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Pharmacokinetics of Cefuroxime in Synovial Fluid

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ABSTRACT Cefuroxime is frequently used as preoperative antibiotic prophylaxis and may be used for the treatment of septic arthritis. A prerequisite for successful treatment of septic arthritis is the ability of an antibiotic agent to penetrate into the target site. Therefore, the concentration of cefuroxime in synovial fluid was evaluated. Ten patients who underwent elective knee arthroscopy were included in this study. Patients were treated with a single dose of 1,500 mg cefuroxime intravenously, and subsequently, the concentrations in plasma, the interstitial fluid of muscle tissue, and synovial fluid were measured by using microdialysis. Pharmacokinetic/pharmacodynamic calculations to predict bacterial killing were performed using the epidemiologically defined MIC_{90} for clinical isolates and CLSI breakpoints. Cefuroxime penetrated excellently into muscle tissue (ratio of the area under the concentration-time curve [AUC] for muscle tissue/AUC for free plasma, 1.79) and synovial fluid (ratio of the AUC for synovial fluid/AUC for free plasma, 1.94). The cefuroxime concentration was greater than the MIC_{90} for *Staphylococcus aureus* and *S. epidermidis* strains (≤2 mg/liter) over the complete dosing interval (the percentage of the dosing interval during which the free cefuroxime concentration exceeded the MIC for the pathogen [fT_{MIC}]). CLSI defines staphylococci with MICs of ≤8 mg/liter to be susceptible to cefuroxime. For staphylococci with MICs of ≤8 mg/liter, the fT_{MIC} in plasma was 52.5%, while the fT_{MIC} in muscle tissue and synovial fluid was 93.6% and 96.3%, respectively. Cefuroxime may be used to treat septic arthritis caused by susceptible bacterial strains (MIC ≤ 8 mg/liter). The activity of cefuroxime in septic arthritis might be underestimated when relying exclusively on plasma concentrations.

KEYWORDS *in vivo* pharmacokinetics, drug tissue concentration, microdialysis, bacteria, septic arthritis

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Antimicrobial efficacy is dependent on the local concentration of an antibiotic at the infection site and its activity against the underlying pathogen. While most studies measure exclusively the plasma concentrations of antibacterial drugs, infections primarily occur in the interstitial space of peripheral compartments or in various body fluids. Local antibiotic drug concentrations at the infection site may differ considerably from the plasma concentrations (1, 2). Hence, measurements of antibiotic concentrations at the infection site deliver valuable information for optimizing the treatment of infections. This is in agreement with the recommendations of major regulatory authorities, like the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), which recommend that the drug tissue concentration, in addition to the drug plasma concentration, be measured (3, 4).

Septic arthritis is a joint-destructive infectious disease with an increasing incidence rate. Presumably, the increase in the number of prosthetic joint arthroplasties performed, the general increase in the incidence of rheumatoid arthritis, and the concom-

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TABLE 1 Patients' characteristics

Characteristic	Value(s)
Mean (SD) age (yr)	34.2 (13.6)
No. of patients of the following sex:	
Male	8
Female	2
No. of patients with the following smoking status:	
Smoker	6
Nonsmoker	4
No. of patients with the following alcohol consumption:	
Infrequent drinking behavior	6
Abstinent	4
No. of patients with a preceding arthroscopy on the knee	2
Mean (SD) BMI[a]	26.0 (5.2)
No. of patients with the following indication for arthroscopy:	
Rupture of cruciate ligament	3
Rupture of meniscus	3
Rupture of cruciate ligament and meniscus damage	2
Rupture of cruciate ligament and cartilage damage	1
Rupture of meniscus and cartilage damage	1

[a]BMI, body mass index.

itant use of immune-suppressive treatment are responsible for this increasing rate (5, 6). Furthermore, the number of sports injuries and the number of arthroscopic surgeries are continuously increasing, and with those increases, the number of associated infections is also increasing. Recently, the prevalence of postarthroscopic septic arthritis was reported to be 0.14% (7). In adults, the knee is the most frequently affected joint in septic arthritis (8). Current treatment guidelines recommend broad-spectrum antibiotic treatment as well as the surgical evacuation of pus (9). However, recommendations concerning the choice of antimicrobial drug are exclusively based on expert opinion rather than on clinical trials, and despite adequate therapy, up to 40% of patients suffer sequelae (10). It is possible that the drug levels at the infection site (i.e., synovial fluid) are inadequate, which might be responsible for the poor outcome. Therefore, this study set out to measure the intra-articular concentrations of cefuroxime by microdialysis (MD) after a single intravenous application of cefuroxime in patients undergoing elective knee arthroscopy for meniscal repair or cruciate ligament reconstruction.

