USE OF NOVOSEVEN® (RECOMBINANT ACTIVATED FACTOR VII) IN ICU

Normal haemostasis

Revised theory of coagulation in the 1990s emphasized the importance of the extrinsic pathway as the initiator of coagulation. The initiation stage occurs after the formation of Tissue Factor (TF) – FVIIa complex, with generation of FXa and small amounts of thrombin, allowing platelet activation and release of FVIII from VWF. Amplification of the response involves production of FIXa on the activated platelet surfaces, catalyzing FXa formation and subsequent large-scale thrombin generation.

What is NovoSeven?

NovoSeven® is recombinant activated human coagulation Factor VIIa (rFVIIa) intended for promoting haemostasis by activating the extrinsic pathway of the coagulation cascade. It is supplied as sterile, white lyophilized powder in single-use vial with the following constitutes per vial: 1200ug rFVIIa, 5.84mg sodium chloride, 2.94mg calcium chloride dihydrate, 2.64mg glycylglycine, 0.14mg polysorbate 80 and 60mg mannitol.

Pharmacodynamics

Action of rFVIIa is two-folded

1. Binding to tissue factor located on the subendothelium, leading to platelet activation and a thrombin burst
2. TF independent – at pharmacologic dose, binds to activated platelets and initiate clotting by generating FXa, leading to a thrombin burst

From its distinct mechanism, haemostasis is promoted only at the site of injury. However, systemic coagulation remains a theoretical concern.

Pharmacokinetics

Vd at steady state - 103 mL/kg
Clearance - 33 mL/kg/hr
T½ - 2.3 hours

Indications and Dosages

Approved for treatment of bleeding episodes in haemophilia A or B patients with inhibitors to Factor VII or Factor IX

IV bolus administration: 90 mcg/kg every 2 hours until hemostasis is achieved or until treatment is judged ineffective. The dose and interval may be adjusted based upon the severity of bleeding. Continuous infusion possibly inferior to bolusing. 30 mcg/kg will normalize the PT, >300mcg/kg is the theoretical dose for maximum thrombin generation. 90-120 mcg.kg is a reasonable compromise because of cost.

The duration of therapy following haemostasis has not been fully established, although the use of continuous infusion at 10-50 mcg/kg/hour for median of 20 days has been described (1,2)

Off-label uses

1. **Warfarin –related bleeding**

   Recommendation from 2004 American College of Chest Physicians (ACCP) Consensus Conference for patients with warfarin related life-threatening bleeding

   - rFVIIa is given with Vit K 10mg. INR is checked after 30 minutes, aim at < 1.2
   - rFVIIa as low as 15 to 20 mcg/kg IV has been used successfully (3,4)
   - Prothrombin complex is cheaper but much more thrombogenic

2. **Spontaneous Intracerebral Haemorrhage**

   A phase IIb randomized controlled trial is undertaken and preliminary result as followed - in subjects with spontaneous ICH confirmed by CT scan within three hours of symptom onset, use of rFVIIa led to a significant reduction in hematoma growth, and significantly improved neurological and functional outcomes at 90 days.

3. **Liver disease (including fulminant hepatic failure)**

   Upper gastrointestinal bleeding - increased bleeding control in patients with Child's B and C cirrhosis, but no overall effect on mortality (5)

4. **Trauma**

   No evidence to support *routine* use when conventional therapy failed. Case series suggest impressive rescues in some seemingly hopeless patients. Laboratory studies suggest that rFVIIa is effective against coagulopathy induced by hypothermia,, acidosis, DIC and dilution. Exact timing of its use not well defined, but currently uses in trauma are confined to "hopelessly" bleeding cases "refractory" to conventional coagulation management. Cost remains a dis-incentive against earlier use.

5. **Others**

   - Thrombocytopaenia
   - Bleeding in neonates
   - Post-operative bleeding
   - Virtually all other cases of severe bleeding not amenable to surgical correction. Exception may include anticoagulation due to large doses of synthetic small-molecule direct thrombin inhibitors eg Argatroban (6)

Reminder

All conventional and appropriate haemostatic management should precede, and continue irrespective of whether rFVIIa is used. rFVIIa should not be a replacement for sound clinical practice

Contraindications

Known hypersensitivity to rFVIIa or any of its components; hypersensitivity to mouse, hamster, or bovine proteins

Side effects

Generally well tolerated
Possible adverse effects < 1%

- Allergic reaction, bradycardia, hypotension, abnormal renal function, vomiting, injection site pain, coagulation disorder, decreased prothrombin
- Disseminated intravascular coagulation (theoretical)

Drug Interaction

Unknown.

Monitoring the effect of rFVIIa

- Near linear relationship between rFVIIa activity and its plasma level, but difficult to measure rFVIIa activity with standard laboratory tests
- (Recommended dose based on target concentration of > 30 U/ml)
- PT will normalize at about 5 U/ml
- aPTT may not normalize, even with peak therapeutic concentrations
- Monitoring is mainly clinical

Reference

1.Santagostino et al. *Relationship between factor VII activity and clinical efficacy of recombinant factor VIIa given by continuous infusion to patients with factor VIII inhibitors*. Thromb Haemost 2001; 86:954

2.Ludlam et al. *A prospective study of recombinant activated factor VII administered by continuous infusion to inhibitor patients undergoing elective major orthopaedic surgery: a pharmacokinetic and efficacy evaluation*. Br J Haematol 2003; 120:808

3.Deveras et al. *Reversal of warfarin-induced excessive anticoagulation with recombinant human factor VIIa concentrate*. Ann Intern Med 2002; 137:884

4.Lin et al. *The use of recombinant activated factor VII to reverse warfarin-induced anticoagulation in patients with hemorrhages in the central nervous system: preliminary findings.* J Neurosurg 2003; 98:737

5.Bosch J et al. *Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial.* Gastroenterology. 2004 Oct; 127(4): 1123-30

6. Malherbe S. et al. *Argatroban as anticoagulant in cardiopulmonary bypass in an infant and attempted reversal with recombinant activated factor VII.* Anesthesiology 2004; 1002):443-5