Small Molecule Antidote for Anticoagulants

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Introduction

PER977 is a synthetic small molecule (~500Da) that:

- Reverses oral apixaban, rivaroxaban, and dabigatran, as well as s.c. fondaparinux and LMWH in vivo
- Reduces blood loss, reversing the anticoagulant activity of apixaban and rivaroxaban in a rat tail transection assay
- Reverses apixaban and rivaroxaban in human blood ex vivo
- Has validated assays for stability measurements and determining plasma concentrations
- Survives heating above sterilization temperatures to 200°C
- Is stable for more than 1 year
- No hERG binding in vitro; neither CYP substrate nor inhibitor; no plasma protein binding; no liver cell metabolism in vitro
PER977 reverses ~100x overdose of rivaroxaban (2mg p.o.) and apixaban (1.25mg p.o) in a rat tail transection model

- Full reversal at a mass ratio of 6.25:1, N=5 *p<0.05
PER977 reverses ~100x overdose of dabigatran etexilate (15mg p.o.) in a rat tail transection model.
PER977 reverses rivaroxaban across a range of human plasma concentrations ex vivo

- PER977 restores Xa activity to an equivalent rivaroxaban concentration below MEC in fresh human plasma
PER977 reverses apixaban across a wide range of plasma concentrations *ex vivo*

- PER977 restores Xa activity to an equivalent apixaban concentration below MEC in fresh human plasma
- Apixaban concentration standards not yet available
PER977 restores Factor Xa activity in a dose-dependent fashion ex vivo in human plasma.

PER977 restores Xa activity to an effective rivaroxaban concentration below MEC.
APTT testing confirms PER977 reverses rivaroxaban in freshly drawn human blood ex vivo
IV PER977 does not influence aPTT *in vivo* over a wide range of doses (rats)

- Male, weight-matched CD rats were dosed with PER977 solution (IV) in the lateral saphenous vein (hind quarters)
- Whole blood aPTT averaged over seven time points spanning 90 min
200mg/kg PER977 IV reverses 10 mg/kg s.c. LMWH extreme overdose \textit{in vivo} (rat)

- PER977 reverses 200x LMWH overdose on a mg/kg basis not accounting for differences between species
200mg/kg PER977 IV reverses 5 mg/kg s.c. fondaparinux *in vivo* (rat)

- Fondaparinux activity in plasma measured by Factor Xa kit

* Indicates below the limit of detection
PER977 Summary

- Reverses rivaroxaban, apxaban, and dabigatran as confirmed by >90% reduction in blood loss in bleeding model (rat tail transection assay)

- Completely reverses apixaban and rivaroxaban (~10:1 :: PER977:anticoagulant) in human blood ex vivo as measured by 510k-cleared anti-Xa kit

- Exhibits a dose-dependent reversal of apixaban and rivaroxaban in human blood ex vivo

- Rivaroxaban reversal in freshly drawn human blood confirmed by aPTT measurements ex vivo

- Reverses s.c. LMWH and fondaparinux anticoagulation in vivo (rats)