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USE of RECOMBINANT FACTOR VIIa in UNCONTROLLABLE HAEMORRHAGE

A Position Statement of the NSW Therapeutic Assessment Group Inc.

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EXECUTIVE SUMMARY

Recombinant factor VIIa (NovoSeven[®]) has been commercially available through recombinant technology since March 1999. The approved indication in Australia is haemostasis or prophylaxis (surgery) in patients with inhibitors to coagulation factors VIII or IX.

The effectiveness of the drug is clinically proven in double-blinded, randomised clinical trials *only for haemophilia*. However, there are many case reports, and some small case series in the literature of use of factor VIIa for patients with life- threatening bleeding other than haemophilia. A number of clinical trials in indications other than haemophilia are currently in progress, both internationally and in Australia, including cirrhotic and non cirrhotic liver transplants, upper GIT bleeds (oesophageal varices), trauma, post-partum haemorrhage, intracerebral haemorrhage, paediatric cardiopulmonary bypass and bone marrow transplants.

At this time, diagnosis of the specific defect, and therapy with specific coagulation factors, plasma, or platelets, remain first line therapies for patients with uncontrollable haemorrhage.

When these measures fail it may be reasonable to use rFVIIa as an attempted "rescue" therapy for massively transfused patients with persistent bleeding despite appropriate blood component transfusion, haemostatic measures, pharmacological measures and surgical intervention. This would include patients who have received more than 10 units of packed cells in 24 hours, or replacement of blood volume within 3 hours, and also situations where insufficient packed cells are available. Experience based solely on case reports indicates a haemostatic effect of rFVIIa in doses of 60-120µg/kg. One or two bolus injections may be enough to decrease bleeding significantly.

The decision to use rFVIIa should be made in consultation with a haematologist. A full blood count and coagulation profile (APTT,INR and fibrinogen) should be available prior to use of rFVIIa and should be repeated after the product is given, to assess response. Additional fresh frozen plasma, platelets, or cryoprecipitate may need to be given after rFVIIa.

1. INTRODUCTION

1.1 Normal Haemostasis and the role of factor VIIa

Current models of haemostasis suggest that cells rather than proteins control coagulation, which is thought to occur in three overlapping stages: initiation, amplification and propagation. Tissue factor/ factor VIIa ('extrinsic pathway') initiates coagulation on the surface of TF-bearing cells. The small amount of thrombin formed on these cells amplifies the procoagulant signal by activating cofactors (factor V and factor VIII) and factor XI, and enhances platelet activation. In the propagation phase, the factor VIIIa/ factor IXa complex activates factor X on the platelet surface, and it is this factor Xa that is thought to be responsible for the large-scale thrombin production that leads to fibrin clot formation¹

In the absence of factor VIII or IX ('haemophilia'), insufficient factor Xa is produced on the surface of the platelet to generate enough thrombin to form a fibrin clot, and thus bleeding can occur. However, recent work has demonstrated that high-dose factor VIIa can effectively 'replace' factors VIIIa and IXa on the platelet surface, thereby restoring platelet-surface Xa generation and subsequent platelet surface thrombin generation. It is this property of factor VIIa that led to its use in haemophiliac patient with inhibitors and more recently it has also been used in patients with non haemophiliac bleeding disorders. The potential mechanisms of action of factor VIIa include enhanced platelet thrombin generation as well as enhanced platelet aggregation.

Clearance of rFVIIa is approximately 30-35 ml/kg/h in adults and greater in children², requiring repeated dosing approximately every 2 hours for maintenance of efficacy. The recommended route of administration is as bolus injections, which produce high plasma levels following injection.

1.2 Approved Indications

Recombinant factor VIIa (eptacog alpha; rFVIIa; NovoSeven[®], Novo Nordisk) has been commercially available through recombinant technology since March 1999- developed for the prevention of spontaneous bleeding episodes and for diminution of intra-operative blood loss in the 15-25% of patients with haemophilia who have inhibitors (antibodies) of clotting factors VIII and IX. The approved indication in Australia is haemostasis or prophylaxis (surgery) in patients with inhibitors to coagulation factors VIII or IX.

2. CLINICAL EVIDENCE

In researching this document the Medline, Embase, and Cochrane databases were searched to September 2002. No guidance documents were available from organisations such as CCOHTA and NICE.

Recombinant factor VIIa is clinically proven in double-blinded, randomized clinical trials *only for hemophilia*. However, there are now over 20 case reports, and also some small case series, of its use in patients with life- threatening bleeding other than haemophilia. A number of clinical trials for indications other than haemophilia are currently in progress,

both internationally and in Australia. These include cirrhotic and non cirrhotic liver transplants, upper GIT bleeds (oesophageal varices), trauma, post-partum haemorrhage, intracerebral haemorrhage, paediatric cardiopulmonary bypass and bone marrow transplants. (Personal Communication, Jean Young, Novo Nordisk, October 2002). A website (NovoSeven Extended Use Data Collection System) has been set up for physicians to register off-label use in their patients, in order to secure structured outcome data collection in these patients. See www.haemostasis.com.

