

LIVER, PANCREAS, AND BILIARY TRACT

Recombinant Factor VIIa Corrects Prothrombin Time in Cirrhotic Patients: A Preliminary Study

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Background & Aims: Cirrhotic patients with a prolonged prothrombin time (PT) are known to have low levels of factor VII. Because the current modalities to correct this problem are not ideal, recombinant factor VIIa (rFVIIa) may be useful in correcting the prolonged PT observed in the coagulopathy of cirrhosis. The aim of this study was to evaluate the effectiveness of rFVIIa in nonbleeding volunteer patients with the coagulopathy of cirrhosis. **Methods:** A preliminary, single-center, dose-escalation trial was performed. Cirrhotic patients with a PT of >2 seconds above the upper limit of the reference value received an intramuscular injection of vitamin K. Ten patients whose PT did not correct to within 2 seconds above the control of the upper limit of the reference value were given three successive dosages of rFVIIa (5, 20, and 80 µg/kg) during a 3-week period. **Results:** The mean PT transiently corrected to normal in all three dosage groups. No adverse effects were noted. There was no evidence of the induction of disseminated intravascular coagulation. **Conclusions:** This preliminary trial shows rFVIIa to be effective in transiently reversing the prolonged PT in a select group of nonbleeding cirrhotic patients. These preliminary observations support conducting a large-scale efficacy trial.

The coagulopathy of cirrhosis is a leading factor contributing to the high morbidity and mortality associated with liver disease in the United States.^{1,2}

The liver is the principal site of synthesis and clearance of coagulation factors, components of the fibrinolytic system, and naturally occurring anticoagulants. The most frequently encountered hematologic abnormalities in cirrhotic patients include thrombocytopenia, a prolonged prothrombin time (PT), and hyperfibrinolysis.³ Cirrhotics with low platelet counts and/or prolonged PTs generally do not experience spontaneous bleeding. These patients are, however, at increased risk of severe bleeding episodes from routine procedures, such as dental extractions and liver biopsies. Variceal bleeding, a common

complication of cirrhosis, carries a worse prognosis in cirrhotic patients with an underlying coagulopathy.⁴ Unfortunately, the treatment and prevention of bleeding episodes in cirrhotic patients with prolonged PTs remains unsatisfactory because treatment does not correct the underlying defect.

Patients with cirrhosis and a prolonged PT have been shown to have low levels of factor VII.⁵ Recombinant factor VIIa (rFVIIa) was developed for the treatment of bleeding in patients with hemophilia A and B with inhibitors against factors VIII and IX, respectively.⁶⁻⁹ It is manufactured by a recombinant DNA technique and is identical in structure and activity to human factor VII.¹⁰ rFVIIa has been shown to induce hemostasis in dogs with hemophilia A and B.¹¹ Its clinical utility has been shown in reducing prolonged PTs in acenocoumarol-treated healthy volunteers,^{12,13} in the treatment of hemophilia, and in congenital factor VII-deficient patients with critical bleeding episodes or who require major surgery.¹⁴⁻²⁵

Previous data indicate that treatment with rFVIIa may be useful in patients with liver disease who have altered synthesis of vitamin K-dependent coagulation factors, as well as dysfibrinogenemia and depressed levels of other clotting factors. Therefore, our aim was to evaluate the safety, pharmacokinetics, and efficacy of rFVIIa in correcting the prolonged PT in nonbleeding patients with cirrhosis.

Materials and Methods

Patients

Thirteen consecutive cirrhotic patients with PTs of >2 seconds above the upper limit of the reference value were

Abbreviations used in this paper: aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; FFP, fresh frozen plasma; PT, prothrombin time; rFVIIa, recombinant factor VIIa.

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screened at the University of Miami School of Medicine Hospital System during the period of February 1995 through March 1995.

Subjects were eligible for inclusion if they (1) had a PT of ≥ 2 seconds above the upper limit of the reference value; (2) had advanced liver disease or presumed liver cirrhosis, defined as Child's score of B or C; (3) were ages 18 years or older; and (4) were able to provide informed consent before screening.

Patients were excluded if they had any of the following: (1) a known hypersensitivity to vitamin K or rFVIIa or any of its components; (2) any overt bleeding, including active bleeding from the gastrointestinal tract; (3) treatment with prothrombin-complex concentrates within 7 days before screening; (4) treatment with 1-desamino-8-D-arginine vasopressin or anti-fibrinolytics within 3 days before screening; (5) an α -fetoprotein level of greater than two times normal within 3 months of screening; (6) a positive pregnancy test result; (7) known malignant disease, including hepatocellular carcinoma; (8) myocardial infarction or stroke within 6 months of screening or advanced atherosclerosis; (9) serum creatinine of > 2 mg/dL; or (10) a positive human immunodeficiency virus antibody test.

Study Design

The study was a single-center, dose-escalation trial with each subject receiving three injections of rFVIIa. The study duration was 24 days per patient. At screening (day 1), a physical examination of each patient, including a complete patient history, was performed, and informed consent was obtained. Serum electrolytes, liver chemistries, complete blood count, α -fetoprotein, PT, factor IX, factor X, prothrombin, protein C, and human immunodeficiency virus antibody were assessed. A serum pregnancy test was performed on all women.

