Reversal of oral anticoagulation by PCC, aPCC and rFVIIa in vitro

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Background

Reversal of pharmacologic anticoagulation is an issue that arises when an anticoagulated patient has a major bleeding or when an emergency surgery needs immediate correction of coagulation. However, the new oral anticoagulants (NOAC) Rivaroxaban (anti-FXa) and Dabigatran (anti-FIIa) lack specific antidotes and only limited data is available regarding the antidotal effect of non-specific haemostatic agents. Therefore, in this ex vivo study reversal of anticoagulant activity after the administration of either 20 mg Rivaroxaban or 150 mg Dabigatran was tested in vitro using two different PCC (Beriplex®, Cofact®), aPCC (FEIBA®; factor eight inhibitor bypassing activity) or rFVIIa (NovoSeven®) at various concentrations.

Methods

Subjects

10 healthy caucasian subjects (female: n=5; male: n=5) were first randomized to receive either 20 mg Rivaroxaban, 150 mg Dabigatran or 5 mg Apixaban in one oral dose. The patients had to abide a 7-day wash-out period before administration of the respective second drug.

Methods

Citrated venous blood was taken right before (H0) and 2 hours after administration (H2) of either Dabigatran or Rivaroxaban. The potential of 4 commercially available haemostatic agents to reverse the anticoagulant effect of the NOACs was evaluated.

- Beriplex: 0.25; 0.5 (corresp. to 25 U/kg); 1; 2 U/mL
- Cofact: 0.25; 0.5 (corresp. to 25 U/kg); 1; 2 U/mL
- FEIBA:0.25; 0.5; 1 (corresp. to 80 U/kg); 2 U/mL
- NovoSeven: 1.25; 2.5; 5; 10 µg/mL (a dose of 90-100 µg/kg corresponds to a plasma level of about 2 µg/mL)

Thrombin generation in platelet-rich plasma (PRP) using Calibration Automated Thrombinography (CAT) was the primarily applied assay, along with the parameters aPTT, PT, thrombin time, Rivaroxaban- and Dabigatran levels and Ecarin time. Parameters of interest concerning the thrombin generation assay (TGA) were the endogenous thrombin potential (ETP), Peak (maximum reaction velocity) and lag time (LT; length of the latent phase). Thrombin generation in platelet poor plasma was initiated by adding 1 pM tissue factor and 4 µM phospholipids.

