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Population pharmacokinetics of cefuroxime and uptake into hip and spine bone of patients undergoing orthopaedic surgery

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Abstract

Objectives To reduce the incidence of peri- or postoperative infections in orthopaedic surgery, patients are prophylactically treated with antibiotics. Here, we wanted to know whether effective bone and intervertebral disc concentrations of cefuroxime are reached.

Methods Patients undergoing surgery of hip ($N = 40$; 62.5% male) or spine ($N = 40$; 55% male) were pretreated with 1.5 g of the second-generation cephalosporin cefuroxime before surgery. We studied plasma population kinetics and bone and intervertebral disc (C5/6 till L5/S1) concentrations of cefuroxime using high-performance liquid chromatography.

Key findings The plasma kinetics of cefuroxime in 80 patients was analysed using a population approach. The clearance amounted to 7.86 l/h. The peripheral and central volumes of distribution were estimated as 8.45 and 10.4 l, respectively. The concentrations in hip samples amounted to 9.8 ± 0.6 μg/g in cancellous bone and 8.9 ± 0.8 μg/g in cortical bone. Cefuroxime concentrations in vertebral bone and intervertebral discs were calculated as 9.6 ± 1.3 and 8.9 ± 1.1 μg/g, respectively.

Conclusion Even if a majority of patients undergoing hip or spine surgery probably achieved adequate concentrations of cefuroxime, not all patients reached bone concentrations of cefuroxime above a recommended breakpoint for susceptible germs at the time of surgery.

Introduction

Osteomyelitis and spondylodiscitis are rare but feared complications of orthopaedic surgery. Postoperative spondylodiscitis may account for 30% of all cases of pyogenic spondylodiscitis with an incidence ranging from 0.24% up to 3.6%.[1,2] The incidence of hip joint infections after surgery is reported between 1 and 2%.[3] Antibiotics have been clearly shown to decrease the incidence of infections in orthopaedic surgery: in one study 1.7% of patients with prophylactic penicillins suffered from surgical site infections whereas 8.9% in the control group.[4] Orthopaedic infections are typically caused by Gram-positive bacteria notably strains of *Staphylococcus aureus* and *Staphylococcus epidermidis* but many other organisms like *Streptococcus* strain or Gram negative germs like *Escherichia coli*, strains of *Pseudomonas* and *Klebsiella* species have been incriminated.[5] Nevertheless, hospitals use typically cephalosporins of the first generation like cefazolin (1–2 g) or of the second generation of cephalosporins like cefuroxime (1.5 g).[5] Alternatively, sometimes ceftriaxone[6] or levofloxacin,[7] clindamycin and vancomycin are employed as prophylactic antibiotics in orthopaedic surgery.[5]

In human volunteers, the time to peak plasma concentration of cefuroxime was dose independent and occurred at about 30 min with a terminal half-life between 60[8] and 120 min.[9] Within 6 h after intravenous injection, 90% of cefuroxime was detected unchanged in the urine of humans.[8] The volume of distribution of cefuroxime in humans was about 11 l/1.73 m^2.[8] Prophylactic treatment

with cefuroxime reduced the incidence of bone infections in clinical studies.[10]

However, the germs that cause bone infections reside typically in bone or nearby tissues like intervertebral discs and only in sepsis germs reach typically the blood. Hence, a correlation of dosage of cefuroxime, bone concentration, intervertebral concentrations and plasma concentration is desirable in order to predict which plasma concentrations are necessary to reach bactericidal or at least bacteriostatic concentrations in bone or the vicinity of bone (intervertebral discs). Indeed, such studies have been published in animals: in pigs, cefuroxime penetrated poorly into bone.[11] In the present work, we studied cancellous bone and the cortical bone of hip and bone and intervertebral discs from spine surgery patients and asked whether sufficiently high concentrations of cefuroxime are obtained in the tissues to inhibit the usual bacterial pathogens in these surgical situations. To the best of our knowledge, this is the first study to estimate cefuroxime concentrations in bone and intervertebral discs in comparison with plasma concentrations of cefuroxime in human patients. Similar data are apparently currently only available in intervertebral discs of pigs (cervical vertebrae C2–C4).[12]