RESULTS

Ten subjects aged 20 to 61 years undergoing elective knee arthroscopy were enrolled in the trial described here. Table 1 shows the patients' characteristics and, in particular, their indications for arthroscopy.

The mean values of the pharmacokinetic (PK) parameters for cefuroxime in serum, muscle tissue, and synovial fluid are presented in Table 2. The time profiles of the cefuroxime concentrations in plasma, muscle tissue, and synovial fluid are shown in Fig. 1. While the maximum concentration (C_{max}) of cefuroxime in plasma was achieved

TABLE 2 Mean values of PK parameters after a single infusion of 1,500 mg cefuroxime

Compartment	AUC_{0-8} (mg · h/liter)	$AUC_{muscle\ tissue}$/ $AUC_{free\ plasma}$	C_{max} (mg/liter)	T_{max} (h)	$t_{1/2}$ (h)	CL (liters/h)	*V* (liters)
Total plasma	151.0 ± 37.2		103.0 ± 24.7	0.5	1.35 ± 0.5	10.4 ± 3.0	19.7 ± 8.0
Free plasma	101.2 ± 24.9		69.0 ± 16.5	0.5	1.35 ± 0.5		
Synovia	192.2 ± 86.2	1.94 ± 0.87	57.3 ± 27.7	1.5 ± 0.7	3.1 ± 1.2		
Muscle	178.5 ± 74.0	1.79 ± 0.66	67.1 ± 33.0	1.1 ± 0.2	4.9 ± 2.4		

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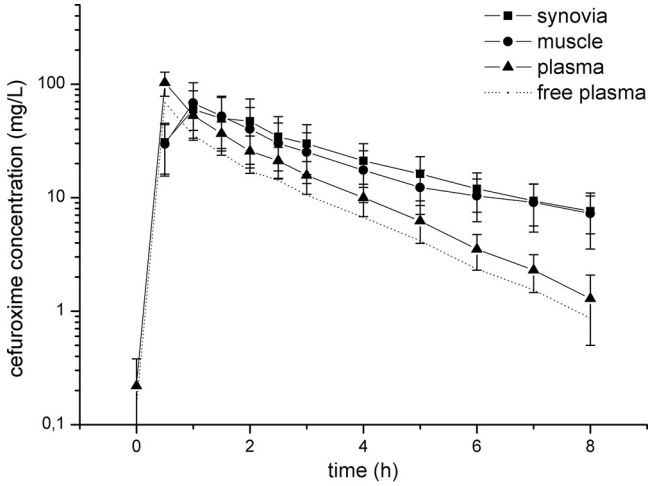

FIG 1 Concentration-time profiles of cefuroxime in synovial fluid, muscle tissue, and plasma. A plasma protein binding rate of 33% was assumed, as previously described (11).

at the end of the infusion, the C_{max}s of cefuroxime in muscle tissue and synovial fluid were measured 1 h after the end of the infusion.

The average relative recovery of cefuroxime was 13.2% and 18.2% in muscle tissue and synovial fluid, respectively. For calculation of the unbound fraction, plasma protein binding of 33% was assumed, as previously described (11). After a single infusion of cefuroxime, the areas under the concentration-time curves (AUCs) for muscle tissue ($AUC_{muscle\ tissue}$) ($P = 0.028$) and synovial fluid ($AUC_{synovia}$) ($P = 0.009$) were significantly higher than the AUC for plasma for cefuroxime not bound to protein ($AUC_{free\ plasma}$). This is underlined by the mean ratio of the $AUC_{muscle\ tissue}$ to $AUC_{free\ plasma}$ of 1.9 for synovial fluid and 1.8 for muscle tissue. Table 3 depicts the PK/pharmacodynamic (PD) calculations for relevant susceptible bacterial strains.

