Background

Mast cell-derived heparin proteoglycans (Hep-PG):
- attenuate platelet-collagen interactions under blood flow
- reduce platelet thrombosis on collagen surfaces in vitro and at vascular injury sites in vivo

APACs are semisynthetic Hep-PG mimetics with dual antiplatelet and anticoagulant action

In vitro APAC:
- inhibited collagen-induced platelet aggregation in PRP and procoagulant activity in calibrated automated thrombogram
- prolonged aPTT and thrombin time in plasma

In vivo locally administered APAC reduced acute thrombosis in two baboon models:
- In a modified Folt’s model: crush injury site remained patent under stenosis (30-90%) with APAC (for 120 min); whereas UFH-treated artery repeatedly occluded
- AV-shunt with an extracorporeal collagen-coated graft: APAC inhibited platelet deposition (34%), delayed thrombosis, reduced distal thrombus propagation (63%) and fibrin formation (50%) in situ

Methods

Male SD rats were dosed with APAC (APAC2, Aplagon, Helsinki, Finland) or UFH (Heparin Leo, Leo Pharma, Ballerup, Denmark) at 0.128 - 7.3 mg/kg.
- Blood samples were drawn pre and post dose at 60 min, 90 min, 6h, 24h and 48h for aPTT and PT analysis
- Distribution and retention were studied by PET/CT scan with 64Cu-NOTA-labeled APAC or UFH
- At 48h rats were euthanized and kidneys, liver, lungs and spleen were harvested for 64Cu radioactivity counting

Aim

Pharmacokinetic and pharmacodynamics profiling of APAC in rats

RESULTS

APAC is distributed to the kidneys and liver alike UFH

APAC has longer clearance time than UFH at high dose

- APAC clearance (T1/2) was 15min at Low (0.128 mg/kg) and Medium (0.48 mg/kg) dose, and 1h at High Dose (7.3 mg/kg)
- UFH (Heparin) T1/2 was 23-28min at both low and high doses

Conclusions

- APAC and UFH mainly accumulated in the kidneys and liver following the traditional heparin elimination route
- Our anticipated clinical dose is around 0.5 mg/kg
- APAC prolonged aPTT, while PT only modestly elevated
- APAC had at 2.5-fold clearance time over UFH suggesting some retention at the high dose only

APAC as an anticoagulant

- APAC or UFH had no effect on aPTT at low doses
- At 7.3 mg/kg
  - aPTT was prolonged by 6- and 4-fold with APAC and UFH, respectively
  - PT was prolonged by 1 to 1.3-fold for both APAC and UFH
  - aPTT remained elevated for 90min while PT reverted at 6h aPTT and PT were returned to baseline

References

1. Lassila R et al. JVB, 17:3578-87, 1997

Representative example: PET (bottom) and PET/CT (top) co-registration images obtained following administration via the tail vein of 0.128 mg/kg of [64Cu]-NOTA-APAC (ki = kidneys, li = liver, sp = spleen, vc = vena cava)