One week after screening (day 8), all subjects with an initial PT of > 2 seconds above the upper limit of the reference value had a repeat PT. Safety data that included vital signs, discussion of adverse reactions, and laboratory testing were obtained. Laboratory testing included a platelet count, fibrinogen, fibrinopeptide A, D-dimer, antithrombin III, and prothrombin fragment 1 + 2. All patients who continued to have a PT of > 2 seconds above the upper limit of the reference value were given a 10-mg intramuscular dose of vitamin K.

On day 10 (2 days after the vitamin K injection), the PT was retested, and those subjects whose PTs remained 2 seconds above the upper limit of the reference value were eligible to receive the initial dose of 5 μ g/kg body wt rFVIIa. Before intravenous injection of rFVIIa, blood for the following analyses was drawn: serum electrolytes, liver chemistries, complete blood count, PT, activated partial thromboplastin time, coagulation factor VII:C, factor IX, factor X, prothrombin (factor II), platelets, fibrinogen, antithrombin III, D-dimer, fibrinopeptide A, and prothrombin fragment 1 + 2 (F1 + 2). Platelets, fibrinogen, antithrombin III, D-dimer, fibrinopeptide A, and F₁₊₂ were followed up for 8 hours after rFVIIa injection. This procedure was repeated on days 17 and 24 with injections of 20 wt and 80 μ g/kg body wt rFVIIa, respectively. All blood

samples were drawn by a direct venipuncture with a 20-gauge needle from the opposite arm used for the injection of rFVIIa. The tourniquet time for the drawing of all blood samples at a given time was < 1 minute per blood draw.

This protocol was approved by the Institutional Review Board at the University of Miami School of Medicine.

Materials

rFVIIa (NovoNordisk, Copenhagen, Denmark) was supplied as a powder for injection preparation in 2-mL vials. The preparation contains no foreign proteins, and each vial was reconstituted immediately before use in 2.2 mL sterile water. Reconstituted rFVIIa contains 0.6 mg/mL rFVIIa (1.2 mg/2 mL). rFVIIa was administered as a slow intravenous injection during 2 minutes.

Coagulation Assays

PT and activated partial thromboplastin time (aPTT) were analyzed in an ACL 1000 Automated Coagulation Laboratory (Lexington, MA) using IL PT-fibrinogen and IL aPTT reagents according to the manufacturer's instruction. The normal range for aPTT is 26–36.2 seconds. The normal range for PT is 11.8–14.4 seconds. Platelet counts were measured according to the routine technique (H-2 Technicon; Bayer Corp., Tarrytown, NY). The normal range is 150,000–400,000 per milliliter. Fibrinogen was analyzed in a Fibrometer by the method of Clauss.²⁶ The normal range is 1.8–4.0 g/L. Antithrombin III was analyzed using Actichrome AT anti-IIa chromogenic antithrombin activity kit from American Diagnostica Inc. (Greenwich, CT).²⁷ The normal range is 60%–140%.

Coagulation factor VII was measured in a one-stage clotting method using factor VII-deficient plasma as a test base and rabbit thromboplastin in an ACL 300/3000 instrument as described previously.²⁸ The normal range is 0.54–1.23 U/mL (1 U/mL = 100%). D-dimers were analyzed using Dimertest Gold EIA kit from American Diagnostica Inc.²⁹ The normal range is < 0.5 μ g/mL. Fibrinopeptide A was analyzed using Asserachom FPA from Diagnostiga Stago (American Bioproducts Co., Parsippany, NJ).³⁰ The normal range is ≤ 3 ng/mL. Fragment 1 + 2 was analyzed using Dade Prothrombin Fragment 1 + 2 enzyme-linked immunosorbent assay kit from Baxter Diagnostics Inc. (Miami, FL).³¹ The normal range is ≤ 1.2 nmol/L. Coagulation factor X and prothrombin (factor II) were analyzed using factor X- and factor II-deficient plasma, respectively, in the PT method.³² The normal range for factor X is 60%–100%, whereas that for factor II is 60%–150%. Coagulation factor IX was analyzed using factor IX-deficient plasma in the aPTT method.³³ The normal range is 60%–100%. Protein C was analyzed in a Fibrometer using Anticlot C kit from American Diagnostica Inc.³⁴ The normal range is 72%–106%.

Statistics

All statistical analyses were performed using programs of the SAS Institute (SAS User's Guide: Statistics Version 6;

Table 1. Patient Characteristics

Patient	Sex	Age (yr)	Liver disease	Child-Pugh	Initial PT (s) (NL, 11–14.4 s)
1	F	39	HCV	B	17.4
2	M	29	HBV	C	20.6
3	M	51	NASH	B	16.4
4	M	44	HCV	B	17.7
5	F	29	AIH	C	22.1
6	M	48	HCV	C	16.6
7	M	57	HCV	C	18.8
8	M	40	ETOH	C	19.4
9	M	62	ETOH	C	28.9
10	M	46	HCV	C	16.8

AIH, autoimmune hepatitis; ETOH, alcoholic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; NL, normal.

