

Case Report

Correction of both prothrombin time and primary haemostasis by recombinant factor VII during therapeutic alcohol injection of hepatocellular cancer in liver cirrhosis

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We evaluated the efficacy of recombinant factor VII to correct impaired haemostasis in a patient with liver cirrhosis requiring an invasive procedure. A test intravenous bolus of 80 µg/kg of recombinant factor VII was given to a Jehovah's Witness, with a solitary 4.4-cm hepatocellular carcinoma and underlying hepatitis C virus cirrhosis, in an attempt to correct his haemostatic disorders and safely inject the tumour with alcohol. An extensive portal block had precluded consideration of liver transplantation. Haemostasis was evaluated by clotting assays, bleeding time and thromboelastography 10 min before and 10 min and 1, 2, 4, 8 and 24 h after factor VII infusion. Parameters of both coagulation (prothrombin time) and platelet function (bleeding time and the α and ma parameters of thromboelastography) were improved 10 min after factor VII infusion; improvements lasted 4 to 8 h or

more. Platelet count did not change and there was no evidence of disseminated intravascular coagulation. The improvements in haemostatic parameters correlated significantly with the increases in factor VII plasma concentrations ($p < 0.04$). Factor VII clearance was 25.1 U/h/kg and its half-life was 5.8 h. The same dose of recombinant factor VII was given to the patient 1 week later, just before the alcohol injections. The patient had no subsequent bleeding or other complication, with no change in haemoglobin levels over 24 h. Thus, recombinant factor VII represents a therapeutic advance, as it can correct fully both coagulation and platelet function defects in cirrhosis and allow invasive procedures to be performed safely.

Key words: Cirrhosis; Coagulation; Factor VII; Platelets; Thromboelastography.

THE LIVER has a central role in the maintenance of normal haemostatic mechanisms, so that impaired haemostasis, as expressed by low platelet count (PLT) and/or prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT), is almost always present in patients with advanced liver disease (1). Although cirrhotic patients with low PLT and/or prolonged PT do not frequently experience spontaneous bleeding, they are certainly at increased risk of severe bleeding during common invasive procedures (2). Fresh frozen plasma and/or platelet transfusions have been the two conventional therapeutic options to reduce the risk of bleeding during invasive pro-

cedures in such patients (1,2). However, it may be difficult to correct haemostasis in cirrhosis using blood products because the transfusion volume required is too large. Moreover, since both fresh frozen plasma and platelets are human blood products, there is always a risk of transmitting infection of unknown or undetectable agents, while a minority of patients decline any kind of human products for religious reasons.

Deficiencies of the vitamin K-dependent coagulation factors are considered to play a key role in the development of the hypocoagulable state in cirrhosis (1). Factor VII has the shortest half-life and its levels have been suggested as a good prognostic marker for the severity of liver disease (1,2). Recombinant activated factor VII (rFVIIa) has been developed for the treatment of patients with haemophilia A and B, particularly those with inhibitors against factors VIII and IX, respectively (3). Recently, administration of a single dose of rFVIIa was shown to correct the prolonged PT

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and aPTT in non-bleeding cirrhotic patients in a dose-dependent manner (4). Infusion of rFVIIa has also been shown to decrease or stop bleeding in patients with thrombocytopenia (5). However, the efficacy of rFVIIa in a therapeutic setting in patients with cirrhosis and impaired haemostasis and its effect on the haemostatic plug *in vivo* has been reported only in abstract in one patient undergoing cataract surgery (6).

We report the beneficial effect of rFVIIa in a Jehovah's Witness with hepatocellular cancer and underlying hepatitis C virus cirrhosis, which allowed us to treat the tumour safely with alcohol injections despite the patient's impaired haemostasis.

Case Report

A 50-year-old man was diagnosed to have hepatitis C virus-related cirrhosis and a solitary hepatocellular carcinoma of the right lobe of the liver, 4.4 cm in diameter. An extensive portal block precluded consideration of orthotopic liver transplantation. The total bilirubin was 42 $\mu\text{mol/l}$ (1–17), albumin 32 g/l (35–50), alkaline phosphatase 298 u/l (35–130), aspartate transaminase 97 u/l (15–40), alanine transaminase 118 u/l (15–40). Alcohol injections of the tumour were the only therapeutic option, but a PT of 20 s (control 13 s) and a PLT of $80 \times 10^9/\text{l}$ (150–400) made these unsafe. The anti-thrombin III antigen was 37 u/dl (80–140) and activity 26 u/dl (80–140). Since the patient declined any human-derived product for religious reasons, he was given rFVIIa in an attempt to correct his haemostatic disorders and to perform the procedure safely.

