Pharmacologic Interventions for the Management of Critical Bleeding

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Hospital pharmacists are often consulted for their knowledge about coagulation and therapeutic interventions for the management of critical bleeding. Many pharmacotherapies are available for this purpose, both systemic and topical, and others are in development. These agents and their mechanisms of action are reviewed, and perspectives are provided regarding their use in various clinical settings. Also provided are associated precautions to promote safe use. Current controversies surrounding pharmacotherapeutic agents used to control serious bleeding (e.g., in various types of surgery, trauma, obstetrics, and intracranial hemorrhage) are also discussed.

Key Words: critical bleeding, hemostatic agents, pharmacy.

Patients with acute blood loss are often considered medical or surgical emergencies that demand immediate attention to assess and control bleeding. A keen understanding of state-of-the-art interventions, as well as their limitations and risks, by health care professionals is imperative. These interventions include unimodal or multimodal strategies for using blood products, volume replacement products or expanders, and systemic and topical pharmacotherapies that promote hemostasis. Blood products are reviewed elsewhere in this supplement; this article addresses pharmacotherapies used to manage critical bleeding.

Systemically administered agents include desmopressin acetate, vitamin K$_1$ (phytonadione), conjugated estrogens, and agents that exhibit antifibrinolytic as well as antiinflammatory properties: aprotinin, epsilon-aminocaproic acid (EACA), and tranexamic acid. Topical agents such as thrombin and fibrin sealants, of which there are several products available, with others in clinical development, are useful primarily as adjunctive therapy to control surgical bleeding when conventional methods fail. Clotting factors, recombinant or purified from plasma (e.g., factors VII, VIII, and IX), are appropriate to replace missing clotting factors in patients with genetic or acquired coagulation disorders. Factors VIII and IX are specifically reserved for patients with hemophilia A and B, respectively, and are not used to manage critical bleeding in patients who normally possess adequate amounts of these endogenous factors; therefore, these agents are not discussed here. By contrast, off-label use of recombinant factor VIIa (rFVIIa) is widespread to treat uncontrolled bleeding and to establish and/or maintain hemostasis in patients unresponsive to conventional methods.

Of the many pharmacotherapies used to minimize uncontrolled bleeding, some have not been evaluated extensively—or under all circumstances in which they are used—in controlled clinical trials. Moreover, many agents are controversial in that they may or may not improve outcomes, are associated with significant risks, and/or are very expensive. These therapies and the recent evidence and controversies pertaining to their use in patients with different types of critical bleeding are reviewed.

Systemic Antifibrinolytic and Antiinflammatory Agents

Aprotinin, Epsilon-Aminocaproic Acid, and Tranexamic Acid

Among the antifibrinolytic and antiinflammatory agents used to treat critical bleeding,
Aprotinin is perhaps the most extensively studied. Aprotinin is indicated for patients undergoing cardiopulmonary bypass who are at high risk for perioperative blood loss and transfusion. Use of aprotinin is also prevalent in liver transplantation where it decreases blood loss and transfusion requirements and reduces tissue-type plasminogen activator (t-PA) production, preventing endothelial damage in the graft. Whereas the primary mechanism of aprotinin action is due to protease inhibition (including plasmin and kallikrein; Figure 1), it may also maintain platelet function and decrease fibrinolysis during cardiopulmonary bypass, inhibit the extrinsic clotting cascade by suppressing tissue factor expression, and exert antiinflammatory effects by modulating cytokine effects such as increasing levels of interleukin (IL)-10 and decreasing levels of IL-6, IL-8, and tumor necrosis factor-α. Tranexamic acid and EACA are lysine analogs that inhibit plasminogen activators and plasmin at higher doses (Figure 2). Like aprotinin, these agents have also been shown to exhibit antiinflammatory effects by inhibition of IL-6 and IL-8.