SAS Institute Inc., Cary, NC). A three-factor analysis of variance (ANOVA) was performed using dose of the experimental drug as one factor, time after treatment as the other factor, and subject as the blocking factor. To compare the means at the various time periods within a dose level, Bonferroni multiple comparison procedure was used.

Results

Patient Characteristics

Ten of 13 cirrhotic patients screened met the entry criteria and were enrolled in the trial. The mean subject age was 45 years (range, 29–62 years). Eight patients were men, and 2 were women. Three subjects were Child's B cirrhotics, and 7 were Child's C cirrhotics. The etiology of cirrhosis was as follows: 5 with hepatitis C; 2 with alcoholic liver disease; and 1 each with autoimmune hepatitis, hepatitis B, and nonalcoholic steatohepatitis (Table 1). Initial hematologic data are shown in Table 2. All 10 patients had plasma levels of factor VII below the normal range. A more inconsistent pattern was observed for factors II, IX, and X. Nine of the 10 patients completed the trial. One patient, subject 8, received the 5- and 20- $\mu\text{g}/\text{kg}$ dosages of rFVIIa. In the period between the 20- and 80- $\mu\text{g}/\text{kg}$ dose, a suitable donor liver became available, and this subject successfully underwent a liver transplantation.

Table 3. Mean PT^a With Administration of rFVIIa

Dose ($\mu\text{g}/\text{kg}$)	Predose PT	Postdose PT						
		10 min	30 min	2 h	4 h	6 h	8 h	12 h
5	20.9	12.1	12.7	14.6	16.7	17.9	18.2	18.7
	(17.1–31)	(9.9–15.2)	(10.4–16.1)	(12.9–18.2)	(14.2–23)	(14.8–24)	(15.2–24)	(14.5–23.8)
20	20.5	12.3	12.4	13.7	14	15	15.6	16.8
	(17–31.2)	(9.4–13.9)	(9.3–14.7)	(10.5–17.7)	(11.4–17.7)	(12.1–19.4)	(12.1–20.7)	(14.8–19.2)
80	20.2	9.9	10	10.7	11.1	11.8	13.6	14.2
	(17.1–28.6)	(8.6–11.1)	(8.7–11.9)	(9–18)	(9.3–13.1)	(9.9–13.7)	(10.1–14.6)	(11.3–17.8)

NOTE. PT ranges are in parentheses.

^aNormal range, 11–14 seconds.

Table 2. Initial Hematologic Data Before Initial Administration of rFVIIa

Patient	Factor VII (U/mL)	Factor IX (%)	Factor X (%)	Prothrombin (%)	Protein C (%)
Normal	0.54–1.23	60–100	60–100	60–150	72–106
1	0.4	94.5	67	88	35
2	0.37	64	61	63	36
3	0.24	30	86	40	15.6
4	0.25	52.5	49	42	31
5	0.38	22	49	29	19.2
6	0.23	27.8	66	40	26
7	0.26	36	60	32.1	11.6
8	0.11	73	54.5	70	14.8
9	0.45	21.7	28	16.7	8.2
10	0.2	23	46	32	29

PT

The PTs are shown in Table 3. The period of time during which the PT normalized showed a dose-dependent pattern. After a dose of 5 $\mu\text{g}/\text{kg}$, the mean PT normalized for 2 hours ($P < 0.0001$); after 20 $\mu\text{g}/\text{kg}$ for 6 hours ($P < 0.0001$); and after 80 $\mu\text{g}/\text{kg}$ for 12 hours ($P < 0.0001$) (Figure 1).

aPTT

As shown in Figure 2, aPTT shortened significantly after rFVIIa administration in doses of 20 and 80 $\mu\text{g}/\text{kg}$ ($P < 0.05$). Although the aPTT normalized after administration of the 20- and the 80- $\mu\text{g}/\text{kg}$ doses, no normalization occurred after administration of 5 $\mu\text{g}/\text{kg}$. The levels found before the 80- $\mu\text{g}/\text{kg}$ dose varied with a range of 32–71 seconds. One patient with an initial aPTT of 71 seconds resulted in a higher baseline value for the 80- $\mu\text{g}/\text{kg}$ patient group.

Platelets, Fibrinogen, and Antithrombin III

No statistically significant changes were observed in the platelet count, fibrinogen, or antithrombin III at any dose level.

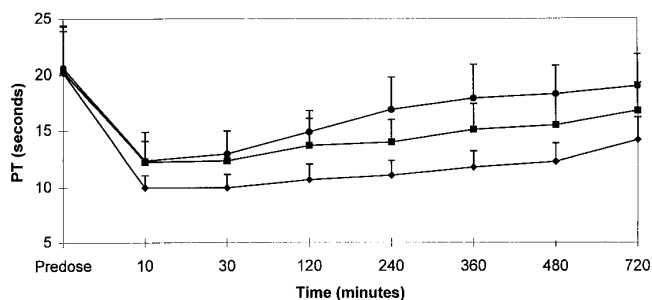


Figure 1. PT values at predose of rFVIIa and at 10, 30, 120, 240, 360, 480, and 720 minutes after the dose of rFVIIa. The doses of rFVIIa were 5 (●), 20 (■), or 80 µg/kg (◆).

