

Potential of Activated Prothrombin Complex Concentrate and Activated Factor VII to Reverse the Anticoagulant Effects of Rivaroxaban in Primates

Andras Gruber^{1,2}, Ulla M Marzec¹, Ulf Buetehorn³, Stephen R Hanson¹, Elisabeth Perzborn³

¹Division of Biomedical Engineering, Oregon Health and Science University School of Medicine, Portland, USA; ²Division of Medicine, Oregon Health and Science University School of Medicine, Portland, USA; ³Bayer HealthCare AG, Wuppertal, Germany

Introduction

- Rivaroxaban is a novel, oral, once-daily anticoagulant that directly inhibits Factor Xa. It has been approved in Canada and the European Union for the prevention of venous thromboembolism after elective hip and knee replacement surgery
- Bleeding is a potential side-effect of all anticoagulant therapies, including rivaroxaban¹
 - Standard strategies to control bleeding consist of delaying the next dose or discontinuation, mechanical compression, surgical intervention, fluid replacement and hemodynamic support, or blood product or component transfusion
- Both activated prothrombin complex concentrate (APCC; FEIBA® [Baxter HealthCare Corp., Westlake Village, CA, USA]) and recombinant human activated Factor VII (rFVIIa; NovoSeven® [Novo Nordisk, Copenhagen, Denmark]) have demonstrated hemostatic effects in rat models of high-dose rivaroxaban (higher than would be administered in clinical practice)^{2,3}

Objective

- Because bleeding emergencies (defined as life-threatening bleeding events) may occur in patients receiving rivaroxaban, we determined whether APCC and rFVIIa could attenuate the antihemostatic effects of rivaroxaban in non-human primates if standard strategies fail to control bleeding

Methods

- Juvenile male baboons (8.5–11.6 kg, N=11) were used to investigate the pharmacokinetic and pharmacodynamic profile of high-dose rivaroxaban (0.6 mg/kg intravenous bolus followed by a continuous infusion of rivaroxaban 0.6 mg/kg for 60 minutes)
- Baboons received either 50 U/kg APCC (2 U/kg/min, n=7) or 210 µg/kg bolus rFVIIa (n=7) 30 minutes after the start of rivaroxaban administration
- The hemostatic effects of APCC and rFVIIa after administration of high-dose rivaroxaban were assessed by measurement of prothrombin time (PT), bleeding time (BT), and plasma thrombin–antithrombin complex (TAT) levels

Results

Effect of High-Dose Rivaroxaban on Hemostasis

- Steady-state conditions were obtained after 15 minutes of continuous infusion of high-dose rivaroxaban, and were maintained until the end of infusion (after 60 minutes)
- At steady state, PT increased 3.16- to 3.58-fold times baseline, and BT increased 2.19- to 3.01-fold times baseline ($p < 0.001$ for both)
- No adverse events, except the occasional rebleeding of BT wounds, were observed

Effect of APCC on Hemostasis

- In the APCC group, BT increased 2.02-fold±0.56 times baseline, and PT increased 3.04±0.26 times baseline 30 minutes after the infusion of high-dose rivaroxaban (Table 1; Figure 1)
- On completion of APCC infusion, BT returned to baseline (1.02-fold±0.33 times baseline) before increasing again to 1.65-fold±0.94 times baseline (Table 1; Figure 1A)

Table 1. The effect of APCC and rFVIIa on BT, PT, and TAT concentration in baboons anticoagulated with high-dose rivaroxaban (n=7 each)

Time	BT (x-fold change from baseline)	PT (x-fold change from baseline)	TAT concentration (µg/L)
APCC			
Baseline	1.00	1.00	3.51±0.08
30 minutes after rivaroxaban	2.02±0.56*	3.04±0.26*	3.01±1.37
At the end of APCC infusion	1.02±0.33	2.20±0.29*	10.35±1.41*
20 minutes after the end of APCC infusion	1.65±0.94	2.28±0.29*	ND
rFVIIa			
Baseline	1.00	1.00	7.35±4.17
30 minutes after rivaroxaban	2.54±0.79*	3.17±0.42*	2.95±0.79
5 minutes after rFVIIa	1.68±0.80	2.38±0.41*	2.58±0.52
30 minutes after rFVIIa	1.96±1.26	2.48±0.49*	4.00±1.12

* $p < 0.05$ (paired t-test) compared with pretreatment baseline. Values are given as mean ± standard deviation. APCC, activated prothrombin complex concentrate; BT, bleeding time; ND, no data; PT prothrombin time; rFVIIa, recombinant activated Factor VII; TAT, thrombin–antithrombin complex.

