The potential role for recombinant factor VIIa in cardiac surgery

Recombinant factor VIIa (rFVIIa, Novoseven®, Novo Nordisk®, Denmark) is established for the management of bleeding episodes in haemophiliac patients with inhibitors.[1,2] Interest has been growing in the use of this drug for the management of severe intractable bleeding following major trauma and surgery.[3] The potential benefits of this drug are that it is a recombinant product, avoiding the potential immunological and infective complications of allogeneic transfusion, and that it has a mechanism of action that should limit its effects to the site of tissue injury.[4-6]

Cardiac surgical services are high users of allogeneic transfusion, with up to 80% of patients undergoing even routine cardiac surgery being given an allogeneic transfusion (Carbery *et al.*, NATA [Network for Advancement of Transfusion Alternatives] Meeting, Rome, 2002). These patients are at particular risk for coagulopathic bleeding as a result not only of pre-operative drug-induced platelet dysfunction but also of the effects of cardiopulmonary bypass (CPB), including hyperfibrinolysis, platelet dysfunction and a reduction in circulating coagulation factors.[7,8] During complex cardiac surgery, all of these effects are exacerbated by prolonged CPB and long periods of hypothermia.

The management of coagulopathic bleeding after cardiac surgery usually relies on the administration of allogeneic haemostatic products. This can be ameliorated by stopping antiplatelet agents and warfarin before surgery and the intra-operative use of antifibrinolytic agents proven to reduce patient exposure to transfusion after cardiac surgery.[9-11] In the context of limited resources and an increasing demand for allogeneic products, the search for safe and effective alternatives to allogeneic transfusion is of great importance.[12,13]

Site-specific action

Experimental trials of the mechanism of action of rFVIIa demonstrated that it primarily has effects at the site of initial injury. This was at first thought to work via a tissue factor-dependent pathway, leading to activation of factor X and, in the presence of FVa, the generation of thrombin.[14] However, more recent evidence suggests that the supra-normal levels of rFVIIa administered clinically cause a thrombin burst following the generation of a pro-thrombinase complex on the surface of activated platelets (figure 1). This can occur not only in the absence of factors VIII and IX (explaining its efficacy in haemophilia patients) but in the presence of thrombocytopaenia or platelet dysfunction.[15,16]

Interest in the use of rFVIIa in the non-haemophiliac population stemmed from the apparent ability of the drug to act in a site-specific manner in the absence of some of the usual factors required for coagulation. In other words it may represent a 'universal haemostatic'.[17] The first reported use of rFVIIa outside haemophilia was the management of an Israeli soldier who, following an extensive gunshot wound, had persistent life-threatening bleeding in spite of multiple surgical attempts at haemostasis coupled with large quantities of conventional haemostatic products.[18] A dose of 60 µg/kg of rFVIIa was given 'in a desperate attempt to control the bleeding'. This had an immediate effect in reducing bleeding levels, and the bleeding was fully controlled after one further dose of rFVIIa.

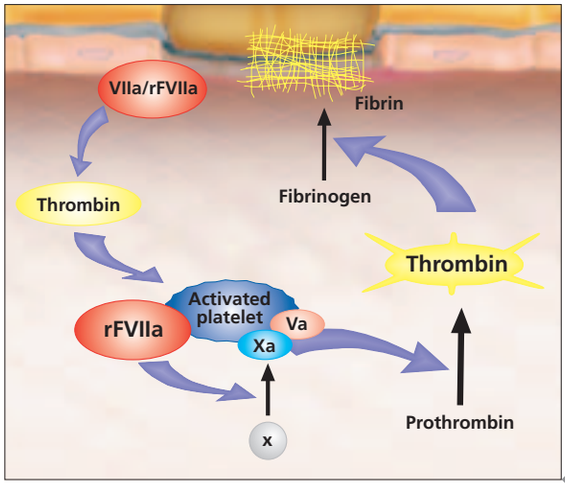
Since then, a case series of 19 patients (10 with blunt trauma and nine with penetrating trauma) has been reported on the successful use of rFVIIa in this setting.[19] In this group of patients four of the total did not respond to the rFVIIa and exsanguinated, but overall there was a 68.4% survival rate. There have also been experimental studies on pigs given severe liver injuries that show the efficacy of rFVIIa in terms of elevation of arterial pressure, reduction in blood loss and a trend to survival advantage.[20,21] A double-blind, randomised controlled trial of the use of rFVIIa for traumatic bleeding is due to be published soon.

