FEIBA reverses the effects of a high dose of rivaroxaban in rats

Elisabeth Perzborn, Hanna Tinel
Global Drug Discovery, Cardiology Research, Bayer HealthCare AG, Wuppertal, Germany

Introduction

Rivaroxaban is a novel, oral, direct Factor Xa inhibitor in late-stage development for the prevention and treatment of thromboembolic disorders. Its antithrombotic activity has been demonstrated in several animal models of venous and arterial thrombosis at doses that do not increase bleeding time.[1] However, as with all anticoagulants, high doses of rivaroxaban can promote bleeding.[1] The activated prothrombin complex concentrate FEIBA® (Factor VIII Inhibitor Bypassing Activity; Baxter BioScience) has been found to reverse the anticoagulant activity of the direct thrombin inhibitor melagatran in rats.[2]

Objective

- To determine whether an activated prothrombin complex concentrate such as FEIBA can reverse the anticoagulant effects of a high dose of rivaroxaban using a mesenteric bleeding-time model in rats

Methods

Surgical technique

- Study drugs were injected into the jugular vein of anaesthetized male Wistar rats (250–300 g)
- Mesenteric bleeding times were measured after cutting small branched mesenteric arteries using microsurgery scissors, while the intestinal surface was superfused with warmed (37°C) 0.9% NaCl solution

Drug administrations

- Rivaroxaban was dissolved in polyethylene glycol/H_2O/glycerol (996 g/100 g/60 g) and FEIBA was dissolved in water for injection
- In one study, rats (n=10–12 per dose regimen) received rivaroxaban 2 mg/kg i.v. with FEIBA 50 or 100 U/kg i.v. or the appropriate vehicle 5 minutes before initiation of bleeding
- In a second study, rats (n=10 per dose regimen) received rivaroxaban 2 mg/kg i.v. 5 minutes before initiation of bleeding, and FEIBA (50 or 100 U/kg i.v) or vehicle 1 minute after the induction of bleeding

Bleeding time measurements

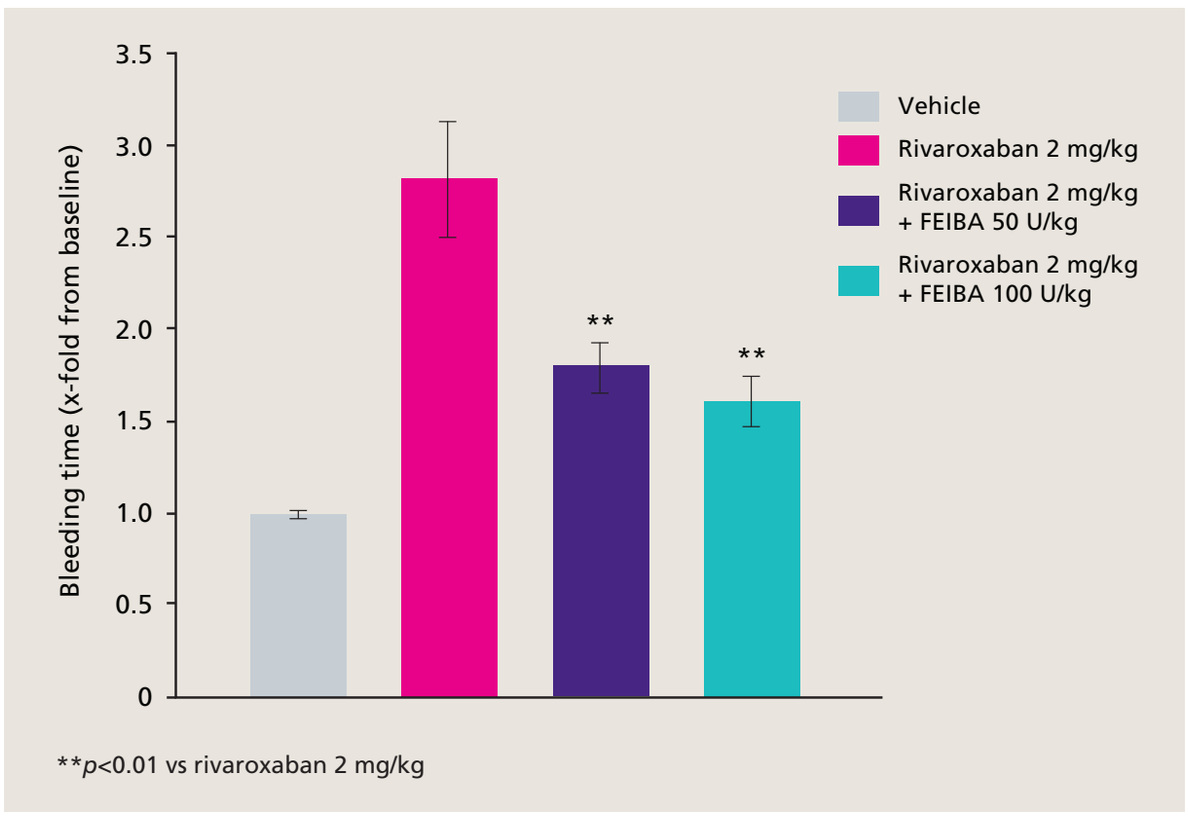
- Bleeding time was measured from the time of arterial incision to cessation of free-flowing blood from the incision
- Bleeding times were obtained from three control vessel incisions before drug administration (to calculate an average 'baseline' value)
- Bleeding time after i.v. infusion of the study drugs was determined from an incision in one artery

