

April/May 2005

## Welcome to the Newsletter of the Haemostasis Registry

### What is the Haemostasis Registry?

The Haemostasis Registry is a national registry aiming to collect data on the use of recombinant activated factor VII (rFVIIa, marketed under the brand name NovoSeven®) in patients with critical bleeding.

FVIIa is a naturally occurring initiator of haemostasis. Its recombinant form, rFVIIa, is approved for the treatment of spontaneous and surgical bleeding in patients with haemophilia with antibodies to either factor VIII or factor IX. It has been extensively used amongst haemophiliacs and enhances clotting at the site of bleeding through the formation of a firm fibrin clot, without systemic activation of the coagulation cascade.

Recently various case series and case reports have suggested the efficacy of rFVIIa in non-haemophiliac patients with life-threatening bleeding. Initially these were mostly patients with serious trauma, but more recently the use of rFVIIa has spread to other clinical settings where critical bleeding has occurred. These include bleeding after cardiac surgery, liver transplantation, severe post-partum haemorrhage and intracerebral haemorrhage.

Patients with uncontrolled bleeding and coagulopathy, despite large transfusions and surgical intervention have significant mortality rates. In addition, transfusion of blood and blood products is known to be correlated with increased morbidity and mortality and increased costs to the health care system, not just in blood products themselves, but also in extended ICU and hospital stays.

The main concern associated with the use of rFVIIa, as with all pro-

thrombotic agents, is the potential for an increased risk of systemic thrombosis. In preliminary case series, however, the rate of serious adverse thrombotic events has been very low, which may be related to the mechanism of action of rFVIIa which acts after exposure of TF (tissue factor) at the site of bleeding. One of the purposes of the Haemostasis registry is to collect data to identify the possible adverse effects associated with using rFVIIa.

The purpose of the Registry is to collect systematic and prospective data from patients treated with rFVIIa in Australia and New Zealand with the aim of:

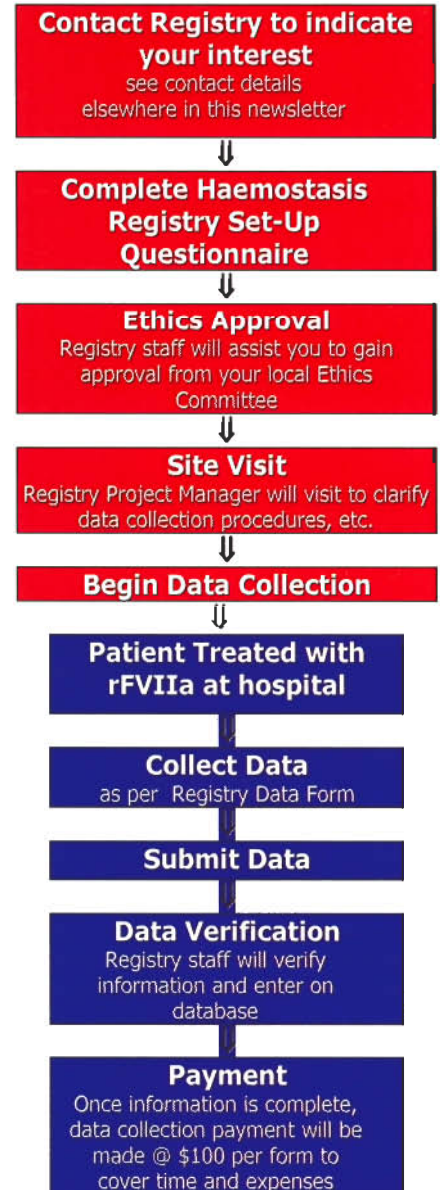
- investigating the safety and efficacy of rFVIIa in various bleeding indications
- monitoring the extent, indications for, dosages and appropriateness of use
- providing information to assess cost-effectiveness
- generating new information to support clinical use
- providing supportive data for Regulatory Authority submissions.

The Haemostasis Registry is supported by an unrestricted Educational Grant provided by Novo Nordisk Pharmaceuticals Pty Ltd.

### Department of Epidemiology and Preventative Medicine

The Monash University Department of Epidemiology and Preventative Medicine is well placed to undertake the establishment and management of the Haemostasis Registry. The Department has a wealth of experience in the management and analysis of data registries and is currently responsible for the management of over ten data registries. Our staff includes a variety of medical specialists and pharmacologists as well as statisticians, bioethicists and database specialists.

### How will the Registry Work?



### Ethics Approval

Approval has been granted by the Monash University Standing Committee On Ethics In Research Involving Humans (SCERH) and the Alfred Hospital Ethics Committee. We are hoping within the next few months to have approval to collect data at another 5-6 hospitals around Australia.

