Abstract

Introduction: Urokinase (UK) and tissue plasminogen activator (tPA) mediate thrombolytic actions by activating endogenous plasminogen. Thrombomodulin (TM) complexes with thrombin to activate Protein C and thrombin activatable fibrinolysis inhibitor (TAIFI). Activated Protein C (APC) modulates coagulation by digesting factors V and VIII and activates fibrinolysis by decreasing PAI-1 functionality. Recombinant versions of TM (rTM) has been developed for therapeutic purposes.

Aim: To compare the effects of rTM and APC on urokinase and tPA mediated thrombolysis utilizing thromboelastography.

Materials and methods: Native whole blood was activated using a diluted intrinsic activator (APTT reagent, Triniclot). The modulation of thrombolysis by tPA and UK (Abbott, Chicago, USA) was studied by supplementing these agents to whole blood and monitoring TEG profiles for 3 hours. To investigate effect of APC (Haematologic Technologies, VT, USA) and rTM (Asahi Kasei Pharma, Tokyo, Japan) these agents were also supplemented to the activated blood. The modulation of UK and UK induced thrombolysis by APC and rTM was also studied.

Results: In comparison to rTM, APC produced a stronger anticoagulant effect in terms of r time, k time, angle and MA. Fibrinolysis was assessed in terms of LY30(%) and LY60 (%). At concentrations of up to 2.5ug/ml rTM and APC did not produce any direct fibrinolytic effects. APC also produced strong augmentation of the lytic of effects of tPA and urokinase in a concentration dependent fashion. rTM at concentrations of less than 10ug/ml produced strong augmentation of the lytic process by both tPA and UK. APC did not produce any direct fibrinolytic effects. APC

Conclusions: These studies demonstrate the differential anticoagulant and procoagulant effects of APC and rTM. APC is a stronger anticoagulant than rTM and facilitates thrombolysis. rTM is a much weaker anticoagulant and modulates clot stability branding it resistant to fibrinolysis. These observations suggest that while APC may impair hemostasis, rTM restores hemostasis via TAIFI activation.

Materials & Methods

Activated Protein C of human plasma origin was purchased from Hematologic Technologies (Burlington, Vermont USA), Recombinant version of thrombomodulin (TM) was obtained from (Asahi Kasei Pharma Tokyo, Japan), normal whole blood was drawn from healthy donors. UK and tPA were obtained from commercial vendors, the effect of both APC and rTM were studied on the UK and tPA induced fibrinolysis in whole blood and plasma based systems upon activation with tissue factor in TEG analysis.

Summary

These studies suggest that APC is a stronger anticoagulant in comparison to rTM; furthermore, whereas the APC facilitated the lytic process rTM restores the clot stabilization in both the tPA and UK induced fibrinolytic states. Therefore the effect of these agents can be differentiated in terms of their modulation of the fibrinolytic process. In contrast to APC the rTM at therapeutic concentrations is capable of modulating the fibrinolytic process and retards the excessive fibrinolysis. These findings may have safety implications to differentiate the two agents.