Results

Fig. 1A

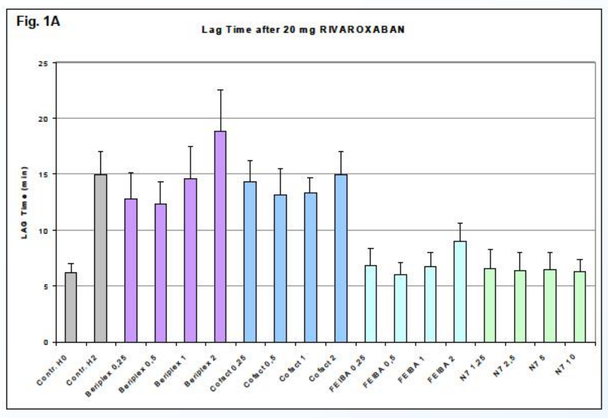


Fig. 1B

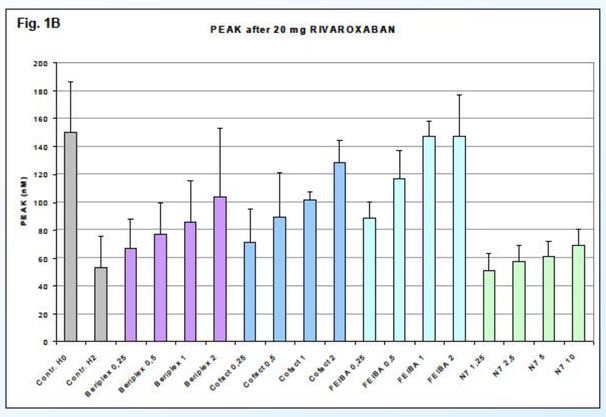


Fig. 1C

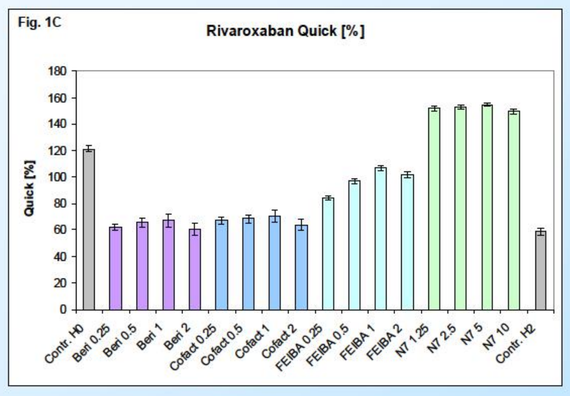


Fig. 1D

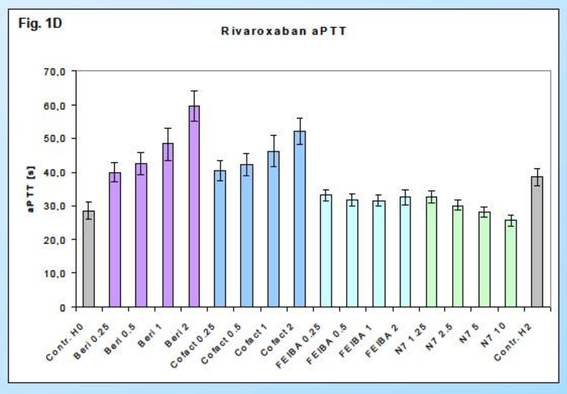


Fig. 2A

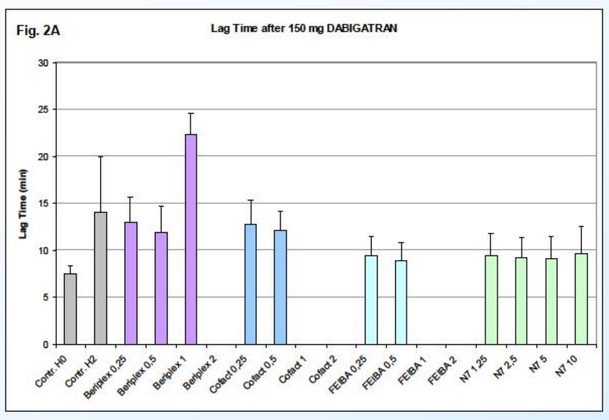


Fig. 2B

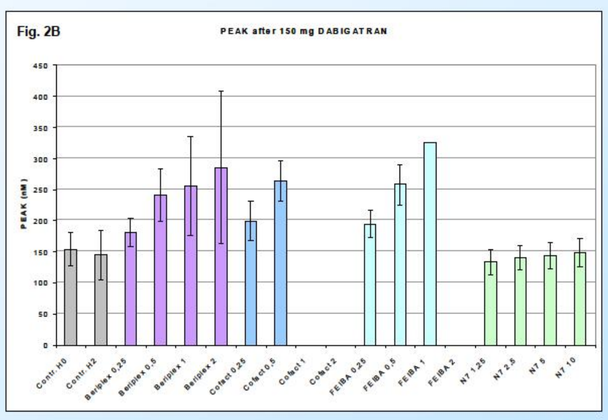


Fig. 2C

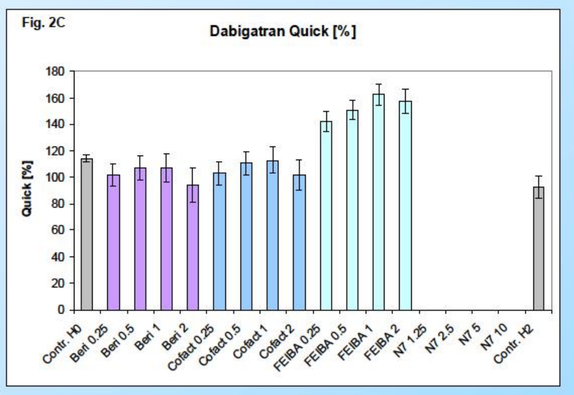


Fig. 2D

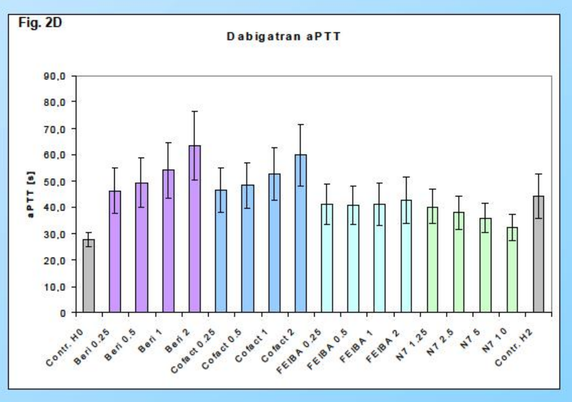


Fig. 3A

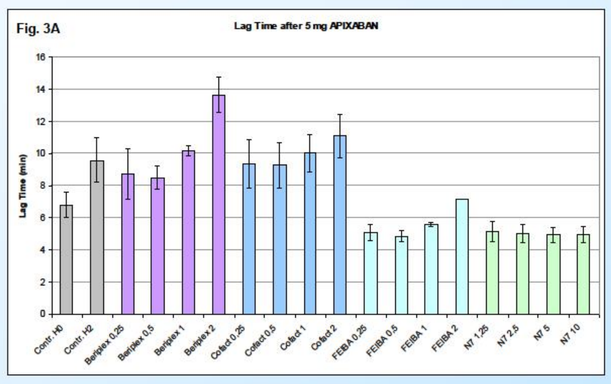


Fig. 3B

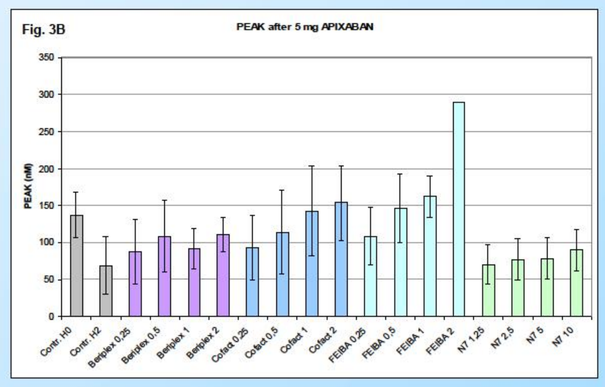


Fig. 3C

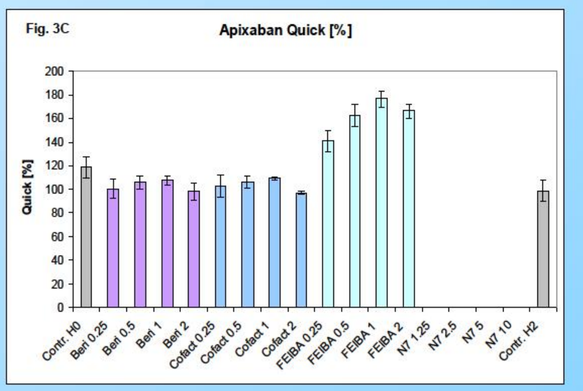
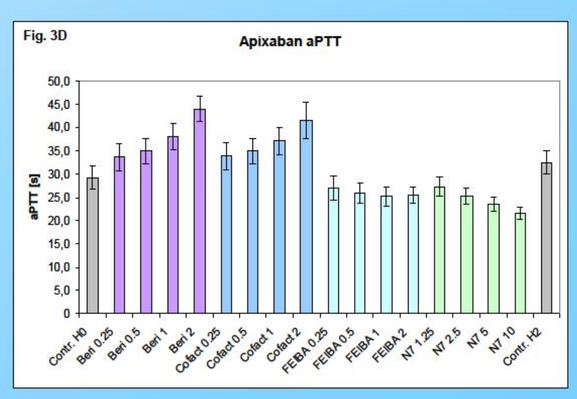


Fig. 3D



2 hours after administration (H2), the FXa-inhibitors Rivaroxaban and Apixaban showed remarkable inhibitory effects on the TGA parameters Peak and Lag time in PRP, with a more pronounced inhibitory effect on the Peak. In contrast, Dabigatran at H2 showed no effect on the Peak whereas LT was significantly prolonged.

Anticoagulant -induced (Rivaroxaban, Dabigatran and Apixaban) inhibition of Peak was reversed by FEIBA in a concentration dependent manner with an overcorrection for the Dabigatran-treated samples (Fig. 2B). Regarding anticoagulant-prolonged lag time all concentrations of FEIBA were responsible for a significant LT-reduction close to baseline (Fig. 1-3A). The PCC's Cofact and Beriplex dose-dependently increased the Peak (Fig. 1-3B) with overcorrection for the Dabigatran-samples (Fig. 2B). However, they had no antidotal effect on the lag time (Fig. 1-3A). In contrast, all concentrations of rFVIIa were responsible for a significant LT-reduction close to baseline (Fig. 1-3A), whereas rFVIIa did not correct Peak (1-3B).

