

PROTHROMBIN COMPLEX CONCENTRATE REVERSES THE EFFECTS OF HIGH-DOSE RIVAROXABAN IN RATS

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Background/Aims: Rivaroxaban, an oral, direct Factor Xa inhibitor, does not increase bleeding time (BT) over baseline at antithrombotic doses in arterial and venous thrombosis animal models; however, as with any anticoagulant, BTs may be prolonged at high doses. We investigated whether a prothrombin complex concentrate (PCC) could neutralize the anticoagulant effects of high-dose rivaroxaban. **Materials and Methods:** Mesenteric BTs were first measured at baseline in anaesthetized rats. High-dose rivaroxaban (2 mg/kg) was then injected intravenously 5 minutes before cutting the vessel. After 1 minute, the animals received either PCC (Beriplex 25 or 50 U/kg; n=10 per dose group) or vehicle (n=7). BTs were measured as time taken for continuous blood flow to cease for >30 seconds (maximum observation time: 30 minutes). Prothrombin time (PT) and thrombin-antithrombin complex (TAT) were also measured in blood taken from anaesthetized rats (n=10) that had received the same injections but had not been used for determining BT. **Results:** Rivaroxaban alone significantly prolonged BT 5.4±1.4-fold relative to baseline (861±213 seconds vs 162±10 seconds; $p<0.01$). PCC 50 U/kg almost completely normalized rivaroxaban-induced BT prolongation to 1.5±0.4-fold relative to baseline (242±56 seconds vs 165±6 seconds; $p>0.05$); PCC 25 U/kg had no effect on rivaroxaban-induced BT prolongation. Rivaroxaban alone significantly increased PT compared with control (91±3 seconds vs 14.4±0.3 seconds; $p<0.001$); coadministration of PCC 50 U/kg partially reversed rivaroxaban-induced PT prolongation (71±2 seconds; $p<0.001$ vs rivaroxaban alone). TAT levels were significantly decreased by rivaroxaban compared with control (3±0.3 µg/ml vs 21±4 µg/ml, respectively; $p<0.001$); coadministration of PCC 50 U/kg completely reversed inhibition of thrombin formation (TAT 25±1 µg/ml). **Conclusions:** PCC reversed the anticoagulant effects of high-dose rivaroxaban in rats when administered to bleeding animals, suggesting that this PCC may have the potential to reverse bleeding caused by high-doses of rivaroxaban in humans, if necessary.

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