Factor VII

Factor VII levels increased in a dose-dependent manner (Figure 3), which correlated well with the shortening of PTs. The pharmacokinetic parameters, clearance, mean residence time, and half-life were independent of dose ($P > 0.05$), whereas the maximum drug concentration in plasma and the area under the curve increased linearly with the dose (Table 4).

D-Dimer

The mean predose levels varied between the dose groups, showing lower levels on days 10 and 17 (predose, 20 and 80 µg/kg, respectively). These wide ranges were caused by a large variation between the patients and also a large inpatient variation. Thus, 2 patients had extremely high D-dimer levels, 1220 and 980 ng/mL, respectively, before any rFVIIa was administered (predose, 5 µg/kg). These 2 patients had decreasing levels throughout the observation time after having been administered 20 and 80 µg/kg of rFVIIa.

The only significant increases in D-dimer levels were found at 6 and 8 hours after the administration of 80 µg/kg rFVIIa ($P < 0.0001$) (Figure 4). However, the SD was high. Three of 8 patients examined at 8 hours after the administration of the 80-µg/kg dose had de-

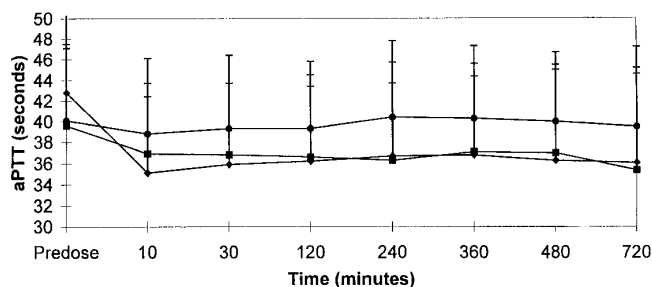


Figure 2. aPTT values at predose of rFVIIa and at 10, 30, 120, 240, 360, 480, and 720 minutes after the dose of rFVIIa. The doses of rFVIIa were 5 (●), 20 (■), or 80 µg/kg (◆).

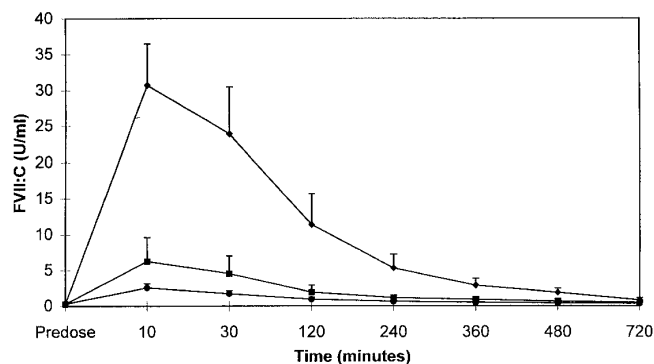


Figure 3. Plasma levels of coagulation factor VII (FVII:C) (in U/mL) after injection of various doses of rFVIIa (5 [●], 20 [■], or 80 µg/kg [◆]) at 10, 30, 120, 240, 360, 480, and 720 minutes after the injections were given.

creased D-dimer levels compared with the first predose levels.

Fibrinopeptide A

Predose levels of fibrinopeptide A varied in the three dose groups (Figure 5). As for the D-dimer levels, the variation between patients was extensive. After doses of 20 and 80 µg/kg, significant increases in fibrinopeptide A were observed at 6 hours after the administration. After 80 µg/kg, the lowest predose mean value significantly increased at 30 minutes and 4 and 8 hours but not at 2 hours.

Prothrombin Fragment 1 + 2

No statistically significant changes in fragment 1 + 2 levels were observed at the 5- and 20-µg/kg dose levels (Figure 6). At the 80-µg/kg dose, a significant increase was observed at 2 and 4 hours ($P < 0.0001$).

Adverse Effects

No adverse effects were observed in any of the patients treated with rFVIIa.

Volume of rFVIIa

The volume of rFVIIa administered after reconstitution varied from 2 to 14 mL and was dependent on patient weight and the dosage administered.

Discussion

The progressive loss of liver parenchymal cells seen in cirrhosis is associated with the decreased synthesis of the vitamin K-dependent coagulation factors, factors II, VII, IX, and X, and protein C.^{3,35,36} The deficiency is usually more marked for factor VII than for factors II, IX, and X. Our study confirms these findings because below normal levels of factor VII were observed in all

Table 4. Pharmacokinetic Parameters

Dose ($\mu\text{g}/\text{kg}$)	Clearance ($\text{mL} \cdot \text{h}^{-1} \cdot \text{kg}^{-1}$)	MRT (h)	Half-life (h)	C_{max} (U/mL)	AUC ($\text{U} \cdot \text{h}^{-1} \cdot \text{mL}^{-1} \cdot \text{kg}^{-1}$)
5	32.9 ± 16.9	3.11 ± 1.3	2.37	2.28 ± 0.56	5.13 ± 1.64
20	43.7 ± 20.0	4.01 ± 2.33	3.23	6.06 ± 3.25	15.71 ± 5.84
80	34.9 ± 16.5	3.01 ± 0.48	2.87	30.80 ± 6.08	76.14 ± 22.90

NOTE. Values are expressed as means \pm SD.

