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Bone penetrance of locally administered vancomycin powder in a rat femur fracture model

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ABSTRACT

Introduction: Locally delivered, crystalline vancomycin has been suggested as a potential prophylactic measure against the development of deep and superficial surgical site infection. Clinical expectations regarding the duration and peak of drug concentration in local tissues following administration are unknown. Our goal was to develop concentration vs time curves for locally administered vancomycin powder in a high-energy, open femur fracture rat model in local tissues and to compare that data to two well performed similar, systemic administration studies.

Methods: After approval for animal research, 24 adult Sprague-Dawley rats sustained closed, midshaft femoral fracture under anesthesia. Fractures were caused via blunt guillotine with 750 g metal rod dropped 50 cm. Injured hindlimbs were surgically opened at fracture to simulate open injury and stabilized using 0.054 Kirschner wires. Vancomycin powder was administered using weight-based protocol (goal: 25 mg/kg). Rats were sacrificed in groups of 4 at 4, 8, 24, 48, 72, 96 h. Samples harvested included rat-tail venous blood prior to sacrifice, and femoral bone and anterior thigh soft-tissue were harvested post-mortem. High Performance Liquid Chromatography (HPLC) was performed on all samples.

Results: Concentration vs. time curves demonstrated that the surrounding soft-tissues demonstrated highest maximum concentration (1.5 mg vancomycin/g muscle). Bone reached maximum average of 199 μg vancomycin/g femur: approximately 13% of maximal soft-tissue absorption. Plasma reached maximum concentration of 1.8 μg/mL plasma. All peaks at t = 4 h. Within 48 h, average muscle vancomycin concentration dropped to 3 μg/g muscle (0.2% maximum muscle concentration) and the average bone concentration dropped to 1.9 μg/g femur (0.9% maximum bone concentration). Vancomycin was undetectable on all samples at 96 h. Comparison to classical animal studies suggest local delivery to bone exceeds that of IV dosing for approximately 48 h and may peak near concentrations of 10^2 multiples.

Conclusions: Locally administered vancomycin provides drug delivery in excess of IV dosing for approximately 48 h after intervention. Exponential decay demonstrates rapid removal of drug to near undetectable levels in bone, plasma, and local soft tissue thereafter in a rat model. Local delivery may generate concentrations exceeding that achievable by steady state systemic dosing for 48 h.

Introduction

Bone and soft tissue infections are a significant clinical problem in the world of orthopaedics. Implant related infections occur in an estimated 112,000 patients annually and cost the American health care industry over $1.2 billion annually [1,2]. Vancomycin is regarded as a workhorse drug used to treat soft-tissue gram positive infections, especially in the case of methicillin resistant Staph aureus isolates. However, intravenous delivery of vancomycin is known to deliver antibiotics to remote tissue sites slowly [3], taking days to reach steady state concentrations. Additionally, as systemic dosing of vancomycin is limited by toxicity to the renal system; the gradient into soft tissues cannot be increased indefinitely. Many gram positive infections are biofilm forming

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infections, and there is real concern that drug concentrations at the implant surface from systemic administration cannot reach sufficient concentrations [4–6]. As a result, there have been many efforts to address the problem of treatment of infections and prevention of infections through local delivery of vancomycin at the site of surgery.

Buchholz et al. [7] advocated for the concept of local antibiotic therapy in the form of antibiotic impregnated cement. Their findings, supporting the utility of local cement-mediated delivery, were confirmed by Elson et al. in two landmark papers in the Journal of Bone and Joint Surgery [8,9]. Antibiotic beads were the next major step in local administration, as the smaller spheres allowed for a greater phase surface area allowing for greater local antibiotic delivery, yet this too produces a foreign body that ultimately requires removal; the antibiotic within the cement will eventually reach phase equilibrium with the surrounding tissue and the cement becomes a static foreign body. The drive to deliver local antibiotics without requiring additional surgery was eventually satisfied by powdered crystal formulation of antibiotics. O'Neil et al. [10] were the first to described their clinical success in reducing surgical site infections in spine wounds using powdered vancomycin in a high risk trauma cohort. O'Neil's research has triggered a burst of clinical research within the past 5 years into spine wound prophylaxis [11,12], including studies from the US military [13] and the AO Research Institute [6] studying the effect of vancomycin on biofilms, as well as research on local delivery of gentamycin [14–16] and clinical research on the effect of local prophylaxis on deep infection rates in tibial plateau treatment [17].

