

CASE REPORT

Recombinant FVIIa in the management of intracerebral haemorrhage in severe thrombocytopenia unresponsive to platelet-enhancing treatment

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SUMMARY. Intracranial haemorrhage (ICH) is a dramatic and potentially life-threatening presentation of children with thrombocytopenia. Management is limited to supportive care. Recent evidence suggests that ongoing bleeding following the initial ICH may result in greater neurological morbidity and mortality. Haemostatic agents, including recombinant factor VIIa (rFVIIa), a product licensed for use in patients with haemophilia and inhibitors, may be helpful in reducing bleeding in children with refractory thrombocytopenia.

We present the case of a 16-year-old girl with severe refractory immune thrombocytopenia, who

presented with a major ICH and responded to treatment that included rFVIIa and platelet transfusions. The dose of rFVIIa was empirically chosen and based on reported cases in the literature. The case highlights a number of issues regarding off-label use of rFVIIa and demonstrates the need to prospectively collect accurate information on the off-label use of this new potentially useful medication.

Key words: intracranial haemorrhage, off-label use, rFVIIa, thrombocytopenia.

Recombinant-activated factor VII (rFVIIa; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) is a novel haemostatic agent licensed for use in the management of bleeding in patients with haemophilia and inhibitors. Off-label indications for rFVIIa have increased as the effectiveness of rFVIIa as a haemostatic agent has been demonstrated in a number of clinical settings including bleeding in patients following massive trauma, surgery and warfarin overdose (O'Connell *et al.*, 2003; Hedner, 2000). Several case reports show that rFVIIa has been effective in the treatment of bleeds in patients with platelet dysfunction and severe thrombocytopenia (Gerotziapas *et al.*, 2002; Billio *et al.*, 2002; Culic, 2003; Klamroth *et al.*, 2002; Minniti & Weinthal, 2001;

Vidarsson & Onundarson, 2000; Waddington *et al.*, 2002; Watson *et al.*, 2002).

Intracranial haemorrhage (ICH) is a major cause of morbidity and mortality in both patients with normal coagulation and in patients with underlying coagulopathy (Mayer, 2002; Schmidt *et al.*, 1994). Effective treatments are limited. Early treatment with rFVIIa may have a role in improving the outcome of these patients.

We report the use of rFVIIa in a teenager with severe refractory immune thrombocytopenia presenting with massive ICH. We highlight the potential value of rFVIIa in this setting and raise potential issues regarding the expanding indications for rFVIIa.

CASE REPORT

The case is a 16-year-old girl with a longstanding history of a systemic autoimmune disorder manifesting as polyarticular juvenile rheumatoid arthritis, chronic immune thrombocytopenia purpura, chronic villous atrophy with malabsorption and chronic interstitial

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pneumonitis. As a result of thrombocytopenia, she has suffered from gum bleeding, epistaxis and recurrent gastrointestinal bleeding associated with precipitous drops in her haemoglobin requiring hospitalizations and red cell transfusions. In an attempt to moderate her autoimmune disease, she received various immunosuppressive agents, including multiple doses of intravenous gammaglobulin, corticosteroids and cyclophosphamide with no improvement. She underwent an autologous bone marrow transplantation at 11 years of age. Recently, she was treated with anti-CD20 and anti-TNF α monoclonal antibodies, but her autoimmune disorder persists, and she continues to have chronic severe refractory thrombocytopenia with a platelet count below $10 \times 10^9 \text{ L}^{-1}$. She has had a variety of treatment-related complications including severe growth retardation secondary to chronic corticosteroid use.

The patient presented with a 36-h history of severe headache, light-headedness, nausea and vomiting. There was no history of trauma or complaints of hearing or vision disturbances. Examination showed a mildly drowsy and disorientated girl with marked growth retardation and widespread petechiae. She was not hypertensive. A complete blood count showed a haemoglobin of 11.1 g dL^{-1} , a white blood cell count of $21.5 \times 10^9 \text{ mL}^{-1}$ and a platelet count of $4 \times 10^9 \text{ L}^{-1}$. At the time, she was not on anticoagulants or medications known to interfere with platelet function.