Materials and Methods

Study protocol

A prospective, open-label study was conducted with 80 patients undergoing hip or spine surgery. 1.5 g of cefuroxime was administered intravenously for 10 min between 15 and 60 min (exactly measured) before skin incision. Blood was drawn from the cubital vein just before infusion of cefuroxime and eight times thereafter in hourly intervals (exact times of blood withdrawal were carefully written down in the operation theatre for subsequent statistical analysis). Bone samples were taken from the hip or from the spine. In patients undergoing hip surgery, we had for surgical reasons the opportunity to obtain a second cancellous bone sample at a later time point of the operation (bone 2). Moreover, from some patients, with a splittable forceps, we obtained tissue from the nucleus pulposus of the intervertebral disc. We took one and only one sample from the nucleus pulposus of the patients. Mean time of bone sampling with regard to the end of cefuroxime infusion is shown in Table 1. The study was approved by the local institutional research board and ethics committee (EudraCT number: 2016-001511-20). We have included patients (women and men) from 27 to 70 years which were, for clinical reasons, undergoing electively a hip or spine surgery in the participating centre (Table 2). Written informed consent was obtained before any procedure from all patients.

Table 1 Time of bone sampling relative to the end of cefuroxime infusion

	Spine (n = 40)		Hip (n = 40)		
	Intervertebral disc (n = 36)	Bone	Bone 1	Bone 2	Combined
Time (min)					
Mean	69.58	60.41	35.30	55.48	54.59
SD	29.22	22.41	12.32	15.81	24.17

Table 2 Patient characteristics (N = 80)

Patients	All	Hip	Spine
Men (n)	47	25	22
Women (n)	33	15	18
Age (years)	59 ± 11.5	65 ± 9.1	54 ± 10.9
BMI (kg/m^2)	27.2 ± 4.0	27.7 ± 3.5	26.6 ± 4.3

Age and BMI (body mass index) are given as mean ± SD.

We have excluded patients with anaemia, children and young adults that are still growing, breast-feeding women, patients with leucocytopenia, patients with thrombocytopenia, patients taking at admission to the hospital diuretics or aminoglycoside antibiotics. Women were postmenopausal. Exclusion criteria were prior traumatic surgery, past or present osteomyelitis, impaired function of the heart (>New York Heart Association classification II), impaired function of the kidney (creatinine blood levels >130 μmol/l), impaired function of the liver (high glutamine-oxalacetic transaminase value), high body mass index (>35 kg/m^2), allergy against cephalosporins or allergy against β-lactam antibiotics. These exclusion criteria were predefined in the protocol submitted to the local ethics committee. The complete list of inclusion/exclusion criteria is presented in Table 3.

Sample preparation

Processing of samples for high-performance liquid chromatography measurement was done similarly as in previous studies from our laboratory.[6,7] 150 μl of plasma were mixed with 600 μl methanol. Samples were centrifuged at 20 000 *g* for 30 min, and 100 μl of the supernatant was used subsequently. After removing the bone or disc samples, they were cleaned free of adhering tissue and rinsed with isotonic sodium chloride solution to get rid of any remaining blood. The bone and disc samples were collected and stored at −20°C until further processing. Frozen tissue was cut in a custom-made dissecting machine into smaller samples. For hip samples, cancellous bone was separated from cortical bone manually. One could ask whether cross contamination of cortical and cancellous bone might have occurred. This seems unlikely: the frozen bones were

