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Pharmacokinetics of single-dose cefuroxime in porcine intervertebral disc and vertebral cancellous bone determined by microdialysis

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Abstract

BACKGROUND: Pyogenic spondylodiscitis is associated with prolonged antimicrobial therapy and high relapse rates. Nevertheless, tissue pharmacokinetic studies of relevant antimicrobials in both prophylactic and therapeutic situations are still sparse. Previous approaches based on bone biopsy and discectomy exhibit important methodological limitations.

PURPOSE: The objective of this study was to assess the C3–C4 intervertebral disc (IVD), C3 vertebral body cancellous bone, and subcutaneous adipose tissue (SCT) pharmacokinetics of cefuroxime by use of microdialysis in a large animal model.

STUDY DESIGN: This was a single-dose, dense sampling large animal study of cefuroxime spine penetration.

METHODS: Ten female pigs were assigned to receive 1,500 mg of cefuroxime intravenously over 15 minutes. Measurements of cefuroxime were obtained from plasma, SCT, vertebral cancellous bone, and IVD for 8 hours thereafter. Microdialysis was applied for sampling in solid tissues.

RESULTS: For both IVD and vertebral cancellous bone, the area under the concentration curve from zero to the last measured value ($AUC_{0–last}$) was significantly lower than that of free plasma. As estimated by the ratio of tissue $AUC_{0–last}$ to plasma $AUC_{0–last}$, tissue penetration (95% confidence interval) of cefuroxime was significantly incomplete for the IVD 0.78 (0.57; 0.99), whereas for vertebral cancellous bone 0.78 (0.51; 1.04) and SCT 0.94 (0.73; 1.15) it was not. The penetration of cefuroxime from plasma to the IVD was delayed, and the maximal concentration and the elimination of cefuroxime were also reduced compared with both SCT and vertebral cancellous bone. Because of this delay in elimination of cefuroxime, the time with concentrations above the minimal inhibitory concentration ($T_{>MIC}$) was significantly longer in the IVD compared with the remaining compartments up to MICs of 6 μg/mL.

CONCLUSIONS: Microdialysis was successfully applied for serial assessment of the concentration of cefuroxime in the IVD and the vertebral cancellous bone. Penetration of cefuroxime from plasma to IVD was found to be incomplete and delayed, but because of a prolonged elimination, superior $T_{>MIC}$ was found in the IVD up to MICs of 6 μg/mL.

Keywords: Cefuroxime; Intervertebral disc; Microdialysis; Pharmacokinetics; Tissue penetration; Vertebra

Introduction

Pyogenic spondylodiscitis is a relatively rare disease, but the incidence is increasing [1–3]. The estimated incidence varies between 0.4 and 2.4/100,000 persons per year in developed countries [4,5]. Postoperative pyogenic spondylodiscitis accounts for approximately 30% of all cases of pyogenic spondylodiscitis and, depending on the

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surgical procedure, the incidence varies between 0.24% and 3.6% [6,7]. Despite prolonged antimicrobial therapy, relapse rates remain high, suggesting that antimicrobial penetration may be insufficient [8,9]. Indeed, evidence-based treatment guidelines are currently lacking for both treatment and perioperative antimicrobial prophylaxis. This stresses the need for tissue pharmacokinetic studies of relevant antimicrobials.

Assessment of intervertebral disc (IVD) and bone penetration of antimicrobials is challenging. So far, bone biopsy and discectomy have been the predominant approaches [10–14]. These methods do, however, suffer from important limitations, which may reduce applicability of the findings [11,12,15,16]. Recently, the well-known pharmacokinetic tool, microdialysis (MD), has been successfully applied for assessment of antimicrobial bone concentrations [17–24]. Microdialysis is a catheter-based technique, which allows for continuous sampling of the unbound fraction of water-soluble drugs in the interstitial space, and as such, it offers attractive advantages compared with other methods. No previous studies have assessed IVD pharmacokinetics of antimicrobials by means of MD.