2.1 Recombinant factor VIIa in situations with impaired thrombin generation (other than haemophilia)

Since factor VIIa enhances thrombin generation on the platelet surface, an exogenous source is potentially of benefit in situations of impaired thrombin generation eg patients with platelet disorders. There have been case reports of success in achieving haemostasis after administration of rFVIIa for thrombocytopenia³, thrombocytopenia refractory to platelet transfusion owing to antibodies to platelet antigens⁴, some states of platelet dysfunction⁵ and in Glanzmann thrombasthenia⁶

2.2 Surgery and severe trauma resulting in profuse bleeding

Recombinant factor VIIa has been used (in conjunction with surgery) for patients with necrotizing pancreatitis⁷, hip arthroplasty in a patient with cirrhosis & thrombocytopenia⁸, rectal haemorrhage⁹, pulmonary haemorrhage¹⁰, skull base hemangiopericytoma¹¹, bleeding after open heart surgery¹², stab wounds¹³ and postpartum haemorrhage¹⁴.

Haemorrhage is a major cause of trauma-related death, and presents in most patients as a combination of diffuse coagulopathic bleeding and bleeding from vessels that require surgical treatment¹⁵. Recombinant factor VIIa is approved in Israel for compassionate use in patients suffering from massive, life threatening bleeding as a result of trauma or surgery and a case series of 9 trauma patients¹⁵ and also 9 surgical patients¹⁶ have been reported.

Australian experience in treatment of massive bleeding in ten non-haemophiliac adult patients has recently been presented¹⁷. The median dose was 100µg/kg (range 32-180 µg/kg) and median time after onset of bleeding was 14 hours. Two patients received a second dose of factor VIIa. Transfusion requirements were reduced or eliminated in the majority of patients following factor VIIa administration and 6 of 10 patients survived the episode of massive haemorrhage.

2.3 Acquired factor VIIa deficiency

This may result from a defect in the normal synthesis of factor VII, such as reported in patients receiving oral anticoagulant therapy and in patients with impaired liver function¹⁸. Cirrhotic patients are at an increased risk of bleeding from routine procedures such as liver biopsy and also during major surgery such as liver transplantation¹⁸. Recombinant factor VIIa has been used in patients with cirrhosis with normalization of prothrombin time¹⁹. A pilot study undertaken to examine the effects of an 80 µg/kg bolus of rFVIIa given at the beginning of surgery in liver transplantation patients found that red blood cells requirements were significantly reduced in those patients who received the drugs as

compared to those who did not²⁰. Severe bleeding refractory to standard haematological or haemostatic support is common in patients undergoing bone marrow transplantation (BMT). The use of rFVIIa in 3 patients with intractable bleeding undergoing BMT has been reported²¹, as has its use in children with liver disease²²

A 40µg/kg dose has been used in paediatric patients²². Doses of 60-260 µg/kg IV have been used for adult patients. Frequency of administration has varied widely, from a stat dose, to 'every 2 hours for 21 hours', to 'every 4-24 hours for 14 days' (see Table 1).

3. ADVERSE EVENTS

Few thrombotic events have been reported in the more than 170,000 doses of rFVIIa given, and predisposing factors such as previous cardiovascular disease and advanced age were present in most cases¹⁸. There is a theoretical possibility of induction of systemic pathologic thrombosis when using factor VIIa, thus some authors believe it is contraindicated in patients with severe disseminated intravascular coagulation (DIC) or crush injuries. Caution has been advised in the use of rFVIIa for bleeding after open heart surgery²³. The drug has been given to a limited number of healthy volunteers without safety problems²⁴.

The product information states that contraindications to use of NovoSeven[®] include known hypersensitivity to NovoSeven[®] or any of its components, or known hypersensitivity to mouse, hamster or bovine proteins. Patients who receive NovoSeven[®] should be kept under close observation in case they develop signs and symptoms of untoward activation of the coagulation system or thrombosis. Any findings of this nature indicate that the dosage should be reduced or treatment stopped, depending on the patient's symptoms. In pathological conditions in which tissue factor can be expected in circulating blood, there is the possibility of a thrombogenic potential or induction of DIC in association with NovoSeven[®] treatment. Such situations may include patients with advanced atherosclerotic disease, crush injury, septicaemia or DIC. The PI also states that caution should be exercised in prescribing NovoSeven[®] for patients who have significant hypersensitivity to platelets and/or blood products. However, these patients will have of necessity, already been exposed to most blood products available, prior to use of rFVIIa.

4. RECOMMENDATIONS

To date, clinical efficacy of rFVIIa, has only been proven in double blind randomized clinical trials in patients with haemophilia. By the very nature of many of the trauma situations in which rFVIIa would be potentially useful, it would be virtually impossible to conduct a double-blind randomised trial. Thus, for diagnoses other than haemophilia, the evidence base consists of case reports and small case series, and optimal dosage regimens especially in paediatric patients are not well established. Efficacy has not been demonstrated for patients without a preoperative coagulation disorder, in whom abnormal intra-operative bleeding develops.

