

## In Vivo Microdialysis Assessment of Systemic and Local Vancomycin Levels in Rats

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**INTRODUCTION:** The rising incidence of peri-prosthetic joint infections motivates the development of strategies for sustained antibiotic release through local administration. Among these antibiotics, vancomycin is significant due to its efficacy against methicillin-resistant *Staphylococcus aureus* (MRSA) infections. However, the pharmacokinetic and pharmacodynamic (PK-PD) parameters of locally administered antibiotics, especially with intraarticular administration, remain largely unknown. This study focuses on assessing vancomycin concentrations in peri-prosthetic tissues of the joint using microdialysis in a rat model following local administration. The goal is to determine the PK-PD parameters for vancomycin, thereby providing valuable insights into its intraarticular and systemic concentrations when employed in clinical drug delivery devices.

**METHODS:** The following experimental procedures were approved under MGH IACUC protocol 2022N000108 (n=6 animals, 3 compartments each). A 3-4 cm skin incision was made on the right femur to expose joint structures. A craniofacial screw (1.3 mm diameter, 11 mm length) was implanted into the tibial canal. The microdialysis (membrane 10 mm, >20 kDa cut-off, polyarylethersulfone, Harvard Bioscience) catheters were positioned in skin (subcutaneous adipose tissue), muscle (right hindlimb), and tibia bone tissues (**Figure 1**). Vancomycin (50 mg/ml in 100  $\mu$ l saline) was administered via intra-articular injection, and sampling continued (every 30 min) using the microdialysis system for approximately 8 hours. Retrodialysis by drug (calibration) was performed using a vancomycin concentration of 10  $\mu$ g/mL. The vancomycin concentration in the dialysates and calibration samples were determined by Liquid Chromatography with tandem mass spectrometry (LC-MS-MS).

**RESULTS SECTION:** The half-life in skin and muscle was approximately 1.5 hours while the concentration was above MIC (~1  $\mu$ g/ml) for about 4 hours (n=4-6; **Figure 2, Table 1**). The maximum as well as the average concentration were higher in muscle than that in the skin (**Figure 2**). Together with the forthcoming bone concentration and plasma profiles, these data provide the PK/PD parameters to incorporate in devising the appropriate concentration profiles in devices with the ability to sustain vancomycin release over longer periods than the bolus injection applied here.

**DISCUSSION:** The dosing guidelines of antibiotics as well as other drugs are largely based on systemic administration and modelling. However, it is crucial to understand the pharmacokinetics of locally administered drugs because of growing interest in using local administration to minimize systemic side effects while enhancing local efficacy against infections. Microdialysis is a unique method for the determination of local drug concentrations longitudinally. Here we present the first-time use of microdialysis in an orthopaedic rat model with local administration of an antibiotic, presenting clear and quantitative ranges for efficacy. Our limitation is the lack of synovial fluid concentrations due to the small volume in the rats. While this prevents us from directly comparing to *in vitro* predictions as well as previous data with systemic administration, our results have clinical significance because dosing guidance is based on therapeutic concentrations in the local tissues.

**SIGNIFICANCE/CLINICAL RELEVANCE:** This pilot study serves as a seminal step in the exploration of *in vivo* microdialysis as a tool for refining antimicrobial strategies in orthopaedics. The ability to obtain real-time, tissue-specific drug concentration data could guide treatment approaches, offering more effective and targeted interventions for musculoskeletal infections.

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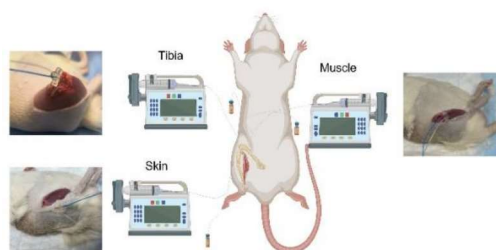


Figure 1. Microdialysis system in vivo.

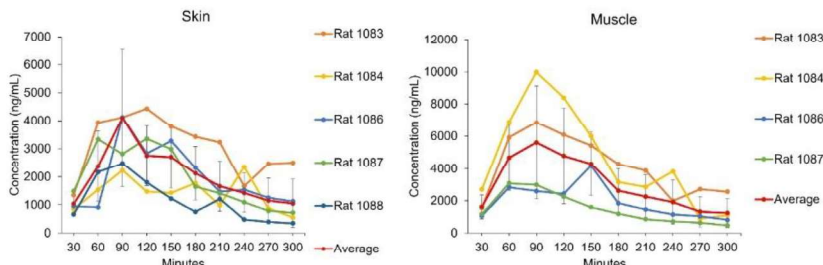


Figure 2. Mean concentration-time profiles for skin and muscle. Error bars are  $\pm 1$  standard deviation.

Skin (Rat ID)	1083	1084	1086	1087	1088	1090	Average	Muscle (Rat ID)	1083	1084	1086	1087	Average
AUC <sub>0-last</sub> (min· $\mu$ g/mL)	907.20	409.29	580.70	566.86	335.70	548.60	558.06	AUC <sub>0-last</sub> (min· $\mu$ g/mL)	1213.82	1332.19	565.72	430.74	885.62
C <sub>max</sub> (ng/mL)	4429.56	2354.56	4121.03	3352.23	2484.67	8801.14	4257.20	C <sub>max</sub> (ng/mL)	6833.70	9985.11	4166.03	3079.53	6016.09
T <sub>max</sub> (min)	120.00	240.00	90.00	120.00	90.00	90.00	125.00	T <sub>max</sub> (min)	90.00	90.00	150.00	60.00	97.50
T <sub>1/2</sub> (min)	177.69	28.72	110.00	75.60	73.46	67.28	88.79	T <sub>1/2</sub> (min)	124.49	61.88	71.69	82.50	85.14

Table 1. Pharmacokinetic (PK) parameters for skin and muscle. AUC<sub>0-last</sub>, area under the concentration-time curve from 0 h to the last measured value; C<sub>max</sub>, peak drug concentration; T<sub>max</sub>, time to C<sub>max</sub>; T<sub>1/2</sub>, half-life at beta phase.