After the lag time needed for tissue penetration to take place (i.e., after 60 min), a strong correlation between free cefuroxime plasma concentrations and local concentrations in synovial fluid ($R = 0.97$, $P < 0.001$) and muscle tissue ($R = 0.99$, $P < 0.001$) was found (Fig. 2).

In total, 7 subjects reported 8 adverse events. None of the adverse events was graded serious or was associated with the microdialysis procedure or the study drug.

DISCUSSION

This study showed the excellent penetration of cefuroxime into synovial fluid and muscle tissue. Cefuroxime was chosen for this study because it is frequently used for perioperative antibiotic prophylaxis and, furthermore, can be used to combat septic arthritis.

The cefuroxime plasma concentrations measured within this population were similar to previously reported plasma concentrations (12). The mean cefuroxime tissue concentrations in synovial fluid and muscle tissue exceeded the mean cefuroxime

TABLE 3 Mean cefuroxime fT_{MIC} for relevant bacteria in plasma, synovial fluid, and muscle tissue

Compartment	fT_{MIC} (%) for bacteria for which the MIC was:		
	2 mg/liter	8 mg/liter	64 mg/liter
Total plasma[a]	95.0 ± 21.7	61.2 ± 12.8	5.0 ± 8.0
Free plasma[a]	85.4 ± 19.0	51.4 ± 10.4	0
Synovia[b]	100	96.3	0
Muscle[b]	100	93.6	1.9

[a]Calculated as previously described (22).
[b]Estimated from the shapes of the mean concentration-time curves.

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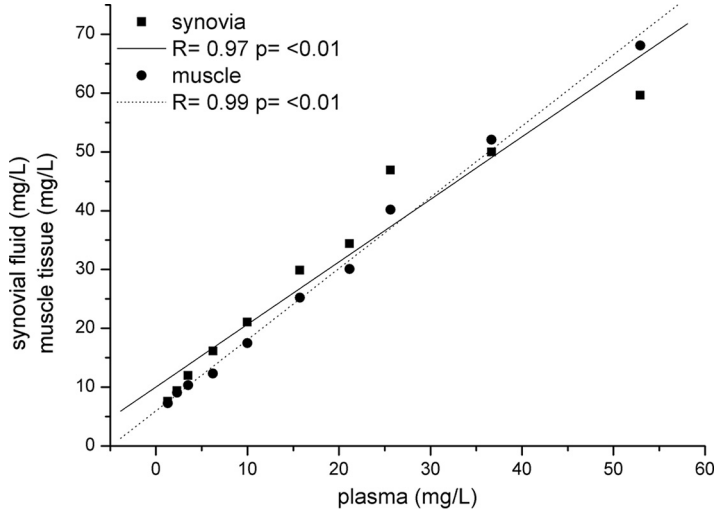

FIG 2 Correlation of mean plasma and tissue concentrations at individual time points.

plasma concentration after 1 h and for the entire following dosing interval, indicating excellent tissue and synovial fluid penetration. It might be surprising that the tissue concentrations exceeded the plasma concentrations during the entire observation period, since the tissue concentrations of cephalosporins are generally similar to or less than the free plasma concentrations (13, 14). However, the favorable tissue pharmacokinetics of cefuroxime, including tissue concentrations that exceed plasma concentrations, have also been observed in a study investigating cefuroxime in morbidly obese patients (15).

While the C_{max} in tissues was slightly lower than that in plasma, the terminal elimination half-life ($t_{1/2}$) was profoundly extended in tissues compared to the plasma $t_{1/2}$. The prolonged $t_{1/2}$ led to increased $AUC_{synovia}$ and $AUC_{muscle\ tissue}$ compared to the $AUC_{free\ plasma}$ (Table 2).

Nevertheless, the linear regression model showed a strong correlation between free cefuroxime concentrations in plasma and cefuroxime concentrations in synovial fluid and muscle tissue, indicating that tissue concentrations might be estimated on the basis of the plasma concentration when other dosing schedules are employed.

