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Recombinant activated factor VII use in the emergency department

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ABSTRACT

Recombinant activated factor VII (rFVIIa) has recently gained wide attention as a potent prohaemostatic agent for patients with excessive or life-threatening blood loss. Originally licensed for the treatment of patients with bleeding haemophilia with antibodies to factor VIII or IX, rFVIIa is now being used on an off-label basis to thwart blood loss in a variety of other clinical situations. Despite concerns over the drug's cost, risk profile and the lack of large-scale clinical trials validating its use, more and more patients are being treated with rFVIIa in the emergency department. With few clinical trials available to guide its administration, emergency physicians must weigh the existing evidence when considering whether to use rFVIIa for their patients with bleeding. This paper reviews the current literature regarding rFVIIa as it pertains to the practice of emergency medicine.

There is a saying in medicine that all bleeding stops eventually. Emergency physicians are trained to recognise and control bleeding quickly, knowing that early intervention is the cornerstone of treatment. The mainstays of emergency department (ED) management traditionally involve tamponade, aggressive volume and blood product replacement and rapid reversal of existing coagulopathies until definitive haemostasis can be achieved.

In recent years recombinant activated factor VII (rFVIIa) (NovoSeven; NovoNordisk, Princeton, NJ, USA) has received much attention for its ability to enhance haemostasis in patients with profuse or life-threatening haemorrhage. Originally approved to treat bleeding episodes in haemophilia patients with alloantibodies to factor VIII or IX, rFVIIa has been increasingly used on an off-label basis for patients with traumatic, surgical and coagulopathic bleeding (box 1).¹ In many cases rFVIIa has reportedly helped achieve haemostasis when massive transfusions of blood products proved ineffective.

Concerns have been raised, however, over the potential for thrombotic complications with rFVIIa and the lack of large-scale clinical trials validating its safety and efficacy for off-label uses.² rFVIIa is also very expensive, costing up to \$4500 per 4.8 mg vial. The recommended initial dose for an 80 kg patient might cost \$9000. In addition, with its relatively short half-life of 2.7 h, multiple doses may be necessary.

Although few randomised trials are available to guide its administration, off-label use of rFVIIa is increasing, driven by clinicians who believe that existing data and anecdotal experience justify its use in a variety of clinical situations.^{1,3}

Haematologists, surgeons, anaesthesiologists and intensivists are the providers most commonly using rFVIIa off-label; notably, in almost 30% of cases the drug is being administered in the ED.¹

Emergency physicians are often the first to encounter bleeding patients and will play an increasing role in determining when rFVIIa should be used.⁴ It is therefore imperative that emergency care providers become familiar with the drug, its clinical utility, administration and risk profile. This review summarises the current evidence regarding the use of rFVIIa in the ED so that emergency physicians can make informed decisions when caring for bleeding patients.

METHODS

A search was made of PubMed/MEDLINE (January 1966–February 2008), The Cochrane Library and Aries Knowledge Finder for English language clinical and basic science studies examining rFVIIa in the treatment of severe haemorrhage or blood loss in situations relevant to the daily practice of the emergency physician. The electronic search used the MeSH terms “recombinant factor VIIa”, “factor VIIa” AND “haemorrhage”, “intracerebral haemorrhage”, “gastrointestinal bleeding”, “trauma”, “warfarin”, “DIC” as well as other search terms relevant to the ED physician. The references of all articles were cross-examined for further relevant publications relating to ED use of rFVIIa. Two authors (BCD and MED) reviewed the selected references individually for relevance and content. A third author (PEF) performed a subsequent review of all articles. Any discrepancies were resolved by committee.

Articles were included in the review based on the methodological quality of the research and the direct relevance to ED practice. Primary research topics (see subheadings below) were chosen based on the availability of evidence from one or more randomised clinical trials or the indication among the literature that a significant number of physicians are currently using rFVIIa in a given manner (ie, for reversal of anticoagulation) that justifies a review of the available evidence for such use. Some indications with a limited amount of evidence stemming mainly from case reports (ie, use of rFVIIa in postpartum haemorrhage) were not included in this review for the sake of brevity.

