Effects of Blast Overpressure on Development of Wound Infections and Evaluation of PK/PD and Efficacy of Standard-of-Care Antibiotics

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Abstract

Introduction: During previous conflicts 70% of wounds sustained by service members resulted from blast-related injuries. These wounds are often complicated by infections requiring battlefield-ready, standard-of-care (SOC) antibiotics. Blast overpressure (BOP) exposure or primary blast causes a whole-body trauma that can affect immune response, infection development, and treatment. Previous research demonstrated reduced clearance of cefazolin in BOP-exposed mice however, other battlefield SOC antibiotics such as ertapenem (ert) and moxifloxacin (moxi) have not been evaluated for the effects of BOP on pharmacokinetics/pharmacodynamics (PK/PD) or efficacy against wound infections. The frequent association of *Staphylococcus aureus* (*Sa*) and *Klebsiella pneumoniae* (*Kp*) with combat wound infections prompted us to examine the PK/PD and efficacy of SOC antibiotics post-BOP in *Sa* and *Kp* wound infection models.

Methods: Novel, combat-relevant wound infection models were developed incorporating BOP. Prior to the creation of full thickness excisional wounds, anesthetized mice were exposed to 19 psi of BOP. Wounds were inoculated with *Sa* or *Kp,* treated with human-equivalent doses of ert or moxi, and monitored for 48 hours and 24 hours, respectively. Infection development and efficacy were determined via CFU analysis, comparing BOP and sham groups. Post euthanasia, the effects of BOP on the PK/PD of ert and moxi were evaluated by measuring concentrations of antibiotics in the liver and plasma using UPLC-MS/MS.

Results: BOP exposure did not lead to observable differences in PK/PD for ert or moxi compared to the sham group. Moxi was efficacious against *Kp* wound infections, with no differences in bacterial burden observed in the wound or organs between sham and BOP groups. However, ert treatment did not lead to the clearance of infection in either group. Notably, BOP altered *Kp* infection dynamics, as bacterial burden in the organs was lower in the BOP group despite a similar burden in the wounds.

Conclusions: In contrast to previous cefazolin research, BOP had no effect on PK/PD of ert or moxi, suggesting the effect of BOP may be antibiotic-specific. Moxi efficacy against *Kp* wound and systemic infections suggests it may remain effective for patients exposed to BOP and with full-thickness wounds. Most notably, this project established a wound infection model to study the effects of BOP on bacterial dissemination and drug efficacy, which will have far-reaching applications for future combat casualty care.

Materials and Methods

Pharmacokinetics/Pharmacodynamics of Antibiotics after Blast Exposure

- Mice were exposed to 19 psi of blast overpressure or sham procedures while under anesthesia
- 1-hour post-blast or sham mice were administered either ertapenem (IV) or moxifloxacin (oral gavage
- Post humane euthanasia, blood and organs were collected at pre-determined time points to measure antibiotic concentrations in the plasma and liver via UPLC-MS/MS

Antibiotic efficacy against Wound Infections and Dissemination after Blast Exposure

- Mice were exposed to 19 psi of blast overpressure or sham while under anesthesia
- Immediately following blast exposure mice were given EthiqaXR® (extended-release buprenorphine) as an analgesic prior to wounding with a 6mm biopsy punch
- Wounds were topically infected with either *Sa* or *Kp*
- 1 hour post infection mice were treated with ertapenem for *Sa* infection or moxifloxacin for *Kp* infection
- Wound beds and organs were harvested after humane euthanasia for CFU enumeration at 48 hours for *Sa* infected mice or 24 hours for *Kp* infected mice

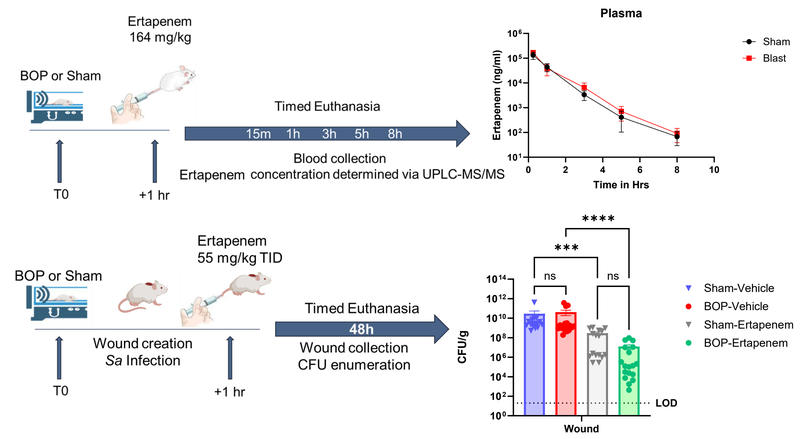
Conversion of human dose to mouse dose antibiotics

- Recommended human dose for ertapenem is 1g via IV or IM [1]
- Recommended human dose for moxifloxacin 400 mg via PO [1]

