The occurrence of hemorrhages associated with warfarin anticoagulation therapy is well known and presents a considerable therapeutic challenge.1,17,22 As the medical indications for prolonged anticoagulation therapy expand, neurological surgeons are frequently called on to manage hemorrhages in the CNS in patients who require reversal of anticoagulation with perioperative therapy such as vitamin K, plasma, or prothrombin complex concentrates.3,15 Although these treatments are effective, there are wide variations in doses, volumes, and rates of reversal, as well as potential complications such as anaphylaxis, fluid overload, transmission of infective agents, or thromboembolism.2,3,11,15,19 In this report we describe the use of rFVIIa (Novo Seven; Novo Nordisk, Copenhagen, Denmark) for the perioperative reversal of anticoagulation induced by warfarin sodium (Coumadin; DuPont, Wilmington, DE) in four patients with hemorrhages in the CNS. This report is preliminary; the clinical experience is anecdotal and does not identify the optimal dose or timing. Nevertheless, the outcomes in this series of patients indicate that rFVIIa may offer a significant improvement in the surgical management of these difficult cases.

Clinical Material and Methods

Patient Population
The four patients in this series were treated consecutively during 2002; their clinical characteristics are outlined in Table 1. All patients were being treated with orally administered warfarin sodium for DVT, although the patient in Case 1 had additional indications, including an artificial heart valve, atrial fibrillation, and a history of congestive heart failure. Patients had been receiving warfarin therapy for periods of 1 month to 3 years. There were two men and two women; their ages ranged from 53 to 68 years. The first patient suffered a spontaneous hemorrhage; the remaining patients' hemorrhages were associated with trauma. Results of additional preoperative coagulation studies, including platelet counts, activated partial thromboplastin times, and fibrinogen levels, were normal.

Results

Treatment With rFVIIa
The first patient presented with midlevel cervical quadriplegia and respiratory distress associated with a cervical epidural hematoma. Twelve hundred micrograms of rFVIIa was administered by slow intravenous push, along with 2 U
FFP over a 6-hour period, with normalization of the INR. An additional 2 U FFP and 1200 µg rFVIIa were administered for prophylaxis over a 24-hour period after surgery while the INR remained normal. The second patient presented with a severe paraparesis caused by a lumbar SDH. Initial administration of 1200 µg rFVIIa followed by 1 U FFP resulted in normalization of the INR before surgery. An additional 2 U FFP and 1200 µg rFVIIa were administered over a 27-hour period after surgery, without changes in the INR. The third patient required immediate surgical intervention for the evacuation of an SDH; 1200 µg rFVIIa was administered before surgery and 2 U FFP were given during surgery. The INR normalized during surgery, and the patient required no further therapy. The fourth patient presented with headaches, confusion, and an acute dominant-hemisphere SDH. His neurological condition was stable, although his INR remained elevated, despite the administration of 5 U FFP. A follow-up computerized tomography scan revealed additional hemorrhage; 1200 µg rFVIIa was administered just before surgery, with normalization of the INR during the procedure. Postoperatively, the INR increased to preoperative levels and an additional unit of FFP was administered within 12 hours. The INR continued to be slightly elevated, but the patient’s condition remained stable and no further treatment was necessary.

Blood loss during surgery was less than 100 ml for all patients. Warfarin therapy was resumed after 10 days in the first patient and was discontinued in the remaining three.

**Postoperative Outcome**

The first patient fared poorly; she suffered from significant quadriparesis and required a tracheostomy. She began rehabilitation but died suddenly 6 weeks postsurgery; necropsy did not reveal a thromboembolism. The second patient improved; at follow-up review she was using a walker for assisted ambulation and had voluntary control of bladder and bowel function. The two remaining patients had uneventful recoveries and resumed preoperative activities.

