Dose escalation effects of intravenous APAC, a heparin proteoglycan mimic, in healthy participants

Y Mehta[1], R Saxena[1], S Goel[1], J George[1], A Amarsheda[1], A Kumar[2], A Chatterjee[2], S Patel[2], S Sharma[2], A Jouppila[3,4], M Koskinen[5,6] N Meyers[7], and R Lassila[4,6,8]

Medanta, Delhi, India, [2]Cadila, Ahmedabad, India, [3]Clinical Research Institute HUH, [4]Research Program Unit in Systems Oncology, Medical Faculty, Helsinki Univ, [5]Helsinki Univ, [6]Diagnostic Centre of HUH, [7]Boyds, Crewe UK, [8]Aplagon Ltd, Helsinki, Finland

INTRODUCTION

AntiPlatelet, AntiCoagulant APAC, mimics natural antithrombotic mast-cell heparin proteoglycans being a conjugate of unfractionated heparin (UFH) and human serum albumin (HSA)

APAC targets vascular injury sites, acts as local antithrombotic especially under arterial flow conditions and inhibits inflammation and complement system

In essence, APAC is a dual von Willebrand factor (VWF) and thrombin inhibitor

AIMS

- To report results of Phase-I clinical study of single, ascending IV bolus injections of APAC in healthy participants
- To assess safety and dose responses on platelet aggregation and coagulation activity

HEALTHY PARTICIPANTS

- 30 healthy males (10/cohort) were IV-dosed APAC 0.1, 0.25 and 0.5 mg/kg and followed clinically for 24 h to 5 days, with laboratory assessment up to 12h

CONCLUSIONS

- Clinical safety study of IV doses of APAC was successful without adverse events
- The half-life of relevant clinical doses are about 90 min
- Clinical laboratory follow up was feasible with several routine markers of which TT, ACT and ROTEM InTEM CT and MCF are suitable and the most sensitive
- The antithrombotic effects of APAC were dose-dependent and transient, aligning with our ongoing studies for vascular interventions and thrombo-inflammation

METHODS

Study identifier: CTRI/2023/04/051500

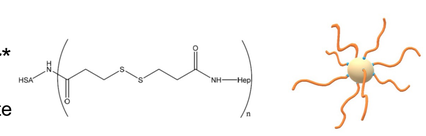
- Complete blood cell counts,
- Routine clinical chemistry
- Coagulation analysis:
  - activated partial thromboplastin time (APTT) prothrombin time (PT)
  - thrombin time (TT)
  - activated clotting time (ACT)
  - antiFIIa/antiFXa activities (Biophen assay, antithrombin supplemented)
- ROTEM, InTEM
- VerifyNow
- Platelet aggregation by collagen (2 µg/mL), ristocetin, arachidonic acid (AA), adrenaline and adenosine-5 diphosphate (ADP)

MECHANISM OF ACTION OF APAC

STRUCTURE OF APAC

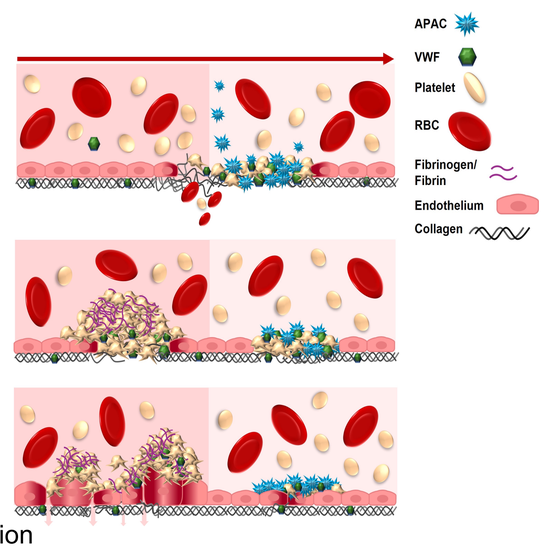
UFH chains linked to HSA via disulphide bonds by cross-linker*

*N-succinimidyl 3-(2-pyridyldithio)propionate



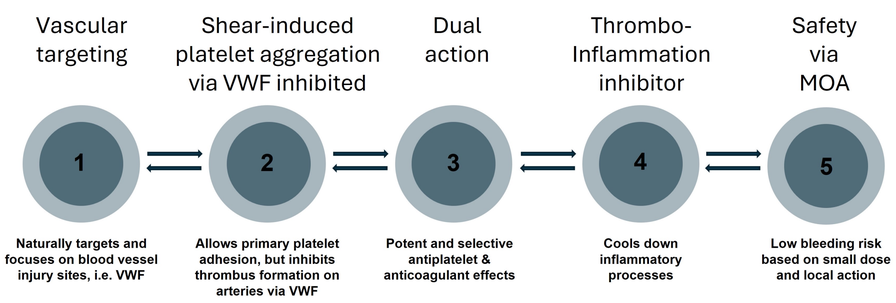
APAC targets injury sites under high blood flow conditions allowing primary platelet adhesion and hemostasis

