

Reversal of Warfarin-Induced Excessive Anticoagulation with Recombinant Human Factor VIIa Concentrate

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Background: Bleeding associated with warfarin anticoagulation correlates directly to duration and degree of international normalized ratio (INR) elevation above the therapeutic range. Safe and rapid reversal of excessive anticoagulation is occasionally needed to treat or avoid hemorrhagic complications.

Objective: To evaluate the efficacy and safety of human recombinant factor VIIa (rFVIIa) concentrate in persons requiring rapid reversal of the effects of warfarin.

Design: Uncontrolled case series.

Setting: Academic medical center.

Patients: 13 patients with critically increased INRs requiring immediate reversal of warfarin-induced anticoagulation.

Measurements: Prothrombin time and INR were measured before and after administration of varying doses of rFVIIa.

Results: Critically prolonged INR and bleeding complications were treated successively and rapidly in all patients, regardless of rFVIIa dose (range, 15 to 90 $\mu\text{g}/\text{kg}$ of body weight). Indications for use of rFVIIa included an INR greater than 10 in high-risk persons ($n = 5$), clinical hemorrhage ($n = 4$), and diagnostic or therapeutic procedures ($n = 4$).

Conclusion: Safe, rapid, and effective administration of rFVIIa corrects critically prolonged INRs and can avert or reverse bleeding associated with warfarin anticoagulation.

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Warfarin, the most widely prescribed oral anticoagulant therapy in North America (1), is administered to treat or prevent primary and secondary venous and arterial thromboembolic complications. Prolonged use for many years may be necessary, particularly for treating symptomatic hypercoagulability, chronic atrial fibrillation, maintaining mechanical prosthetic heart valves, and preventing acute myocardial infarction and stroke (2). Warfarin therapy has a narrow risk-to-benefit profile. Its complex pharmacokinetics are influenced by concurrent medications, ethanol ingestion, variability of vitamin K intake and absorption, and hepatic disease (3). Therefore, it is not surprising that the most common complication of warfarin use is adverse bleeding (4).

For patients receiving warfarin, estimated yearly risks are 0.6% for fatal bleeding, 3.0% for major hemorrhage, and 9.6% for minor events (5). The incidence of bleeding complications is directly proportional to the intensity of anticoagulation (6) and time spent at a high international normalized ratio (INR) (7). Various strategies have been implemented to reverse warfarin-induced excessive anticoagulation. In a patient with a prolonged INRs without active bleeding but with an anticipated high risk for bleeding, the INR can be decreased slowly by administering an exogenous source of vitamin K₁ (8).

The reversal of active bleeding or excessively elevated INRs in patients with a high risk for bleeding requires rapid replacement of vitamin K–dependent coagulation proteins. This replacement has traditionally been achieved by transfusing fresh-frozen plasma (9) or prothrombin complex concentrates (10). Problems associated with transfusing fresh-frozen plasma are the long time necessary to administer large volumes, a patient's inability to tolerate increases in intravascular volumes, and the potential for transmission of pathogenic blood-borne viruses (11) or pri-

ons. Prothrombin complex concentrates work very rapidly but may be thrombogenic (12) and may transmit non-lipid-enveloped pathogens. Therefore, it is important to identify alternative agents that are safe, reliable, and rapidly acting.

We describe the successful use of recombinant factor VIIa (rFVIIa) concentrate in 13 adults receiving warfarin who required rapid reversal of a critically prolonged INR and excessive anticoagulation.

METHODS

Recombinant FVIIa

NovoSeven (Novo Nordisk, Princeton, New Jersey) is a genetically engineered concentrate of human coagulation FVIIa, which is structurally similar to native human plasma-derived FVIIa. The FVII zymogen is synthesized in vitro by a baby hamster kidney-cell line, which is then auto-activated through sequential ion exchange chromatography. This process also enhances eradication of any contaminating murine viruses. No exogenous human serum proteins are used in the manufacturing procedure (13).

The rFVIIa product was developed to achieve hemostasis in persons with hemophilia who have allogeic antibody inhibitors directed against factor VIII or IX. Essentially, rFVIIa, complexed with tissue factor on phospholipid-rich membranes of activated platelets, mediates conversion of coagulation factor IX to IXa and factor X to Xa. Subsequently, the prothrombinase complex (factors Xa and Va and phospholipid) produces a procoagulant "burst," which is derived from prothrombin conversion to thrombin (14). Thrombin then proteolyzes fibrinogen to fibrin, which is essential for thrombus formation and cross-linking. Clot stability is further promoted by rFVIIa-

induced activation of thrombin-activated fibrinolytic inhibitor.