MECHANISM OF ACTION

Activated factor VII is a recombinant human coagulation factor synthesised *in vitro* using baby hamster kidney cells (NovoSeven product information). It is structurally similar to human

Box 1 Off-label uses of recombinant activated factor VII

- ▶ Trauma
- ▶ Gastrointestinal/variceal bleeding
- ▶ Intracranial haemorrhage
- ▶ Massive obstetrical haemorrhage
- ▶ Reversal of anticoagulation
- ▶ Perioperative haemostasis
- ▶ Platelet disorders

plasma-derived factor VIIa, a vitamin K-dependent coagulation protease produced in the liver.

Pharmacological doses of rFVIIa are thought to enhance coagulation specifically at the site of injury by binding to exposed tissue factor on damaged endothelium.⁵ The FVII/tissue factor complex activates factor IX into factor IXa and factor X into factor Xa resulting in a burst of thrombin production at the point of intimal injury. Thrombin generation in turn activates localised platelets, factor V and factor VIII leading to the creation of fibrin and a haemostatic plug. Some research has suggested that rFVIIa also binds directly to activated platelets at the site of injury, activating factor X in a tissue factor-independent pathway.⁶ Again the result is thrombin formation, conversion of fibrinogen to fibrin and creation of a clot. The clot is further stabilised by rFVIIa-induced activation of fibrinolytic inhibitors (fig 1).⁷

POTENTIAL INDICATIONS FOR rFVIIa IN THE EMERGENCY DEPARTMENT

Haemophilia with inhibitors

Several clinical trials have shown the safety and efficacy of rFVIIa for patients with bleeding haemophilia with inhibitors, which remains the only indicated and FDA approved use of the drug.^{8,9} A randomised double-blind clinical trial performed by Lusher *et al* tested the safety and efficacy of two different rFVIIa dosages (35 µg/kg and 70 µg/kg) for treating bleeding patients

with haemophilia A or haemophilia B, both with and without FVII antibody inhibitors.⁸ rFVIIa treatment was rated efficient or excellent in 71% of bleeding episodes (n = 145). Hay *et al*⁹ reported results of the compassionate use of rFVIIa for patients with acquired haemophilia between 1990 and 1995 in 32 international centres. rFVIIa was used as second-line therapy for patients with acquired haemophilia in whom first-line treatments had failed to control bleeding. They reported an effective or partial response for 88% of bleeding episodes after 8 h of treatment and for 92% after 24 h of treatment, highlighting the efficacy of rFVIIa as second-line salvage treatment in patients with acquired haemophilia.⁹

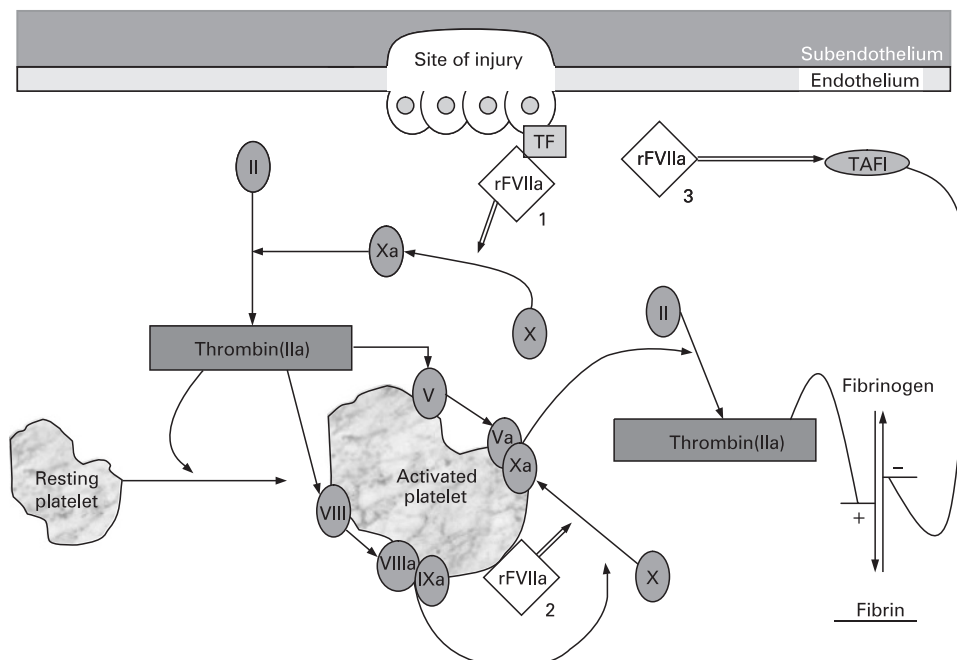
Dosing among the rFVIIa haemophilia trials varies. Lusher *et al*⁸ showed both 35 µg/kg and 70 µg/kg unit doses to be safe and effective for patients presenting with spontaneous joint, muscle or mucocutaneous bleeding. Up to 6 unit doses were administered per bleeding episode at an interval of 2.5 ± 0.5 h. In the study by Hay *et al* both dosing and frequency of administration varied on a case-by-case basis; the minimum rFVIIa dosage administered was 45 µg/kg and the median initial rFVIIa dose was 90.4 µg/kg (range 45–181 µg/kg) with a median of 28 doses administered per bleeding episode (range 1–541).⁹ The authors suggest that the optimal dosing lies between 35 µg/kg and 90 µg/kg, depending upon the severity of the bleeding.⁹