Regarding clotting assays Rivaroxaban had a more pronounced effect on Quick (Fig. 1C) than on aPTT (Fig. 1D). In contrast, the FXa-inhibitor Apixaban had less effects on Quick (Fig. 3C) and aPTT (Fig. 3D) (in the tested dose of 5 mg). As expected Dabigatran produced the most pronounced effect on the aPTT (Fig. 2D).
rFVIIa and aPCC (FEIBA) showed a higher reversal effect in the clotting assays (Quick and aPTT) than the PCC's (Beriplex and Cofact). Surprisingly, at high PCC concentrations aPTT was prolonged over baseline (Fig. 1-3D) whereas Quick was not influenced (Fig. 1-3C), independent of the tested anticoagulant.

Conclusion

All tested haemostatic agents (Beriplex, Cofact, FEIBA, rFVIIa) showed significant reversal of anticoagulant activity already at low therapeutic concentrations for all tested anticoagulants (Apixaban, Dabigatran and Rivaroxaban) on thrombin generation in platelet-rich plasma. The clotting assays Quick and aPTT were not suitable to illustrate the antidotal effect of the tested haemostatic agents, especially for the PCC's Beriplex and Cofact.

WFH2014 61--P-M

Novel therapeutic agents

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DOI: 10.3252/pso.eu.WFH2014.2014

Poster presented at: WFH 2014 World Congress, Melbourne, Australia, May 11-15

PosterSessionOnline.com