APAC inhibits platelet aggregation under high blood shear rate mediated via collagen, VWF and thrombin and
Is a potent anticoagulant, especially against thrombin, dependent on heparin



APAC cools down inflammation

INTERACTIVE AND MULTIFUNCTIONAL APAC



RESULTS

- No adverse events, dose limiting toxicities or safety concerns were observed in clinical or laboratory data
- PT did not change, but ACT (Fig. 1), APTT and TT (Fig. 2) dose-dependently and transiently aligned with dose-escalated anticoagulant effects
- ACT and TT were the most sensitive markers of APAC doses (Fig.1, 2)
- Accordingly, the antiFIIa/antiFXa activity ratio varied between 2.5 to 3.1 at the same time
- ROTEM InTEM clotting time and clot firmness time were transiently prolonged at ≥ 0.25 mg/kg of APAC, and maximum clot firmness (MCF) was reduced by 12-57% at 0.5 mg/kg
- Platelet aggregation inhibition (15-25%) with many of the agonists was short-lived (15-30 min) occurring only at the highest APAC dose
- APAC did not induce responses in VerifyNow to either AA or ADP

Figure 1. Activated Clotting Time (ACT) along APAC IV dosing

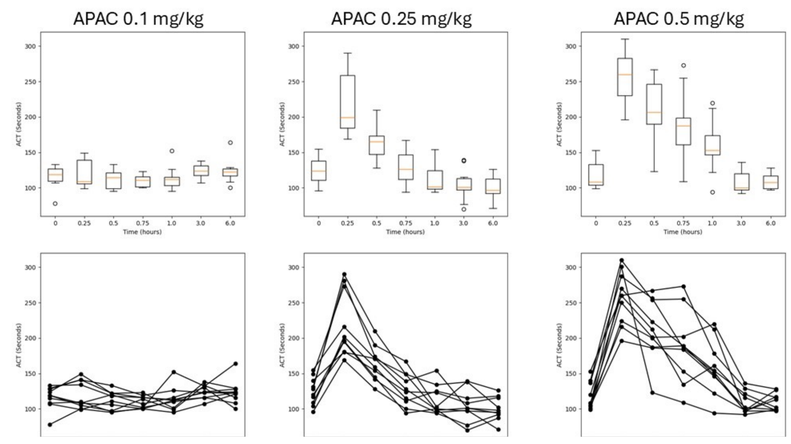
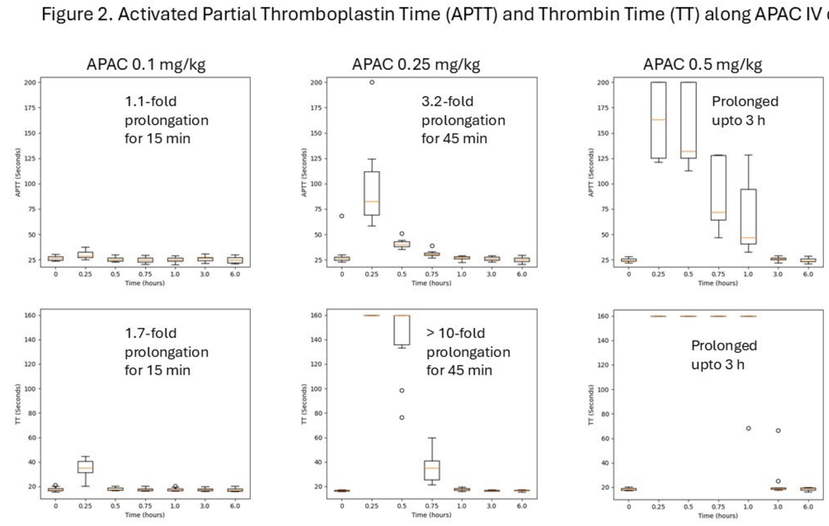


Figure 2. Activated Partial Thromboplastin Time (APTT) and Thrombin Time (TT) along APAC IV dosing



CONTACT

Riitta Lassila riitta.lassila@kolumbus.fi

www.aplagon.com

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