Overall, evidence for the use of rFVIIa in patients with haemophilia has shown that it is effective as a primary or adjunctive therapy in controlling spontaneous bleeding without a preponderance of adverse thrombotic side effects.

Trauma

Uncontrolled bleeding is the leading cause of death in trauma.¹⁰ Early control of bleeding and treatment of traumatic coagulopathy have the potential to decrease mortality. A potent procoagulant medicine such as rFVIIa has potential utility here as an adjunct to surgical damage control and aggressive fluid resuscitation and angiographic embolisation. In 2001 Martinowitz *et al*¹¹ published a series of seven cases in which rFVIIa was used as an adjunct to surgical haemostasis. Since

Figure 1 Mechanism of action of recombinant activated factor VII (rFVIIa). rFVIIa encourages haemostasis through three separate mechanisms: (1) direct binding to exposed tissue factor (TF) at the site of vascular injury which results in the activation of free factor X to factor Xa, in turn causing a thrombin burst; (2) binding to activated platelets resulting in the conversion of factor X to factor Xa which in turn links with factor Va to further encourage thrombin formation; (3) upregulation of thrombin-activated fibrinolysis inhibitor (TAFI) which mitigates clot breakdown.



then there have been numerous case series and reports describing the use of rFVIIa in traumatic bleeding and coagulopathy, but only one significant randomised trial.

Boffard *et al*¹² simultaneously conducted two double-blind randomised controlled trials examining the efficacy and safety of rFVIIa in penetrating and blunt trauma. Eligibility criteria were patients aged 16–65 years presenting with “severe” trauma, defined as that requiring administration of 6 units of packed red blood cells (RBCs) within 4 h of admission to the trauma service. Patients with severe head injuries (Glasgow Coma Score <8), extreme metabolic acidosis (pH <7.0), a history of myocardial infarction or extensive prehospital blood transfusion (≥ 8 units RBCs) were excluded. Two hundred and seventy-seven patients were randomised to receive three subsequent intravenous injections of rFVIIa (200, 100, 100 $\mu\text{g}/\text{kg}$) starting after the eighth unit of packed cells was transfused and at 1 and 3 h after the first dose. The authors reported that transfusion requirements during the first 48 h were significantly reduced in the blunt trauma group (by ~ 2.6 units PRBC) and the need for massive transfusion (defined as >20 units PRBC) was reduced by nearly 20%. A similar trend was seen in a subset of patients with penetrating trauma. Mortality and mean clinical parameters (prothrombin time (PT), activated partial thromboplastin time), however, did not differ significantly between groups. Post hoc subgroup analyses by the same investigators concluded that patients with traumatic coagulopathy may derive some additional benefit from rFVIIa, as might patients with a higher likelihood of survival on presentation.^{13 14} Thromboembolic adverse events (pulmonary embolism, deep venous thrombosis) occurred in six patients receiving rFVIIa and six receiving placebo.

Despite decreased transfusion requirements, patients in the study by Boffard *et al*¹² did not receive a mortality benefit with rFVIIa use. Multicentre prospective studies are underway that will better define patient selection, dosage, timing of administration and monitoring for rFVIIa in trauma patients with uncontrolled bleeding. Preliminary guidelines have recently been published by Martinowitz *et al* in advance of these studies.¹⁵

Intracerebral haemorrhage

Intracerebral haemorrhage (ICH) is arguably the most debilitating form of acute stroke, with over one-third of affected patients dying within 1 month of onset and only 20% regaining long-term functional autonomy.¹⁶ Current treatment of ICH is mostly supportive. Ongoing bleeding and haematoma expansion contribute to poor clinical outcomes but may be mitigated by early procoagulant therapy.¹⁷ The use of rFVIIa in ICH has recently been evaluated in two large-scale industry-sponsored clinical trials.^{16 18}