Efficacy

An extensive Cochrane Library meta-analysis compared the efficacy of aprotinin (61 trials), tranexamic acid (18 trials), and EACA (four trials). Aprotinin and tranexamic acid decreased the relative number of red blood cell transfusions by 30% (relative risk [RR] 0.70, 95% confidence interval [CI] 0.55 to 0.88).

Figure 1. Proposed mechanism of action of the serine protease inhibitor, aprotinin. As shown by the broken lines, aprotinin inhibits the following: release or activation of factors initiated by factor XII contact with a negatively charged surface (contact system), kallikrein-mediated plasminogen activation, and plasmin-mediated conversion of fibrin to fibrin-degradation products. (From reference 36 with permission. Copyright© 1998 Massachusetts Medical Society. All rights reserved.)

Figure 2. Proposed mechanism of action of the antifibrinolytics, aminocaproic acid and tranexamic acid. In the top panel, activation of fibrinolysis is depicted. This occurs when plasminogen binds to fibrin at a lysine-binding site and is converted to plasmin. In its activated form, plasmin catalyzes fibrin degradation to fibrin-degradation products. In the bottom panel, the antifibrinolytic agents are shown blocking the lysine-binding site and subsequent activation of plasminogen to plasmin. Plasmin is not generated and fibrin is not degraded into its split products. (From reference 36 with permission. Copyright© 1998 Massachusetts Medical Society. All rights reserved.)
confidence interval [CI] 0.64–0.76) and 34% (RR 0.66, 95% CI 0.54–0.81), respectively. Transfusion volume was reduced by an average of 1 unit (aprotinin 1.1 units, 95% CI 0.69–1.47, tranexamic acid 1.03 units, 95% CI 0.67–1.39). A nonsignificant trend toward decreased red blood cell transfusions was observed in the EACA group (RR 0.48, 95% CI 0.19–1.19); however, only four studies representing 208 patients were included. Noting the underrepresentation of tranexamic acid and EACA studies and the potential for publication bias, the authors concluded that these agents may be as effective as aprotinin in preventing postoperative blood loss in patients undergoing cardiac surgery.

Other meta-analyses, systematic reviews, and studies comparing systemic antifibrinolitics in cardiac surgery have been performed, some of which reached similar conclusions. Moreover, EACA and tranexamic acid (albeit to a lesser extent) are less costly than aprotinin. However, one group noted that aprotinin and tranexamic acid, but not EACA or desmopressin, were effective in reducing red blood cell transfusion requirements. Another group cited the poor quality of trials, the possibility of bias, and lack of large comparative trials as reasons not to draw definitive conclusions as to whether aprotinin should be replaced by the less costly lysine analogs.

Safety

According to a 2004 meta-analysis, aprotinin in patients undergoing cardiac surgery decreases stroke risk, suggesting a neuroprotective effect. By contrast, two recent observational studies concluded that aprotinin increases stroke risk and other thrombotic complications, as well as the risk for renal complications, none of which were seen with EACA or tranexamic acid use. These two studies were the focus of a United States Food and Drug Administration (FDA) advisory committee meeting in September 2006. The FDA analyzed published studies as well as data from the manufacturer’s global safety and efficacy database and concluded that aprotinin does not increase the risk of renal, cardiovascular, or cerebrovascular events. However, shortly after the advisory committee meeting, the FDA was made aware of additional safety data involving 67,000 patients that strongly suggested aprotinin increases the risk of death, renal failure, heart failure, and stroke.

In a follow-up observational study, long-term survival was assessed in patients receiving aprotinin, tranexamic acid, or EACA versus no therapy to prevent bleeding for coronary artery bypass graft (CABG) surgery. Only patients in the aprotinin group had a significant increase in 5-year mortality versus control (hazard ratio 1.48, 95% CI 1.19–1.85), a finding confirmed by multivariate logistic regression analysis. Since death occurred even in patients surviving the hospitalization, one proposed explanation for the delayed effect on mortality was thrombosis that occurred during surgical revascularization and later manifested clinically. Conclusions from this study are limited by caveats that apply to all observational studies and by the fact that 13% of patients were lost to follow-up between 6 weeks and 5 years.