A test dose of 80 $\mu\text{g/kg}$ of rFVIIa (NovoSeven, NovoNordisk, Copenhagen, Denmark) was given as a slow intravenous injection over 2 min and changes of haemostasis were evaluated by: a) routine tests: PT and international normalized ratio (INR), aPTT, PLT, fibrinogen, fibrin degradation products (before rFVIIa and at 10 min, 1 h, 2 h, 4 h, 8 h and 24 h after rFVIIa) and bleeding time (before rFVIIa and at 1 h and 8 h after rFVIIa); and b) by thrombelastography (TEG) (at all time points).

TEG enables a global assessment of haemostasis to be made from a single whole blood sample (7). TEG was performed by a single operator in a computerised thrombelastograph (Haemoscope Corp. & Launch Diagnostic, UK), as recommended by the manufacturer and according to the technique already described in our previous reports (8). The native TEG was measured with no anticoagulant or Celite added. The TEG was allowed to run for at least 1 h after maximum amplitude on the TEG tracing was achieved. The TEG parameters which were generated and recorded auto-

matically by computer were the following: 1) reaction time (r), which is related functionally to plasma clotting factors and circulating inhibitory activity; 2) clot formation time (k), which is affected by the activity of the intrinsic clotting factors, fibrinogen and platelets; 3) alpha angle (α), which reflects the absolute strength of the fibrin clot and is a direct function of platelets and plasma components residing on the platelet surface; 4) maximum amplitude (ma), which is a direct function of the maximum dynamic properties of fibrin and platelet number and function; and 5) clot lysis index (CLI), which reflects loss of clot integrity as a result of lysis and is an excellent marker of fibrinolysis (6).

Factor VII plasma levels were also measured at all time points. A one-stage parallel line bio-assay using factor VII-deficient plasma as a test base and rabbit thromboplastin was used. The normal range is 0.54–1.23 U/ml. Briefly, doubling dilutions were made of patient plasma in Owren's buffered saline; 100 μl of diluted plasma was mixed with 100 μl of factor VII-deficient plasma (Diagen, Diagnostic Reagents Ltd, Thane, Oxon, UK) and 100 μl of rabbit brain thromboplastin (PT HS PLUS, Instrumentation Laboratories) and brought to 37°C; 25 μl of 0.025 M calcium chloride was then added and the time to clot formation determined on an ACL 300/3000 coagulometer (IL Warrington, UK). The same procedure was carried out with a standard reference plasma. Time of each plasma (test and standard) was plotted against dilution on log linear graph paper to obtain two parallel lines. By reference to the standard plasma line, the factor VII content of test plasma was determined.

Spearman's correlation analysis was used for evaluation of the relationships between the changes of haemostatic parameters and the changes of factor VII plasma concentrations.

The test dose of rFVIIa resulted in improvement of all haemostatic parameters, except PLT. The improvements in haemostatic parameters were all detected at 10 min and lasted for several hours (Table 1). In particular, PT and INR remained within normal levels up to at least 8 h and aPTT showed slight improvement for up to 2 h. The r , k and α parameters of TEG showed improvements for up to 4 h; the ma parameter of TEG increased for the first 4 h and slightly decreased thereafter, but remained at values higher than those before the rFVIIa infusion up to 24 h. The bleeding time also improved for up to at least 8 h. There was no evidence of disseminated intravascular coagulation: no change in fibrinogen levels or fibrin degradation products, and no increase of the CLI parameter of TEG.

TABLE 1

Changes in parameters of haemostasis after a single injection of 80 µg/kg recombinant activated factor VII (rFVIIa) in a patient with liver cirrhosis

Haemostatic parameters	Before rFVIIa*	Time after rFVIIa infusion					
		10 min	1 h	2 h	4 h	8 h	24 h
Prothrombin time (PT), s	19.6	10.5	10.4	11.0	11.3	12.9	16.9
International normalized ratio (INR)	1.5	0.8	0.8	0.9	0.9	1.0	1.3
Activated partial thromboplastin time (aPTT), s	42.0	36.0	38.3	41.0	45.0	40.9	44.4
Platelet count (PLT), $\times 10^9/l$	88	83	88	81	81	98	114
Thromboelastography (TEG) parameters							
<i>r</i> (reaction time), mm	28.5	13.5	11.0	18.0	18.0	31.5	33.5
<i>k</i> (clot formation time), mm	15.5	6.0	5.5	5.0	7.0	13.0	16.0
<i>ma</i> (maximum amplitude), mm	71.0	89.0	96.0	93.5	90.0	80.0	79.0
α (angle), degrees	27.0	54.0	49.5	67.6	49.5	29.0	23.5
CLI (clot lysis index), %	<5%	<5%	<5%	<5%	<5%	<5%	<5%
Fibrinogen, g/dl	1.2	1.1	1.2	1.2	1.2	1.3	1.4
Fibrin degradation products	<0.25	<0.25	<0.25	<0.25	<0.25	<0.25	<0.25
Bleeding time, min	10.5	–	6.5	–	–	8.0	–
Factor VII plasma levels, U/ml	0.49	33.5	23.0	11.0	5.7	2.3	0.7

*Haemostatic parameters were measured 10 min before rFVIIa infusion.