- A sustained reduction of PT was seen after APCC infusion; 2.20-fold±0.29 times baseline at the end of infusion, and 2.28-fold±0.29 times baseline 20 minutes later (Table 1; Figure 1B)
- TAT levels increased from baseline after APCC administration despite the high concentration of rivaroxaban in circulation ($p < 0.001$; Table 1)

Effect of rFVIIa on Hemostasis

- In the rFVIIa group, high-dose rivaroxaban prolonged BT to 2.54-fold±0.79 ($p < 0.019$) times baseline 30 minutes after the infusion (Table 1; Figure 2A)
- After an infusion of rFVIIa, BT was partially shortened (34%), and PT was reduced (Table 1; Figure 2)
- Circulating TAT levels did not change significantly after rFVIIa bolus administration (Table 1)

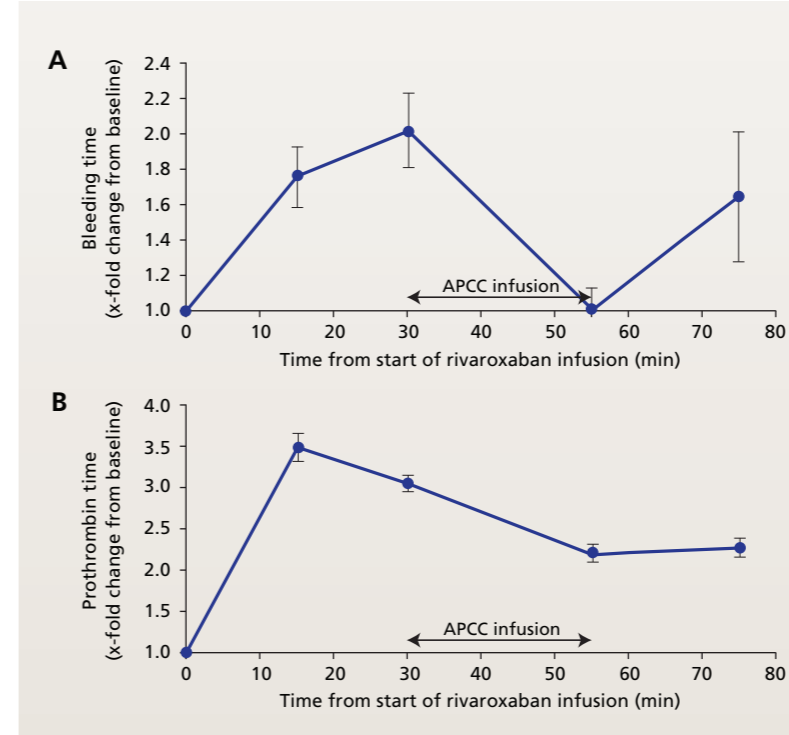


Figure 1. Effect of activated prothrombin complex concentrate (APCC) infusion (50 U/kg over 25 minutes) in baboons (n=7) anticoagulated with high-dose rivaroxaban. (A) Bleeding time; (B) prothrombin time. Values are shown as mean ± standard error of the mean.

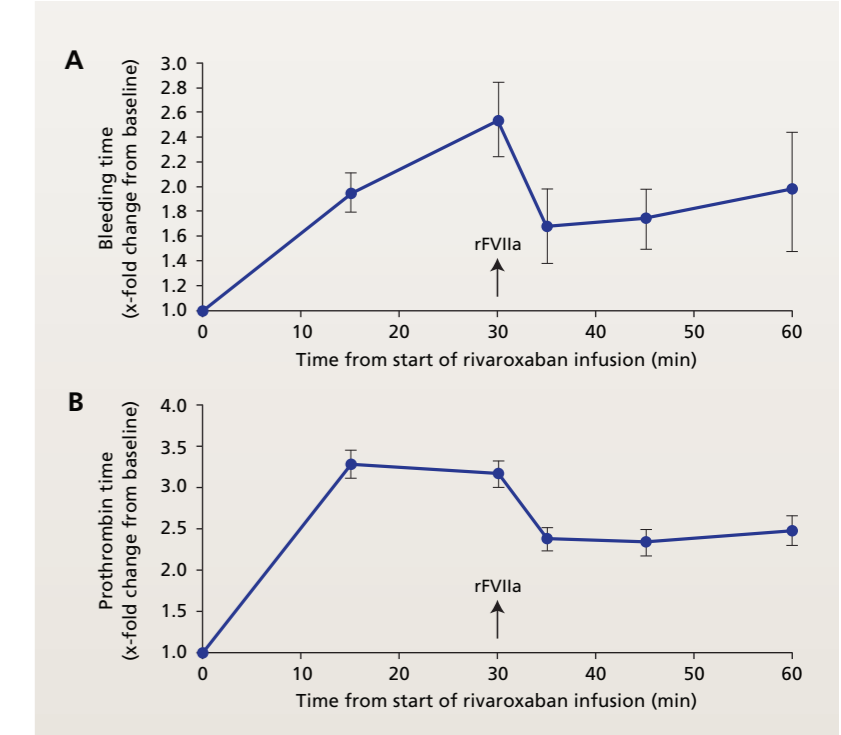


Figure 2. Effect of recombinant activated Factor VII (rFVIIa) injection (210 µg/kg at 30 minutes) in baboons (n=7) anticoagulated with high-dose rivaroxaban. (A) Bleeding time; (B) prothrombin time. Values are shown as mean ± standard error of the mean.

Conclusions

- Administration of APCC or rFVIIa rapidly reversed the effect of high-dose rivaroxaban on markers of hemostasis impairment in baboons
- The effect of rFVIIa on BT was continuous, in contrast to that of APCC
- APCC and rFVIIa may provide potential hemostatic antidotes during bleeding emergencies in patients receiving rivaroxaban
- Whether APCC and rFVIIa could achieve reversal of rivaroxaban anticoagulation without increasing the risk of thrombus formation remains to be established

References and Disclosures

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- Perzborn E. *Pathophysiol Haemost Thromb* 2008;36:A40.
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