Prothrombin time (PT)

- In a separate study, PT was determined in platelet-poor plasma taken from rats (n=6 per dose regimen) that received the study drugs (rivaroxaban 2 mg/kg i.v. with FEIBA 50 or 100 U/kg i.v., FEIBA 50 or 100 U/kg i.v. alone, or the appropriate vehicle)
- FEIBA was administered 6 minutes after dosing with rivaroxaban, and blood samples taken 5 minutes after FEIBA administration

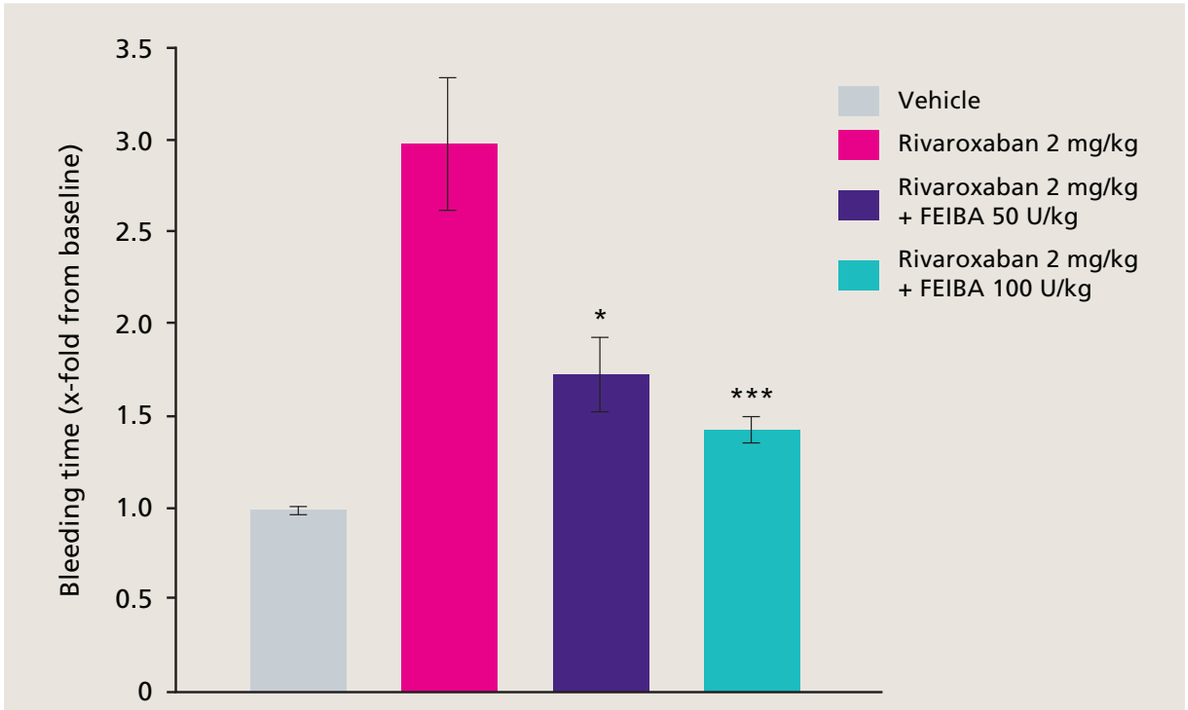
Statistical analysis

- Statistical analysis of the bleeding time data was performed using the non-parametric Mann–Whitney test
- Statistical analysis of the PT data was performed using analysis of variance followed by the Tukey's multiple comparison test
- *P*<0.05 was considered statistically significant. Data are expressed as mean± standard error of the mean (SEM)