Table 3 Inclusion and exclusion criteria of the study

Subject inclusion criteria	Subject exclusion criteria
Adult patients	Patients who are unable to consent
Women and men	Patients unwilling to consent
Undergoing an elective hip replacement therapy	Patients who retracted their consent
Knee or spine surgery	Pregnant women
Undergoing elective knee replacement therapy	Patients with impaired renal or liver function
Signed informed study consent form	Patients with anaemia
Legally competent patient	Children
	Young adults
	Breast-feeding women
	Patients with leucocytopenia
	Patients with thrombocytopenia
	Patients hypersensitive to cefuroxime cephalosporins or beta-lactame antibiotics
	Patients with traumatic surgery
	Patients with past or present osteomyelitis
	Patients with impaired cardiac function
	Patients with high body mass index
	Patients taking diuretics or aminoglycoside antibiotics
	Patients with candida infections
	Patients with colitis
	Patients with other abdominal infections

individually inspected, and in each case, the cortical bone was of sufficient size to be visually discernible from the cancellous bone. Their anatomical aspect is quite different. Moreover, we started the homogenization only after bones from all study patients had been collected. Furthermore, we first homogenized cortical samples from all patients and then cancellous samples from all patients. In brief, deep-frozen tissue samples were pulverized in a mortar precooled in liquid nitrogen and then grinded three times for 30 s each with a microdismembrator S (Sartorius, Göttingen, Germany) in liquid nitrogen at full speed. To 100 mg of bone or disc homogenates 1.9 ml of the mobile phase (see next paragraph). The mixture was homogenized two times for 60 s with a sonificator (Bandelin) at 75% maximum power. Homogenates were cleared by centrifugation for 10 min at 4600 *g* at 4°C, and the supernatants were immediately analysed by reversed-phase high-performance liquid chromatography (HPLC).

High-performance liquid chromatography detection of cefuroxime

The level of cefuroxime was monitored by reversed-phase HPLC. The chromatographic system (nearly identical to that used in our earlier studies)[6,7] consisted of a reverse phase column Vertex plus Knauer (25DD181SBJ), 25 cm length 4 mm width; Knauer, Berlin, Germany), a degasser (Series 1100, Hewlett Packard; Agilent Technologies, Böblingen, Germany), LS2200 VWR Hitachi, L-7100 pump Merck-Hitachi, a detector (series 1050 Hewlett Packard) and the HPLC-Manager-Software D-6000 (Merck-Hitachi). The column was isocratically eluted with a flow rate of 0.5 ml/min at 30°C. The mobile phase consisted of 25% methanol and 75% aqueous 67 mM KH_2PO_4 (pH = 5.0). Detection of cefuroxime was carried out at 270 nm. The detection limit for an injection of 100 µl of cefuroxime dilution amounted to 5 ng and under these experimental condition the assay was linear from 10 ng/100 µl up to 300 ng/100 µl, the highest concentration studied.

Pharmacokinetic analysis

Based on a two-compartment model for cefuroxime disposition after intravenous administration the parameters clearance (CL), distribution clearance (CL_{cp}) and volumes of the central (V_c) and peripheral compartments (V_p) were estimated. The steady-state distribution volume is given by:

$$V_{ss} = V_c + V_p$$

The cefuroxime data (n = 80) were analysed by a population approach with maximum likelihood estimation via the EM algorithm implemented in the software ADAPT 5.[13] The MLEM program provides estimates of the population mean and intersubject variability as well as of the individual subject parameters (conditional means). Standard errors (precision %RSE) of the parameters are estimated when sufficient information is available from the data (reasonable ratio of the number of subjects to the number of parameters estimated). We assumed log-normally distributed model parameters and that the measurement error has a standard deviation that is a linear function of the measured quantity:

$$\mathrm{VAR}_i = [\sigma_0 + \sigma_1 C(t_i)]^2$$

where VARi is the variance of the *i*th data point, σ_0 and σ_1 are the are the variance parameters and $C(t_i)$ is *i*th model predicted value.

