

Prothrombin Complex Concentrate Reverses the Effects of High-Dose Rivaroxaban in Rats

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Introduction

- ◆ Rivaroxaban is a highly selective, reversible, oral, direct Factor Xa inhibitor that dose-dependently inhibits Factor Xa activity, thrombin generation, and thrombus formation^{1,2}
- ◆ Rivaroxaban does not increase bleeding times over baseline at doses that are antithrombotic in animal models of venous and arterial thrombosis¹
- ◆ As with any anticoagulant therapy, high doses of rivaroxaban prolong bleeding times¹

Objective

- ◆ To investigate if a prothrombin complex concentrate (PCC) neutralizes the *in vivo* anticoagulant effects of high-dose rivaroxaban

Methods

- ◆ The effects of PCC (25 U/kg or 50 U/kg; Beriplex®; CSL Behring, Marburg, Germany) on rivaroxaban-induced bleeding were assessed in an *in vivo* rat model of mesenteric bleeding
- ◆ Bleeding times were measured before (baseline) and after treatment following vessel incision in anesthetized Wistar rats

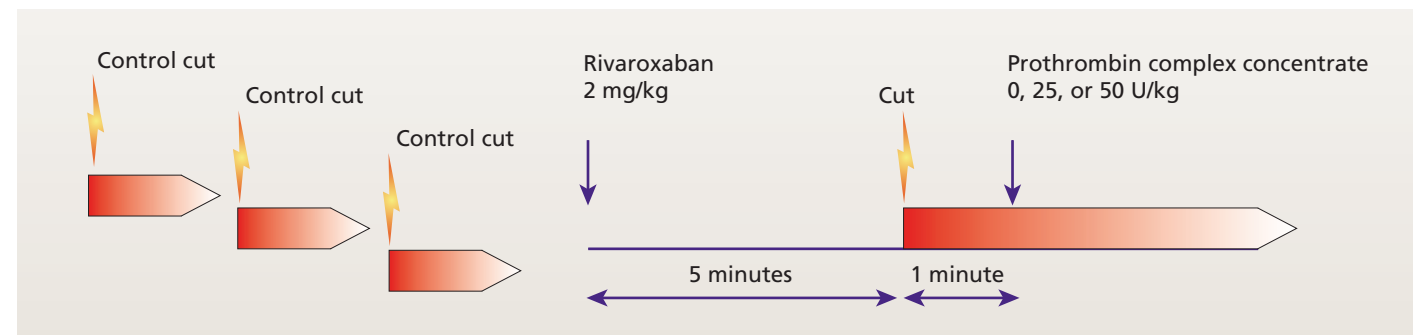


Figure 1. Study protocol

- ◆ Individual small arteries branching from the superior mesenteric artery visualized by a stereomicroscope were cut by microsurgery scissors while the intestinal surface was superfused with 0.9% NaCl
- ◆ Baseline bleeding times were measured in three different vessels in each animal before the injection of high-dose rivaroxaban (2 mg/kg)
- ◆ Five minutes later a small vessel was cut and after 1 minute the animals received either PCC (25 U/kg or 50 U/kg; n=10 rats) or vehicle (n=7 rats) (Figure 1)
- ◆ Bleeding times were measured as time taken for continuous blood flow to cease for >30 seconds (maximum observation time of 30 minutes)
- ◆ Prothrombin time (Neoplastin® Plus; Roche Diagnostics, Basel, Switzerland) and thrombin-antithrombin complex (Enzygnost TAT; Dade Behring, Marburg, Germany), a marker of thrombin formation, were also measured in blood from anesthetized rats (n=10) that had received the same injections but had not been used for determining bleeding time

Results

- ◆ High-dose rivaroxaban (2 mg/kg) significantly prolonged bleeding time 5.4±1.4-fold relative to baseline (baseline: 162±10 seconds; rivaroxaban: 861±213 seconds; $p<0.01$) (Figure 2)

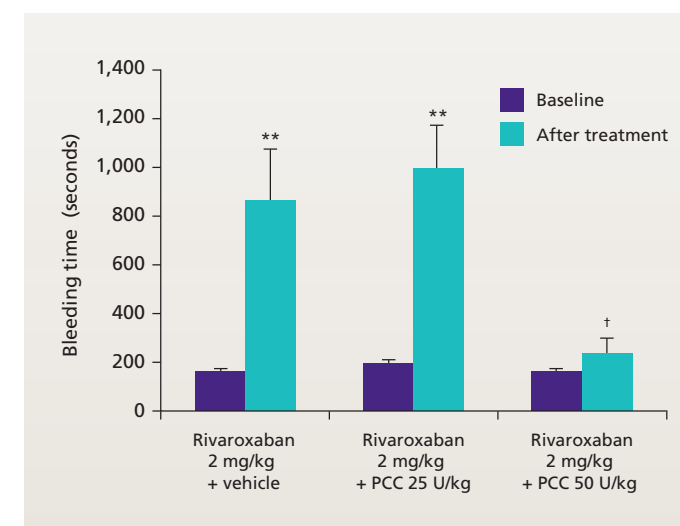


Figure 2. Mesenteric bleeding times before (baseline) and after intravenous injection of vehicle or PCC (25 U/kg or 50 U/kg) in rivaroxaban 2 mg/kg pretreated rats 1 minute after the start of bleeding. Values are presented as mean ± standard error of the mean (n=7 for rivaroxaban + vehicle and n=10 for rivaroxaban + PCC). ** $p<0.01$ versus baseline, † $p>0.05$ (no difference with baseline).