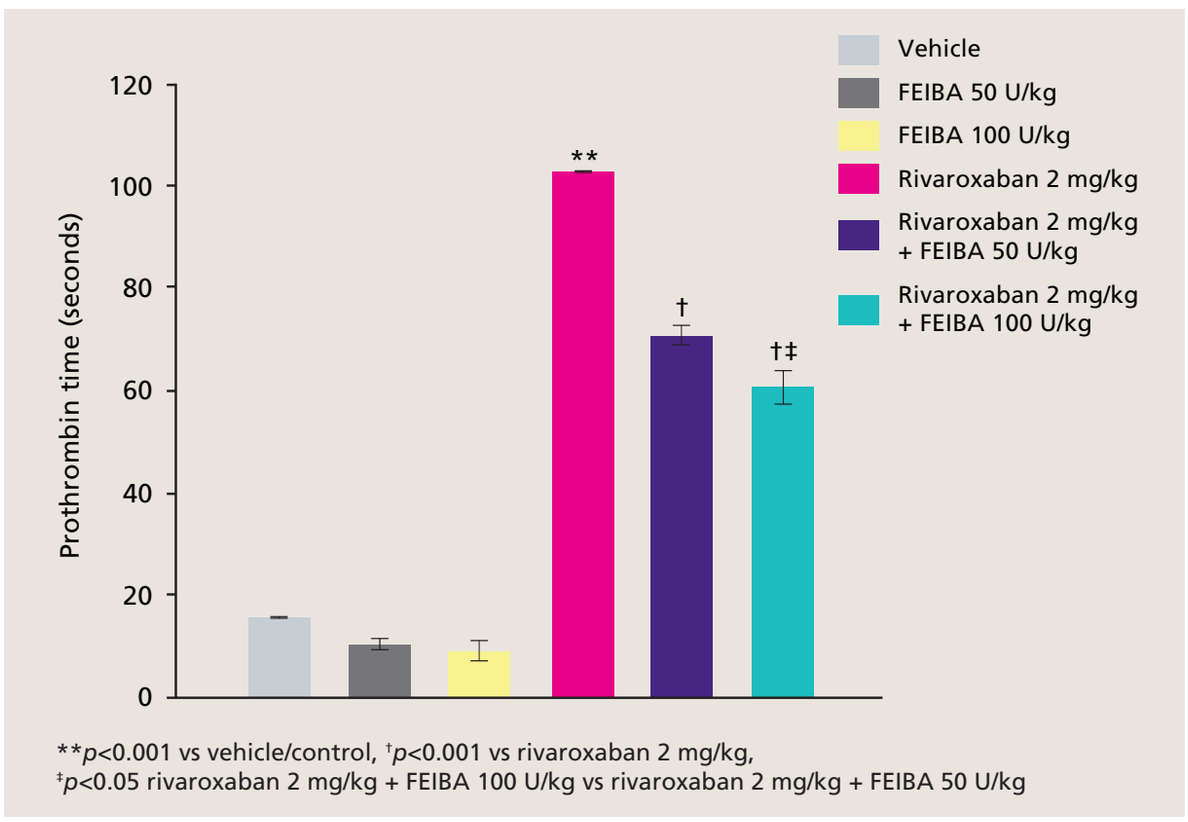
***p*<0.01 vs rivaroxaban 2 mg/kg

Figure 1. Mesenteric bleeding time after intravenous administration of both rivaroxaban and FEIBA, 5 minutes before induction of bleeding. Values are shown as mean±standard error of the mean.



**p*<0.05 vs rivaroxaban 2 mg/kg, ***p*<0.001 vs rivaroxaban 2 mg/kg

Figure 2. Mesenteric bleeding time after intravenous administration of rivaroxaban 5 minutes before induction of bleeding and FEIBA 1 minute after the start of bleeding. Values are shown as mean±standard error of the mean.



***p*<0.001 vs vehicle/control, †*p*<0.001 vs rivaroxaban 2 mg/kg,
‡*p*<0.05 rivaroxaban 2 mg/kg + FEIBA 100 U/kg vs rivaroxaban 2 mg/kg + FEIBA 50 U/kg

Figure 3. Prothombin time in seconds and with rivaroxaban 2 mg/kg i.v. and/or FEIBA 50 or 100 U/kg i.v. or the appropriate vehicle. Values are given as mean±standard error of the mean.

Results

- Administration of both rivaroxaban 2 mg/kg and FEIBA 50 or 100 U/kg 5 minutes before the mesenteric incision reduced the prolongation of bleeding time from 2.82±0.31-fold over baseline to 1.80±0.12-fold, and to 1.61±0.14-fold over baseline, respectively (Figure 1)
- FEIBA also reduced the prolongation of bleeding time associated with rivaroxaban when it was applied 1 minute after the initiation of bleeding: 50 U/kg reduced bleeding time from 2.98±0.36-fold over baseline to 1.73±0.20-fold over baseline, and 100 U/kg reduced it to 1.43±0.07-fold over baseline (Figure 2)
- Rivaroxaban 2 mg/kg significantly prolonged PT compared with vehicle: 103.5±3.4 seconds vs 15.7±0.3 seconds, respectively ($p<0.001$). FEIBA alone reduced PT, although not significantly (Figure 3)
- Rivaroxaban-induced prolongation of PT was partially and dose-dependently reversed by FEIBA (Figure 3)

Conclusions

- **FEIBA is effective in partially reversing prolonged bleeding time associated with rivaroxaban in rats, both when administered before or even after the initiation of bleeding**
- **FEIBA doses of 50 and 100 U/kg produce similar reductions in the prolongation of bleeding time associated with rivaroxaban**
- **FEIBA is effective in partially reversing prolongation of PT associated with rivaroxaban in rat plasma in a dose-dependent manner**

References and disclosures

1. Perzborn E *et al*. *J Thromb Haemost* 2005;3:514–521.
2. Elg M *et al*. *Thromb Res* 2001;101:159–170.

This study was supported by Bayer HealthCare AG. All authors are employees of Bayer HealthCare AG.
Rivaroxaban is in clinical development and not yet licensed.

Poster P061 presented at the 20th International Congress on Thrombosis (ICT), Athens, Greece; 25–28 June 2008