The model fits to the data were assessed by the goodness-of-fit plot, standardized residuals vs predicted concentration and individual fits. Model discrimination was carried out using Akaike's information criterion. The two-compartment model fitted the concentration-time data very well as demonstrated by the goodness of fit, and standardized residual plots, as well as by examples of individual fits.[14]

Drugs and materials

For the bolus infusions, 1.5 g cefuroxime was dissolved in 15 ml water for injections. The drug is sold as Cefuroxim-ratiopharm p.i. and manufactured by Ratiopharm GmbH (Graf-Arco-Str 3, D-89079 Ulm, Germany). Cefuroxime (PZN 3647788 Cefuroxim Hikma 750 mg) was used as a chromatographic standard. All other chemicals were of the best grade commercially available.

Results

Table 2 presents demographic data of the patients included in this study namely age, sex and body mass index. There were no significant differences related to gender, or hip and spine surgery groups with regard to standard clinical parameters. Figure 1a depicts the measured plasma data (from all 80 patients that is combining patients with hip and spine surgery) together with model predicted mean plasma concentration-time curves for these patients. The individual blood sampling times together with the corresponding cefuroxime concentrations are also given (Figure 1a). Exemplary, for better clarity, the individual surgical times for hip surgery (n = 40) with the corresponding cefuroxime concentrations of cancellous bone samples are given (filled dots in Figure 1a). Figure 1b shows the goodness-of-fit plot for observed data and the predicted plasma concentrations of cefuroxime based on conditional estimates.

The estimates of clearance (CL) and central and peripheral volume of distribution are characterized by an interpatient variability of 37, 54.5 or 42.7%, respectively (Table 4). The diagram in Figure 2a shows the concentrations (median, 5–95 percentiles, 95% confidence interval) of cefuroxime in the cancellous and cortical hip bone, spine bone and intervertebral discs. The mean concentrations (±SEM) were 9.82 ± 0.58 μg/g (cancellous hip bone), 8.93 ± 0.83 μg/g (cortical hip bone), 9.63 ± 1.37 μg/g (spine bone) and 8.92 ± 1.11 μg/g (intervertebral discs). No significant differences between cancellous and cortical hip bone samples as well as between cancellous hip bone-1 and bone-2 samples or between hip and spine samples were observed ($P > 0.05$ ANOVA with Bonferroni's Multiple Comparison Test). The mean concentrations of cefuroxime in the intervertebral discs were not different from the concentrations in vertebral bone. However, very low values were only seen in intervertebral discs (Figure 2a). That is in 14 of the 40 patients studied, the concentration of cefuroxime in the intervertebral disc was below a concentration of 6 μg/g, usually regarded as necessary for preventive action against nosocomial infections.[15] A cut off concentration of 6 μg/ml of cefuroxime was not reached in 13 out of 40 patients in the hip bone (referring to cortical bone), while