Patients

Between 1 September 1999 and 31 October 2001, we considered administration of rFVIIa concentrate in patients referred to the Hematology Service of Georgetown University, Washington, DC, for evaluation and rapid reversal of anticoagulation effects produced by warfarin. Recombinant factor VIIa was prescribed when clinically significant bleeding was precipitated or exacerbated by anticoagulation; when persons assessed to be at high risk for bleeding (INR > 10) could not tolerate infusions of fresh-frozen plasma because of intravascular volume constraints or comorbid conditions; when very rapid warfarin reversal was required; or when interruption of anticoagulation was deemed risky but temporary moderation of warfarin was indicated (for example, for invasive therapeutic or diagnostic procedures).

The dose of rFVIIa to be administered was based on the patient's weight, rounded off to the closest vial size (1.2 mg and 4.8 mg). The first patient received 90 $\mu\text{g}/\text{kg}$ of body weight, the recommended dose for persons with hemophilia and alloantibody inhibitors. Subsequent patients were treated with progressively lower doses as it became apparent that even doses in the 15 to 20 $\mu\text{g}/\text{kg}$ range (Table) provided adequate hemostasis. Recombinant factor VIIa was administered intravenously over 3 to 5 minutes. Prothrombin time and INR were obtained before and after treatment in all persons in order to monitor the effects on coagulation. In addition, factors II, VII, IX, and X activity levels were concurrently measured in four patients. One patient received rFVIIa on two separate occasions.

RESULTS

Thirteen adult patients received decreasing single doses of rFVIIa concentrate as our experience and confidence in the product increased (Table). In all patients, the INR was immediately reduced after a single infusion (Figure). Prothrombin times and INRs slowly increased with time after administration of rFVIIa but remained below baseline levels for all patients. Subsequent management of patients after rFVIIa administration was individualized according to clinical situation and treatment goals. Most patients resumed warfarin therapy at appropriately adjusted doses within 12 hours after the INR normalized. Patients with an INR greater than 10 also received supplemental vitamin K₁ for long-term protection against relapse.

Four vitamin K–dependent coagulation proteins (factors II, VII, IX, and X) were assayed in four patients 1 hour before and 1 hour after rFVIIa infusion. The activity of these proteins was markedly deficient, which is consistent with the effects of warfarin. Of interest, the activity level of factors II, IX, and X did not appreciably increase after rFVIIa treatment. However, FVII activity increased dramatically (by more than 500%) (data not shown).

Context

Traditional treatments (fresh-frozen plasma, prothrombin complex concentrate) for rapid reversal of excessive anticoagulation from warfarin are limited by inconvenience and potentially serious side effects.

Contribution

This prospective case series showed that a single infusion of human recombinant factor VIIa concentrate (rFVIIa) immediately reduced international normalized ratios without adverse effects in 13 patients who needed rapid reversal of excessive warfarin-induced anticoagulation for various reasons.

Cautions

Before changing treatment policy on the basis of these preliminary findings, physicians should watch for controlled studies that compare outcomes, side effects, and costs in patients treated with rFVIIa versus traditional therapies.

—The Editors

The clinical scenarios in this series varied but were typical of a large hospital experience. Four patients presented with clinically significant hemorrhage, consisting of retroperitoneal bleeding, severe protracted epistaxis, tongue laceration, and an expanding facial and soft palate hematoma. Immediate cessation of bleeding was clinically apparent after rFVIIa administration. Five patients required rapid reversal of anticoagulation effects before invasive, diagnostic, or surgical interventions. These included removal of an arterial femoral sheath, removal of epidural and central venous catheters, closed fixation of a femoral neck fracture, and electrophysiologic studies with pacemaker placement. No adverse bleeding occurred in any persons during or after surgery. In several patients who had recurrent hypercoagulable events or had previous episodes of heparin-induced thrombocytopenia, the risk for bleeding was reduced without complete reversal of anticoagulation effects. Hemorrhagic complications were averted in patients with significant comorbid conditions (Table) and a high risk for bleeding, including an INR greater than 10, recent upper gastrointestinal bleeding or history of peptic ulcer disease, quantitative and qualitative platelet dysfunction, hemodialysis, and congestive heart failure.

All patients had indications for chronic or lifelong use of warfarin before treatment with rFVIIa (Table). Most patients had received anticoagulation for at least 3 months. In one patient, initiation of warfarin therapy after surgery produced excessive anticoagulation effects within 3 days.

