Investigation of Mode of Action of sugammadex effects on coagulation

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INTRODUCTION

The selective muscle relaxant binding agent sugammadex (Bridion®) is associated with transient and limited prolongation of activated partial thromboplastin time (APTT; 11%) and prothrombin time (PT; 17%) in humans. However, no sugammadex effects were observed on a standard thrombin generation test (TGT). Moreover, no increased bleeding risk is observed in in surgical patients upon sugammadex treatment[1]. These observations warrant identification of the mechanism by which sugammadex affects coagulation.

AIM

To unravel the Mode of Action (MoA) by which sugammadex affects coagulation.

METHODS

In vitro coagulation experiments with plasma from healthy male volunteers:

- Plasma spiked with sugammadex (Org 25969) to cover concentrations for the clinical doses of 2, 4 and 16 mg/kg (25, 50 and 200 µg/mL, respectively);
- Assays: APTT, PT, standard and tissue factor-enriched TGT, Prothrombinase induced Clotting Time (PiCT) and factor Xa generation.

[1]Anesthesiology, 2014;121(5):969-77

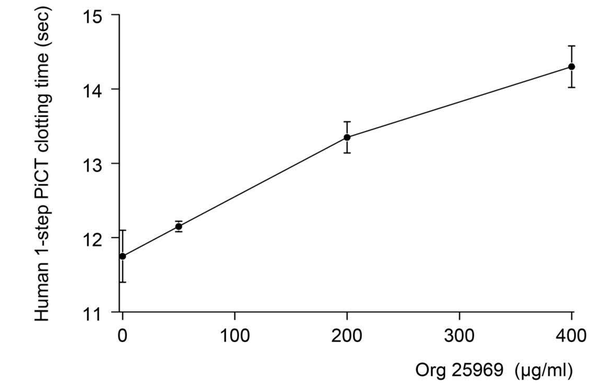

Figure 1: Sugammadex effect on (top) clotting time determined with 1-step PiCT test using human factor Xa, (middle) intrinsic factor Xa generation test using APTT reagent and (bottom) expression of sugammadex effects on APTT and PT in apparent factor X reduction using calibration curves with factor X deficient plasma dilutions in plasma from healthy subjects.

RESULTS

- Sugammadex prolonged APTT and PT concentration–dependently: up to 10 seconds in APTT and 2.5 seconds in PT at 200 µg/mL. This was similar in antithrombin or heparin cofactor II depleted plasmas;
- TGT was delayed by 11-12 seconds at 200 µg/mL sugammadex, but only in a tissue-factor enriched test;
- Sugammadex inhibited human factor Xa PiCT by approximately 1.7 seconds at 200 µg/mL (figure 1, top), but did not inhibit bovine factor Xa PiCT, suggesting species-dependence;
- Sugammadex specifically inhibited factor Xa generation via the intrinsic activation coagulation route (figure 1, middle) and not the extrinsic route;
- Effects of 200 µg/mL sugammadex on APTT and PT correlated with an apparent reduction in factor X of 90% and 46% respectively (figure 1, bottom).

CONCLUSIONS

Sugammadex inhibited factor Xa generation in the intrinsic pathway and decreased factor Xa activity in the common pathway. TGT was only inhibited when high tissue factor was used.

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