**Discussion**

The coumarin anticoagulants act by inhibiting the synthesis of vitamin K–dependent clotting factors and anticoagulant proteins C and S. Their anticoagulant effect occurs within 24 to 72 hours, with a duration of action of up to 1 week.13 The prevalence of treatment with these drugs has been estimated at approximately 0.5% in the general population, with an incidence of major hemorrhages of 3.8% per year and hemorrhages in the CNS at the rate of 1% per year.2,22 Up to 14% of spontaneous hemorrhages in the CNS have been associated with orally administered anticoagulant medications8,15 with a mortality rate close to 80%.17 The pharmacological effects of these drugs are usually monitored by checking the one-stage prothrombin time, with calculation of the standardized INR.2,19 In patients with hemorrhages in the CNS, rapid reversal of the anticoagulation effect, as indicated by the INR, is imperative to reduce the risk of rebleeding or perioperative hemorrhage.2,8

Several treatments are available for reversal of warfarin anticoagulation therapy. The administration of vitamin K is effective, but its action can be delayed up to 24 to 48 hours, and anaphylaxis may occur with intravenous administration. Recently the use of factor IX complex concentrate associated with the administration of FFP in patients receiving warfarin therapy has been shown to increase the rate of reversal and shorten the period of correction of the INR when compared with the use of FFP alone.3 This preparation contains high concentrations of the vitamin K–dependent clotting factors, but it carries an additional risk of viral contamination4,6 and a potentially increased risk of thromboembolic complications due to activated factor complexes.14 We routinely use FFP at our institution as replacement anticoagulant therapy. The administration of vitamin K is pharmacological effect, as indicated by the INR, is imperative to reduce the risk of rebleeding or perioperative hemorrhage.2,8

The use of rFVIIa when administered every 2 hours has been shown to be safe and effective in patients with he-

### Table 1

Clinical characteristics, treatments, and outcomes in four consecutive patients with CNS hemorrhages associated with warfarin anticoagulation§

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Preexisting Condition</th>
<th>Diagnosis</th>
<th>Time to Op†</th>
<th>Initial INR</th>
<th>Tx Before or During Op</th>
<th>INR After Initial Tx</th>
<th>Postop Tx (hrs)</th>
<th>Outcome (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64, F</td>
<td>artificial heart valve, atrial fibrillation, CHF, DVT</td>
<td>acute cervical EDH, C3–6</td>
<td>6 hrs</td>
<td>5.6</td>
<td>2 U FFP, 1200 µg rFVIIa preop</td>
<td>1.0 preop</td>
<td>2 U FFP + 1200 µg rFVIIa (24)</td>
<td>death (1.5)</td>
</tr>
<tr>
<td>2</td>
<td>68, F</td>
<td>DVT</td>
<td>acute lumbar SDH, L1–3</td>
<td>8.5 hrs</td>
<td>2.9</td>
<td>1200 µg rFVIIa preop, followed by 1 U FFP</td>
<td>1.0 inmed preop</td>
<td>2 U FFP + 1200 µg rFVIIa (27)</td>
<td>good (5)</td>
</tr>
<tr>
<td>3</td>
<td>66, M</td>
<td>chronic ethanolism, DVT</td>
<td>acute cortical SDH</td>
<td>45 mins</td>
<td>1.9</td>
<td>1200 µg rFVIIa, followed by 2 U FFP during op</td>
<td>1.0 at end of op</td>
<td>none</td>
<td>excel-lent (3)</td>
</tr>
<tr>
<td>4</td>
<td>53, M</td>
<td>headache, confusion, CLL, DVT</td>
<td>acute cortical SDH</td>
<td>17 hrs</td>
<td>2.8</td>
<td>5 U FFP preop, followed by 1200 µg rFVIIa immed preop</td>
<td>2.8, reduced to 1.7 immed preop, reduced to 0.8 during op</td>
<td>1 U FFP (12)</td>
<td>excel-lent (2)</td>
</tr>
</tbody>
</table>