## Recent Publications and Clinical Trials

### Intracerebral Haemorrhage

Early in 2005, Mayer and colleagues (*N Engl J Med* 2005; 352:777-85) published a report of an international multi-centre trial involving 399 patients with ICH and including six Australian clinical centres. Patients were randomly assigned to receive either a placebo or 40, 80 or 160µg/kg of rFVIIa. Mayer and colleagues found that giving rFVIIa within four hours of the onset of ICH limited haematoma volume, reduced mortality and improved outcome at 90 days. There was an associated small increase in the frequency of thromboembolic adverse events.

### Trauma

At present the evidence of efficacy of rFVIIa in trauma springs largely from case reports, but a recent large randomised controlled trial has been conducted in trauma- stratified to blunt and penetrating groups. This trial is due to be published during 2005.

### Cardiac Surgery

Large volumes of blood are required for patients undergoing cardiac surgery where coagulopathic bleeding is a high risk because of the complexity of the surgery, the bypass process and the preoperative use of anti-platelet or anticoagulant drugs. Case studies have reported the use of rFVIIa as a rescue therapy in these situations. A pilot study was reported by Herbertson (*Blood Coagulation & Fibrinolysis* 2004; 15:S31-32) where 20 patients were prospectively given rFVIIa (90µg/ kg) after cardiopulmonary bypass and after administration of protamine. Results of this and larger randomized trials are yet to be published.

### Other

In 2003, Friederich and colleagues (*Lancet* 2003;361:201-05) reported the results of a small trial in patients undergoing retropubic prostatectomy. Thirty-six patients were randomized to receive either a placebo or 20 or 40 µg/kg of rFVIIa in the early operative phase. The results showed that the patients receiving rFVIIa lost less blood than those receiving the placebo. None of the patients receiving the 40 µg/kg dose required any transfusion. This study reported no adverse events.



## Cost of Blood Transfusion

In addition to the potential to save lives by stopping life threatening haemorrhage, rFVIIa may have a potential role in reducing blood loss in non-life threatening situations.

In the year 2003/2004, blood and blood related products used in approved indications in Australia cost around \$500 million. (*Source: Annual Report 2003-04 National Blood Authority*). This is funded through the Federal Government (63%) and the State and Territory Governments (37%). However, the cost of blood transfusion can be considered to be much higher if on-costs are included. These include the costs in the hospital of medical and administrative staff, storage, administration and monitoring of blood component supply and use, and laboratory costs associated with blood product use.

In addition, blood transfusion has been reported to be a risk factor for: mortality, ICU admission, ICU length of stay and hospital length of stay (*J. Trauma* 2003;54:898-907) all of which may be considered to add significantly to both the financial and human cost of blood transfusion. Any possibilities to reduce the necessity or amount of blood transfusion while still maintaining positive outcomes should be seriously considered by the medical community.

## Bibliography

The Haemostasis Registry is keeping an up to date bibliography of publications related to the use of rFVIIa. We hope to have this bibliography up on our web site shortly. In the interim, please contact us to obtain information on publications.

## Registry Steering Committee

The Steering Committee for the Haemostasis Registry is comprised of those with an interest in the clinical use of rFVIIa, those involved in the commercial production and the clinical trials of rFVIIa, those with expertise in the management of Registries, and Registry Staff.

The Chair of the Steering Committee is Professor James Isbister who is Emeritus Consultant in Haematology and Transfusion Medicine at Royal North Shore Hospital, Clinical Professor of Medicine, University of Sydney, Adjunct Professor, University of Technology, Sydney



PROF. JAMES ISBISTER

The other members of the Steering Committee are;

- Professor Peter Cameron,  
Monash University, Department of Epidemiology and Preventative Medicine
- Professor John McNeil,  
Monash University, Department of Epidemiology and Preventative Medicine
- Professor Hatem Salem,  
Blood Diseases Group, Department of Medicine, Monash University
- Dr Gary Jankelowitz,  
Medical Advisor, Novo Nordisk Pharmaceuticals
- Ms Wendy Thomas,  
Haematology Project Manager, Novo Nordisk Pharmaceuticals
- Dr Louise Phillips,  
Haemostasis Registry Project Manager, Monash University, Department of Epidemiology and Preventative Medicine
- Mr Andrew Hannaford,  
Haemostasis Registry Database Manager, Monash University, Department of Epidemiology and Preventative Medicine

## CONTACT US:

### haemostasis registry

Monash University, Department of Epidemiology and Preventative Medicine, 3<sup>rd</sup> Floor Burnet Building, The Alfred Hospital, Commercial Road, Melbourne, 3004

### Chief Investigator:

Professor Peter Cameron

### Project Manager:

Dr Louise Phillips

Phone: 03 9903 0551

Fax: 03 9903 0576

email: [louise.phillips@med.monash.edu.au](mailto:louise.phillips@med.monash.edu.au)

Website: [www.med.monash.edu/epidemiology/traumaepi/haemostasis.html](http://www.med.monash.edu/epidemiology/traumaepi/haemostasis.html)