Clinical evidence

In elective surgery, case reports on the successful use of rFVIIa have included patients who were bleeding following liver surgery and orthopaedic surgery.[22,23] To date, only one randomised, double-blind, placebo-controlled trial of the use of rFVIIa in the non-haemophiliac population has been published.[24] This investigated the effect of rFVIIa on peri-operative blood loss in 36 patients undergoing retropubic prostatectomy. The investigators found that peri-operative blood loss was reduced in the groups given rFVIIa, with a significantly greater effect at a dose of 40 µg/kg compared to 20 µg/kg. In the 40 µg/kg group no patients required allogeneic red cell transfusion (p=0.001, when compared to placebo).

Cardiac surgical patients share some of the causative fac-

Figure 1. The mechanism of action of rFVIIa. The combination of rFVIIa and exposed tissue factor initiates the coagulation process with the generation of a small amount of thrombin. This leads to the amplification stage, during which platelets become activated, leading to a large thrombin burst and the stabilisation of a localised fibrin clot



Key: rFVIIa = recombinant factor VIIIa
Courtesy of Novo Nordisk®

tors for coagulopathic bleeding with other surgical and trauma patients, notably hypothermia, activation of inflammation and dilutional effects. However, as has been previously stated, they also have additional risks for the development of coagulopathic bleeding, most especially from a functional platelet defect. The published experience of rFVIIa in cardiac surgery has included a total of 14 patients to date (12 adults and two children).[25-33] These case reports have included a wide spectrum of cardiac surgical procedures. All patients received rFVIIa on a compassionate basis to manage life-threatening bleeding that was unresponsive to standard haemostatic product transfusion and surgical intervention. Therapeutic effect was achieved at a variety of doses ranging from 30 µg/kg to 107 µg/kg.[25,27]

Within our unit we have used rFVIIa for the management of severe intractable cardiac surgical bleeding unresponsive to standard therapy in 15 patients. Types of surgery included root replacements, acute dissections, and combined valve replacement and coronary grafting. Effective haemostasis was secured in 11 patients, with an overall survival to hospital discharge of 60%.[34] Recently, we have completed a randomised, double-blind, placebo-controlled pilot study on the elective use of rFVIIa in patients undergoing complex non-coronary cardiac surgery where the patient was felt to be highly likely to receive allogeneic transfusion. Following CPB and reversal of the effects of heparin, patients were randomised to receive either 90 µg/kg of rFVIIa or equivalent volumes of normal saline. Two out of nine patients in the rFVIIa group received an allogeneic transfusion, compared to eight out of 10 patients in the placebo group (relative risk of transfusion of 0.27; 95% CI 0.07–0.9; p=0.02).[35] There were no apparent thrombotic complications, and there was one death in the placebo group from multiple organ failure.

There remain concerns regarding the use of rFVIIa in cardiac surgical patients.[36] Coronary plaques are known to express tissue factor and therefore could pose a potential site for the generation of thrombin following rFVIIa administration.[37] In addition, there are concerns regarding potential generalised systemic activation of coagulation. To date, only small numbers of patients with coronary artery disease have received rFVIIa, and there have been no reported coronary thrombotic events related to rFVIIa administration in this group. No evidence for the generation of a generalised prothrombotic state following rFVIIa administration has been forthcoming. Most of the safety data on rFVIIa so far have come from the haemophiliac population, in whom there have been relatively few reported adverse events. Clear unequivocal safety data for the non-haemophiliac population are not yet available.

The future

Research so far on the use of rFVIIa to manage cardiac surgical bleeding (and other surgical and traumatic causes of bleeding) is providing intriguing insights into its possible applications in the future. For patients who were previously considered to be at very high risk of receiving an allogeneic transfusion, this drug may offer the potential for transfusion-free surgery. However, at present the absence of large multicentred trials on the efficacy and safety of this drug in these novel settings will limit its use to the management of bleeding that is unresponsive to more conventional treatments. Currently, we believe that if all other avenues for the management of life-threatening bleeding in the cardiac surgical patient have been explored, then the use of rFVIIa should be considered.