In addition to potential thrombotic and renal complications, aprotinin is a potent allergen that can produce hypersensitivity reactions, including anaphylaxis and death. Approximately half of all patients who have had a single exposure to aprotinin have detectable aprotinin-specific serum immunoglobulin G antibodies. Previous exposure to aprotinin is therefore the major risk factor for sustaining a hypersensitivity reaction, although fatal reactions have occurred even during administration of a test dose. The aprotinin prescribing information now contains a black-box warning about anaphylaxis and that aprotinin is contraindicated in patients who may have been exposed in the previous 12 months. Some fibrin sealants also contain aprotinin and similar warnings may apply, although such reactions may be less likely with topical use.

Until the FDA releases further analysis of aprotinin data, this agent should be used only in patients for whom the risk of bleeding outweighs aprotinin-related risks. Several questions also remain unanswered; in particular, why do the findings in the follow-up observational study differ from those of numerous previously published studies suggesting that aprotinin is safe? One explanation is that studies are not adequately powered to assess safety, or the study duration may be too short to detect adverse events. Is there a dose-related increase in adverse effects of aprotinin, as suggested by the authors of the observational study? Finally, future safety studies should include specific details of the surgical procedure such as cross-clamp time, blood pressure during the procedure, and other parameters that may contribute to the risk of adverse outcomes independent of the antifibrinolytic used.
Intravenous infusions of aprotinin consist of a loading dose, a pump-priming dose, and a maintenance dose. Expressed in kallikrein inhibitor units (KIU), loading and pump-priming doses are generally 1–2 x 10^6 KIU. The usual maintenance dosage is 0.5 x 10^6 KIU/hour, continuing until the patient arrives in the intensive care unit (ICU). In two meta-analyses of clinical trials of aprotinin usage in cardiac surgery, the high-dose aprotinin regimen (i.e., full Hammersmith dosing) was clearly the most common. The rationale for the high dose is to maintain sufficient inhibition of a greater number of circulating serine proteases and presumably effect a greater degree of hemostasis. This regimen, however, may be associated with higher mortality than half-dose aprotinin and with little-to-no incremental benefit. High-dose aprotinin is also most commonly used in hepatic and orthopedic surgery, although one study that used no loading dose and only 0.2 x 10^6 KIU/hour as a maintenance dose in orthotopic liver transplantation reported that fibrinolysis was adequately controlled and blood product transfusion was reduced.

Most dosing data for tranexamic acid also derives from cardiac surgery studies. For example, a meta-analysis that reviewed 12 trials showed that most used a 10-mg/kg bolus and 1-mg/kg/hour infusion for 10–12 hours. A recent meta-analysis citing 17 comparative trials with tranexamic acid also noted that these doses were commonly used, but 15–20-mg/kg or 2.5-g loading doses and maintenance doses of 2–3 mg/kg/hour were also used. In orthopedic surgery, tranexamic acid bolus doses ranged from 10–15 mg/kg, and maintenance doses ranged from 2–40 mg/kg/hour in hepatic surgery.

Reported doses of EACA used in cardiac surgery trials are more variable than either aprotinin or tranexamic acid. Loading doses of 5–10 g or weight-based doses of 80–150 mg/kg have been used. Maintenance doses of 2 g/hour are the most common but range from 1–2.5 g/hour; doses by weight range from 2.5–30 mg/kg/hour. Although not always used, pump-priming doses of 2.5–10 g or 80 mg/kg have been reported. Epsilon-aminocaproic acid has been less well studied in liver transplantation; however, in one study comparing its efficacy with tranexamic acid and placebo, a dose of 16 mg/kg/hour was used, with no benefit over placebo. Finally, in a small, open-label pilot study of EACA for intracerebral hemorrhage, hematoma expansion was greater in patients who received EACA within 12 hours of symptom onset compared with placebo. Moreover, 60% of EACA-treated patients had hematoma expansion compared with 22% of nontreated patients.