A CT scan performed within 3 h of presentation to hospital demonstrated a large ($4.8 \times 2.9 \times 4.3 \text{ cm}$), intra-axial cerebral haemorrhage over the left parieto-occipital region. (Fig. 1) There was associated oedema and mass effect. Additionally, there were three smaller haemorrhages in the right cerebral parenchyma. The haematology service was consulted, and she was immediately treated with platelet transfusions, fresh frozen plasma and intravenous tranexamic acid. Additionally, she was commenced on rFVIIa ($122 \mu\text{g kg}^{-1}$ every 2 h). She was given high-dose intravenous dexamethasone and admitted to the paediatric intensive care unit where aggressive medical management continued. Intravenous gammaglobulin was not given because of the patient's previous lack of response and in the current setting of fluid restriction. Neurosurgical intervention was deemed too risky in light of her refractory severe thrombocytopenia. Fortunately, with medical treatment for raised intracranial pressure (ICP), her condition stabilized. Throughout the subsequent 3 weeks, haemostatic support continued and included rFVIIa ($122 \mu\text{g kg}^{-1}$) every 4–8 h, and then daily for the final 5 days of admission. Despite platelet transfusions, the highest platelet count that she attained was



Fig. 1. Massive intracerebral haemorrhage in the left parieto-occipital region.



Fig. 2. Improved intracerebral haemorrhage two weeks later.

$35 \times 10^9 \text{ L}^{-1}$. Serial neuro-imaging demonstrated no further haemorrhage and resolving ICH. (Fig. 2)

During the 22 days of her admission, this 19.7 kg girl received 124 800 μg of rFVIIa along with 98 U of platelets, 1.5 L of fresh frozen plasma and daily tranexamic acid given every 6 h. The patient was discharged after 3 weeks with no residual neurological side effects. Her platelet count on discharge was $5 \times 10^9 \text{ L}^{-1}$.

DISCUSSION

Intracranial haemorrhage, defined as bleeding into the brain, is the deadliest, most disabling and least treatable form of stroke (Mayer, 2002). Treatment for ICH is generally supportive, including blood pressure control and possibly surgical removal of the intracranial clot (Daverat *et al.*, 1991). A number of studies have shown that the mortality of ICH is related to the size of the intracranial haematoma and that the best predictor of 30-day mortality in patients with ICH is haematoma size (Broderick *et al.*, 1993; Daverat *et al.*, 1991). Bleeding in ICH was previously thought to be completed within minutes of the onset of ICH. Recent prospective studies involving repeat CT scans on patients with ICH and normal coagulation have shown that haematoma growth can continue beyond the first 3 h of presentation (Brott *et al.*, 1997). Hemostatic therapy might reduce ongoing bleeding and improve outcome in patients with ICH. The rationale for this therapy is even more convincing in patients with underlying bleeding disorders presenting with ICH.

rFVIIa is an effective recombinant haemostatic agent that mediates its effect via interaction with endogenous tissue factor ultimately leading to thrombin generation (Roberts *et al.*, 1998). High doses of rFVIIa also activate platelets and promote conversion of prothrombin to thrombin. rFVIIa is currently licensed for use in the management of bleeding in patients with haemophilia and inhibitors, and there is significant experience demonstrating its effectiveness in this setting (Lusher, 2000). The use of rFVIIa is being investigated in a number of off-label settings including the control of bleeding in the setting of trauma, liver transplantation and following cardiac surgery. Since the licensing of rFVIIa in 1996, more than 500 000 doses have been used worldwide, with only 24 thrombotic adverse events reported (Dejgaard, 2003). Unfortunately, rFVIIa has a very short half-life of 1.3 h in children and 2.7 h in adult patients (Hedner, 2000). The other major obstacle to its use is its cost (Morenski *et al.*, 2003).