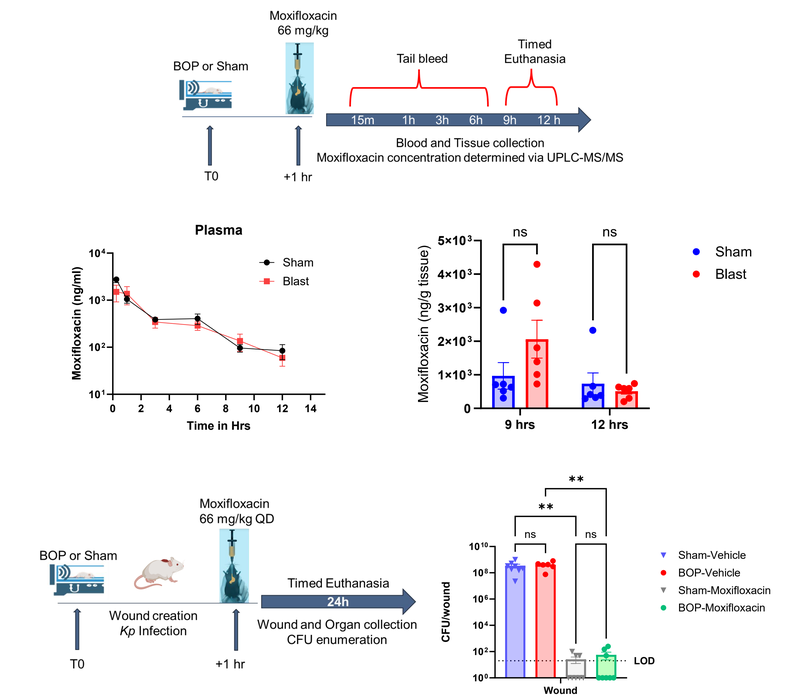
Species	Reference body weight (kg)	To convert dose in mg/kg to dose in mg/m², divide by K_m	To convert human dose in mg/kg to AED in mg/kg, either	
			Multiply human dose by	Divide human dose by
Human	60	37		
Mouse	0.02	3	12.3	0.081

Data adapted and modified from Food and Drug Administration guidelines. AED = Animal equivalent dose [2]

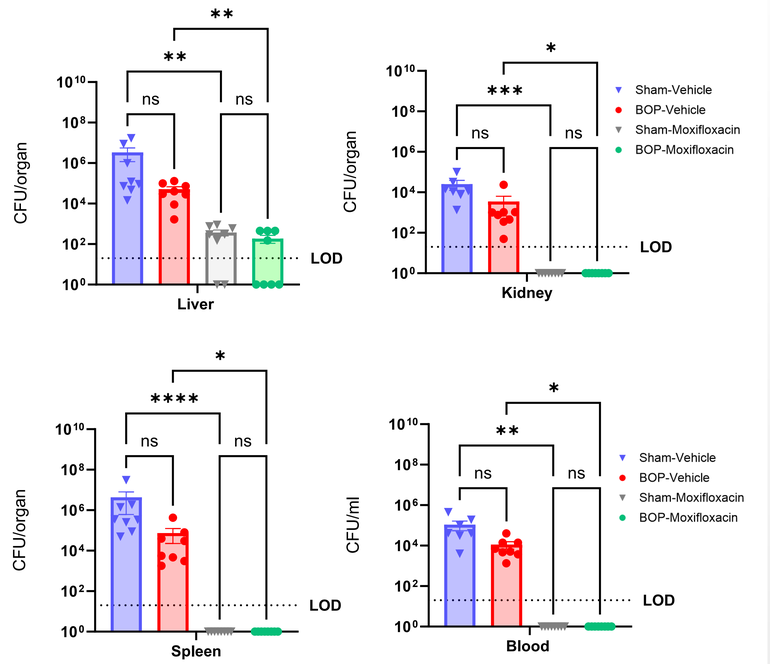
BOP Model Development for *Sa* Wound Infection, and Ertapenem PK/PD and Efficacy



BOP Model Development for *Kp* Wound Infection, and Moxifloxacin PK/PD and Efficacy



Efficacy of Moxifloxacin against Disseminated *Kp* Wound Infections Post BOP



Summary

- Developed in vivo BOP model to analyze PK/PD of antibiotics
- BOP did not yield differences in antibiotic concentration suggesting treatment strategies will not need to be altered for blast related wound infections
- Developed in vivo BOP wound infection model to test infection development and antibiotic efficacy
- BOP resulted in lower bioburden in the organs of mice infected with *Kp*
- Moxifloxacin resulted in *Kp* clearance in both the control group and the BOP group while ertapenem resulted in lower *Sa* bioburden

1. Causbie, J. M., Wisniewski, P., Maves, R. C., and Mount, C. A. (2024) Prophylactic antibiotic use for penetrating trauma in prolonged casualty care: A review of the literature and current guidelines. *J Trauma Acute Care Surg* **97**, S126-S137
2. US Food and Drug Administration; 2005. USFDA. Guidance for Industry: Estimating the Maximum Safe Starting Dose in Adult Healthy Volunteer

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