Cefuroxime exhibits time-dependent bacterial killing. The maximum effect can be achieved when the free plasma concentration continuously exceeds the MIC for the target pathogens. Therefore, the percentage of the dosing interval during which the free cefuroxime concentration exceeds the MIC for the pathogen (fT_{MIC}) is the PK/PD parameter that best correlates with clinical efficacy. While PD targets for joint infections are not available, in a mouse thigh infection model, optimal bacterial killing by cephalosporins was shown when the fT_{MIC} was at least 40 to 50% (16).

While the cefuroxime concentrations in plasma fell beneath the MIC_{90} for susceptible bacteria (2 mg/liter for both *S. aureus* and *S. epidermidis*) at the end of the observation period, cefuroxime concentrations in muscle tissue and synovial fluid remained above the MIC_{90} over the whole dosing interval. Therefore, septic arthritis caused by *S. aureus* and *S. epidermidis* strains susceptible to cephalosporins may effectively be treated with cefuroxime.

The average $fT{>}MIC_{90}$ in plasma for staphylococci susceptible to cefuroxime according to the CLSI breakpoint (8 mg/liter) was 52.5%. This is just slightly above the minimal fT_{MIC} required for bacterial killing. However, the $fT{>}MIC_{90}$ in synovial fluid and muscle tissue was 96.3% and 93.6%, respectively, indicating that in the case of septic arthritis caused by staphylococci with an MIC of ≤8 mg/liter, cefuroxime treatment should be successful, although plasma levels might be on the lower limit of the targeted concentrations. The MIC_{90} for methicillin-resistant *S. epidermidis* (MRSE) was

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also defined to be 8 mg/liter. Therefore, although the treatment of septic arthritis due to MRSE with cefuroxime cannot be recommended, in at least some patients, treatment could be successful. The $fT>MIC_{90}$ of methicillin-resistant *S. aureus* (MRSA) (64 mg/liter) was too short or the level was not even reached in all compartments in which the concentration was measured.

It should be mentioned that the use of fT_{MIC} as a PK/PD parameter to predict bacterial efficacy is validated only for drug plasma concentrations and not for drug tissue concentrations. However, only the free concentration of an antibiotic at the site of infection exerts a killing effect. Therefore, one might suspect that the fT_{MIC} derived from the tissue concentration also delivers accurate information regarding the antimicrobial activity to be expected. In the particular case of staphylococci, the fT_{MIC} for staphylococci (including MRSE) with an MIC of 8 mg/liter was substantially higher in synovial fluid and muscle tissue than that predicted by the fT_{MIC} in plasma. Therefore, when fT_{MIC} is used exclusively on the basis of the plasma concentrations, the activity of cefuroxime in tissues might be underestimated.

This study had several limitations. This study was performed in a group of generally healthy subjects. The tissue penetration of antimicrobial agents may be significantly impaired by local or systemic inflammation (17), and therefore, the ability of cefuroxime to penetrate into inflamed tissues should be investigated in distinct patient populations. Further, only the concentration in muscle tissue and synovial fluid and not that in synovial tissue was obtained. However, introduction of an MD probe into the cartilage would not be considered feasible from an ethical perspective.

In this study, samples for PK analysis were collected only up to 8 h postdosing. Given that the $t_{1/2}$ of cefuroxime was substantially prolonged in tissues, it is unclear whether the terminal slopes of the concentration-time curves were captured.

When fT_{MIC} was estimated, one-compartment kinetics were assumed. Multicompartment modeling might have yielded more accurate results; however, establishment of a multicompartmental model to calculate cefuroxime pharmacokinetics was beyond the scope of the current study.

As seen in Fig. 1, the C_{max} in plasma was achieved at 30 min postdosing, while the C_{max} in muscle tissue and synovial fluid was measured only after 60 min. Hence, the tissue penetration of cefuroxime into tissues was delayed by roughly 30 min. Therefore, comparisons were performed only for concentrations measured after concentration hysteresis was already achieved, i.e., after 60 min.

In conclusion, we present the results of the first study investigating the synovial fluid concentrations of cefuroxime throughout the dosing interval. This study showed that the activity of cefuroxime in septic arthritis might be underestimated when reliance is exclusively based on the concentrations measured in plasma. On the basis of the results of the present pharmacokinetic study, cefuroxime seems to be a valid treatment choice in patients with septic arthritis when bacterial resistance can be ruled out. Clinical studies and PK/PD modeling should verify the present data.