AUC, area under the curve; C_{max} , maximum drug concentration in plasma; MRT, mean residence time.

10 patients. Normal and variably decreased levels of factors II, IX, and X were noted in these same patients. Factor VII has the shortest half-life of these clotting factors (5–6 hours) and is therefore the first factor to decrease with impaired hepatic synthesis.³⁶ Factor VII is the major initiator of hemostasis,^{37,38} and factor VII deficiency is readily reflected by a prolonged PT. The impaired production of factors II and X and fibrinogen in cirrhotic patients may also contribute to the prolonged PT observed in cirrhosis.^{3,39}

The current treatment of the coagulopathy caused by cirrhosis in an actively bleeding patient is based on the replacement of missing coagulation proteins through the administration of fresh frozen plasma (FFP) containing all the vitamin K–dependent coagulation factors as well as a number of other plasma proteins. This treatment is far from ideal. FFP needs to be administered in large volumes and paradoxically may worsen the complications of portal hypertension by increasing portal pressure.⁴⁰ Because FFP is made from human blood products, the risk of transmitting infection, both known and as yet undiscovered, must be considered. Parenteral vitamin K is routinely administered to patients with cholestasis to stimulate the production of vitamin K–dependent clotting factors. However, this modality is rarely effective in correcting the prolonged PTs observed in cirrhotic patients because of the extent of hepatocellular destruction.

Furthermore, any correction of the coagulopathy provided by the administration of vitamin K will take up to 3 days to be effective. Therefore, the administration of vitamin K is not indicated for the treatment of acute bleeding.⁴¹

Our study is the first to show that administration of rFVIIa alone corrects the prolonged PT associated with cirrhosis. Cirrhotic patients have an acquired factor VII deficiency as well as moderate deficiencies of factors II, IX, and X. Because the factor VII deficiency is the most pronounced deficiency, replenishment with rFVIIa should correct the prolonged PT observed in cirrhosis.

As our results show, administration of a single injection of rFVIIa corrected the prolonged PTs in all patients at 10 minutes at all dose ranges. The time period during which the PT remained normal varied from 2 hours with the lowest dose to 12 hours in the highest dose. This ability to control the duration of effect by varying the rFVIIa dose may prove to be important in the clinical application of this product.

Normal individuals have a factor VII plasma level of approximately 0.4 $\mu\text{g}/\text{mL}$, corresponding to 1 U/mL.⁴² Of this, approximately 4 ng/mL exists in the already activated form, factor VIIa. After tissue damage, normal hemostasis is initiated by the formation of complexes of factor VIIa and tissue factor. This complex then activates factors IX and X and converts zymogen factor VII into

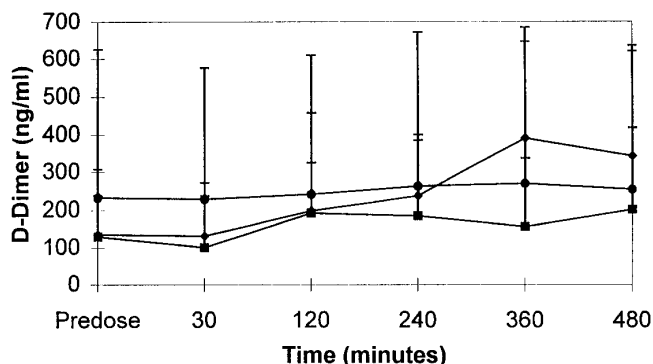


Figure 4. D-dimer levels in plasma before and at 10, 30, 120, 240, 360, and 480 minutes after administration of rFVIIa (5 [●], 20 [■], or 80 [◆] $\mu\text{g}/\text{kg}$).

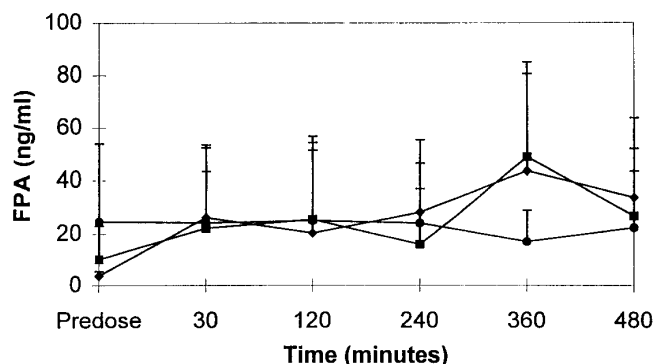


Figure 5. Plasma levels of fibrinopeptide A (FPA) before and at 30, 120, 240, 360, and 480 minutes after administration of rFVIIa (5 [●], 20 [■], or 80 [◆] $\mu\text{g}/\text{kg}$).