In the phase II multicentre prospective trial by Mayer *et al*¹⁶ 399 adults presenting with acute ICH documented by CT scan within 3 h of the onset of symptoms were randomised to receive 40 $\mu\text{g}/\text{kg}$ ($n = 108$), 80 $\mu\text{g}/\text{kg}$ ($n = 92$) or 160 $\mu\text{g}/\text{kg}$ ($n = 103$) of rFVIIa or placebo ($n = 96$) within 1 h of baseline imaging. Haematoma volume at 24 h increased more in the placebo group than the three treatment groups combined (29% vs 14%, $p = 0.01$), with the larger doses demonstrating the greatest effect. Subgroup analysis of the results showed an even more pronounced haemostatic effect (growth of haematoma 13% vs 34%, $p = 0.004$) in those subjects treated within 3 h of symptoms. In this study, treatment with rFVIIa was associated with a 16% absolute reduction in the incidence of death or severe disability (modified Rankin scale score of 4–6) after 90 days. It is important to note, however, that this was a phase

II trial designed primarily to assess drug safety and not significantly powered to directly examine neurological outcomes and mortality. The primary outcome measure, the overall incidence of adverse events, was not significantly different between the placebo and treatment groups.

To the surprise and disappointment of many, the results of the phase III trial failed to show any benefit of rFVIIa over placebo in reducing death and disability at 3 months.¹⁸ The results did, however, show a significant dose-related reduction in haematoma growth. The phase III trial, Factor VII for Acute Haemorrhagic Stroke Treatment (FAST), was conducted in 26 countries and randomised 841 patients to placebo vs rFVIIa at doses of 20 $\mu\text{g}/\text{kg}$ or 80 $\mu\text{g}/\text{kg}$. All patients were treated within 4 h of symptom onset. The placebo group had a mean increase of 26% in haematoma volume compared with 18% in the 20 $\mu\text{g}/\text{kg}$ group ($p = 0.09$) and 11% in the 80 $\mu\text{g}/\text{kg}$ group ($p < 0.001$). The combined end point of death or severe disability was 24% in the placebo group, 26% in the 20 $\mu\text{g}/\text{kg}$ group and 29% in the 80 $\mu\text{g}/\text{kg}$ group. Examined by themselves, mortality and disability rates were also similar in the three groups. There was no difference in the overall rate of thromboembolic events.

In comparison with the phase II study, the phase III FAST trial did include more elderly patients and patients with a history of myocardial infarction and stroke. Nonetheless, the mortality of the control group in the phase III trial was lower than that in the phase II trial (19% vs 29%) and the absolute increase in arterial thromboembolic adverse events with rFVIIa treatment remained the same. Post hoc analyses did show an outcome benefit in the small group of younger patients (<70 years old) treated with rFVIIa earlier (<2.5 h), most likely representing the effects of the drug on halting active bleeding; however, the authors admit this deserves further study.

Reversal of anticoagulation

In the ED bleeding complications of anticoagulant therapy, specifically with warfarin, are encountered routinely. For all patients taking warfarin, conservative estimates suggest an annual incidence of 0.6% for fatal bleeding and 3.0% for major haemorrhage.¹⁹ Age and intensity of warfarin therapy are both independent predictors of the risk of bleeding, and the ED population is generally older and more likely to be over-anticoagulated than the general public.^{20 21} Serious bleeding in these patients presents a significant therapeutic challenge requiring rapid reversal of their coagulopathy in the setting of multiple co-morbidities.

Accepted options for rapid coagulopathy reversal include infusions of fresh frozen plasma (FFP), prothrombin concentrates and vitamin K. Each of these options has drawbacks. For instance, the full effect of vitamin K administration on reversal of the international normalised ratio (INR) has been shown to take up to 24 h, so it must be used together with faster acting agents.²² FFP can achieve rapid reversal but requires relatively large rapid volume infusions that can precipitate pulmonary oedema in elderly patients and those with heart disease.²³ FFP also carries the risk of blood-borne infection and transfusion reactions and must be thawed. Prothrombin concentrates have been associated with a risk of thrombogenesis and disseminated intravascular coagulopathy (DIC) and are not widely available in the USA.²⁴