MATERIALS AND METHODS

This single-center phase 1 MD study was performed at the Medical University of Vienna in accordance with the Declaration of Helsinki and the guidelines of the International Conference of Harmonization good clinical practice. The ethics committee of the Medical University of Vienna approved the study protocol and the informed consent form (EK-1063/2012) before the study was initiated. All subjects provided written informed consent before inclusion.

Study population. The study population included 10 male and female patients aged 20 to 61 years with no clinically relevant medical history that were undergoing elective knee arthroscopy. Physical examination, body weight, vital signs, blood laboratory tests, urinalysis, and a 12-lead electrocardiography were performed during the screening evaluation visit. For female subjects of childbearing potential, a pregnancy test was performed. Subjects were excluded if they had a history of a clinically relevant disease, had significantly abnormal clinical findings during the screening physical examination, were intolerant to β-lactam antibiotics, were pregnant, or had received any investigational drug within 30 days prior to inclusion in the study.

Study medication. Cefuroxime (Cefuroxim Astro, 1,500 mg; Astro-Pharma GmbH, Vienna, Austria) was diluted in 250 ml of saline solution and administered over 30 min by use of an automatic infusion apparatus. After completion, 100 ml physiological saline solution was infused over the same infusion line to guarantee that the complete dosage had been applied.

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Study design. Subjects were admitted to the ward of the Department of Trauma Surgery of the Medical University of Vienna on the day before surgery. Subjects fasted overnight before surgery, and in the morning of the study day, a peripheral venous catheter was inserted into a vein of each arm. A standard arthroscopy including either meniscus or ligament repair was performed as described previously (18). An MD probe was inserted aseptically into the synovial space of the knee, and another MD probe was inserted into the skeletal muscle of the same thigh. In the postanesthesia care unit, cefuroxime was applied as described above. Cefuroxime concentrations in plasma and the interstitial fluid of muscle tissue and synovia were measured at regular intervals for up to 8 h. Subjects were released from the ward in the following days at the discretion of the surgeon. Within 2 weeks after arthroscopy, a follow-up evaluation was performed.

Sampling for concentration determination. Cefuroxime plasma concentrations were measured at the baseline, at 30-min intervals for up to 3 h, and thereafter hourly for up to 8 h after infusion. Cefuroxime concentrations in synovial fluid and muscle tissue were measured by the MD technique. As described previously, this method is based on the exchange of molecules between the perfusion fluid of an MD probe and the extracellular space of the tissue into which the MD probe is implanted (19, 20). Exclusively non-protein-bound molecules are able to diffuse across the semipermeable membrane located at the tip of the MD probe and can be collected for subsequent analysis. CMA 63 MD probes with a 20,000-Da-molecular-mass cutoff (CMA, Sweden) were used. By employing a microinfusion pump (CMA microdialysis pump 107; CMA, Sweden), the probes were rinsed with saline solution at a low flow rate of 2 μl/min. Cefuroxime concentrations were determined predosing and at 0 to 0.5 h, 0.5 to 1 h, 1 to 1.5 h, 1.5 to 2 h, 2 to 2.5 h, 2.5 to 3 h, 3 to 4 h, 4 to 5 h, 5 to 6 h, 6 to 7 h, and 7 to 8 h postdosing. At the end of the sampling period, the probes were calibrated by retrodialysis before removal. The retrodialysis method relies on the assumption that the process of diffusion across the semipermeable membrane is quantitatively equal in both directions. This implies that the fraction of the interstitial drug concentration that is recovered in the collected microdialysate sample, which is referred to as relative recovery, can be calculated according to the following equation: percent relative recovery = 100 − [100 × (analyte concentration$_{out}$/analyte concentration$_{in}$], where concentration$_{out}$ is the concentration of the analyte within the dialysate and concentration$_{in}$ is the concentration of the analyte within the perfusion fluid. Interstitial cefuroxime concentrations were calculated as follows: interstitial concentration = 100 × (sample concentration/relative recovery) (19).