§ CHF = congestive heart failure; CLL = chronic lymphocytic leukemia; EDH = epidural hematoma; immed = immediately; Tx = treatment.
† Time elapsed between neurosurgical consultation and surgery.
Reversal of warfarin anticoagulation in neurosurgical patients

mophilia and nonhemophilic disorders of thrombin generation. In several reports a remarkable effect has been demonstrated in patients with massive trauma, extensive cardiac surgery, or during craniotomy for a large hemangiopericytoma. rFVIIa has also been used to prevent recurrent aneurysmal subarachnoid hemorrhage. Its use in the reversal of warfarin-induced anticoagulation, however, has been described in only one anecdotal report. This patient experienced severe epistaxis and throat hemorrhage while being treated with warfarin for DVT. Two doses of rFVIIa at 80 µg/kg body weight that were administered within 30 minutes stopped the bleeding with no additional therapy. Additional data were not outlined in that report. Because human serum or proteins are not used in rFVIIa preparations, there is no risk of blood-borne contamination.

The effects of rFVIIa have been shown to be tissue factor–dependent and tissue factor–independent, with the latter mechanism occurring by activation of factor X on activated platelets. Both of these hemostatic actions promote the formation of a stabilized fibrin plug. Its use in patients receiving warfarin therapy is based on the fact that factor VII has the shortest half-life (4–6 hours) of all the vitamin K–dependent factors, and an increase in factor VII activity would be expected to reduce the INR in a reasonably short time. It has been used in experimental animals in doses of 50 µg/kg, which reduce the prothrombin time after a single dose of warfarin. In human volunteers with stable INRs greater than 2 due to oral anticoagulating agents, doses of rFVIIa as low as 5 µg/kg body weight normalized the INRs for a 12-hour period.

In this series we demonstrate an erratic but eventually successful learning curve. After the clinical reversal of anticoagulation therapy in the first patient, rFVIIa was administered initially in the second patient along with a single unit of FFP; the INR normalized just before surgery. The continued administration of rFVIIa and FFP postoperatively in both the first and second patients may not have been necessary because the INRs remained normal during this period. The precise relationship, however, between the effect of rFVIIa on the INR and hemostatic efficacy is not established. In the third patient, rFVIIa was administered just before emergency surgery, along with FFP during surgery. It is unlikely that the INR would have normalized rapidly during surgery after administration of FFP alone, and postoperatively no further therapy was needed. In the fourth patient, rFVIIa effectively normalized the INR despite the high volume of FFP administered preoperatively. The dose for rFVIIa was chosen arbitrarily at 1200 µg, or the contents of a small, single-use vial. This translated to a range of approximately 16 to 22 µg/kg body weight for all patients. Although this dose is much lower than that used in patients with hemophilia or massive trauma, it is consistent with dosages used in the reversal of elevated INRs in human volunteers receiving oral anticoagulants. Because the recommended interval for each dose of rFVIIa for patients with hemophilia is 2 hours, the addition of FFP may reduce the need for continued perioperative use of rFVIIa. Cost remains a consideration; the cost to our hospital for the 1200-µg single-use vial of rFVIIa is approximately $1100, whereas the cost of a single unit of FFP is approximately $40. This expense must be weighed against the potential benefit of rapid, although short-term reversal of anticoagulation.

No thromboembolic complications were seen in these patients, which corroborates earlier clinical experience. None of our patients, however, showed additional clotting abnormalities, which could increase the risk of thromboembolic complications. Although experience in patients with massive trauma or during craniotomy indicates that rFVIIa may be a universal hemostatic agent, this cannot be confirmed based on our series.

Acknowledgment

We gratefully acknowledge Mrs. JoAnna Gass for her secretarial assistance on this manuscript.

References


J. Neurosurg. / Volume 98 / April, 2003 739


Manuscript received August 14, 2002. Accepted in final form November 18, 2002. Address reprint requests to: William C. Hanigan, M.D., Department of Neurosurgery, University of Illinois College of Medicine at Peoria, P.O. Box 1649, Peoria, Illinois 61656. email: joanna.gass@osfhealthcare.org.