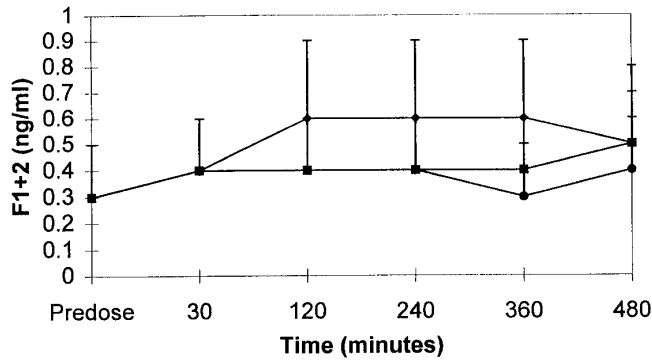


Figure 6. Plasma levels of fragment 1 + 2 (F 1 + 2) before and at 30, 120, 240, 360, and 480 minutes after administration of rFVIIa (5 [●], 20 [■], or 80 [◆] µg/kg).

factor VIIa.³⁷ The cirrhotic patients included in the present study had factor VII levels of approximately one-fourth the normal concentration. Accordingly, a seriously impaired initial hemostasis should be expected in these patients. Although the decreased levels of the other coagulation factors (factors II, V, and X and fibrinogen) may have contributed to the prolonged PT observed in our study, the substantially lower factor VII concentration appears to be the major contributor, as indicated by the prompt normalization of the PT after a single injection of rFVIIa. The increase in factor VII plasma levels after rFVIIa administration was dose dependent as measured by a test using soluble tissue factor specific for factor VIIa.⁴³

In the present study, PT was used to detect a beneficial effect of rFVIIa on the coagulation system because the international normalized ratio has not proven valid for comparison of patients with liver disease.⁴⁴ In the present study, the shortening of the PT correlated well with increased plasma levels of factor VII. The PT increased as factor VII levels returned to baseline. These phenomena suggest an important role for factor VII in maintaining a normal PT. A dose-dependent normalizing effect of single doses of rFVIIa on the international normalized ratio has been reported in a study of warfarin-treated volunteers with international normalized ratios between 2 and 3.¹³

The potential risk of initiating the coagulation cascade leading to disseminated intravascular coagulation (DIC) with the administration of activated coagulation factors was one of our major concerns. Chronic, low-grade DIC has been described in patients with cirrhosis.^{45,46} The ability to determine the presence of DIC in cirrhosis is difficult because the defective synthesis of coagulation proteins in cirrhosis may stimulate the consumption of these proteins.⁴⁷⁻⁴⁹ Indicators of DIC, such as elevated levels of fibrinopeptide A, fragment 1 + 2, and D-dimers,

are commonly increased in cirrhosis, leading to further confusion between these diagnoses.³ In the present study, significantly increased concentrations of D-dimer and fibrinopeptide A were observed after administration of the 80-µg/kg dose of rFVIIa. However, the interpatient as well as inpatient variations were extensive with several patients showing decreased levels of these proteins throughout the study. Fragment 1 + 2 increased after administration of the 80 µg/kg dose of rFVIIa at time points 2 hours and longer. Local activation of coagulation secondary to rFVIIa complexing with tissue factor at exposed sites of injury may have led to the release of the prothrombin peptide fragment 1 + 2. The results of these tests are highly dependent on blood sampling and, therefore, may vary widely. None of our patients showed any clinical signs of DIC, and no changes occurred in antithrombin III, fibrinogen, or platelets, providing strong evidence against any systemic activation of the coagulation system.

rFVIIa appears to offer several advantages over FFP in the correction of the coagulopathy of cirrhosis. FFP is derived from pooled blood products, and the exact factor composition of each unit is highly variable. Because decreased factor VII levels appear to be the main factor contributing to the prolonged PT found in cirrhotics, it is conceivable that the low levels of factor VII in some units of FFP may not adequately correct the PT. rFVIIa is the product of recombinant technology, and therefore, the risk for the transmission of blood-borne disease present with the use of FFP is nonexistent with rFVIIa. rFVIIa is effective in small volumes, and its administration should not increase portal pressure. The range of volume of rFVIIa used in our study was 2–14 cc, which is in marked contrast to the average 240 mL/U of FFP. The duration of effect of a unit of FFP is 3–4 hours,⁵⁰ whereas the duration of effect of rFVIIa was dose dependent, with the shortest mean effect being 120 minutes in the lowest dose range and 720 minutes in the highest dose range. Because no side effects were observed after any of the doses, the higher dose may be the preferred one.

The pharmacokinetic parameters, clearance, mean residual time, and half-life were independent of dose and were in the same range as found by Lindley et al.,⁷ thus indicating that liver failure does not influence the pharmacokinetics of rFVIIa.

In our current era of cost-containment medicine, the relative cost of rFVIIa must be compared with the relatively low cost of FFP. Because this is a preliminary study, we did not include a cost analysis of rFVIIa in our analysis. Although the price of rFVIIa is approximately \$700.00 per milligram in Denmark, there are currently

no estimates as to the cost of rFVIIa once it becomes available in the United States. Undoubtedly, the increased cost of rFVIIa must be balanced against the potential risk of the transmission of yet unknown infectious agents that accompanies the use of FFP.

rFVIIa appears to be a safe and effective tool in correcting the PT of advanced Child's B and C cirrhotics. The duration of effect is dose dependent. This study, performed on end-stage nonbleeding cirrhotic patients, cannot be extrapolated to include bleeding patients. Further controlled trials are required to evaluate this new medication in the setting of acute bleeding, as well as its use before elective procedures such as liver biopsy, dental extraction, and routine surgery.