Pharmacokinetics is defined as the study of drug absorption, distribution, metabolism and excretion as a function of time [3]. While two studies have developed basic pharmacokinetic data on local delivery of vancomycin into healthy tissue, no studies exist

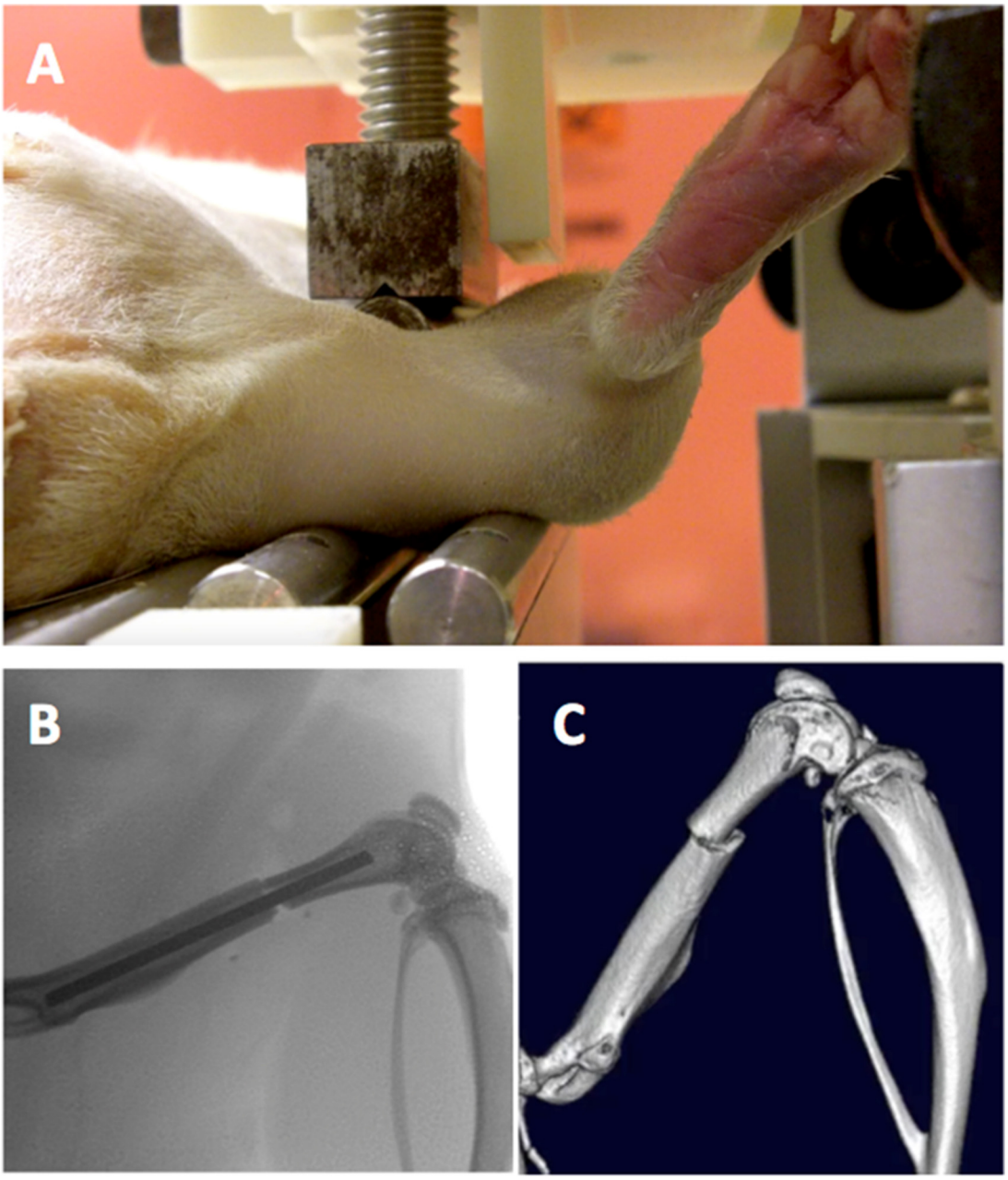

Fig. 1. (A) Rat limb positioned on blunt guillotine; (B) X-ray of femur fracture; (C) Micro-CT of femur fracture.

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