- ◆ PCC 50 U/kg almost completely normalized rivaroxaban-induced bleeding time prolongation to 1.5±0.4-fold (242±56 seconds versus baseline [165±6 seconds]; $p>0.05$ versus baseline). PCC 25 U/kg had no effect on increased bleeding time (Figure 2)

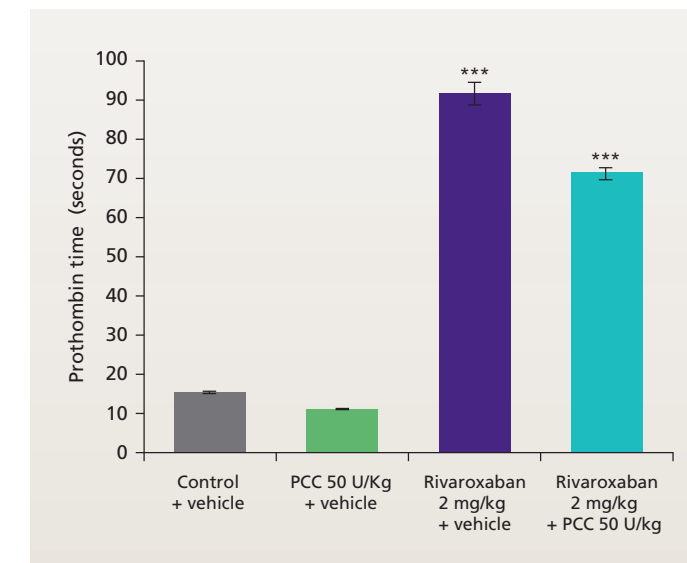


Figure 3. Effect of PCC 50 U/kg on rivaroxaban-induced prolongation of prothrombin time in rats. Values are presented as mean ± standard error of the mean (n=10). *** $p<0.001$ versus control.

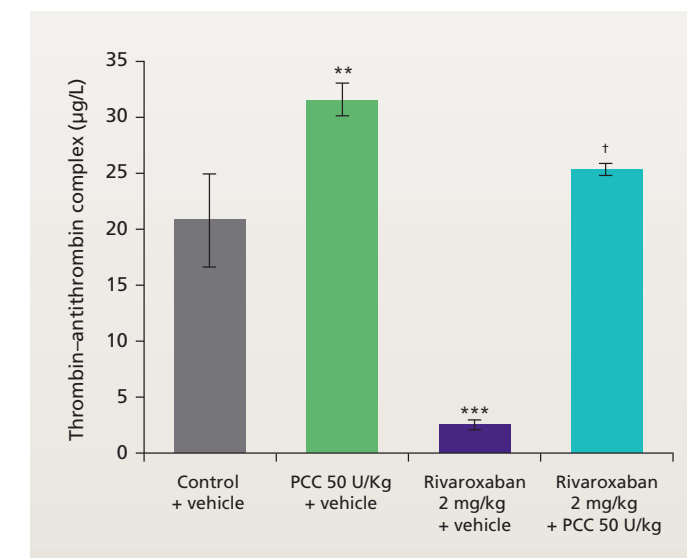


Figure 4. Effect of PCC 50 U/kg on rivaroxaban-induced inhibition of thrombin generation in rats. Values are presented as mean ± standard error of the mean (n=10). ** $p<0.01$, *** $p<0.001$ versus control, † $p>0.05$ (no difference with control).

Conclusions

- ◆ Prothrombin complex concentrate 50 U/kg reversed the anticoagulant effects of high-dose rivaroxaban in rats by reducing bleeding time and completely reversing the inhibition of thrombin-antithrombin complex formation
- ◆ Prothrombin complex concentrate may have the potential to reverse bleeding caused by high doses of rivaroxaban, if necessary

- ◆ Rivaroxaban alone significantly increased prothrombin time compared with control (91±3 seconds versus 14.4±0.3 seconds, respectively; $p<0.001$); co-administration of PCC 50 U/kg partially reversed rivaroxaban-induced prothrombin time prolongation (71±2 seconds) (Figure 3)
- ◆ Thrombin-antithrombin complex levels were significantly decreased by rivaroxaban compared with control (3±0.3 µg/mL versus 21±4 µg/mL, respectively; $p<0.001$); co-administration of PCC 50 U/kg completely reversed the inhibition of thrombin formation (thrombin-antithrombin complex: 25±1 µg/mL) (Figure 4)

References

1. Perzborn E et al. *J Thromb Haemost* 2005;3:514–521.
2. Gerotziapas GT et al. *J Thromb Haemost* 2007;5:886–888.

Disclosure of conflict of interest

This study was supported by Bayer Schering Pharma AG and Johnson & Johnson Pharmaceutical Research & Development, L.L.C. The data contained within this poster do not support or recommend the use of rivaroxaban in indications or countries in which it is not licensed.

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