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Pharmacokinetics of Sivelestat in a Combat-Relevant Polytrauma Rat Model

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Introduction

- Combat-relevant polytrauma produces a severe systemic injury state characterized by soft tissue damage, fracture, hemorrhagic shock, inflammation, and multiorgan stress.[1]
- Acute kidney injury (AKI) is a clinically important consequence of severe trauma and hemorrhagic shock, yet therapeutic options that directly target the inflammatory mechanisms driving trauma-induced AKI remain limited.
- Trauma-associated inflammation rapidly activates neutrophils, which can release neutrophil elastase, reactive oxygen species, and neutrophil extracellular traps that amplify renal tubular injury.[2]
- Sivelestat is a selective neutrophil elastase inhibitor with clinical-use precedent outside the United States, including approval in Japan and Korea for acute lung injury/ARDS associated with systemic inflammation; however, it is not FDA-approved.
- By inhibiting neutrophil elastase, sivelestat may attenuate inflammatory tissue injury after polytrauma and represents a candidate therapy for trauma-induced AKI.
- However, the pharmacokinetics of sivelestat have not been defined in combat-relevant polytrauma, where hemorrhage, shock, and evolving organ dysfunction may substantially alter systemic drug exposure.
- Therefore, this study evaluated the plasma pharmacokinetics of sivelestat in a rat model of combat-relevant polytrauma as a translational step toward PBPK model development, dose optimization, and future clinical evaluation.

Objectives

- Characterize plasma sivelestat pharmacokinetics in a rat model of combat-relevant polytrauma.
- Compare sivelestat exposure in polytrauma rats with healthy rat reference data at the same dose.
- Generate pharmacokinetic data to support PBPK model development, dose optimization, and future translational studies of sivelestat for trauma-induced acute kidney injury.

Methods

- Adult male Sprague-Dawley rats (N=10) were used to evaluate the pharmacokinetics of sivelestat in a combat-relevant polytrauma model.
- Polytrauma in rats was induced using a combined injury model consisting of soft tissue injury, fibula fracture, and pressure-controlled hemorrhage.
- The first dose of sivelestat (2 mg/kg) was administered intravenously (i.v.) immediately after hemorrhage, followed by three additional doses (2 mg/kg) i.v. or intraperitoneally (i.p.) at 6, 24, and 48 hours after injury (Figure 1).
- Blood samples were collected at baseline before drug administration and at 2.5, 24, 48, and 72 hours after the initial sivelestat dose.
- The concentration of sivelestat was measured using high-performance liquid chromatography-mass spectrometry.
- Plasma PK parameters were calculated using the noncompartmental analysis (NCA) with PKanalix version 2021R1 (Antony, France, Lixoft SAS, 2021, http://lixoft.com/products/PKanalix/) software.
- Pharmacokinetic data from healthy rats following intravenous administration at the same dose were used as a reference for comparison.

Methods

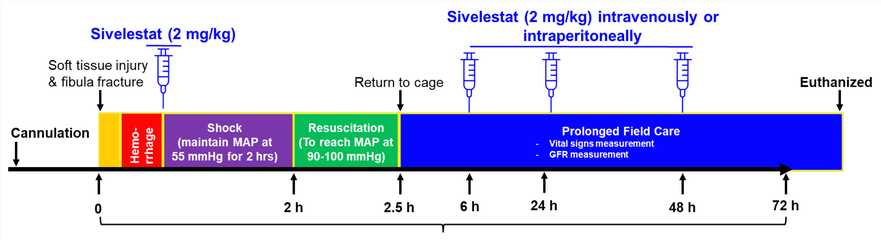

Figure 1. Sivelestat administration and pharmacokinetic sampling schematic

Results

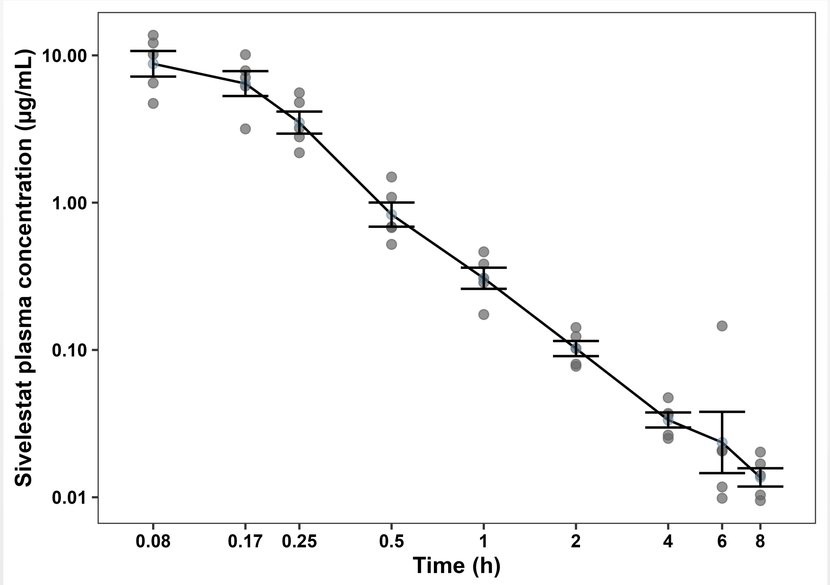

Figure 2. Plasma concentration vs. time profile of sivelestat in healthy rats after intravenous administration. Sivelestat plasma concentrations are shown as individual observed data points following sivelestat intravenous administration (2 mg/kg) in rats. Time and concentration are presented on logarithmic scales. Individual observations are shown as gray circles. The solid black line represents the geometric mean concentration at each sampling time point, and error bars represent the standard error around the geometric mean.