For these reasons, rFVIIa has emerged as a potentially promising agent for rapid reversal in warfarin-related haemorrhage. Doses as low as 15–20 $\mu\text{g}/\text{kg}$ have been shown to normalise the INR of an anticoagulated patient within minutes (note that normalisation of INR or PT alone does not

automatically imply reversal of anticoagulant; the effectiveness of rFVIIa is measured most reliably by clinical effect).²⁵ Several case series have reported the successful use of rFVIIa for the reversal of warfarin-associated bleeding.^{26, 27} Brody *et al* retrospectively described 12 patients on warfarin with intracranial bleeding treated with rFVIIa (70 µg/kg on average) in addition to vitamin K and FFP and compared them with 15 concurrently admitted patients who received FFP and vitamin K alone.²⁶ The median time from presentation to documented INR <1.3 was 9 h in the rFVIIa group and 32 h in the control group. One patient with end-stage renal disease developed DIC while on rFVIIa; one patient who received FFP and vitamin K alone developed pulmonary oedema.

Freeman *et al* reported seven consecutive patients with warfarin-related intracranial haemorrhage in a retrospective study treated with an average dose of 62 µg/kg rFVIIa.²⁷ Six of these patients also received FFP and vitamin K. The INR in five of these patients was reduced to <1.5 in less than 5 h; one patient needed a second dose and another patient had a normal INR when first checked at 8 h.

Data from the studies by Brody *et al* and Freeman *et al* are drawn retrospectively from small heterogeneous groups of patients without uniform dosages or time to rFVIIa administration. While preliminary evidence from these reports supports the use of rFVIIa as an adjunctive therapy in patients with warfarin-related ICH, prospective clinical trials must be conducted to evaluate the efficacy of rFVIIa in this situation before widespread use is adopted. Additionally, these trials should thoroughly evaluate the incidence of serious adverse events with the use of rFVIIa in patients on warfarin who are at a high risk of developing thrombotic complications.

Gastrointestinal bleeding

Acute gastrointestinal bleeding is another common presentation in the ED requiring prompt intervention. Particularly vulnerable are patients with underlying coagulation abnormalities such as those resulting from long-standing cirrhosis or warfarin therapy where reversal of coagulopathy is paramount. Rapid prohaemostatic intervention via rFVIIa may have the potential to improve outcomes in this population.

Recombinant FVIIa has been tested in one randomised placebo-controlled trial as an adjunctive therapy in cases of severe gastrointestinal blood loss in patients with cirrhosis. Bosch *et al*²⁸ examined the use of rFVIIa in 245 cirrhotic patients at 26 hospitals across Europe. Patients with active signs of upper gastrointestinal bleeding who were scheduled to undergo exploratory endoscopy within 12 h of the onset of bleeding were randomised to receive eight doses of 100 µg/kg rFVIIa at intervals up to 30 h vs placebo in conjunction with standard supportive therapy. Patients with advanced cirrhosis

(Child-Pugh score ≥12) were excluded. rFVIIa failed to show a beneficial effect on a composite end point composed of (1) failure to control bleeding within 24 h, (2) failure to prevent rebleeding within 24 h to 5 days, and (3) death within 5 days among the entire study population. A subgroup analysis showed that patients with variceal bleeding did benefit from rFVIIa therapy as measured by a decrease in the occurrence of the composite end point (23% vs 8%, $p = 0.03$) and in the failure to control bleeding within 24 h (11% vs 0%, $p = 0.01$). The incidence of adverse thrombotic events was similar between the groups (6%).

The results from the trial by Bosch *et al* indicate that rFVIIa is not efficacious for the reversal of upper gastrointestinal bleeding in all patients with cirrhosis. The findings from their subgroup analysis in patients with variceal bleeding warrant further exploration before widespread application of rFVIIa in this population is undertaken.

Additional uses

The direct action of rFVIIa on platelets suggests its potential utility in patients with functional platelet disorders and thrombocytopenia.²⁹ Indeed, there are a number of studies describing its successful use in patients with Glanzmann thrombasthenia, autoimmune and drug-induced thrombocytopenias and Bernard-Soulier syndrome.^{30, 31} These disorders are relatively rare and heterogeneous enough to make prospective trials difficult. At this time there is limited clinical evidence to support the use of rFVIIa in the setting of these coagulopathies.