References

- United States Department of Health and Human Services. Monthly vital statistics report (September 26) 1989;38(Suppl 5).
- Carr JM. Disseminated intravascular coagulation in cirrhosis. *Hepatology* 1989;10:103-110.
- Paramo AJ, Rochae E. Hemostasis in advanced liver disease. *Semin Thromb Hemost* 1993;19:184-190.
- Kelly DA, Summerfield JA. Hemostasis in liver disease. *Semin Liver Dis* 1987;7:182-191.
- Joist JH. Hemostatic abnormalities in liver disease. In: Colman RW, Hirsh J, Marder VJ, Salzman EW, eds. *Hemostasis and thrombosis*. 3rd ed. Philadelphia: Lippincott, 1994:906-920.
- Hedner U, Kisiel W. Use of human factor VIIa in treatment of two hemophilia patients with high titer inhibitors. *J Clin Invest* 1983;71:1836-1841.
- Lindley CM, Sawyer WT, Macik BG, Lusher J, Glazer S. Pharmacokinetics and pharmacodynamics of recombinant factor VIIa. *Clin Pharmacol Ther* 1994;55:638-648.
- Hedner U, Bjoern S, Bernvil SS, Tengborn L, Stigendahl L. Clinical experience with human plasma derived factor VIIa in patients with hemophilia A and high titer inhibitors. *Hemostasis* 1989;19:335-343.
- Hedner U, Glazer S. Management of hemophilia patients with inhibitors. *Hematol Oncol Clin North Am* 1992;6:1035-1046.
- Thim L, Bjoern S, Christensen M, Nicolaisen EM, Lund-Hansen T, Pederson AH, Hedner U. Amino acid sequence and post-translational modification of human factor VIIa from plasma and transfected baby hamster kidney cells. *Biochemistry* 1988;27:7785-7793.
- Brinkhous KM, Hedner U, Garris JB, Diness V, Read MS. Effect of recombinant factor VIIa on the hemostatic defect in dogs with hemophilia A, hemophilia B and von Willebrand's disease. *Proc Natl Acad Sci USA* 1989;86:1382-1386.
- French P, Nony P, Erhardtson E, Delair P, Girard P, Dechavanne M, Boissel JP, Glazer S. Dose effect of recombinant factor VIIa in healthy subjects pre-treated with acenocoumarol (abstr). *Thromb Haemost* 1995;73:984.
- Erhardtson E, Nony P, French P, Dechavanne M, Boissel JP, Lyng Hansen LL, Hedner U, Glazer S. Further safety information on the use of factor VIIa in acenocoumarol treated volunteers: a phase 1 study (abstr). *Blood* 1994;84(Suppl 1):67a.
- Hedner U, Glazer S, Pingel K, Alberts KA, Blombach M, Schulman S, Johnsson H. Successful use of rFVIIa in a patient with severe hemophilia during synovectomy (letter). *Lancet* 1988;2:1193.
- Macik GB, Hohnaker H, Roberts H, Griffin AM. The use of recombinant activated factor VII for treatment of a retropharyngeal hemorrhage in a hemophiliac patient with a high titer inhibitor. *Am J Hematol* 1989;32:232-234.
- Bell BA, Birch K, Glazer S. Experience with recombinant factor VIIa in an infant hemophiliac with inhibitors to FVIII:C undergoing emergency central line placement: a case report. *Am J Pediatr Hematol Oncol* 1993;15:77-79.
- Schmidt ML, Smith HE, Gamerman S, DiMichele D, Glazer S, Scott JP. Prolonged recombinant activated factor VII treatment for severe bleeding in a factor IX deficient patient with an inhibitor. *Br J Hematol* 1991;78:460-463.
- Hedner U, Feldstedt M, Glazer S. Recombinant factor VIIa in hemophilia treatment. In: Lusher JM, Kessler CM, eds. *Hemophilia and von Willebrand's disease in the 1990s*. New York: Elsevier, 1991:283-292.
- Hedner U, Glazer S, Falch J. Recombinant activated factor VII in the treatment of bleeding episodes in patients with inherited and acquired bleeding disorders. *Transfus Med Rev* 1993;2:78-83.
- Macik BG, Lindley CN, Lusher J, Sawyer WT, Glazer S. Safety and initial clinical efficacy of three dose levels of recombinant factor VIIa: results of a phase 1 study. *Blood Coagul Fibrinolysis* 1993;4:521-527.
- Schulman S. A therapeutic alternative for hemophiliacs with inhibitors. *Acta Pediatr* 1992;81:564-565.
- Lusher JM. Recombinant factor VIIa in the treatment of internal bleeding in patients with factor VIII and IX inhibitors. *Haemostasis* 1996;26(Suppl 1):124-130.
- Rice KM, Savage GF. Novo Seven in central nervous system bleeds. *Haemostasis* 1996;26(Suppl 1):131-134.
- Ingerslev J, Friedman D, Gastineau D, Gilchrist G, Johnsson H, Lucas G, McPherson J, Preston E, Scheibel E, Shuman M. Major surgery in hemophiliac patients with inhibitors using recombinant factor VIIa. *Haemostasis* 1996;26(Suppl 1):118-123.
- Bech RM, Anderson PM, Glazer S, Hedner U. Recombinant factor VIIa for the treatment of congenital factor VII deficient patients (abstr). *Thromb Haemost* 1995;73:983A.
- Clauss A. Gerinnungsphysiologische Schnellmethode zur Bestimmung des Fibrinogens. *Acta Haematol* 1957;17:237-246.
- Abildgaard U, Lie M, Odegard OR. A simple amidolytic method for the determination of functional active antithrombin III. *Scand J Clin Lab Invest* 1976;36:109-112.
- Hansen LL, Nielsen FE, Hedner U. Validation of a method for determination of recombinant FVIIa coagulant activity in plasma using a one stage clotting assay (abstr). *Thromb Haemost* 1993;69:865A.
- Douglas JT, Eisenberg PR. Characterization of cross-linked fibrin degradation products in patients treated with fibrinolytic agents. *Fibrinolysis* 1993;7(Suppl 2):28-31.
- Soria J, Soria C, Ryckewaert JJ. A solid phase immuno enzymological assay for the measurement of human fibrinopeptide A. *Thromb Res* 1980;20:425-435.
- Shi O, Sio R, Lin S, Yu K, Arbutnutt K, Ruiz J, Gaur P. Performance characteristics of an ELISA for prothrombin 1 + 2 (abstr). *Thromb Haemost* 1991;65:1118A.
- Owren PA. *Transactions of the 5th Conference of Blood Clotting and Allied Problems*. Flynn JE, ed. New York: Josiah Macy, Jr., Foundation, 1952:98.
- Procter RR, Rapaport SI. The partial thromboplastin time with kaolin. *Am J Clin Pathol* 1961;36:212-219.
- Martinoli JL, Stocker K. Fast functional protein C assay using Protac, a novel protein C activator. *Thromb Res* 1986;43:253-264.
- Blanchard RA, Furie BC, Jorgensen M, Kruger SF, Furie B. Acquired vitamin K dependent carboxylation deficiency in liver disease. *N Engl J Med* 1981;305:242-248.
- Kloczko J, Mian M, Wojtukiewicz MZ, Babiuch L, Bielawiec M, Galar M. Plasma protein C as a marker of hepatocellular damage in alcoholic liver disease. *Haemostasis* 1992;22:340-344.
- Rapaport SI. The tissue factor pathway: how it has become a "prima ballerina." *Thromb Haemost* 1995;74:7-17.

