

CASE REPORT

Successful outcome of a cirrhotic patient with postoperative haematuria treated with a single high dose of recombinant factor VIIa

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Summary. Recombinant factor VIIa (rfVIIa) has been widely used for the treatment and prevention of bleeding episodes in haemophiliacs with high-titre inhibitors. High single doses are the treatment of choice for joint and muscle bleeds in those patients. There are only a few reports on the value of rfVIIa in cirrhotic patients with haemostatic impairment but this drug can consistently correct

the prothrombin time in these individuals. We report a case of a good response to a single high dose of rfVIIa in a patient with advanced liver disease who suffered from severe refractory postoperative haematuria.

Keywords: haematuria, liver cirrhosis, recombinant factor VIIa.

Recombinant factor VIIa (rFVIIa) has proved to be successful for the treatment and prevention of bleeding episodes in haemophilic patients with high-responding inhibitors to factor VIII or IX [1–5]; favourable haemostatic responses have also been reported in other patients with various congenital or acquired bleeding disorders.

We report a case of a cirrhotic patient with refractory postoperative haematuria who responded to a single high dose of rFVIIa.

Case report

Our patient was a 58-year-old man with Child–Pough stage B liver cirrhosis who underwent surgery (transurethral resection) due to a urine bladder malignancy (transitional cell carcinoma) in April 2001. A preoperative analytical screen revealed only

a mild anaemia (haemoglobin level 11.7 g dL^{-1}) and thrombocytopenia ($112 \times 10^9 \text{ L}^{-1}$) as well as a borderline prothrombin time (PT) of 14.3 s and prothrombin time ratio (PT_r) of 1.25 s (normal range for PT 9.5–14 s) consistent with chronic liver disease. Surgery was immediately followed by profuse haematuria leading to severe anaemia requiring transfusion of 9 U of red cell concentrates (RCC); bleeding did not cease in spite of infusion of 10 U of fresh frozen plasma (FFP), two further endoscopic surgical procedures and selective arterial embolization. Seven weeks after initial surgery, the patient had received a number of infusions of different blood and plasma products because of recurrent episodes of haematuria (Fig. 1). When the patient was referred to the Hospital Miguel Servet his haemoglobin level was 8.7 g dL^{-1} , platelet count $83 \times 10^9 \text{ L}^{-1}$ and his PT 20 s (PT_r 1.9 s); activated partial thromboplastin time remained within the normal range. No evidence of any specific inhibitor to any haemostatic factor was elicited. A single intravenous bolus infusion of 480 kIU rFVIIa ($137 \mu\text{g kg}^{-1}$) was prescribed; 4 hours later, bleeding had stopped and did not reappear any more. A shortening of the PT to 15.8 s

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Accepted 12 October 2001

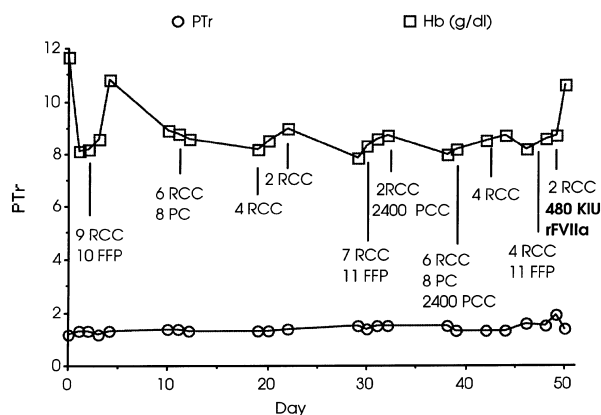


Fig. 1. Timing of postoperative episodes of haematuria, laboratory results (PTr and haemoglobin levels) and relationship with infusion of blood products in our patient. RCC, red cell concentrates; FFP, fresh frozen plasma; PC, platelet concentrates; PCC, prothrombin complex concentrate; PTr, prothrombin time ratio. Haematuria occurred on days 1, 2, 10, 11, 20, 22, 29, 30, 31, 32, 38, 42, 44, 46, 48 and 49.

(PTr 1.4 s) was noticed after the infusion of rFVIIa (Fig. 1). No further infusions of the drug were required in the absence of any other bleeding over the following days.

Discussion

Patients affected by severe liver disease often face clinical situations that mean a potentially serious challenge to their frequently weak haemostatic system. Treatment of those individuals who do not show a response to vitamin K consists of the administration of desmopressin, fresh frozen plasma (FFP), prothrombin complex concentrates (PCC) and occasionally platelet concentrates (PC), when clinically required. FFP contains variable amounts of different clotting factors and it is usually unable to fully correct the international normalized ratio (INR) without infusing large amounts of fluid into the patient [6–8], which is not recommended in a large number of such patients. High doses of PCC are often required in order to provide the haemostatically necessary FVII supply, but hypercoagulable states associated with venous thromboembolic disease [9], arterial thrombotic episodes (including nine fatal myocardial infarctions) [10] and the development of disseminated intravascular coagulation [9,10], have been reported following the use of large amounts of these concentrates. In addition they carry a low, but potential, risk of transmission of viral infections.

Infusion of rFVIIa has been shown to be effective in transiently correcting the prothrombin time in nonbleeding individuals with advanced liver disease who were treated with different doses of this drug (5, 20 and 80 $\mu\text{g kg}^{-1}$) [2,3]. The correction time of PT duration was found to be dependent on the dose of FVIII given. The experience reported with rFVIIa in this latter group of patients (especially with their use in the setting of invasive procedures) is limited; current experience however, suggests a potential value of even low doses [8] for haemostatic treatment prior to any type of major or minor elective surgery (such as dental extractions, central venous access devices insertion procedures or liver biopsies in patients with severe haemostatic impairment) [4,7], as well as gastrointestinal bleeding due to oesophageal varices and haemostatic coverage of liver transplant [11].

Some isolated reports of a good therapeutic outcome in cirrhotic patients with serious or even life-threatening haemorrhagic episodes unresponsive to conventional treatment (FFP, PCC, PC), following the infusion of rFVIIa at a dose of 20 $\mu\text{g kg}^{-1}$ given at 4–6 h intervals, have been published [5]. There is no general agreement regarding the indications or the more appropriate dosing schedule of rFVIIa in patients suffering from liver cirrhosis [5,11]. In our patient a single bolus high-dose infusion had the same therapeutic efficacy that could have been expected from lower intermittent doses [5]; single high doses have also been found to be an excellent therapeutic option for haemarthrosis and muscle bleeds in haemophiliacs with inhibitors [12]. Our finding needs confirmation in a trial including a larger group of patients with liver cirrhosis but, for the time being, single high doses of rFVIIa can be considered for the treatment of cirrhotic patients with severe bleeding who do not readily respond to conventional haemostatic treatment; a potential adjuvant role for drugs like DDAVP or antifibrinolytics in that setting could also be assessed.

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