In the present study, MD was used to assess the C3–C4 IVD, C3 vertebral body cancellous bone, and subcutaneous adipose tissue (SCT) pharmacokinetics of cefuroxime in a large animal model. The primary end points were tissue penetration and the time with concentrations above the minimal inhibitory concentration ($T_{>MIC}$), which is the main pharmacokinetic/pharmacodynamic index for cephalosporins [25].

Materials and methods

This study was conducted at the Institute of Clinical Medicine, Aarhus University Hospital, Denmark. The study was approved by the Danish Animal Experiments Inspectorate and carried out according to existing laws. Chemical analyses were performed at the Department of Biochemistry, Aarhus University Hospital.

Microdialysis

Briefly, MD is based on diffusion of molecules across a semipermeable membrane located at the tip of a probe. Because of continuous perfusion of the probe, non-equilibrium conditions will be present during experiments. Accordingly, the concentration of the drug in the dialysate will only represent a fraction of the actual concentration in the tissue. This fraction is referred to as the relative recovery (RR). The RR can be determined by various calibration procedures, which is a prerequisite if absolute tissue concentrations are to be determined. In this study, retrodialysis by drug was applied for calibration [26]. In-depth description of MD can be found elsewhere [27,28].

Microdialysis equipment from μ-Dialysis AB (Stockholm, Sweden) was used. Specifically, the catheters used were CMA 63 (membrane lengths: 10 and 30 mm with a 20-kDa molecule cutoff), and CMA 107 precision pumps produced a flow rate of 1 μL/min.

The RR was calculated by using the following equation:

$$RR(\%) = 100 \times \left(1 - \frac{C_{out}}{C_{in}}\right)$$

where C_{out} is the concentration in the dialysate, and C_{in} is the concentration in the perfusate.

In the data analysis, the measured concentrations were attributed to the midpoint of the sampling intervals. The absolute tissue concentrations (C_{tissue}) were obtained by correcting for RR using the following equation:

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

Individual catheter calibration was performed for all the catheters at location.

Animals, anesthetic, and surgical procedures

Ten female pigs were included in the study (Danish Landrace Breed 75–77 kg). The pigs were kept in general anesthesia by a combination of propofol (500–600 mg/h by continuous infusion) and fentanyl (0.35–0.45 mg/h by continuous infusion). The pH was monitored and kept within a range of 7.35–7.46 throughout the entire study by regulating the ventilation. The body temperature was kept within the range of 36°C–38.9°C.

The surgical procedure was initiated immediately after induction of general anesthesia. With the pigs in supine position, vertebrae C2–C4 were exposed via an anterolateral approach. A Kirschner wire with a fixating device (PEBAX) was drilled into the distal part of the C2. At an angle of approximately 45° to the sagittal plane, a 2-mm drill hole was made in the middle of C3 (depth 22±1 mm). With the tip of the catheter protruding approximately 20 mm from the tip of the introducer, the MD catheter (membrane length: 10 mm) was attached to a splittable introducer using endo clips. In this way, the membrane was free of the splittable introducer. The MD catheter with the splittable introducer was then placed in the drill hole and fixed to the fixating device in C2 for support to prevent subsequent dislocation of the catheter. The IVD between C3 and C4 was used for IVD measurements. By guidance of fluoroscopy, and again at an angle of approximately 45° to the sagittal plane, a splittable introducer with a needle was introduced into the IVD parallel to, and in the middle of the adjacent end plates. When penetrating the annulus fibrosus, loss of resistance was clearly felt. The needle was then retracted, and the splittable introducer was advanced into the nucleus pulposus until resistance from the opposite wall of the annulus fibrosus was felt. A 10-mm MD catheter was then introduced into the nucleus pulposus through the splittable introducer. Concurrently, the splittable introducer was pulled back until the membrane was exposed in the IVD in full length. The MD catheter was attached to the splittable introducer by endo clips. Correct location of the MD catheters was verified by fluoroscopy before and at the end