Each dose of the protein is expensive (acquisition cost around \$A1050 for 1.2mg vial or \$4200 for 4.8mg vial). Thus a stat dose of 60µg/kg (bottom of adult range cited in case reports for bleeding in non haemophiliac patients) for an 80kg patient would cost \$4200.

- At this time, diagnosis of the specific defect, and therapy with specific coagulation factors, plasma, or platelets, remain first line therapies for patients with uncontrollable haemorrhage.
- When these measures fail it may be reasonable to use rFVIIa as an attempted "rescue" therapy for massively transfused patients (patients who have received more than 10 units of packed cells in 24 hours, or replacement of blood volume within 3 hours) with persistent bleeding despite appropriate blood component transfusion, haemostatic measures (including efforts to correct hypothermia and hypocalcaemia), pharmacological measures (eg antifibrinolytics) and surgical intervention. This would also include situations where insufficient packed cells are available.
- The decision to use rFVIIa should be made in consultation with a haematologist.
- A full blood count and coagulation profile (APTT, INR and fibrinogen) should be available prior to use of rFVIIa and should be repeated after the product is given, to assess response. Additional fresh frozen plasma, platelets, or cryoprecipitate may need to be given after rFVIIa.
- Experience based solely on case reports indicates a haemostatic effect of rFVIIa in doses of 60-120µg/kg. One or two bolus injections often seem to be enough to decrease bleeding significantly.

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Table 1 Case reports and case series of Factor VIIa use in non haemophiliac patients

Investigator	Patient Details	Dose and frequency of rfVIIa
Chuansumrit ²²	Pre-term infant; intraventricular haemorrhage; extraperitoneal haematoma;	40µg/kg; repeated at 7 hours
Kenet ¹⁶	Case series of 9 patients aged 6 to 84, treated for surgery-related bleeding	80-150µg/kg given from 1-34 hours from initiation of uncontrolled bleeding event.
Svartholm ⁷	- severe necrotising pancreatitis - 50 year old female with massive haemorrhage from splenic artery	- 120µg/kg repeated at 5 hours
Sanchez ⁹	65 year old male with liver cirrhosis; rectal haemorrhage	70µg/kg IV 30 min before surgery
Kamphuisen ¹⁰	44 year old male	60µg/kg IV; repeated at 12 hours
Chuansumrit ²²	children with liver disease	40µg/kg combined with FFP (fresh frozen plasma) in 5 children with liver disease to control bleeding episodes and provide haemostasis for invasive procedures
Sanchez ⁹	Rectal Haemorrhage 65 year old male with liver cirrhosis; impaired coagulation, epistaxis, haematomas and rectal haemorrhage	70µg/kg IV given 30 mins prior to surgery
Poon ⁶	Glanzmann thrombasthenia	use has been reported to International registry on FVIIa and congenital platelet disorders
Kamphuisen ¹⁰	44 year old male suicide attempt; Pulmonary haemorrhage	60µg/kg IV repeated at 12 hours.
Gerlach ¹¹	Skull base hemangiopericytoma 64 year old woman;	120µg/kg within an interval of 2 hours
Hendriks ¹²	65 year old male Bleeding after open heart surgery	90µg/kg bolus.
Investigator	Patient Details	Dose rfVIIa ; frequency
Martinowitz ¹⁵	9 multitransfused trauma patients	Dose varied from 40 to 120µg/kg ; 4 patients received more than one dose. Blood requirements decreased significantly; no clinical evidence of venous or arterial

		thromboembolic complications was observed.
Gerotziafas ²⁵	Ex-vivo effect on prothrombin activation studied in 2 patients with severe thrombocytopenia and life threatening haemorrhage.	Single doses of 90µg/kg; normalisation of aPTT after 30 minutes; fibrinogen and D-dimer levels in plasma were not affected, but factor VIIa administration did induce a decrease of Ivy bleeding time and normalisation of clot retraction.
Essex ¹³	Stab wounds	single 90µg/kg dose
White ²⁶	2 patients with Crohn's disease and massive lower GIT bleeding post surgery.	Given 1-2 doses of 90 µg/kg
Vlot ²⁷	Bleeding duodenal ulcer male	given 90µg/kg every 2 hours for 21 hours.
Blatt ²¹	3 Bone marrow transplant patients treated for: haemorrhagic cystitis(3), GIT bleeding (2) pulmonary haemorrhage (1)	Boluses of 90-270 µg/kg; ensuing doses of 90 µg/kg every 4-24 hours for 3-14 days; while maintaining platelets above 50,000/mm ³ .
Moscardo ²⁸	Intractable obstetric haemorrhage; severe abdominal bleeding associated with DIC.	Given 90µg/kg every 3 hours for 9 doses, with no significant side effects.
Mousa ¹⁴	Postpartum haemorrhage: protocol for management (second-line-failure to control bleeding.	Includes factor VII 90µg/kg

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