Correlation of factor VII concentrations (using Spearman correlation) with PT: $r = -0.96$, $p < 0.001$; INR: $r = -0.98$, $p < 0.001$; aPTT: $r = -0.68$, $p = 0.09$; PLT: $r = -0.51$, $p = 0.24$; *r* TEG parameter: $r = -0.85$, $p = 0.016$; *k* TEG parameter: $r = -0.82$, $p = 0.023$; *ma* TEG parameter: $r = 0.79$, $p = 0.036$; α TEG parameter: $r = 0.83$, $p = 0.02$; bleeding time: $r = -1.0$, $p < 0.001$.

Factor VII plasma levels were at the maximum concentration at 10 min and slowly declined thereafter, almost reaching the pre-infusion levels at 24 h. Factor VII clearance was 25.1 U/h/kg, its volume of distribution 97.8 ml/kg at steady state and its half-life 5.8 h. The increases in factor VII concentrations were significantly correlated with improvements in haemostatic parameters ($p < 0.04$ for all correlations) (Table 1).

The same dose of rFVIIa was given to the patient 1 week later, just before the alcohol injection. The patient had no bleeding or any other problem after the injection and there was no change in haemoglobin levels for the next 24 h. Changes in haemostatic parameters were similar to those following the test dose of rFVIIa.

Discussion

This is only the second report of use of rFVIIa to correct haemostasis in a patient with liver cirrhosis in order to perform an invasive procedure safely. The first is published as an abstract related to cataract surgery (6). We confirmed that administration of rFVIIa rapidly corrects the prolonged PT in cirrhotic patients (4). The vitamin K-dependent factors are the first coagulation factors that are reduced in advanced liver disease, with factor VII (the factor with the shortest half-life) being the most sensitive (1,2). Factor VII plays a key role in the initiation of the coagulation cascade, and its deficiency is readily reflected by prolongation of PT (1). Thus, it is expected that administration of rFVIIa will correct the prolonged PT in cirrhotic patients with factor VII deficiency. PT remained within

normal range for at least 8 h in our patient, which is compatible with the findings of Bernstein et al. for the same dosage of rFVIIa (4).

Interestingly, an improvement in haemostatic plug formation was also observed *in vivo*, as the bleeding time shortened and the α and *ma* parameters of TEG improved. Although rFVIIa has been found to decrease bleeding in patients with thrombocytopenia (5), the mechanism of its action on platelets is not clear yet. Since platelet number did not change in our patient, the benefit of rFVIIa was probably due to increased platelet activity. It has recently been shown that a high dose of rFVIIa has platelet activity *in vitro* independent of the tissue factor (9), and it has been suggested that rFVIIa leads to increased local thrombin generation on the surface of activated platelets and possibly to formation of a stable fibrin network, even in the absence of an optimal initial platelet plug (10).

Our patient had a moderate haemostatic impairment with a PT of 20 s, a platelet count of $80 \times 10^9/l$ and an antithrombin III activity of 26 u/l (80–140). Recombinant factor VII has been shown to correct more severely impaired prothrombin times (4), but to date its effect on platelet function in cirrhotic patients has been evaluated only in this patient. Although a beneficial effect on primary haemostasis was found, patients with more severe thrombocytopenia need to be investigated. In non-Jehovah's Witnesses, the use of the blood products, including platelet, transfusions, fresh frozen plasma or cryoprecipitate have been used routinely and still represent standard therapy (1,2). The cost of rFVIIa is high (£680 per milligram), i.e. £3800

for this patient. However, further studies need to determine whether it can be a substitute for current blood products. If so, the real cost would be less.

In conclusion, rFVIIa represents a therapeutic advance, as it can rapidly correct both coagulation and platelet function defects in liver cirrhosis. It may be effectively used in cirrhotic patients with severe haemostatic disorders in order to safely perform invasive procedures. Controlled trials are needed to evaluate the efficacy of this new medication in the prevention of bleeding during surgical procedures such as dental or routine surgery and in the management of acute bleeding in patients with cirrhosis.

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