Pharmacokinetics of Depot Administered Vancomycin Powder in a Rat Femur Fracture Model: Retention Time is Brief

Zachary Working, MD[1]*; Hunter Frederiksen, BS*[2]*; Alex Drew, BS*[2]*;*
Catherine Loc Carrillo, PhD[2]*; Erik Kubiak, MD*[1]
[1]*University of Utah Department of Orthopaedics, Salt Lake City, Utah, USA;*
[2]*University of Utah, Salt Lake City, Utah, USA*

Purpose: Adoption of depot vancomycin for prophylaxis against developing wound and hardware-related infections is increasing. While early data suggest that this technique could reduce infection rates, use of powdered vancomycin is being adopted by surgeons in all subspecialties of Oothopaedics despite an absence of research delineating the mechanism in question. The purpose of this study is to understand the pharmacokinetics of locally administered vancomycin powder in a high-energy, open femur fracture model in a rat.

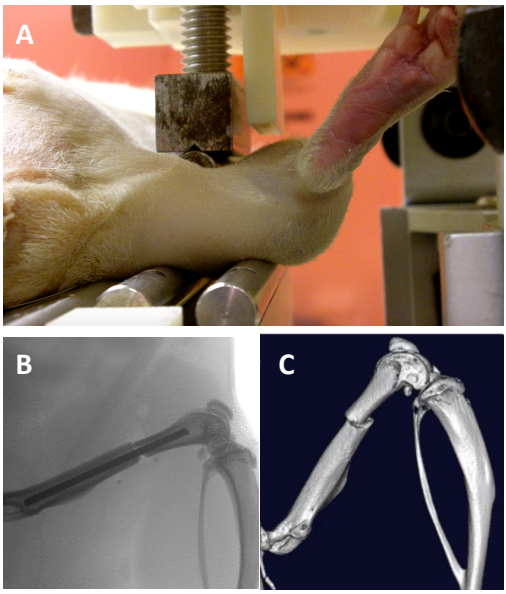
Methods: 24 Sprague Dawley rats sustained a closed, midshaft femoral fracture while under anesthesia (Fig. 1-C). A blunt guillotine apparatus was used to produce a repeatable method where a 750-g metal rod was dropped from a height of 50 cm onto the rat limb (Fig. 1-A). The left hindlimb was then surgically opened at the site of the fracture to simulate an open injury. A .054-in Kirschner wire was inserted into the femur retrograde and anterograde at the site of the fracture (Fig. 1-B). Vancomycin powder was administered using a weight based protocol. Goal dosing was set at 25 mg/kg based on prior studies utilizing vancomycin in a rat model; average total mass of administered vancomycin was 15.2 mg (SD 1.34 mg). The open wound was then closed in a layered fashion. Rats were then sacrificed in groups of 4 at 4, 8, 24, 48, 72, and 96 hours. Blood samples were taken from the rat-tail vein just prior to the time of sacrifice and bone and soft-tissue samples were explanted post mortem. High performance liquid chromatography (HPLC) analysis was performed on the femur, thigh musculature, and plasma to determine the concentration of vancomycin in the samples as a function of time.

Results: All concentration versus time curves shown in Fig. 1-D. The surrounding soft tissue demonstrated the highest maximum concentration, reaching an average of approximately 1.5 mg vancomycin per gram of muscle. Bone reached a maximum average of 199 μg vancomycin per g of femur, approximately 13% of the maximal absorption into soft tissues comparatively. Plasma ultimately reached a maximum concentration of only 1.8 μg per mL of plasma, demonstrating minimal systemic absorption. All maximum concentrations were detected at the first time point postadministration. Removal of the drug from these compartments then proceeded exponentially as a function of time. Within 48 hours, the average muscle vancomycin concentration dropped to 3 μg/g muscle (0.2% of maximum muscle concentration) and the average bone concentration dropped to 1.9 μg/g femur (0.9% of maximum concentration). Vancomycin was undetectable on all samples at 96 hours postadministration.

Conclusion: Depot administered vancomycin is shown to decrease in concentration both at the site of administration and systemically with exponential decay. Within 48 hours, drug decreased to near undetectable levels in bone, plasma, and the surrounding soft tissues in a

See pages 49 - 106 for financial disclosure information.

rat model. Therefore, the act of infection prevention is likely to occur within that time frame. This information is critical in understanding the mechanism of action of locally delivered vancomycin and the difference in pathophysiology between early and late surgical site and trauma-related infections. The rate of removal of the drug and low levels of tissue absorption also brings into question whether depot vancomycin achieves therapeutic dosing or if it is a subtherapeutic treatment modality. Further research will be necessary to answer these questions.



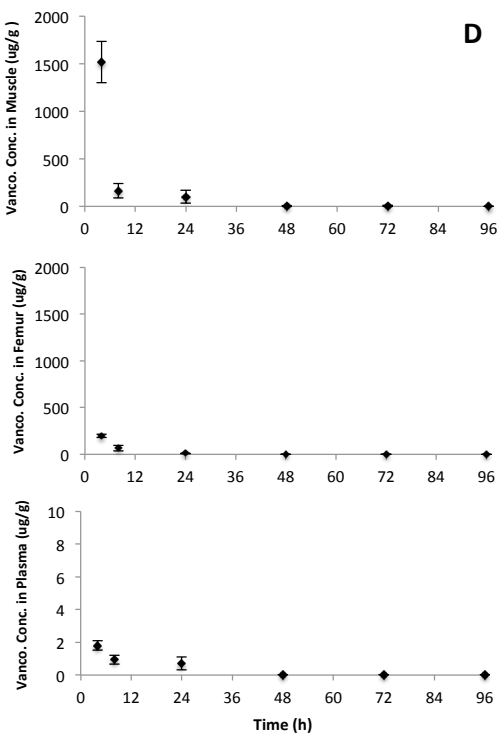


Figure 1. (A) Rat limb positioned on blunt guillotine; (B) X-ray of femur fracture; (C) Micro-CT of femur fracture; (D) Vancomycin concentration in thigh musculature, femur, or plasma over 96 h period after single 25 mg/Kg dose.