DISCUSSION

This series represents the first substantial experience with rFVIIa concentrate to reverse the effects of excessive

Table. Characteristics of 13 Patients Treated with Recombinant Factor VIIa*

Patient	Age	Sex	Reason for Anticoagulation	Comorbid Conditions	Treatment Indication	rFVIIa Dose (Total Dose) <i>μg/kg (μg)</i>	INR		PT	
							Before Treatment	After Treatment	Before Treatment	After Treatment
	<i>y</i>					<i>μg/kg (μg)</i>			<i>s</i>	
1	81	M	Chronic atrial fibrillation, cerebrovascular accident	Chronic renal insufficiency	Retroperitoneal bleeding	90 (6000)	9.95	2.37	51.1	21.4
2	57	F	Chronic atrial fibrillation	Hemodialysis	Closed reduction and internal fixation, left femoral neck fracture	85 (4800)	4.91	1.35	33.3	15.2
3	55	F	Aortic valve replacement	Congestive heart failure	Critically elevated INR, increased risk for hemorrhage, presyncope symptoms	85 (4800)	>20.00	4.20	>60.0	30.2
4	67	F	Congestive heart failure, chronic atrial fibrillation	Peptic ulcer disease, recent upper gastrointestinal bleeding	Profuse, severe epistaxis	70 (3600)	12.96	7.37	>60.0	42.6
5	62	M	Peripheral vascular disease	Coronary artery disease, unstable angina, hemodialysis	Epidural catheter removal	45 (2400)	8.25	1.94	45.6	19
6	55	F	Heparin-induced thrombocytopenia	Chronic lymphocytic leukemia	Tongue laceration	20 (1200)	13.90	5.86	44.8	37.1
7†	41	M	DVT, antiphospholipid antibody syndrome, heparin-induced thrombocytopenia, hirudin antibodies	Chronic renal insufficiency, peptic ulcer disease, recent upper gastrointestinal bleeding	Arterial sheath removal, critically elevated INR, increased risk for hemorrhage	14 (1200) 14 (1200)	3.37 14.93	1.67 3.65	26.5 59.0	17.4 26.5
8	56	M	Cerebrovascular accident, mitral valve replacement	Coronary artery disease, congestive heart failure, pulmonary edema	Expanding facial hematoma, pulmonary edema, neurologic symptoms	12 (1200)	5.81	2.93	29.8	17.8
9	38	M	DVT, methyltetrahydrofolate reductase and factor V Leiden gene mutations	Coronary artery disease	Critically elevated INR, easy bruising, increased risk for hemorrhage	15 (1200)	6.20	2.09	35.8	19.3
10	74	M	Heparin-induced thrombocytopenia, paroxysmal nocturnal hemoglobinuria	Thrombocytopenia, chronic hemolysis, peptic ulcer disease	Electrophysiologic study (ablation), pacemaker placement	12 (1200)	2.57	1.62	21.7	27.0
11	73	F	Chronic atrial fibrillation	Autologous stem cell transplantation	Removal of Hickman catheter	17 (1200)	1.85	0.73	18.0	10.6
12	44	M	Recurrent DVT	Thrombocytopenia, alcohol abuse	Critically elevated INR, increased risk for hemorrhage	15 (1200)	11.87	3.16	51.8	24.4
13	81	F	Cerebrovascular accident	Dilated cardiomyopathy with congestive heart failure	Critically elevated INR, increased risk for hemorrhage	25 (1200)	8.95	3.16	43.1	24.4

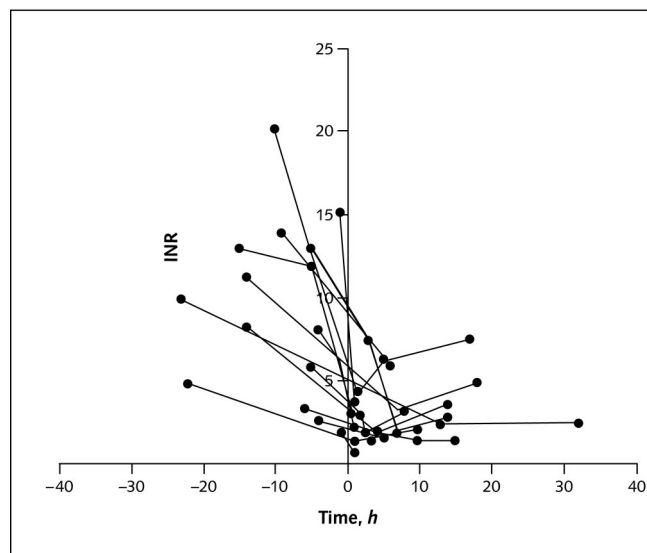
* DVT = deep venous thrombosis; F = female; INR = international normalized ratio; M = male; PT = prothrombin time, rFVIIa = recombinant factor VIIa.

