Should recombinant factor VIIa be used for the treatment of patients with severe blunt trauma?

Recombinant factor VIIa (rFVIIa, NovoSeven; Novo Nordisk, Denmark) was approved by the European Union in 1996 for the treatment of spontaneous bleeding in haemophiliacs with inhibitors to factors VIII or IX. Additional licensed indications have now broadened to include the treatment of patients with factor VII deficiency and Glanzmann's thrombasthenia. Based on the ability of rFVIIa to generate thrombin at the site of injury, there has also been interest in the potential of rFVIIa as a pro-haemostatic agent in patients with acquired coagulopathy. Since rFVIIa was first described in the literature over half of all the publications related to rFVIIa describe its 'off-label' use. In particular, there has been a great deal of interest generated in its role as an adjunctive treatment in traumatic injury.

rFVIIa should be given in blunt traumatic injury

The first account of the off-label use of rFVIIa was a case report published in the *Lancet* by Kenet et al (1999). This documented the successful use of rFVIIa in a soldier with traumatic coagulopathy following a high velocity gunshot wound to the inferior vena cava. Since this time there have been numerous retrospective studies that have been encouraging but only one randomized controlled trial of rFVIIa in bleeding trauma patients (Boffard et al, 2005). Blunt and penetrating trauma were randomized separately; patients were given rFVIIa or placebo after receiving eight units of red blood cells within the first 24 hours of injury. The initial dose of rFVIIa used was 200 µg/kg, followed by 100 µg/kg 1 hour later and an additional 100 µg/kg 2 hours after that. In patients with blunt trauma, there was a significant decrease in both red blood cells transfusion (2.6 units) and number of patients (14% *vs* 33%) requiring massive transfusions (defined as >20 units of red blood cells) in those alive at 48 hours. With the penetrating trauma group there was no significant effect of rFVIIa with respect to red blood cells requirement or massive transfusion.

Importantly, this study also showed a significant reduction in the incidence of acute respiratory distress syndrome in patients with blunt trauma treated with rFVIIa, although this did not translate into mortality benefit. This study allayed some of the concerns about the safety of rFVIIa in non-haemophiliac patients as the incidence of serious adverse events, particularly thromboembolic ones, was not increased.

Consensus guidelines on the use of rFVIIa as an adjunctive treatment for massive bleeding have been published (Vincent et al, 2006). These give a European perspective and recommend that the same dosing regimen used in the Boffard trial (200, 100, and 100 µg/kg rFVIIa given initially, after 1 hour and after 3 hours) should be used in patients with blunt traumatic injury. However, rFVIIa should only be used as an adjunctive therapy to surgical control (and/or embolization), and only when all other attempts to control bleeding have failed. No recommendations were made for penetrating trauma.

rFVIIa should not be given in blunt traumatic injury

A systematic review investigating the role of rFVIIa for the prevention and treatment of bleeding in patients without haemophilia has been published by the Cochrane Collaboration (Stanworth et al, 2007). They concluded that unrestricted, unevaluated administration of rFVIIa outside licensed uses did not seem justified and its wider use should await the results of ongoing and possibly newly commissioned trials. In addition, a report based on passive surveillance of reports describing thromboembolic events for the Food and Drug Administration Adverse Reporting system indicated that many events following rFVIIa occurred off-label and resulted in serious morbidity and mortality (O'Connell et al, 2006).

Further safety concerns have emerged with the results of the Factor Seven for Acute Hemorrhagic Stroke (FAST) study that were presented at the 16th European Stroke Conference in May 2007. This was a phase III trial with 821 patients treated with placebo, 20 µg/kg or 80 µg/kg of rFVIIa. There was no improvement in clinical outcomes with rFVIIa but there was a significant difference in arterial thromboembolic events between placebo and 80 µg/kg of rFVIIa (5% *vs* 10%).

Conclusions

There is a currently a paucity of high quality data regarding safety and efficacy of rFVIIa in blunt traumatic injury and therefore it should not be used routinely. A phase III trial of rFVIIa in traumatic injury is currently underway which may allow more definitive recommendations once the results are published. **BJHM**

Dr MR Duffy *is Locum Consultant in Anaesthesia, Derriford Hospital, Plymouth PL6 8DH*

Boffard KD, Riou B, Warren B et al (2005) Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. *J Trauma* **59:** 8–15

Kenet G, Walden R, Eldad A, Martinowitz U (1999) Treatment of traumatic bleeding with recombinant factor VIIa. *Lancet* **354:** 1879

O'Connell KA, Wood JJ, Wise RP et al (2006) Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA* **295**(3): 293–8

Stanworth SJ, Birchall J, Doree CJ, Hyde C (2007) Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophila. *Cochrane Database Syst Rev* **18**(2): CD005011

Vincent JL, Rossaint R, Riou B et al (2006) Recommendations on the use of recombinant factor VII as an adjunctive treatment for massive bleeding – a European perspective. *Critical Care* **10**(4): R120

Anaesthetic and critical care dilemmas are coordinated by Dr John Orr and Dr Annie Hunningher, Research Fellows at the Centre for Anaesthesia, UCL, London Ideas for future dilemmas can be sent to Rebecca Linssen bjhm@markallengroup.com