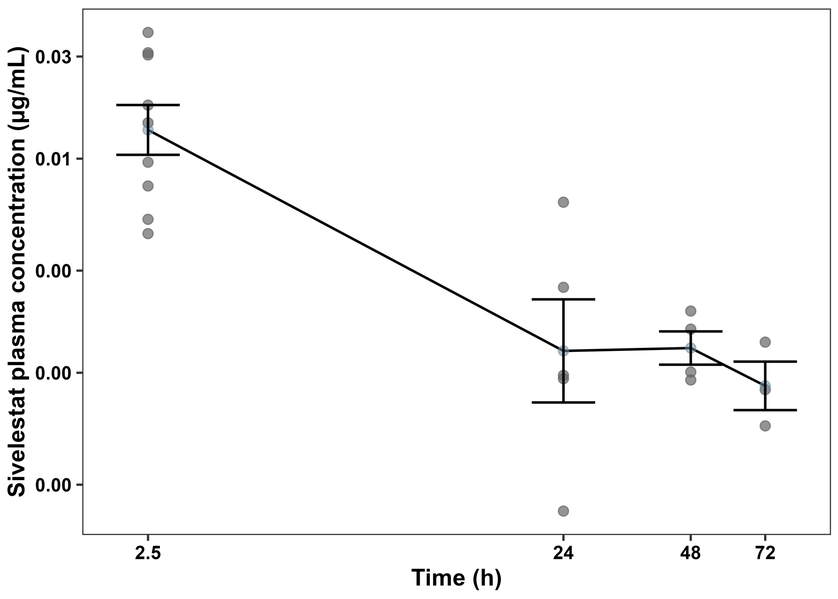

Figure 3. Plasma concentration vs. time profile of sivelestat in rat polytrauma model. Sivelestat plasma concentrations are shown as individual observed data points following sivelestat intraperitoneal administration (2 mg/kg) in rats. Time and concentration are presented on logarithmic scales. Individual observations are shown as gray circles. The solid black line represents the geometric mean concentration at each sampling time point, and error bars represent the standard error around the geometric mean.

Healthy Rat Reference Pharmacokinetics

- Following intravenous administration of sivelestat 2 mg/kg in healthy rats, plasma concentrations declined over time in a multiphasic pattern.
- Mean plasma concentrations were highest during the early sampling period and declined progressively from approximately 8–10 µg/mL at 0.08–0.17 hours to approximately 0.01–0.02 µg/mL by 8 hours.
- Sivelestat remained measurable through 8 hours after intravenous dosing, with concentrations of approximately 0.01 µg/mL at the final sampling time.

Results

Sivelestat Pharmacokinetics in Polytrauma Rats

- In the combat-relevant polytrauma model, systemic sivelestat exposure was markedly lower than the healthy rat reference profile.
- At 2.5 hours after the initial dose, mean plasma sivelestat concentration was 36.39 nM, equivalent to approximately 0.016 µg/mL.
- By 24 hours, mean plasma concentration decreased to 0.0002 µg/mL.
- Sivelestat concentrations were below the limit of quantification at the 48- and 72-hour sampling time points.

Conclusions

- Sivelestat systemic exposure was markedly reduced in polytrauma rats, with low concentrations observed at 2.5 hours and minimal to non-quantifiable concentrations at later sampling times.
- These findings suggest that injury-associated physiological changes after polytrauma may limit sustained systemic sivelestat exposure at the evaluated dosing regimen.
- These data provide an initial pharmacokinetic foundation for developing a rat polytrauma PBPK model to guide future preclinical studies and translational dose selection.

Next Steps

- Develop a rat polytrauma PBPK model to characterize injury-associated changes in sivelestat disposition and predict optimized dosing regimens.
- Conduct dose-escalation and exposure-response studies to identify sivelestat dosing strategies that achieve sustained systemic exposure and mitigate trauma-induced AKI.

Limitations

- This exploratory study was limited by sparse plasma sampling and descriptive comparison with healthy rat reference data rather than formal noncompartmental or model-based PK parameter estimation.

Acknowledgements

- Funded by the U.S. Army Medical Research and Development Command.

References

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Statements

- Research was conducted in compliance with the Animal Welfare Act, the implementing Animal Welfare Regulations, and the principles of the Guide for Care and Use of Laboratory Animals. The Institutional Animal Care and Use Committee approved all research conducted in this study. The facility where this research was conducted is fully accredited by AAALAC International

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