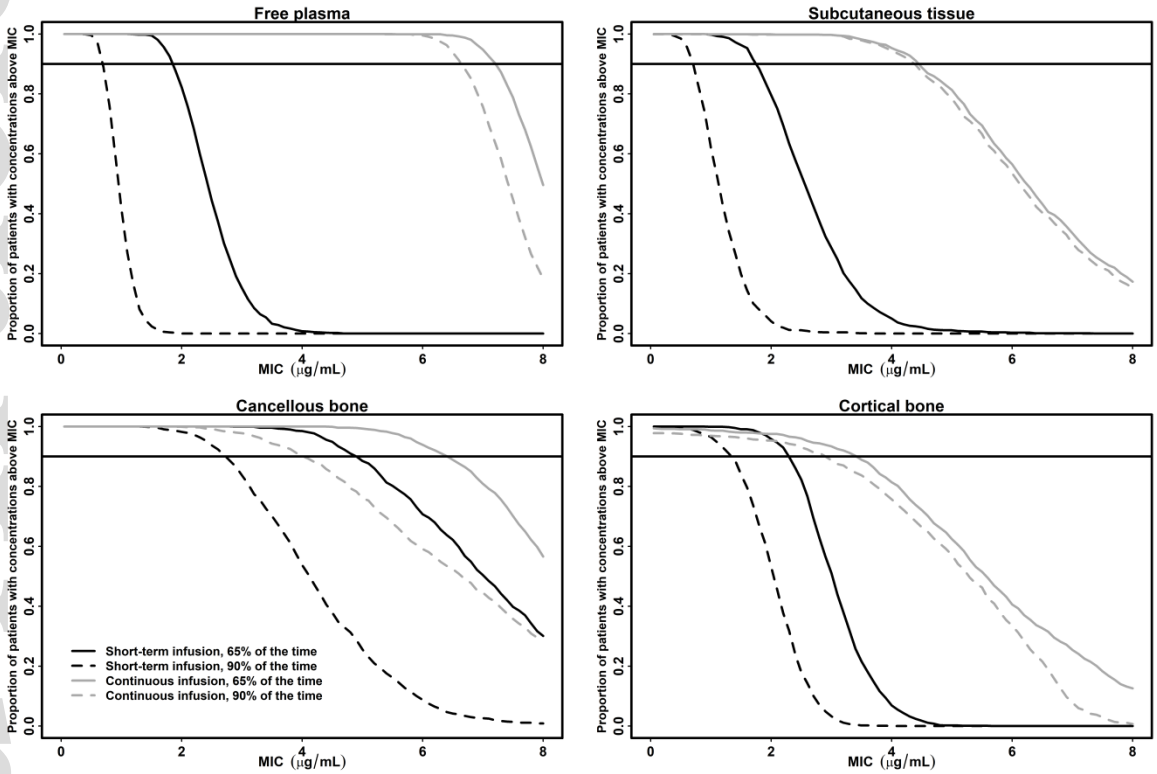

Figure 4. Probability of target attainment in the different tissues. A horizontal line representing 90 % of patients with concentrations above MIC have been inserted.

Table 1

Patient characteristics.

Variable	Short-term infusion	Continuous infusion
Number of patients	9	9
Age (years), mean (range)	68.7 (58 – 76)	70.0 (60 – 75)
Height (cm), mean (range)	180 (170 – 190)	176 (169 – 183)
Weight (kg), mean (range)	99 (73 – 110)	89 (73 – 107)
Body mass index (kg/m^2), mean (range)	30.6 (21.8 – 36.0)	28.7 (23.9 – 35.8)
Plasma creatinine (µmol/l), mean (range)	76 (64 – 99)	87 (68 – 111)
Plasma albumin (g/l), mean (range)	42 (38 – 47)	42 (40 – 46)

Table 2

Comparison of AUC and tissue penetration

Parameter	STI	CI	P-value
Free plasma $AUC_{0-\infty}$ (min µg/mL)	5801 (4902-7277)	5415 (4625-6670)	p = 0.63
SCT $AUC_{0-\infty}$ (min µg/mL)	3016 (1929-4675)	3764 (2164-6426)	p = 0.56
Cancellous bone $AUC_{0-\infty}$ (min µg/mL)	6035 (3718-9831)	6256 (4276-8954)	p = 0.91
Cortical bone $AUC_{0-\infty}$ (min µg/mL)	2630 (1746-3945)	3557 (1375-7262)	p = 0.56
SCT $fAUC_{tissue}/fAUC_{plasma}$	0.52 (0.32-0.83)	0.69 (0.38-1.21)	p = 0.48
Cancellous bone $fAUC_{tissue}/fAUC_{plasma}$	1.03 (0.61-1.74)	1.15 (0.74-1.71)	p = 0.76
Cortical bone $fAUC_{tissue}/fAUC_{plasma}$	0.35 (0.28-0.70)	0.65 (0.25-1.36)	p = 0.50

$AUC_{0-\infty}$, area under the concentration–time curve from 0 to infinity; $fAUC_{tissue}/fAUC_{plasma}$, tissue penetration expressed as the ratio of free $AUC_{0-\infty}$ tissue to free $AUC_{0-\infty}$ plasma. Values are given as mean (95% confidence intervals).