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 12 h

METHODS

- Study identifier: CTRI/2023/04/051500)
- Complete blood cell counts, routine clinical chemistry and 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)

CONCLUSIONS

- Clinical safety study of IV doses of APAC was successful without adverse events
- Clinical laboratory follow up was feasible with several routine markers (TT, ACT and ROTEM)
- The antithrombotic effects of APAC were dose-dependent and transient, aligning with our ongoing studies for vascular interventions and thrombo-inflammation

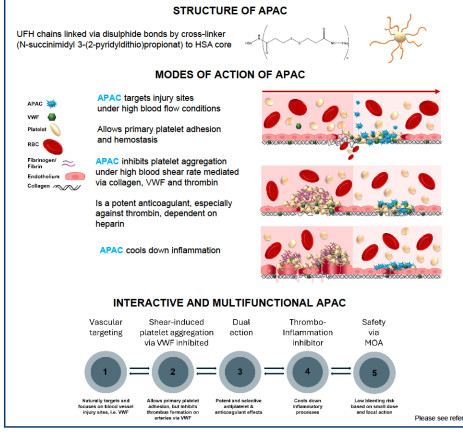
CONTACT

Riitta Lassila riitta.lassila@kolumbus.fi
www.aplagon.com

RESULTS

- No adverse events or safety concerns were observed in clinical or laboratory data

MECHANISM OF ACTION OF APAC



Please see references

- 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 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

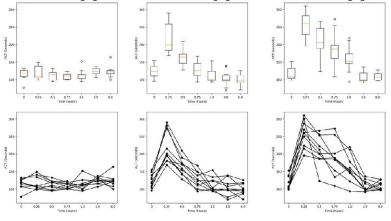
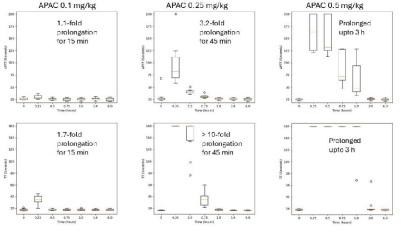


Figure 2. Activated Partial Thromboplastin Time (APTT) and Thrombin Time (TT) along APAC IV dosing



References

Lassila R, Jouppila A. Mast cell-derived heparin proteoglycans as a model for a local antithrombotic. Semin Thromb Hemost. 2014, 40:837

Tuuminen R et al. Dual antiplatelet and anticoagulant APAC prevents experimental ischemia-reperfusion-induced acute kidney injury. Clin Exp Nephrol. 2017, 21:436

Chen J *et al.* Dual antiplatelet and anticoagulant (APAC) heparin proteoglycan mimetic with shear-dependent effects on platelet-collagen binding and thrombin generation. Thromb Res. 2018, 169:143

Barreiro K *et al.* Novel Locally Acting Dual Antiplatelet and Anticoagulant (APAC) Targets Multiple Sites of Vascular Injury in an Experimental Porcine Model. Eur J Vasc Endovasc Surg. 2019, 58:903

Craige S *et al.* Safety and Functional Pharmacokinetic Profile of APAC, a Novel Intravascular Antiplatelet and Anticoagulant. J Cardiovasc Pharmacol. 2021, 78:453

Winzely M *et al.* AFM investigation of APAC (antiplatelet and anticoagulant heparin proteoglycan). Anal Bioanal Chem. 2022, 414:1029

Bonelli N *et al.* Intravenously administered APAC, a dual AntiPlatelet AntiCoagulant, targets arterial injury site to inhibit platelet thrombus formation and tissue factor activity in mice. Thromb Res. 2023, 228:163

Bot I *et al.* Treatment with APAC, a dual antiplatelet anticoagulant heparin proteoglycan mimetic, limits early coilar-induced carotid atherosclerotic plaque development in Apoe-/- mice. Atherosclerosis. 2024, 397:118567

Denorme F *et al.* Pretreatment with a dual antiplatelet and anticoagulant (APAC) reduces ischemia-reperfusion injury in a mouse model of temporary middle cerebral artery occlusion-implications for neurovascular procedures. Acta Neurochir. 2024, 15;166:137

Jouppila A *et al.* Antiplatelet-anticoagulant, APAC, a mimic of endogenous heparin, is an antithrombotic with von Willebrand factor-mediated characteristics. Thromb Res. 2025, 12;250:109318