rFVIIa has been shown to be effective in controlling bleeding in central nervous system haemorrhage in patients with bleeding following neurosurgery and in ICH in patients with haemophilia (Hedner, 2000; Pickard *et al.*, 2000; Rice & Savidge, 1996; Arkin *et al.*, 1998; Wong *et al.*, 2000; Heisel *et al.*, 2002; Karadimov *et al.*, 2003; Mindikoglu *et al.*, 2003; Veshchev *et al.*, 2002). (Table 1) rFVIIa can be given immediately without any need for confirmation of blood group or thawing of blood products and is given in a small volume which is important in the setting of raised ICP where fluid restriction is desired. The dosing schedules, including the duration of therapy, of rFVIIa in the setting of an ICH have varied with some reports describing the use of rFVIIa for up to 14 days. Two multicentre randomized double trials designed to evaluate the efficacy of rFVIIa in patients presenting with acute ICH are in progress.

There are a number of reports describing the successful use of rFVIIa in controlling bleeding in patients with thrombocytopenia (Gerotziafas *et al.*, 2002; Billio *et al.*, 2002; Culic, 2003; Klamroth *et al.*, 2002; Minniti & Weinthal, 2001; Vidarsson & Onundarson, 2000; Waddington *et al.*, 2002; Watson *et al.*, 2002). (Table 2) High concentrations of rFVIIa activate platelets and generate platelet surface factor IXa and Xa, ultimately leading to thrombin generation (Monroe *et al.*, 1998; Kjalke *et al.*, 2001). One open-label study evaluated the effect of rFVIIa on reducing overt bleeding and shortening the skin bleeding time in 82 patients with thrombocytopenia (Kristensen *et al.*, 1996). Of the 82 patients receiving rFVIIa, eight patients had active bleeding, and in all eight, the bleeding lessened with the use of rFVIIa. The skin bleeding time shortened in 52% of the 82 patients.

Our case describes the use of rFVIIa in the context of both thrombocytopenia and ICH. Along with routine supportive medical therapies, our approach was to focus on controlling the initial bleeding with intensive treatment followed by a more prolonged maintenance period to prevent re-bleeding. The patient was given a number of treatments simultaneously, and the specific contribution of rFVIIa to the successful outcome of the patient is unknown. The dose and duration of rFVIIa given was empirical given the absence of evidenced-based literature. The decision to use daily doses of rFVIIa towards the end of the patient's admission, despite the short half-life of rFVIIa, was supported by a report of the successful use of daily rFVIIa in preventing ongoing bleeding in a patient with haemophilia and inhibitors to factor VIII and a target joint (Saxon *et al.*, 2001). It is possible that the clinical half-life of rFVIIa is longer than the reported half-life of 1.3–2.7 h.