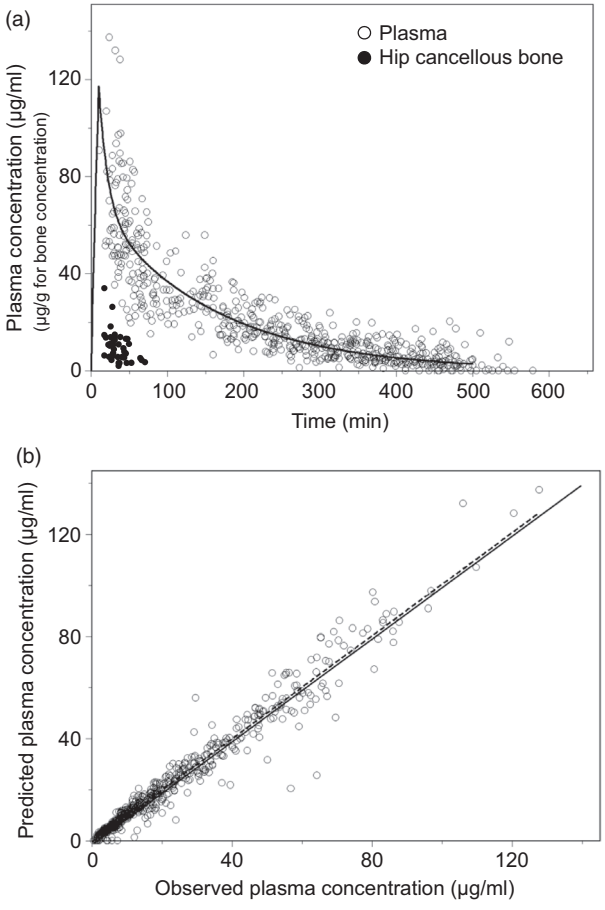

Figure 1 (a) The figure shows the predicted and measured individual concentration-time curve of cefuroxime in plasma (80 patients) based on conditional estimates. Exemplary, for better clarity, the individual surgical times for hip surgery (n = 40) with the corresponding cefuroxime concentrations of cancellous bone samples are given. (b) Goodness-of-fit plot for measured and predicted plasma concentrations.

it was not reached in 12 out of 40 samples of spine bone (Figure 2b). Using Fisher's exact test, we calculated that there was no differences in attaining 6 μg/g in cortical hip

Table 4 Parameter estimates and interindividual variability (errors of the estimates are in parentheses (%))

Model parameter	Symbol (Unit)	Population mean (%RSE)	Interindiv. Variability (CV%) (%RSE)
Clearance	CL (l/h)	7.86 (6)	37 (11)
Central volume of distribution	V_c (l)	10.4 (38)	54.5 (24)
Peripheral volume of distribution	V_p (l)	8.45 (33)	42.7 (18)
Distribution clearance	CL_{cp} (l/h)	22.0 (38)	57.9 (88)
Residual variability[a]	s_0	0.60 (11)	
	s_1	0.17 (5)	

[ad]Measurement error has a variance: $VAR_i = [s_0 + s_1C(t_i)]^2$.

bone compared to spine bone whereas in cancellous hip bone, 6 µg/g were reached more frequently compared to spine bone and intervertebral disc ($P < 0.05$; Figure 2b).

Given the limited time window in which bone concentrations were distributed, the uptake kinetics could not be analysed by using the population approach. Thus, it remains unclear whether the relatively low bone concentrations can be explained by slow drug penetration.

With two exceptions, we have seen all patients in follow-up: no significant side effects were noted in any of the patients in this study.

Discussion

For hip or spine surgery, infections often necessitate a second surgical intervention. Hence, infections are to be avoided by adequate prophylaxis by giving an antibiotic like a cephalosporin. The classical way to assess a useful cephalosporin dosage is to report how long plasma levels, or bone levels or intervertebral disc levels of the cephalosporin are present that are above the MIC for the microbe of interest, in this case, the typical microbes that cause osteomyelitis.[16] If cefuroxime is chosen, the concentration of cefuroxime should usually exceed 6 µg/ml to be effective.[12,15] The main goal in surgical prophylaxis by means of an antibiotic is that effective bactericidal concentrations in serum, cancellous bone and intervertebral discs are maintained as long as a risk of a potential contamination persists. One important result of the present study was that at our present dosage regimen (which is our current clinical routine) in more patients we measured lower cefuroxime concentrations in cortical hip bone, spine bone and intervertebral discs than in cancellous bone, which raises concerns whether the dosages of cefuroxime should be increased. In many cases, the concentrations (of various antibiotics) in cancellous bone are similar or slightly higher than in cortical bone.[17] We noted higher mean concentrations of ceftriaxone in cortical bone compared with cancellous bone in a previous study with a similar design on orthopaedic patients.[6] Few data on the kinetics of cephalosporin penetration into bone tissue are available. Similar estimates of the central and peripheral volume of distribution of cefuroxime were noted in the present study (10.4 and 8.45 l) compared with previous reports: for instance 11.4 and 5.11 l in a Swedish study.[18] However, Viberg *et al.* used a somewhat different design: less samples (5 vs 8) were taken from patients after cefuroxime application, they also studied patients with impaired renal function (receiving half the usual dose of cefuroxime) and gave cefuroxime three times daily 1.5 g cefuroxime (they treated patients in the infectious disease unit with symptoms and signs

