

A factor in combating massive haemorrhage

Biomedical scientist Barry Hill takes a look at how the latest treatment used in the management of haemophilia and other rare bleeding disorders is acquiring a growing reputation in the treatment of all forms of uncontrolled bleeding.

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Congenital haemophilia is a rare bleeding disorder caused by gene mutations on the X chromosome; thus, it affects men almost exclusively. Two types arise: the more common haemophilia A, which affects one person in 5000; and the less common haemophilia B, which affects one person in 30,000. Currently, around 6000 patients in the UK alone are receiving treatment for haemophilia A, and an estimated 400,000 are being treated worldwide.

The clinical presentations of haemophilia A and haemophilia B are virtually identical and are characterised by delayed and prolonged bleeding disorders, classified as mild, moderate or severe. Approximately 70% of haemophilia patients have moderate or severe disease, but virtually all experience prolonged bleeding after trauma or surgery. The severe form usually becomes apparent in the first year of life, while the moderate form is detected during early childhood. The mild form often makes itself known following minor surgery such as tooth extraction.

In most severe cases in the absence of treatment, haemorrhage occurs into the joints and results in loss of mobility or, during major episodes of spontaneous

bleeding, even death. Intracranial haemorrhage accounts for a third of all deaths. Thus, in most patients with haemophilia, it is potentially dangerous to perform even the simplest of surgical procedures without taking preventative measures.

TREATMENT AND HAZARDS

Over the past 30 years, treatment of haemophilia by replacement therapy has changed considerably. Initially, human plasma and cryoprecipitate were utilised, and then later plasma-derived factor concentrates became available. Owing to this improvement in treatment, haemophilia sufferers could look forward to a normal lifespan and were able to undergo most forms of surgical procedure.

However, longstanding problems caused by the transmission of human immunodeficiency virus (HIV) and hepatitis A and C via blood products have resulted in many cases of acquired immune deficiency syndrome (AIDS) and liver disease in the haemophilia population, and thus considerable morbidity and mortality. Viral inactivation was introduced to combat these problems, but now the threat of variant Creutzfeldt-Jakob disease (vCJD) transmission is an added concern. However, the recent advent of recombinant (non-plasma-derived) products has overcome the hazard of pathogen transmission for the majority of patients.

Another serious problem with the use of traditional therapy to treat haemophilia is the development of inhibitors to the replacement clotting factor – so-called refractoriness. This occurs in 15–30% of haemophilia A patients

and in 2–3% of haemophilia B patients. Consequently, inhibitor patients are at increased risk of major and sudden bleeding episodes as, due to this refractory effect, factor replacement therapy becomes ineffective. As a result, inhibitors have become a major cause of morbidity in haemophilia patients.

Thus, it is in the management of acquired haemophilia and in patients with inhibitors where recombinant products have proved invaluable, and they are establishing themselves rapidly as the treatment of choice.

THROMBIN BURST

Recombinant activated human coagulation factor VII (rFVIIa) is a genetically engineered serine protease that can overcome the deficiencies in the coagulation process that these conditions represent. Haemostasis normally begins very soon after endothelial damage, and exposed tissue factor forms a complex with inherent activated FVII that, in combination with several other clotting factors, produces a limited amount of thrombin in the immediate area of the injury (initiation). This activates other clotting factors as well as platelets aggregated at the site of injury (amplification) to produce a large, local thrombin burst (propagation), which leads to the formation of a stable fibrin clot.

The mode of action of therapeutic rFVIIa in patients with FVII deficiency is to replace the missing factor, and so enable initiation of coagulation to occur. In patients with other coagulation deficiencies, where the initiation or amplification phases are affected, higher doses of rFVIIa can bypass those phases and

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interact directly with locally activated platelets to produce the necessary thrombin burst. Essentially, therefore, this reliance on locally activated platelets means that rFVIIa initiates haemostasis locally without causing systemic coagulation. This then results in the rapid formation of an effective haemostatic plug to stem the flow of blood.

Until the introduction of rFVIIa, even minor surgery in patients with inhibitors proved to be very challenging, but now they can undergo even major surgery with only minimal risk of uncontrolled haemorrhage and complications. Although rFVIIa was developed for the treatment of haemophilia, so successful has its impact been in controlling bleeding that it is now enjoying a growing reputation in other important situations.

MASSIVE HAEMORRHAGE

Extensive bleeding invariably results at the site of an injury following major trauma, and similarly this can also occur during emergency or even routine surgical procedures, and also following childbirth. The traditional response to these uncontrolled bleeding episodes has been to use transfusion support with a range of blood products, including red cells, fresh frozen plasma (FFP), cryoprecipitate and platelets. In extreme cases (eg gunshot or knife wounds and serious road traffic accidents) this can sometimes lead to massive transfusions of over 50 units of blood products, often without a favourable outcome due to the difficulty in maintaining the necessary levels of the various clotting factors required.

However, reports are emerging to show that the administration of rFVIIa in these critical circumstances can be very successful in saving lives. Owing to its ability to correct coagulation abnormalities and rapidly arrest bleeding, rFVIIa began to be used as a last resort in these desperate situations. For instance, a case reported in *The Lancet* describes how a young soldier with uncontrolled bleeding from a bullet injury to his vena cava received over 40 units of red cells, plus FFP, platelets and cryoprecipitate, but continued to haemorrhage. However, after administration of two doses of rFVIIa the bleeding was halted and he eventually made a full recovery.

Use of rFVIIa has also been reported in the successful treatment of massive haemorrhage in obstetric cases,

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gastrointestinal bleeding (including variceal haemorrhage) and during major abdominal and cardiothoracic surgery following over-treatment with anticoagulants and following chemotherapy. Clinical trials in many of these areas are underway in an attempt to confirm these initial reports.

Finally, as a result of its ability to reduce or even eliminate the use of blood products during planned surgery, rFVIIa is also an acceptable option to patients who are Jehovah's Witnesses, particularly when used in combination with other blood sparing alternatives (eg cell salvage) in the operating theatre.

WONDER DRUG?

It may be premature to hail rFVIIa as the new universal haemostatic agent, but initial reaction to it by the medical and surgical fraternities has been promising. Already a very valuable licensed tool for use in haemophilia and other bleeding disorders, rFVIIa is also becoming a life-saving agent in trauma and surgery and on the battlefield.

By reducing the requirements for blood

and blood products following trauma or surgery, rFVIIa may have a valuable future role in minimising the effect of the shortfall in UK blood donations following implementation of vCJD safety precautions. Safety is another big plus in its favour, as rFVIIa is a natural coagulation factor produced by DNA technology. Therefore, there is no risk of human viral contamination.

Furthermore, rFVIIa is well tolerated and the frequency of adverse events or side effects following its use is very low, compared with the inherent risks (eg transmission of infection, possible immunosuppression, and the possibility of procedural errors) associated with the use of donated blood products.

However, a major drawback to the use of rFVIIa is cost, as a typical treatment for one patient can cost upward of £3500 to the NHS. But, when this is put into context with factors such as reduced hospital stay and the escalating cost of providing safe transfusion support, then this figure may not be as expensive as it appears. As a result, many hospital blood banks are now beginning to hold small stocks of rFVIIa for emergency cases, and therefore its use is likely to increase enormously over the years to come. ■

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