Table 1. Recombinant factor VIIa (rFVIIa) in intracerebral haemorrhage

	Number of patients	Age (years)	ICH in context of:	Dose schedule (total doses/patient)	Overall success
Majumdar & Savidge (1993)	1	26	Haemophilia with inhibitors	90 µg kg ⁻¹ every 2 h (70 doses)	Control of bleeding
Schmidt <i>et al.</i> (1994)	2 (5 episodes)	2.3 & 6.5	Haemophilia with inhibitors	60–135 µg kg ⁻¹ every 2–4 h for 12–14 days	100% success in controlling bleeding*
Rice & Savidge (1996)	21 (21 episodes)	0–56	Haemophilia/FVII deficiency	80–100 µg kg ⁻¹ (2–332 doses)	Bleeding controlled in 84% of episodes
Arkin <i>et al.</i> (1998)	12 (13 episodes)	1–38	Haemophilia/FVII deficiency	90–120 µg kg ⁻¹ every 2 h (6–184 doses)	Bleeding controlled in 85% of episodes
Pickard <i>et al.</i> (2000)	10†	>18	Bleeding following spontaneous subarachnoid haemorrhage	80 µg kg ⁻¹ followed by an infusion of 3.5–7.0 µg kg ⁻¹ every h	Not described
Wong <i>et al.</i> (2000)	1	0.06	FVII deficiency	15–30 µg kg ⁻¹ every 4 h (9 doses)	Bleeding controlled
Heisel <i>et al.</i> (2002)	5 (8 procedures)	0.17–13	Neurosurgery for brain tumour	74–275 µg kg ⁻¹ (single dose in each patient)	Bleeding controlled in 87% of procedures
Veshchev <i>et al.</i> (2002)	1	52	Warfarin-related coagulopathy	120 µg kg ⁻¹ (single dose)	Bleeding controlled
Morenski <i>et al.</i> (2003)	3	0.1–11	Cerebral injury/coagulopathy	90 µg kg ⁻¹ (single dose in each patient)	Bleeding controlled in all 3 episodes
Karadimov <i>et al.</i> (2003)	3	23–40	Neurosurgery for brain tumour	70–80 µg kg ⁻¹ (single dose in each patient)	Bleeding controlled in all 3 patients
Mindikoglu <i>et al.</i> (2003)	1	68	Cirrhosis associated coagulopathy	90 µg kg ⁻¹ every 6 h (2 doses)	No increase in the size of haematoma

ICH, intracranial haemorrhage.

*The treatment of one patient was complicated by brain stem cerebrovascular accident.

†One patient developed occlusion of middle cerebral artery and trial subsequently suspended pending review of adverse effects.

Table 2. Recombinant FVIIa in patients with thrombocytopenia (treatment was successful in controlling bleeding in all cases)

	Age (years)	Thrombocytopenia in context of:	Dose schedule
Vidarsson & Onundarson (2000)	27	Acute myeloid leukaemia and subdural haematoma, haemoptysis and peri-orbital haematoma	100 µg kg ⁻¹ every 2–4 h for 11 doses
Klamroth <i>et al.</i> (2002)	45	ITP and prophylaxis of intraoperative bleeding for parathyroid adenoma removal	45–90 µg kg ⁻¹ every 2–4 h for 5 days
Minniti & Weinthal (2001)	11	ITP and ICH	50–90 µg kg ⁻¹ every 2 h
	8	ITP and presplenectomy prophylaxis of bleeding	50 µg kg ⁻¹ (single dose)
Billio <i>et al.</i> (2002)	67	Acute myeloid leukaemia and gastrointestinal bleeding	90–120 µg kg ⁻¹ every 3 h (8 doses)
Gerotziakas <i>et al.</i> (2002)	75	ITP complicating chemotherapy and epistaxis	90 µg kg ⁻¹ single dose
	52	Acute lymphoblastic leukaemia and gastrointestinal haemorrhage	90 µg kg ⁻¹ single dose
Watson <i>et al.</i> (2002)	48	Post autologous transplant and gastro-intestinal bleeding	120 µg kg ⁻¹ every 2 h for 36 h
Waddington <i>et al.</i> (2002) Culic (2003)	68	ITP and post splenectomy bleeding	90 µg kg ⁻¹ daily for 3 days
	8	ITP and epistaxis	85 µg kg ⁻¹ single dose

ICH, intracranial haemorrhage ; ITP, immune thrombocytopenia purpura.

Our case highlights issues regarding the off-label use of rFVIIa, and because these off-label indications will increase over time, monitoring the use rFVIIa will become increasingly difficult. In a society continually challenged by financial constraints, the use of rFVIIa for these indications may be challenged, and it will be of major benefit to maintain access to rFVIIa by providing accurate documentation of off-label use. As suggested in a review describing the use of rFVIIa in the management of patients with uncontrolled haemorrhage (O'Connell *et al.*, 2003), better documentation, including indication, dose and frequency of administration, and possible side effects of off-label use of rFVIIa could provide a platform for future scientific studies in order to maximize the clinical benefit of rFVIIa.

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