PK analysis. Kinetica software (version 3.0; Innaphase) was used to calculate the values of the pharmacokinetic (PK) parameters. The maximum concentration (C_{max}) in plasma, the time to C_{max} (T_{max}), the terminal elimination half-life ($t_{1/2}$), and the area under the concentration-time curve (AUC) from 0 to 8 h (AUC_{0-8}) were calculated from nonfitted data by employing the trapezoidal rule. For the AUC from 0 h to infinity (AUC_{0-inf}), individual extrapolation based on the last observed concentration and the elimination rate constant (k_{el}) was performed. In addition, apparent total body clearance (CL) and the apparent volume of distribution (V) were calculated for plasma.

The T_{max}, C_{max}, and AUC_{0-8} were also calculated for synovial fluid and muscle tissue.

Bioanalysis. To quantify the cefuroxime concentrations in the plasma and MD samples, a high-performance liquid chromatography (HPLC) method was developed and validated according to EMA guidelines (21) at the Department of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universität Berlin, Berlin, Germany.

The quantification was achieved on a Thermo Scientific Ultimate 3000 HPLC (HPG-3200SD pump, WPS-3000TSL autosampler, TCC-3000SD column oven, DAD 3000 detector). Cefuroxime was successfully separated from all 26 drugs concomitantly administered in the trial by use of a Thermo Fisher Hypersil Gold phenyl column (100 by 4.6 mm; particle size, 3 μm) and a Thermo Fisher phenyl guard column at 35°C and a gradient method with two mobile phases, Milli-Q water with 0.1% trifluoroacetic acid and Milli-Q water with acetonitrile 30:70 (vol/vol), at a flow rate of 2 ml/min. The autosampler was cooled to 4°C to ensure the stability of all samples. The detection wavelength was set to 271 nm. For one patient who was being treated with urapidil for hypertension, selectivity for cefuroxime was insufficient. Hence, the previously described method was modified: the flow rate was decreased to 1 ml/min, and the gradient was altered to ensure selectivity for the drug administered to this particular patient. All other settings were equal in both methods. Preparation of MD samples consisted of a simple dilution: 30 μl of the sample was mixed with 20 μl of acetonitrile. Plasma sample preparation included protein precipitation by addition of 400 μl of acetonitrile to 100 μl of sample and subsequent centrifugation for 15 min at 13,800 × g. Three hundred microliters of supernatant was evaporated to dryness and afterwards redissolved in a solution of water and acetonitrile 96:4 (vol/vol) to obtain the final solution used for measurement. Twenty microliters was injected for analysis.

Both final quantification methods were successfully validated with good accuracy (inter- and intraday relative error [RE], ≤±10.4% and ≤±15.4% for the lower limit of quantification [LLOQ], respectively), precision (inter- and intraday coefficient of variation [CV], ≤+10.5% and ≤+8.4% for LLOQ, respectively), and stability across the entire concentration range of 0.3 μg/ml to 125 μg/ml.

PK/PD calculations. For calculation of the values of the pharmacokinetic (PK)/pharmacodynamic (PD) parameters, the percentage of the dosing interval during which the free cefuroxime concentration exceeded the MIC for the pathogen (fT_{MIC}) was used as previously recommended (22). The percentage of the time that the concentration was greater than the MIC was calculated as described by Turnidge (22).

S. aureus and *S. epidermidis* are the most frequent causes of septic arthritis. CLSI defines staphylococci with an MIC of ≤8 mg/liter to be susceptible to cefuroxime, while epidemiologic studies revealed MIC_{90}

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values of ≤2 mg/liter for staphylococci. MIC_{90} values for methicillin-resistant *S. aureus* (MRSA) and methicillin-resistant *S. epidermidis* (MRSE) were 8 and 64 mg/liter, respectively (23–25). CLSI breakpoints and MIC_{90} values were used for the PK/PD calculations.

Statistical analysis. Wilcoxon's paired tests were performed with SPSS software (version 24) for the Mac (IBM, USA) for statistical comparison of the main outcome PK parameter ($AUC_{muscle\ tissue}$ to $AUC_{free\ plasma}$). A linear regression model to evaluate the correlation between cefuroxime concentrations in plasma, muscle tissue, and synovial fluid was established using Origin Pro software (version 7; OriginLab Corporation, USA). All data are presented as means ± standard deviations (SDs).

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We have no conflict of interest to declare.

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Pfizer Europe Ltd. did not have an influence on the protocol, the conduct of the study, the results of the study, or the publication of the data.

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