PHARMACOKINETICS AND PHARMACODYNAMICS OF APAC, A DUAL NOVEL ANTIPLATELET AND ANTICOAGULANT HEPARIN COMPLEX

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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*[1]

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[2]

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*[2]

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 60min, 90min, 6h, 24h and 48h for aPTT and PT analysis
- Distribution and retention were studied by PET/CT scan with ^{64}Cu-NOTA-labeled APAC or UFH
- At 48h rats were euthanized and kidneys, liver, lungs and spleen were harvested for ^{64}Cu radioactivity counting

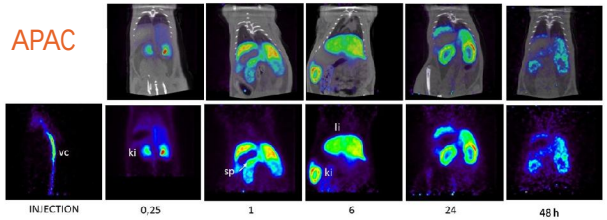
References
1. Lassila R *et al.* ATVB, 17:3578-87, 1997
2. Lassila R & Jouppila A, Semin Thromb Hemost, 40:837–844, 2014

Aim

Pharmacokinetic and pharmacodynamics profiling of APAC in rats

RESULTS

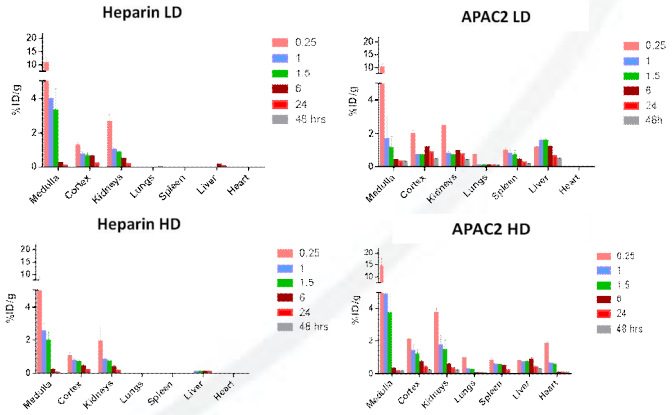
APAC is distributed to the kidneys and liver alike UFH



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

APAC has longer clearance time than UFH at high dose

- APAC clearance ($T_{1/2}$) 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) $T_{1/2}$ 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