Vox Sanguinis

Vox Sang 1998;75:72–73

Factor VII and Activated Factor VII Content of Prothrombin Complex Concentrates

H. Fiedler
Münster, Germany

Hellstern et al. [1] compared the activated factor VII (FVIIa) content of a prothrombin complex concentrate (PCC) that had been involved in three fatal thromboembolic complications with that of another licensed PCC whose complication rate the authors did not impart. They found higher FVIIa values in the first-mentioned preparation. From this observation, the authors concluded that higher FVIIa potencies may contribute to the thrombogenic potential of PCC. Such an inference seems to me to be at variance with the well-established theory that FVIIa in the absence of tissue factor (TF) is not thrombogenic at all [e.g. 2], while in the presence of TF nonactivated FVII is converted into FVIIa within a few seconds [3]. This theoretical consideration is not ruled out by the result of the above-mentioned comparison.

Occasionally, cases of acquired prothrombin complex factor deficiency are due to (or accompanied with) a more or less compensated intravascular activation of the clotting cascade, e.g. by TF exposed to the bloodstream. Under such circumstances, any replenishment of the intravascular FVII pool, even with nonactivated FVII, can lead to the decompensation of the local or disseminated intravascular coagulation process, followed in the worst case by local thrombosis and/or disseminated intravascular coagulation. Therefore, in order to avoid a possible selection bias, the choice of PCC preparations for assessing putative markers of *irregular* (i.e. TF-independent) thrombogenicity should principally be confined to preparations that were involved in thrombogenic events in patients without preexisting elevations of activation markers. The authors did not provide information on how they circumvented this kind of a possible selection bias. Consequently, the utmost inference that can be drawn from the article is that it remains to be determined whether a high FVIIa content of a PCC can make it irregularly thrombogenic.

References

1 Hellstern P, Beeck H, Fellhauer A, Fischer A, Faller-Stöckl B: Factor VII and activated-factor-VII content of prothrombin complex concentrates. Vox Sang 1997;73:155–161.
2 Morrissey JH: Tissue factor interactions with factor VII: Measurement and clinical significance of factor VIIa in plasma. Blood Coagul Fibrinolysis 1995;6/1:S14–S19.
3 Seligsohn U, Østerud B, Rapaport SI: Coupled amidolytic assay for factor VII: Its use with a clotting assay to determine the activity state of factor VII. Blood 1978;52:978–988.

Dr. Harald Fiedler
Stellmacherweg 5
D–48161 Münster (Germany)

Authors' Reply

P. Hellstern, H. Beeck
Institut für Hämostaseologie und Transfusionsmedizin
Klinikum Ludwigshafen GmbH, Ludwigshafen, Germany

Dr. Fiedler claims that it makes no difference whether native factor VII (FVII) or activated factor VII (FVIIa) is infused to patients. It is true that FVIIa by itself has only little proteolytic activity [1]. However, there are several findings indicating that even low levels of FVIIa, but not FVII may serve as a priming function for triggering the clotting cascade [2]. It has been shown that FVIIa at picomolar concentrations can effectively activate FVII bound to tissue factor (TF) [3]. FVIIa itself rapidly forms complexes with TF and phospholipids that are able to activate factors IX and X efficiently. Trace amounts of TF are detectable in the plasma of normal individuals, and substantial amounts of TF exposed to the bloodstream are found in arterial and venous thromboembolism and in disseminated intravascular coagulation (DIC) [4].

It is an important fact that, in contrast to recombinant FVIIa and activated prothrombin complex concentrates (PCC), nonactivated PCC are commonly not administrated to patients with hereditary coagulation factor deficiencies. With the rare exception of hereditary deficiencies of factors II, VII, and X, PCC are used for replacement of vitamin K-dependent clotting factors and inhibitors in liver disease and phenprocoumon or warfarin overdose. Patients suffering from liver disease are prone to DIC. Rapid reversal of oral anticoagulation is accompanied by the risk of recurrent thromboembolism as a consequence of a hypercoagulable state found in most of these patients. Hence, the suggestion of Dr. Fiedler to restrict observations dealing with thrombogenicity to patients without activated hemostasis cannot be accepted, since this would lead to a dangerous underestimation of the thrombogenic potential of PCC.

In spite of the fact that exact features and mechanisms determining thrombogenicity of PCC are presently unknown, it is well conceivable that DIC or hypercoagulability may be deteriorated by PCC containing high activities of activated clotting factors including FVIIa [5]. However, the PCC involved in thromboembolic complications in Germany had further features which are thought to be associated with thrombogenicity. This preparation contained not only high FVIIa potencies, but was also substantially overloaded with FII, while being free of antithrombin and protein S activity [6, 7].

In a previous comparative study, the preparation in question had already attracted attention by causing severe cardiovascular complications in rabbits [8]. The lots involved in these complications were also overloaded with prothrombin and free of antithrombin. Meanwhile, one life-threatening and seven fatal complications associated with the use of this PCC have been observed in Germany [6, 7, Köhler et al.: unpubl. data]. This arouses strong suspicion of a causal relationship, particularly since no fatal complications have been reported in Germany after the application of other licensed PCC during the last 10 years.

KARGER
E-Mail karger@karger.ch
Fax +41 61 306 12 34
www.karger.com

0042–9007/98/0751–0072 $15.00/0

Accessible online at:
http://BioMedNet.com/karger