Letters to the Editor

Conflict of interest

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References


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Recombinant factor VIIa to treat severe bleeding in patients with liver disease: Pitfalls and possibilities

To the Editor:

Patients with liver disease frequently develop substantial changes in their hemostatic system [1]. Recent laboratory and clinical data are compatible with the concept of rebalanced hemostasis in liver disease [2]. According to this concept, the average patient with liver disease is in hemostatic balance due to a concomitant decrease in pro- and anticoagulant pathways. The hemostatic balance in patients with liver disease, however, is much more fragile as compared to the hemostatic balance in healthy individuals. Consequently, patients with liver disease are at risk for both bleeding and thrombosis when the balance is disturbed. Unfortunately, there is currently no clinical or laboratory test able to predict whether a patient with liver disease is at risk for either bleeding or thrombosis.

In a recent commentary in the section “International Hepatology” of this Journal, Thabut and coworkers address the question whether administration of recombinant factor VIIa (NovoSeven, rFVIIa) to patients with liver disease poses them at an increased risk for thrombotic complications [3]. The authors conclude that the use of rFVIIa to patients with uncontrollable bleeding may be justified, and potential thrombotic events should be considered as ‘collateral damage’. Here, we aim to comment on the use of rFVIIa in patients with liver disease to better appreciate the risk-benefit ratio in different clinical scenarios.

Current clinical data do not support prophylactic administration of rFVIIa to prevent excessive bleeding during surgical procedures including partial heptectomy and liver transplantation [4,5]. Also, administration of rFVIIa to patients with variceal bleeding is not indicated based on randomized controlled trials.

Although the average patient with liver disease is in hemostatic balance, there are situations in which severe and uncontrollable bleeding does occur [1]. If the primary cause of bleeding is not surgical and not primarily related to (excessive) portal hypertension, administration of rFVIIa may be beneficial, which is supported by anecdotal reports [6,7]. The main advantage of rFVIIa over other hemostatic therapies, such as blood product infusion, is the low volume, which prevents fluid overload and exacerbation of portal hypertension. In addition, transfusion-related complications such as transfusion-related acute lung injury and other transfusion reactions do not occur when rFVIIa is administered.

The theoretical advantages of rFVIIa when used as a “rescue agent” need to be balanced against a potentially increased risk of thrombosis. We believe that clinical studies are required to establish whether rFVIIa is truly effective in controlling bleeding complications in patients with liver disease. Furthermore, we believe it is important to realise which types of uncontrollable bleeding might benefit from rFVIIa administration, and in which cases therapy with rFVIIa is likely futile.

The patients with uncontrollable bleeding that may benefit from rFVIIa are those patients in whom the bleeding complication is likely a result of an inadequate coagulation system. Examples of this are patients with massive hematomas, patients with bleeding complications after small invasive procedures including dental extraction, liver biopsy, paracentesis and thoracentesis, and patients with bleeding complications during or after larger invasive procedures. In the latter case, it should be excluded that there is a surgical cause for the bleeding complication. Clinically,
a bleeding complication during surgery that is likely attributable to inadequate hemostatic capacity is characterized by multiple simultaneous bleeding sites, persistent oozing from a non-identifiable source, or delayed bleeding following adequate hemostasis. Patients that are theoretically unlikely to benefit from rFVIIa are patients with surgical bleeding, or bleeding complications that are primarily related to pressure effects (such as variceal bleeding).

In those patients with uncontrollable bleeding related to a hemostatic defect, two factors may determine whether rFVIIa might be effective in inducing hemostasis. Firstly, both in vitro studies and clinical studies in trauma patients have established a loss of hemostatic activity of rFVIIa with decreasing pH [8,9]. Patients with severe acidosis, which for example frequently occurs in patients with acetaminophen-induced acute liver failure, may not benefit from rFVIIa. Secondly, rFVIIa likely requires a certain amount of residual endogenous coagulation factors. rFVIIa is believed to exert its hemostatic effect by enhancement of thrombin and fibrin generation in either a tissue factor-dependent or independent manner [10]. For rFVIIa to enhance thrombin and fibrin generation, a certain level of procoagulant proteins (factors X, V, II, and fibrinogen) will be required. In the patient with liver disease, levels of these procoagulants are low, but generally sufficient to support hemostasis. However, severe deficiencies in procoagulants or fibrinogen may occur in patients with severe dilutional- or consumption coagulopathy (including patients with severe sepsis and disseminated intravascular coagulation and patients with uncontrolled bleeding). In such patients, administration of rFVIIa may be futile.

In conclusion, there is a need for carefully designed clinical studies to assess efficacy of rFVIIa administration to patients with liver disease and uncontrollable, hemostasis-related bleeding. Only when these studies show a beneficial effect of rFVIIa, an increased risk of thrombotic events may be considered acceptable ‘collateral damage’. For now, we believe there is little evidence for a widespread use of rFVIIa as a rescue agent in patients with liver disease.

Conflict of interest

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References