38. Ten Cate H, Bauer K, Levi M, Edgington TS, Sublett RD, Barzegar S, Kass BL, Rosenberg RD. The activation of factor X and prothrombin by recombinant factor VIIa in vivo is mediated by tissue factor. *J Clin Invest* 1993;92:1207–1212.
39. Palascak JE, Martinez J. Dysfibrinogenemia associated with liver disease. *J Clin Invest* 1977;60:89–95.
40. Matloff DS. Treatment of acute variceal bleeding. *Gastrointest Clin North Am* 1992;21:103–118.
41. Chopra S, Griffin PH. Laboratory tests and diagnostic procedures in evaluation of liver disease. *Am J Med* 1985;79:221–230.
42. Fair DS. Quantitation of factor VII in the plasma of normal and warfarin-treated individuals by radioimmunoassay. *Blood* 1983;4:784–791.
43. Hansen LL, Nielsen FE, Hedner U. Validation of method for determination of recombinant FVIIa coagulant activity in plasma using a one-stage clotting assay (abstr). *Thromb Haemost* 1993;69:865.
44. Kovacs MJ, Wong A, MacKinnin K, Weir K, Keeney M, Boyle E, Cruikshank M. Assessment of the validity of the INR system for patients with liver impairment. *Thromb Hemost* 1994;6:727–730.
45. Bakker CM, Knot EA, Stibbe J, Wilson JH. Disseminated intravascular coagulation in liver cirrhosis. *J Hepatol* 1992;15:330–335.
46. Violi F, Ferro D, Basili S, Quintarelli C, Musca A, Coedova C, Balsano F. Hyperfibrinolysis resulting from clotting activation in patients with different degrees of cirrhosis. *Hepatology* 1993;17:78–83.
47. Kemkes-Matthes B, Bleyl H, Matthes KJ. Coagulation activation in liver diseases. *Thromb Res* 1991;64:253–261.
48. Coccheri S, Mannuci PM, Palareti G, Gervasoni W, Poggi M, Viganò S. Significance of plasma fibrinopeptide A and high molecular weight fibrinogen in patients with liver cirrhosis. *Br J Hematol* 1982;52:503–509.
49. Paramo JA, Rifon J, Fernandez J, Cuesta B, Rocha E. Thrombin activation and increased fibrinolysis in patients with chronic liver disease. *Blood Coagul Fibrinolysis* 1991;2:227–230.
50. Menitove JE, Gill JC, Montgomery RR. Preparation and clinical use of plasma and plasma fractions. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ, eds. *Williams hematology*. 5th ed. New York: McGraw-Hill, 1995:1649–1954.

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Banti of Banti's Syndrome



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