There are many other potential applications of rFVIIa for bleeding patients in the ED. Most have seen little or no investigation—for example, retroperitoneal bleeding, ruptured abdominal aortic aneurysm, severe and prolonged epistaxis, massive haemoptysis, traumatic brain injury or expanding haematomas. It may also be reasonable to consider rFVIIa for life-threatening haemorrhage in Jehovah's Witnesses and other patients who are opposed to receiving blood or blood products.

DOSING

Standard dosing of rFVIIa in haemophilia patients with acquired inhibitors is 90 µg/kg intravenous (IV) bolus every 2–3 h until cessation of bleeding, but doses between 35 and 120 µg/kg have been used with success.³² Unfortunately there are few experimental data to guide dosing of rFVIIa for off-label uses, so the optimal doses for different indications are unknown. Table 1 shows dosing used in the major randomised trials mentioned above.

In their survey of the off-label use of rFVIIa, MacLaren and colleagues calculated a median initial dose of 76 µg/kg being used for the prevention of bleeding and a median dose of 89 µg/kg being used for bleeding cessation.¹ In general, these results are

Table 1 Dosing of recombinant activated factor VII (rFVIIa) in selected randomised controlled trials

Trial	No of patients	Dosing (µg/kg)	Time	Maximum dose (n)	Arena
Lusher <i>et al</i> ⁶	84	35 or 70	Every 2.5 ± 0.5 h	6	Acquired haemophilia
Hay <i>et al</i> ⁹	38	90.4 (45–181)*	–	28 (1–541)*	Acquired haemophilia
Boffard <i>et al</i> ¹²	301	200, 100, 100	0, 1, 3 h	3	Trauma
Mayer <i>et al</i> ¹⁶	399	40 or 80 or 160	<4 h	1	ICH
Bosch <i>et al</i> ²⁸	245	100	0, 2, 4, 6, 12, 18, 24, 30 h	8	GI bleed

*Doses presented as median (range).

ICH, intracerebral haemorrhage; GI, gastrointestinal.

preliminary and do not support a consensus for the dosing of rFVIIa on an off-label basis.

Available evidence does support the early administration of rFVIIa. Early administration (within 3 h of a bleeding episode) has been shown to limit the volume of haemorrhage as well as the total amount of drug needed to achieve haemostasis.^{16–33} Stein and colleagues found that late haemorrhagic shock, and the acidosis and coagulopathy that accompany it, are predictors of futility in the administration of rFVIIa.¹³

Recombinant factor VIIa is administered intravenously as a bolus over 2–5 min. Repeat dosing is usually based on clinical effect.

SAFETY AND SIDE EFFECTS

Despite a favourable safety profile in the setting of haemophilia, concerns have been raised regarding the potential thrombogenicity of rFVIIa and the risk of adverse events, particularly for unapproved indications.² The prohaemostatic properties of rFVIIa hinge on its ability to bind to tissue factor and activated platelets at sites of vascular injury to promote coagulation and fibrin deposition. In clinical conditions such as DIC, sepsis or atherosclerosis where there is widespread exposure of tissue factor to the circulation, it is believed that rFVIIa administration may result in systemic activation of coagulation and adverse thrombotic events.

In patients with haemophilia with inhibitors, the rate of serious adverse events resulting from rFVIIa administration is less than 1%. There are isolated reports of acute myocardial infarction, ischaemic stroke, pulmonary embolism, internal jugular vein and cephalic-basilic vein thromboses.² Most of these patients were elderly and were known to have either atherosclerosis, hypertension, diabetes or other underlying comorbidities predisposing them towards thrombosis.

Reports from surgical and critical care literature reflect the relative safety of rFVIIa as a haemostatic agent in patients without haemophilia.^{34–36} However, there are case reports of thrombotic events associated with off-label rFVIIa use.³⁷ In the phase II study on rFVIIa in ICH by Mayer *et al*,¹⁶ arterial thromboembolic complications (acute myocardial infarction, cerebrovascular accident) occurred significantly more frequently in patients treated with rFVIIa than controls. Most of these events were minor and patients recovered completely; overall, the frequency of fatal or disabling complications did not differ between the treatment and placebo groups. Nonetheless, there was a trend towards increased thromboembolic events with the highest dose (160 µg/kg).

