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Suppurative Inflammation and Local Tissue Destruction Reduce the Penetration of Cefuroxime to Infected Bone Implant Cavities

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Summary

Treatment of post-traumatic and implant-associated osteomyelitis (IAO) includes surgical debridement, removal of implants and long-term antibiotic therapy. The success of antibiotic therapy relies not only on activity towards the infecting pathogen, but also on sufficient penetration of the target site. The aim of the present study was to characterize the local pathological changes associated with reduced penetration of cefuroxime to infected bone implant cavities. Previously, reduced penetration of systemically administrated cefuroxime was demonstrated in the implant cavity of 10 pigs with *Staphylococcus aureus* IAO present for 5 days. In the present study, a comprehensive histopathological characterization of the peri-implant bone tissue was performed and correlated with the reduced penetration of cefuroxime. In two pigs, the levels of oxygen, pyruvate and lactate was estimated in the implant cavity. A peri-implant pathological bone area (PIBA) developed with a width of 1.2 up to 3.8 mm. PIBAs included: (1) suppuration, resulting in destruction of the implant cavity contour, and (2) a non-vascular zone of primarily necrotic bone tissue. A strong negative correlation was seen between PIBA width and cefuroxime area under the concentration time curves (AUC_[0-last]) and peak concentration of cefuroxime (C_{max}). All metabolic measurements demonstrated hypoxia. In conclusion, subacute suppurative bone inflammation with local tissue destruction can result in decreased penetration of antibiotics and insufficient oxygen supply.

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Introduction

Post-traumatic and implant-associated osteomyelitis (IAO), including periprosthetic infections, are among the most severe orthopaedic conditions (Kapadia *et al.*, 2016). Treatment of IAO includes surgical debridement, removal of implants and long-term antibiotic therapy (Kapadia *et al.*, 2016). The success of antibiotic therapy relies not only on activity towards the infecting pathogen, but also on sufficient

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0021-9975/\$ - see front matter https://doi.org/10.1016/j.jcpa.2017.10.001 penetration of the target site (Landersdorf *et al.*, 2015). Consequently, knowledge of antibiotic penetration of bone following systemic administration is important in order to improve treatment of IAO (Landersdorf *et al.*, 2015). For osteomyelitis systemic post-operative antibiotic treatment is normally recommended for 4–6 weeks (Waldvogel *et al.*, 1970; Norden *et al.*, 1986; Sia and Berbari, 2006; Haidar *et al.*, 2010).

Numerous clinical studies have been conducted in order to quantify antibiotic concentrations in noninfected bones rather than in bones from patients with IAO (Landersdorf *et al.*, 2009). Consequently, the effect of IAO on local bone penetration of antibiotics is largely unknown. It can be speculated that antibiotic penetration to infected bone implants, following systemic administration, may be reduced with the progression of surrounding pathological changes (Tøttrup *et al.*, 2016). Former studies of antibiotic penetration in normal (Tøttrup *et al.*, 2016) and infected bone tissue (Fong *et al.*, 1986) have mainly been based on homogenized bone samples from surgical biopsy samples, but this approach precludes subsequent histopathological evaluation.

Recently, the pharmacokinetic parameters of cefuroxime were obtained by microdialysis in bones from pigs with experimentally-induced IAO (Tøttrup et al., 2016). In this study, microdialysis catheters were placed into infected bone implant cavities and also into healthy cancellous bone tissue. There was a significantly reduced penetration of systemically administrated cefuroxime into the infected implant cavity compared with the healthy bone. Based on the pigs from that study (Tøttrup et al., 2016), the aim of the present study was to characterize the local pathological changes associated with the observed reduced penetration. The pathological bone changes were induced with Staph*ylococcus aureus* as this is one of the most common aetiologies of bone infections in humans (Marculescu, 2010).

Materials and Methods

Bone Material

This study was based on formalin-fixed bone tissue originating from 10 experimental pigs (Tøttrup et al., 2016; Jensen et al., 2017). The pigs were included in a pharmacokinetic study of the penetration of cefuroxime into soft tissue, healthy osseous tissue, infected osseous tissue and infected implant cavities (Tøttrup et al., 2016). Briefly, an implant cavity of 4×27 mm was drilled 10 mm distal and parallel to the growth plate. Firstly, 10 µl of sterile saline containing S. aureus $(10^4 \text{ colony-forming})$ units [CFUs]) was injected into the implant cavity (Table 1) and secondly, a stainless steel implant of 2×20 mm was inserted. The S. aureus strain originated from a porcine lung abscess and has the ability to form a biofilm (unpublished data, current authors). After 5 days, a microdialysis catheter was placed into the implant cavity of the right inoculated tibia and into a new drill hole in the cancellous bone of the healthy, non-inoculated tibia (Table 1). This contralateral drill hole had the same anatomical position, although with a reduced diameter $(2 \times 27 \text{ mm})$. The contralateral drill hole was used only to obtain microdialysis measurements of normal bone tissue. After systemic administration of 1,500 mg of cefuroxime (cefuroxime, Fresenius Kabi, Uppsala, Sweden), dialysates were collected every 30 min for 8 h. The

Timeline and study components	Pigs									
	1	2	3	4	5	6	7	8	9	10
Day 0										
Right tibia: implant insertion and Staphylococcus aureus inoculation	x	х	х	х	х	х	х	х	х	х
Day 5										
Microdialysis (8 h) adjacent to the implant and in a new drill hole of the left tibia representing healthy bone	х	х	х	х	х	х	х	х	х	х
Estimation of cefuroxime concentration	х	х	x	х	х	х	х	х	х	х
Estimation of glucose, pyruvate and lactate concentration	х	х								
Day 5										
Post-mortem examination and histopathological observations	x	х	х	х	х	х	х	х	х	х
Peri-implant pathological bone area thickness (mm)	3.8	3.1	2.6	2.5	2.4	1.9	1.7	1.3	1.3	1.2
Area of vessel-free foci (mm ²)	10.2	13.2	6.2	17.6	9.8	7.5	12.8	6.4	5.8	5.2
Infection based on Fledman's criteria	+	+	+	+	+	+	+	+	+	+
Bacteria	+	+	+	+	_	+	+	+	+	+
Microabscess	+	+	+	_	_	_	_	-	-	_
Osteonecrosis	+	+	+	+	+	+	+	+	+	+
Angiogenesis	+	+	+	+	+	+	+	+	+	+
Small arterioles and veins	+	+	+	+	+	+	+	+	+	+
Small arterioles and veins adjacent to the implant	+	_	+	+	+	$^+$	+	+	+	+
Blood-filled capillaries	+	+	+	+	+	+	+	+	+	+
Blood-filled capillaries adjacent to the implant	+	+	+	+	+	$^+$	+	+	+	+
Collagen production	+	+	+	+	+	+	+	+	+	+
Thrombosis	+	_	_	_	_	_	_	_	_	_

Table 1 Dverview of study design and results

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