Haemophilia (2001), **7**, 589–591

CASE REPORT

In vivo haemostatic effects of activated prothrombin complex concentrate and recombinant factor VIIa in a haemophilia A patient with inhibitors

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Introduction

Side-effects and the lack of suitable monitoring methods complicate the treatment of inhibitor patients with activated prothrombin complex concentrates (APCC) and recombinant factor VIIa (rFVIIa; NovoSeven® Novo Nordisk, Glostrup, Denmark). To assess critically the frequently used dose-monitoring methods and to gain further insights in a possibly different thrombogenic potential, we compared the *in vivo* effects of FEIBA® (factor VIII inhibitor bypassing agent; Baxter Healthcare, CA, USA) and rFVIIa on different dose-monitoring methods (prothrombin time [PT], activated partial thromboplastin time [APTT], thrombelastography, FVII:C, FVIIa) and activation markers (thrombin–antithrombin complexes [TAT], prothrombin fragments F1 + 2, and thrombus precursor protein [TpP]) in a haemophilia A patient with inhibitors.

Case report

We investigated a 72-year-old haemophiliac with alloantibodies (inhibitor titre in Bethesda units [BU] 21 BU mL^{-1}), who normally had to use FEIBA® in very high doses (130 U kg^{-1} bodyweight [bw] twice a day) in case of bleeding. The high cost of treatment and fear of thromboembolic side-effects prompted us to look for an alternative way of treatment, and we decided on rFVIIa. A single dose of FEIBA®, followed 8 days later by a single dose of rFVIIa were applied, both preparations being given at the most commonly used dosage (i.e. FEIBA® 100 U kg^{-1} bw; rFVIIa 96 μg kg^{-1} bw). The patient did not show any signs of bleeding during the whole investigation. Blood samples were obtained before and 5, 30, 60 min, 2, 4, 8 and 24 h after infusion by venepuncture.

Discussion

Both FEIBA® and rFVIIa led to a distinct decrease of PT, APTT (Fig. 1) and r-times of TEG (data not shown). A more distinct shortening of the PT (about 1 s) after infusion of rFVIIa was caused by the much higher content of FVII in rFVIIa than in FEIBA®. A plateau of PT values after application of rFVIIa (0–2 h) was due to the insensitivity of the PT against higher doses of FVII; the PT showed a negative correlation with FVII plasma levels up to about 500% FVII:C. These values are not reflected in the PT [1]. Based on these results, the PT determination seems to be useful in the monitoring of a lower dose rFVIIa therapy, but it is questionable whether FVII:C values below 5 U mL^{-1} can effectively achieve a sufficient haemostasis. The APTT seems to be potentially useful for monitoring of rFVIIa treatment, but the APTT response to rFVIIa administration has shown a high variability among individual patients, depending on the APTT level before administration [2]. TEG has been reported to be more suitable for dose-monitoring than PT and APTT during therapy with rFVIIa because of good dose–response characteristics [3]. Nevertheless, a negative linear correlation between r-times and FVIIa activity could be seen in our investigation only up to FVIIa levels of 5–10 U mL^{-1} (data not shown), indicating that TEG should not be used for high-dose rFVIIa treatment. Better, but also more laborious monitoring methods of rFVIIa therapy seem to be the determination of FVII:C or FVIIa activity. The timecourse of FVII:C seemed to reflect the pharmacokinetic properties of rFVIIa in a better way than PT, APTT or TEG (Fig. 2). Therefore, the sensitivity of the FVII:C determination to

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Accepted 17 September 2001

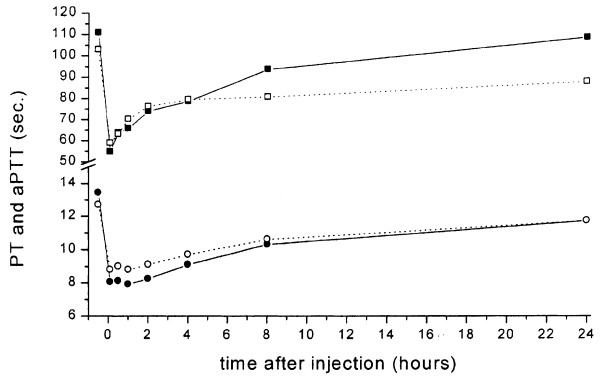

Fig. 1. PT (○) and APTT (□) before and after the application of FEIBA® (100 U kg^{-1} bw), PT (●) and APTT (■) before and after the application of rFVIIa (96 μg kg^{-1} bw) in a haemophilia A patient with alloantibodies.

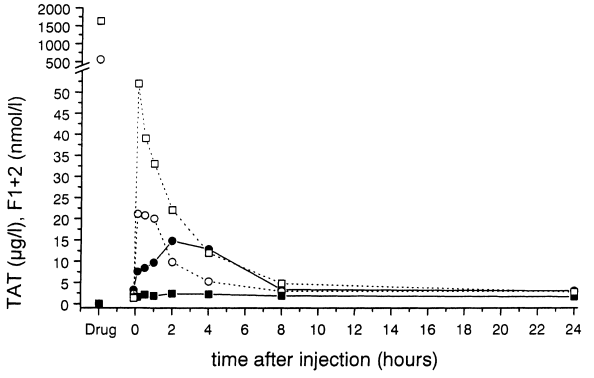

Fig. 3. TAT (○) and F1 + 2 levels (□) before and after the application of FEIBA® (100 U kg^{-1} bw), TAT (●) and F1 + 2 levels (■) before and after the application of rFVIIa (96 μg kg^{-1} bw) in a haemophilia A patient with alloantibodies.