† Patient 7 received treatment twice.

warfarin-induced anticoagulation. Thirteen persons who had been taking warfarin received rFVIIa to treat active, symptomatic bleeding; to ameliorate high risks for bleeding; or to reverse anticoagulation preceding invasive diagnostic or therapeutic interventions. The regimen was safe,

rapidly acting, and effective in all patients. Substantially lower doses than those recommended for persons with hemophilia and alloantibody inhibitors were used to achieve hemostasis, perhaps reflecting the otherwise normal coagulation mechanism in patients with warfarin-induced anticoagulation.

Figure. The international normalized ratios (INRs) of 13 patients relative to treatment with recombinant factor VIIa.



The 0 on the x-axis represents the time at which the dose was administered. Each line represents a patient with his or her INR. The trends in INR and prothrombin time improvement were identical for all patients.

Preclinical studies in rats (15) and normal humans who ingested acenocoumarol (16) have demonstrated the safety and feasibility of rFVIIa use in the clinical setting. Recent anecdotal reports have supported the potential effectiveness of rFVIIa for reversing warfarin-induced excessive anticoagulation to facilitate surgery (17) or treat serious bleeding complications (18, 19). Our series extends the clinical experience with rFVIIa outside the hemophilia population and shows the ease and flexibility of rFVIIa administration in patients who require moderation of anticoagulation effects but are concurrently at increased risk for hypercoagulable events if their anticoagulation was completely reversed. Examples include our patient with active heparin-induced thrombocytopenia and hirudin antibodies and our patients with mechanical heart valves, in whom only brief interruptions of anticoagulation are desirable.

A limitation of using rFVIIa is the inability to monitor or predict hemostatic efficacy in the laboratory. Prothrombin times and FVII activity levels do not correlate. Therefore, we relied on clinical assessment, that is, cessation of bleeding, stability of hematocrit, and other clinical measures. The lack of rFVIIa effects on other vitamin K-dependent clotting factors corroborates the hypothesis that the “thrombin burst” generated on activated platelet surfaces is critical to the hemostatic success of rFVIIa.

Recombinant factor VIIa concentrate will not transmit blood-borne pathogens. Its high specific activity obviates the volume constraints of replacement therapy with fresh-frozen plasma and substantially reduces the time necessary for administration and for achieving adequate hemostasis. Despite the rare reports of hypercoagulable complications

associated with rFVIIa (20), no thromboembolic events were observed in our small series, which included elderly persons with underlying atherosclerosis.

Adequate hemostasis was achieved with very low doses (range, 15 to 20 μg) of rFVIIa. As a result, our regimen is more cost competitive with fresh-frozen plasma. Because rFVIIa concentrate is expensive (approximately \$1.40/ μg Average Wholesale Price in 2002), our Blood Bank monitors requests for rFVIIa with individual patient assessment by hematologists for off-label indications. Institutional guidelines for rFVIIa reversal of excessive warfarin-induced anticoagulation would be prudent.

In summary, rFVIIa concentrate was used successfully and safely to reverse warfarin toxicity in a diverse population of patients. Prospective studies are necessary to determine the most optimal and cost-effective dosing regimen.

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“Are you being properly looked after?” Bergotte asked me. “Who is treating you?” I told him that I had seen, and should probably go on seeing, Cottard. “But that’s not at all the sort of man you want!” he told me. “I know nothing about him as a doctor. But I’ve met him at Mme Swann’s. The man’s an imbecile. Even supposing that that doesn’t prevent his being a good doctor, which I hesitate to believe, it does prevent his being a good doctor for artists, for intelligent people. People like you must have suitable doctors, I would almost go so far as to say treatment and medicines specially adapted to themselves. Cottard will bore you, and that alone will prevent his treatment from having any effect . . . How do you expect Cottard to be able to treat you? He has made allowances for the difficulty of digesting sauces, for gastric trouble, but he has made no allowance for the effect of reading Shakespeare.”

Marvel Proust
Remembrance of Things Past (Within a Budding Grove)
New York: Vintage Books; 1981:614

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