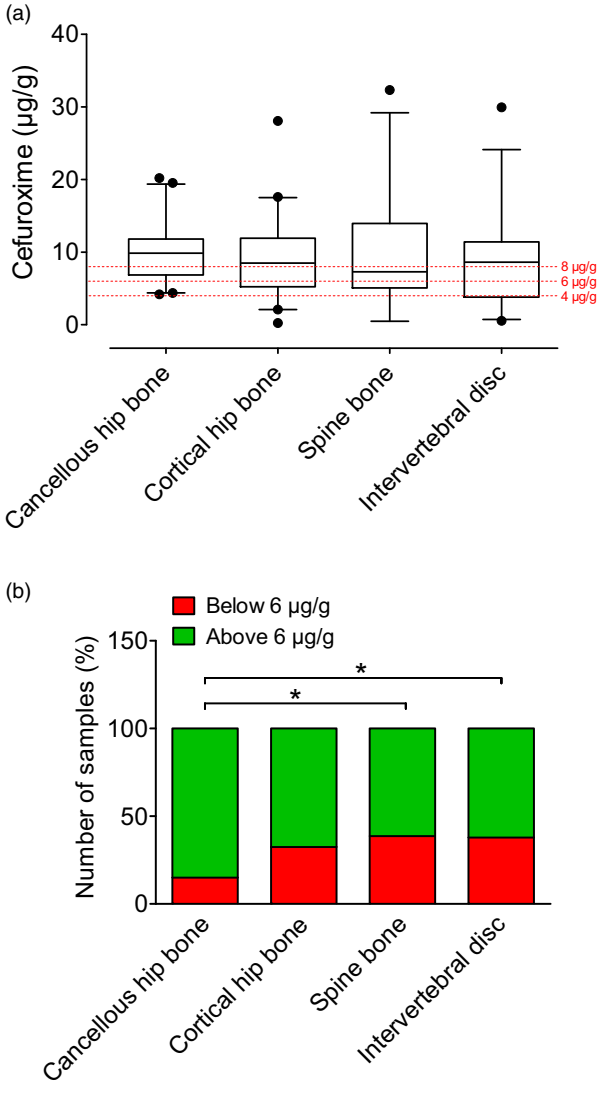

Figure 2 (a) Box and whisker (5–95 percentiles and 95% confidence interval) plot of measured cefuroxime concentrations in cortical hip bone (40 patients), cancellous hip bone (40 patients), spine bone (40 patients) and intervertebral disc (40 patients). Several MICs are shown as dashed lines. (b) Distribution of samples above and below a threshold of 6 µg cefuroxime/g tissue. $*P < 0.05$ using Fisher's exact test. Samples were taken 55 ± 24 min (mean (SD)) after drug infusion. It must be noted that the time that serum levels exceed the MIC ($T >$ MIC) could be a more relevant parameter characterizing cephalosporins than the MIC itself.[16] [Colour figure can be viewed at wileyonlinelibrary.com]

of bacterial infection thought to be treatable with cefuroxime)[18] whereas we gave a single dose of 1.5 g cefuroxime (using prophylactic treatment). Estimates of pharmacokinetic parameters were in accordance with those in earlier studies.[18–20]