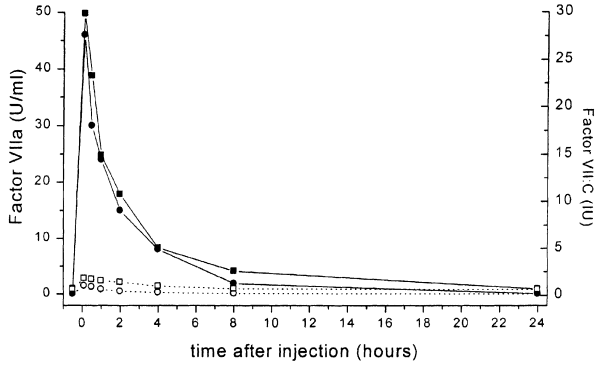

Fig. 2. FVII:C (□) and FVIIa activity (○) before and after the application of FEIBA® (100 U kg^{-1} bw), FVII:C (■) and FVIIa activity (●) before and after the application of rFVIIa (96 μg kg^{-1} bw) in a haemophilia A patient with alloantibodies.

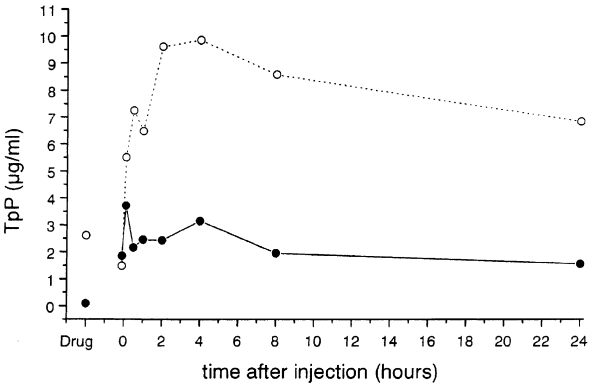

Fig. 4. TpP levels before and after the application of FEIBA® (○) (100 U kg^{-1} bw) and rFVIIa (●) (96 μg kg^{-1} bw) in a haemophilia A patient with alloantibodies.

thromboplastin, FVII-deficient plasma, standards and dilution buffer used has to be considered.

In spite of the short half-life of rFVIIa (about 2.4 h) [1], comparable effects with FEIBA® on PT, APTT and TEG could be observed in our investigation up to 4–8 h after infusion. In contrast, the empirically established application intervals of FEIBA® and rFVIIa differ considerably (FEIBA® 6–12 h; rFVIIa 2–4 h). This fact is in accordance with the observation that no significant correlation between PT and APTT values on the one hand, and the clinical outcome of patients treated with rFVIIa on the other hand, have been observed [2]. In conclusion, it remains questionable whether PT, APTT and TEG can be used to reflect the efficacy of the preparations. Nevertheless, a possible prolongation of the application interval of rFVIIa or shortening of the interval of FEIBA® needs further investigation.

The most important side-effect of inhibitor-bypassing preparations is the occurence of thromboembolic events. TAT, F1 + 2 and TpP levels obtained were substantially higher after infusion of FEIBA® than after rFVIIa (Figs 3 and 4). This can be explained by a postulated mechanism in which activity of rFVIIa is localized at the site of injury and at low doses of rFVIIa, depends on tissue factor (TF) or is TF-independent, on the surface of activated platelets [4]. In contrast to rFVIIa, APCCs cause a generalized activation of coagulation by an FXa-mediated prothrombin activation [5]. However, as already described for F1 + 2 [6], discrete increases of activation markers could also be observed after infusion of rFVIIa, querying the model of a solely local coagulation activation. FEIBA® itself, but not rFVIIa, reveals extremely high concentrations of TAT and F1 + 2. These

exogenously added proteins largely contribute to the rapid increase of the activation peptides after infusion of FEIBA®. Therefore, TAT and F1 + 2 should not be used as markers for the assessment of hypercoagulability in FEIBA® therapy. In contrast to TAT and F1 + 2, the TpP content of FEIBA® is very low, and any time-delayed increase of TpP observed should hence be caused by an *in vivo* activation of coagulation. TpP is an ELISA-based method to measure soluble fibrin polymers, the ultimate soluble precursors of fibrin [7]. It seems to be the most appropriate activation marker for the assessment of hypercoagulable states in therapy with FEIBA®. TpP may even more strongly reflect a clinical relevant activation of coagulation [8], and therefore could indicate a higher *in vivo* thrombogenicity of FEIBA®.

Conclusion

Although an investigation in one patient can not answer all questions, we suggest that further efforts should be made to evaluate appropriate dose-monitoring methods for rFVIIa and FEIBA® therapy. However, it remains questionable whether PT, APTT or TEG are able to reflect the efficacy of the preparations. Furthermore, it could be argued that TAT and F1 + 2 should not be used as activation markers in FEIBA® therapy. As clinically and theoretically assumed, TpP values indicated a lower thrombogenic potential of rFVIIa compared to FEIBA®.

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