A recent review of the FDA's MedWatch database examined reported thromboembolic adverse events associated with rFVIIa.³⁸ MedWatch is only a voluntary listing of observed complications and therefore cannot provide true incidence rates, nor can it adequately describe dosing information, clinical events or patient co-morbidities to help establish causality. Nevertheless, between March 1999 through December 2004, 185 thromboembolic events were reported, 151 of them resulting from off-label use. Among the 50 reported fatalities, 36 (72%) were attributed to thrombotic complications. It is impossible to know which of these patients had co-morbidities or were receiving other procoagulant therapies that may have precipitated these outcomes. The safety of rFVIIa in off-label uses must therefore be systematically addressed in specific patient populations before an evidence-based conclusion can be made regarding its safety profile.

UNCERTAINTIES

Despite recent interest in rFVIIa, there is a paucity of clinical trial data to guide its use beyond the setting of haemophilia. The clinical data that currently exist must be viewed critically considering the likelihood of publication and reporting bias associated with a promising new drug. It is inevitable that the successes of rFVIIa have been touted with greater enthusiasm than its failures.

Multicentre prospective research trials are currently underway to study the safety and efficacy of rFVIIa for traumatic and coagulopathic bleeding in the non-haemophilia population. Additional data regarding effective dosing, frequency of administration and optimal therapeutic window will further aid clinicians in their decision-making. It is important that the safety of rFVIIa be systematically assessed for each clinical situation for which it is used. The significance of various comorbidities and risk factors in the development of thromboembolic complications in these populations must also be rigorously explored.

Another unavoidable issue in the use of rFVIIa is cost. Currently a single 90 µg/kg dose for an 80 kg patient costs \$6773 and many patients require multiple doses. Theoretically, some proportion of this cost should be offset by the costs saved in blood transfusions, operations, interventional radiological procedures, worsening shock and other aspects of persistent haemorrhage. Nevertheless, formal pharmacoeconomic analyses should accompany clinical trials.³⁹ Better characterising the clinical indicators of futility in rFVIIa administration will also be helpful in determining the true cost-effectiveness of this drug per patient treated.

SUMMARY AND RECOMMENDATIONS

In all scenarios other than bleeding haemophilia patients with inhibitors, rFVIIa is not an approved drug. Off-label use of rFVIIa has expanded considerably in recent years due to anecdotal and limited published evidence supporting its effectiveness for bleeding episodes of all kinds. Despite the high hopes and enthusiastic marketing surrounding this new drug, emergency physicians should exercise caution when considering its use. Given the lack of reliable data on the safety and clinical effectiveness of rFVIIa, especially in patients in the ED, we conclude that rFVIIa should only be used for the bleeding patient in extremis, either as an adjunctive treatment or when conventional measures fail. Table 2 provides a summary of ED

Table 2 Potential applications for rFVIIa in the emergency department

Indication	Dosing
Patients with supratentorial or cerebellar intracerebral haemorrhage showing rapid expansion and clinical deterioration; either in an investigational setting or in consensus with neurosurgery	Recommended starting dose: 40–80 µg/kg
Life-threatening bleeding in patients on warfarin when conventional reversal is ineffective or is contraindicated	No standard dose; can start with 15–80 µg/kg depending on initial INR
Life-threatening bleeding in patients with platelet inhibitors, functional or quantitative platelet disorders when conventional treatment is unsuccessful and thrombotic risk factors are absent	No standard dose; can start with 15–80 µg/kg
Trauma patients with life-threatening haemorrhage not responding to conventional measures (in consensus with trauma surgery)	No standard dose; can start with 100–120 µg/kg
Life-threatening variceal bleeding in patients with cirrhosis without additional thrombotic risk factors once conventional measures fail (in consensus with gastroenterology)	No standard dose; can start with 80–100 µg/kg

scenarios where rFVIIa might confer some benefit. The potential benefits of rFVIIa must, of course, be carefully weighed against its risks. Relative contraindications include a history of thrombotic events (eg, pulmonary embolism, acute myocardial infarction, cerebrovascular accident, deep vein thrombosis) or a predisposition towards thrombosis; also, rFVIIa should not be given if the patient is considered medically unsalvageable.¹⁵

Clinical research into off-label uses of rFVIIa is ongoing; current and future trials should focus on the safety and utility of rFVIIa in comparison with conventional treatments. rFVIIa should also be studied specifically in the undifferentiated ED patient population. Data analysis should delineate the role of age, cardiovascular disease and other co-morbidities in the relative effectiveness and thromboembolic risk of rFVIIa. Results from these studies should ultimately inform clinical guidelines. Until ongoing and future clinical trials and safety data are available, rFVIIa use in the ED should be restricted to life-threatening situations in patients for whom the drug offers significantly more benefit than risk.

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