Others have had measured concentrations of cefuroxime in plasma and bone of the same patient and at similar

times. With infusion of 1.5 g of cefuroxime, they observed much higher concentrations in plasma than in cortical bone (femur and tibia) and much higher concentrations in cortical bone than in cancellous bone: they reported that the fall of cefuroxime levels was much faster in plasma than in bone.[21] Another group reported after infusion of 1.5 g cefuroxime at time points between 15 and 37 min concentrations of 15.5–18.6 mg cefuroxime/kg bone (no differentiation between cortical and cancellous bone mentioned) and a bone to serum ratio of cefuroxime of 0.14–0.17.[22] In the manubrium of the sternum of patients undergoing cardiac surgery, infused with 3 g of cefuroxime at an earlier (36 min) and a later (244 min) time point, cefuroxime concentrations amounted to 184 and 4 μg/ml, respectively.[23] In cancellous hip bone, the concentrations of cefuroxime ranged from 1.6, 6.1 to 9.5 μg/g after infusion of three typical doses (0.5, 1.0 and 1.5 g) in each cefuroxime concentration: at 1.5 g the terminal half-life was 1.5 h, the clearance 7.8 l/h and the volume of distribution was 11.3 l.[24]

Our current data extend these data to spinal bone and intervertebral discs.

Others reported a T_{max} (or C_{max}, or $T_{1/2}$) for cefuroxime of 15 min (34 μg/ml; 46 min) in plasma, 45 min (28 μg/ml, 51 min) in vertebral cancellous bone and 57 min (12 μg/ml, 103 min) in intervertebral discs, in pigs.[12] These authors interpreted the data as evidence for a high diffusion coefficient for intervertebral discs in pig.[12] As concerns intervertebral discs, there are some discrepancies in the literature which merit attention: 2 h after infusion of 1.5 g cefuroxime in 8 of 10 patients no measurable concentration of cefuroxime was noted in human intervertebral discs.[25] However, Tai *et al.*[25] used a microbiological assay (inhibition of germ growth in Petri dish) to quantify cefuroxime levels: we used the more sensitive HPLC method[6,7] and this easily explains why we measured cefuroxime in all intervertebral discs studied in the present work. Nonetheless, in our hands as in previous animal studies,[12] cefuroxime concentrations in intervertebral discs are lower (for a given patient and a given time point) than in plasma. This is to be expected because in human adults the intervertebral discs do not contain blood vessels and diffusion is the only process how cefuroxime can enter the intervertebral disc.[26] This could explain the lower penetration to the intervertebral disc, due to the fact, that the antimicrobial penetration to the intervertebral disc is based on diffusion from the vertebral bone endplates. However, the concentrations of cefuroxime were lower than the typical concentrations postulated to be necessary for good protection (6 μg/ml) in 14 from 40 patients. The present results indicate that the use of 1.5 g of cefuroxime as prophylaxis prior to spine surgery, may be insufficient to achieve therapeutic concentrations in the intervertebral disc.

Limitations of the study

We measured total cefuroxime concentrations in bone and intervertebral disc and not the free concentration of cefuroxime. Thus, we systematically overestimate cefuroxime active concentrations and cannot discriminate in bone between intra- and extracellular compartments. Moreover, our kinetic studies do not allow us to predict the pharmacokinetics of cefuroxime in infected bones and intervertebral discs (those were excluded from this study) whereas in osteomyelitis, increased osseous pressure and thrombosed vessels may alter the results.[26] Thus, our data can only be used to recommend dosing of cefuroxime in healthy not in infected tissue. However, in a porcine model, cefuroxime penetrated quite well also in infected cancellous bone.[27] Finally, it must be noted that the time that serum levels exceed the MIC ($T > MIC$) could be more relevant parameter characterizing cephalosporins than the MIC itself[16] but it is hard to imagine that $T > MIC$ would show more favourable result.

Conclusion

In summary, this study indicates that following administration of 1.5 g cefuroxime intravenously, not all patients undergoing hip or spine surgery achieved concentrations of cefuroxime above a recommended breakpoint (6 μg/g)[15,28] for susceptible germs at the time of surgery. The present results indicate that the use of 1.5 g of cefuroxime as prophylaxis prior to spine surgery, may be insufficient to achieve therapeutic concentrations in the intervertebral disc and higher concentrations are probably needed or different antibiotics should be chosen.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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