In Vitro Reversal of the Direct Xa Inhibitor Rivaroxaban Using High Purity Factor X Concentrate (FACTOR X)

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INTRODUCTION

Rivaroxaban (Xarelto ®, Bayer) is one of a number of new specific factor Xa inhibitors. It reversibly inhibits free, prothrombinase bound and clot associated FXa. Reversal of the anticoagulant effect may be necessary in the event of a major bleed or emergency surgery. A recent study has shown that prothrombin complex concentrate (PCC) can correct the prothrombin time (PT) of rivaroxaban in healthy volunteers (Eerenberg 2011).

FACTOR X is a high purity factor X concentrate developed for the treatment of hereditary factor X deficiency. The high factor X potency and low thrombogenic potential of **FACTOR X** hypothetically make it a possible candidate for use in reversal of direct Xa inhibitors. The PT assay has been used to investigate this possibility *in vitro*.

METHODS

Study 1

Commercially available rivaroxaban calibration plasmas (Hyphen Biomed) were spiked with **FACTOR X** or a PCC and the PT measured using Neoplastine CI Plus (Stago) on the ST4.

Study 2

A 10mg Xarelto® tablet was crushed and dissolved in DMSO and then diluted in HEPES buffer to approximately 250ng/mL. This was then added to a normal pooled plasma (1/100 dilution). The rivaroxaban plasma was then spiked with FACTOR X and the PT measured using Neoplastine CI Plus (Stago) or RecombiPlasTin 2G (Instrumentation laboratory) on an ACL9000.

RESULTS

Rivaroxaban showed a concentration dependent increase in the PT times. Addition of FACTOR X reduced the PT times of the Rivaroxaban plasma (Table 1 and Figure 1).

Above 1 IU/mL added factor X there was a poor dose response, however a dose response was seen at lower doses of factor X (Table 2 and Figure 2). There was also a visible difference in the measured response between the two PT assays. This difference was similar to reported effects (Hillarp 2011).

Table 1: Prothrombin Time Results

Rivaroxaban (ng/mL)	Buffer	FACTOR X 1 IU/mL	FACTOR X 2.5 IU/mL	FACTOR X 5 IU/mL	PCC 1.9 IU/mL
0	15.6	14.8	14.2	14.6	12.7
250	33.9	29.2	26.3	28.7	23.4
480	51.6	42.1	39.4	41.3	32.9

Figure 1: Prothrombin Time Results

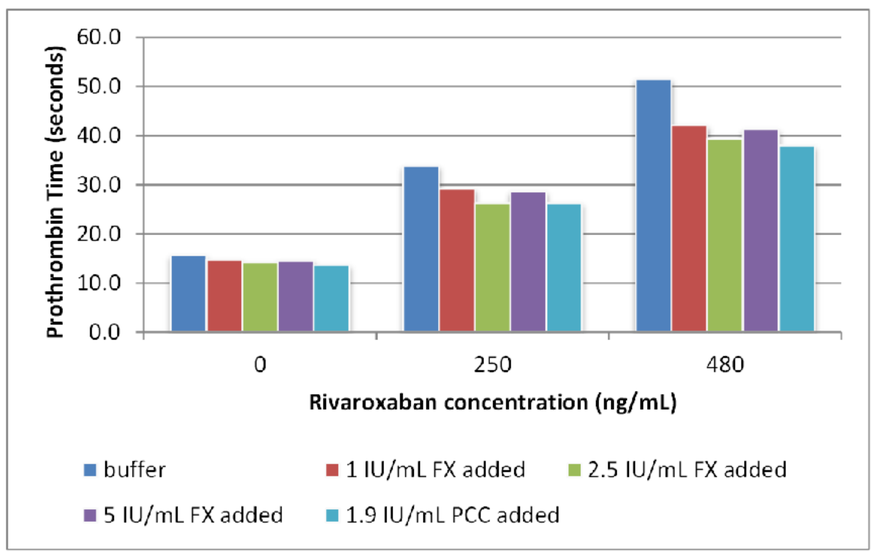
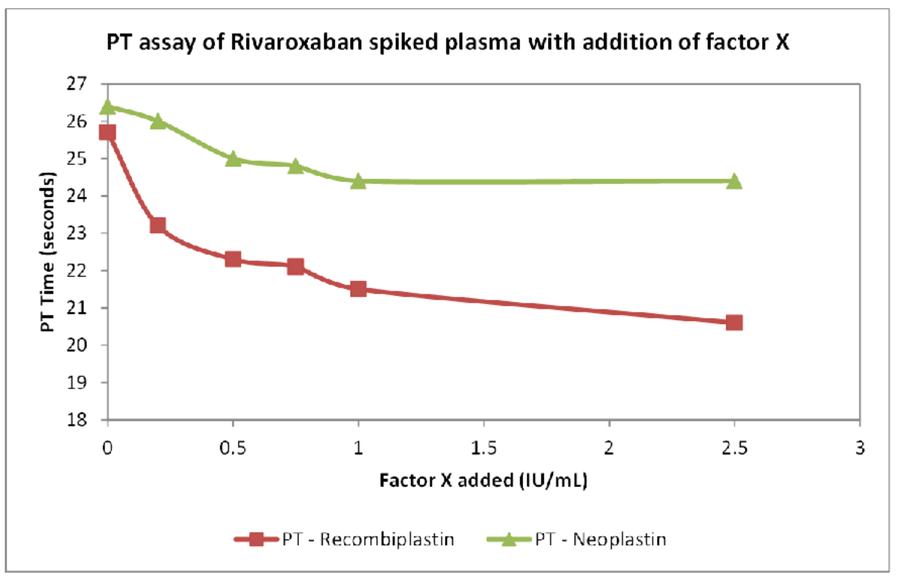


Table 2: Comparison of Prothrombin Time assays

Sample (NPP +)	RecombiPlasTin 2G			Neoplastine CI Plus		
	time (sec)	INR [1]	%	time (sec)	INR [2]	%
0.1% DMSO + buffer	11.3	0.99	101	12.3	1.02	102
Rivaroxaban+ buffer	25.7	2.27	29	26.4	2.85	32
Rivaroxaban+ FX 0.2 IU/mL	23.2	2.05	33	26.0	2.79	32
Rivaroxaban+ FX 0.5 IU/mL	22.3	1.97	35	25	2.64	34.
Rivaroxaban+ FX 0.75 IU/mL	22.1	1.95	36	24.8	2.62	35
Rivaroxaban+ FX 1.0 IU/mL	21.5	1.90	37	24.4	2.56	35
Rivaroxaban+ FX 2.5 IU/mL	20.6	1.82	39	24.4	2.56	35

[1] ISI 1.01 [2] ISI 1.34

Figure 2: Comparison of Prothrombin Time assays



CONCLUSIONS

FACTOR X reduced the PT of the rivaroxaban plasma. Partial correction to the normal range was achieved using these **FACTOR X** doses, confirming the outcomes reported for FVIIa and PCC reversal of edoxaban (Fukuda 2012).

The clinical significance of the PT dose response has yet to be demonstrated in patients anti-coagulated with factor Xa inhibitors.

This study suggests **FACTOR X** may be an effective option for reversal of direct Xa inhibitors, however clinical research is needed to confirm this.

References

Eerenberg E et al. Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate, A Randomised, Placebo-Controlled, Crossover Study in Healthy Subjects. Circulation 2011; 124: 1573-1579.

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Fukuda T et al. Reversal of anticoagulant effects of edoxaban, an oral, direct factor Xa inhibitor, with haemostatic agents. Thromb Haemostat 2012: 107: 253-259

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