Conflict of interest

RG has acted as a consultant and received honoraria from Novo Nordisk®. The haematology department of Southampton University Hospitals NHS Trust has received a research grant from Novo Nordisk®. The company has had no role in design, execution or interpretation of any studies performed.

References

1. Hedner U, Glazer S, Pingel K *et al*. Successful use of recombinant factor VIIa in patient with severe haemophilia A during synovectomy. *Lancet* 1988;**2**:1193.

2. Hedner U, Ingerslev J. Clinical use of recombinant FVIIa (rFVIIa). *Transfus Sci* 1998;**19**:163-76.
3. Erhardtsen E. Ongoing NovoSeven trials. *Intensive Care Med* 2002;**28** (suppl 2):S248-55.
4. Landers DF, Hill GE, Wong KC, Fox IJ. Blood transfusion-induced immunomodulation. *Anesth Analg* 1996;**82**:187-204.
5. Snyder EL, Dodd RY. Reducing the risk of blood transfusion. *Hematology (Am Soc Hematol Educ Program)* 2001:433-42.
6. Hoffman M, Monroe DM 3rd, Roberts HR. Activated factor VII activates factors IX and X on the surface of activated platelets: thoughts on the mechanism of action of high-dose activated factor VII. *Blood Coagul Fibrinolysis* 1998;**9**(suppl 1):S61-5.
7. Mammen EF, Koets MH, Washington BC *et al*. Hemostasis changes during cardiopulmonary bypass surgery. *Semin Thromb Hemost* 1985;**11**: 281-92.
8. Kestin AS, Valeri CR, Khuri SF *et al*. The platelet function defect of cardiopulmonary bypass. *Blood* 1993;**82**:107-17.
9. Henry DA, Moxey AJ, Carless PA *et al*. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2001(1):CD001886.
10. Levi M, Cromheecke ME, de Jonge E *et al*. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. *Lancet* 1999;**354**:1940-7.
11. Laupacis A, Fergusson D. Drugs to minimize perioperative blood loss in cardiac surgery: meta-analyses using perioperative blood transfusion as the outcome. The International Study of Peri-operative Transfusion (ISPOT) Investigators. *Anesth Analg* 1997;**85**:1258-67.
12. Mortimer PP. Making blood safer. *BMJ* 2002;**325**:400-01.
13. DOH. Better Blood Transfusion. London: The Stationery Office, 2002.
14. Bauer KA, Kass BL, Ten Cate H, Hawiger JJ, Rosenberg RD. Factor IX is activated in vivo by the tissue factor mechanism. *Blood* 1990;**76**:731-6.
15. Kristensen J, Killander A, Hippe E *et al*. Clinical experience with recombinant factor VIIa in patients with thrombocytopenia. *Haemostasis* 1996;**26**(suppl 1):159-64.
16. Tranholm M, Rojkjaer R, Pyke C *et al*. Recombinant factor VIIa reduces bleeding in severely thrombocytopenic rabbits. *Thromb Res* 2003;**109**: 217-23.
17. Grounds M. Recombinant factor VIIa (rFVIIa) and its use in severe bleeding in surgery and trauma: a review. *Blood Rev* 2003;**17**(suppl 1):S11-21.
18. Kenet G, Walden R, Eldad A, Martinowitz U. Treatment of traumatic bleeding with recombinant factor VIIa. *Lancet* 1999;**354**:1879.
19. Martinowitz U, Kenet G, Lubetski A, Luboshitz J, Segal E. Possible role of recombinant activated factor VII (rFVIIa) in the control of hemorrhage associated with massive trauma. *Can J Anaesth* 2002;**49**(10):S15-20.
20. Martinowitz U, Holcomb JB, Pusateri AE *et al*. Intravenous rFVIIa administered for hemorrhage control in hypothermic coagulopathic swine with grade V liver injuries. *J Trauma* 2001;**50**:721-9.
21. Lynn M, Jerokhimov I, Jewelewicz D *et al*. Early use of recombinant factor VIIa improves mean arterial pressure and may potentially decrease mortality in experimental hemorrhagic shock: a pilot study. *J Trauma* 2002;**52**:703-07.
22. Silva MA, Muralidharan V, Mirza DF. The management of coagulopathy and blood loss in liver surgery. *Semin Hematol* 2004;**41**(suppl 1):S132-9.
23. Kaw LL Jr, Coimbra R, Potenza BM, Garfin SR, Hoyt DB. The use of recombinant factor VIIa for severe intractable bleeding during spine surgery. *Spine* 2004;**29**:1384-7; discussion 1388.
24. Friederich PW, Henny CP, Messelink EJ *et al*. Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomised trial. *Lancet* 2003;**361**:201-05.
25. Al Douri M, Shafi T, Al Khudairi D *et al*. Effect of the administration of recombinant activated factor VII (rFVIIa; NovoSeven) in the management of severe uncontrolled bleeding in patients undergoing heart valve replacement surgery. *Blood Coagul Fibrinolysis* 2000;**11**(suppl 1):S121-7.
26. Hendriks HG, van der Maaten JM, de Wolf J, Waterbolk TW, Slooff MJ, van der Meer J. An effective treatment of severe intractable bleeding after valve repair by one single dose of activated recombinant factor VII. *Anesth Analg* 2001;**93**:287-9.
27. Naik VN, Mazer CD, Latter DA, Teitel JM, Hare GM. Successful treatment using recombinant factor VIIa for severe bleeding post cardiopulmonary bypass. *Can J Anaesth* 2003;**50**:599-602.
28. Tobias JD, Groeper K, Berkenbosch JW. Preliminary experience with the use of recombinant factor VIIa to treat coagulation disturbances in pediatric patients. *South Med J* 2003;**96**(1):12-16.
29. Tanaka KA, Waly AA, Cooper WA, Levy JH. Treatment of excessive bleeding in Jehovah's Witness patients after cardiac surgery with recombinant factor VIIa (NovoSeven). *Anesthesiology* 2003;**98**:1513-15.
30. Stratmann G, Russell IA, Merrick SH. Use of recombinant factor VIIa as a rescue treatment for intractable bleeding following repeat aortic arch repair. *Ann Thorac Surg* 2003;**76**:2094-7.
31. von Heymann C, Hotz H, Konertz W, Kox WJ, Spies C. Successful treatment of refractory bleeding with recombinant factor VIIa after redo coronary artery bypass graft surgery. *J Cardiothorac Vasc Anesth* 2002;**16**: 615-16.
32. Stratmann G, deSilva AM, Tseng EE *et al*. Reversal of direct thrombin inhibition, after cardiopulmonary bypass in a patient with heparin-induced thrombocytopenia. *Anesth Analg* 2004;**98**:1635-9.
33. Kastrup M, von Heymann C, Hotz H *et al*. Recombinant factor VIIa after aortic valve replacement in a patient with osteogenesis imperfecta. *Ann Thorac Surg* 2002;**74**:910-12.
34. Gill R, Herbertson M, Diprose P. New alternatives for control of severe cardiac surgical bleeding. *Semin Hematol* 2004;**41**(suppl 1):174.
35. Diprose P, Herbertson M, O'Shaughnessy D, Gill R. A pilot double blind placebo controlled trial of the use of recombinant factor VIIa in high transfusion risk cardiac surgery. *Eur J Anaesthesiology* 2004;**21**(suppl 33):9.
36. Dietrich W, Spannagl M. Caveat against the use of activated recombinant factor VII for intractable bleeding in cardiac surgery. *Anesth Analg* 2002;**94**:1369-70; author reply 1370-1.
37. Moons AH, Levi M, Peters RJ. Tissue factor and coronary artery disease. *Cardiovasc Res* 2002;**53**:313-25.

Paul Diprose
Clinical Fellow
Greenlane Department of Anaesthesia
Auckland City Hospital, Private Bag 92-024,
Auckland, New Zealand.

Ravi Gill
Consultant Anaesthetist
Shackleton Department of Anaesthesia,
Southampton University Hospitals NHS Trust,
Tremona Road, Southampton, SO16 6YD.

Correspondence to: Dr R Gill
(email: ravi.gill@suht.swest.nhs.uk)

Br J Cardiol (Acute Interv Cardiol) 2004;**11**:AIC 77–AIC 79