Vasopressin and Somatostatin Analogs

Desmopressin acetate is a selective agonist of the vasopressin-2 (V2) receptor with a much greater antidiuretic than pressor effect (2000–4000:1). Extrarenal V2 receptor activation results in increased circulating levels of factor VIII and von Willebrand factor (vWF), as well as release of t-PA. Desmopressin is indicated to control hemorrhage in patients with mild-to-moderate hemophilia A (factor VIII levels > 5%) and von Willebrand’s disease.

Patients with uremia and prolonged bleeding time have diminished levels of platelet vWF and desmopressin administration will correct this coagulopathy. The recommended dose of desmopressin for this indication is 0.3 µg/kg administered intravenously over 15–30 minutes. This dose may be repeated in 6–8 hours, but subsequent doses within a 24-hour period may lead to tachyphylaxis and paradoxical increase in bleeding time and, therefore, are not recommended. One group suggested that the tachyphylaxis seen with repeated administration may be due to a decreased vWF and factor VIII response, whereas the t-PA response is unchanged. Since desmopressin is a potent diuretic, water retention and hyponatremia may occur with repeated doses.

Studies assessing the use of desmopressin for minimizing blood loss in orthopedic surgery have shown mixed results, as indicated in a published review. For example, for spinal fusion surgery using doses of 10 µg/m² up to a maximum of 20 µg in children or young adults and 0.3 µg/kg in adults, desmopressin has, in some instances, decreased the number of red blood cell transfusions and blood loss, whereas in others, has been ineffective. In total knee or hip arthroplasty, desmopressin has consistently been ineffective as a hemostatic agent.

A recent Cochrane Library review evaluated the use of desmopressin for surgical-related hemostasis. Twenty of the 25 trials included were in patients undergoing cardiac surgery. Most patients received 0.3 µg/kg infused over 10–30 minutes after the cessation of cardiopulmonary bypass. Desmopressin did not decrease the risk of red blood cell exposure, volume of blood loss, or the risk of surgical...
reexploration due to bleeding, leading the authors to conclude that there is no benefit to administering desmopressin in patients undergoing cardiac surgery.

Variceal bleeding is a medical emergency, and vasoactive drugs are considered first-line therapy. Terlipressin and its analogs are potent vasoconstrictors of the splanchnic circulation, causing a decrease in portal venous blood flow and subsequent improvement in variceal bleeding. Because of cardiovascular adverse effects, including myocardial ischemia, vasopressin is not recommended, although coadministration with nitroglycerin may lessen this effect. Terlipressin is an analog of vasopressin with more potent vasoconstrictor activity. Although not currently available in the United States, studies have shown terlipressin to improve morbidity and mortality when administered alone or in combination with sclerotherapy for management of esophageal varices. The availability of terlipressin in the United States is pending review by the FDA of a recently completed phase III clinical trial in type 1 hepatorenal syndrome. If approved, this agent will need to be used with extreme caution in patients with underlying cardiac or pulmonary dysfunction.

The somatostatin analog octreotide has also been shown to decrease recurrent bleeding when combined with sclerotherapy in the treatment of variceal bleeding. The most common dose is a 25–50-µg/kg bolus followed by a continuous infusion of 25–50 µg/hour, with the most frequent adverse effects being gastrointestinal symptoms and hyperglycemia. Meta-analyses have not shown octreotide to affect mortality.

Postpartum hemorrhage is an acute medical emergency for which early pharmacotherapy with oxytocin, a vasopressin analog, is often used to prevent surgical intervention (e.g., hysterectomy). Oxytocin, as well as ergot alkaloids and prostaglandins (e.g., misoprostol), all stimulate uterine contractions and are considered first-line therapy for postpartum hemorrhage. A recent Cochrane Library review failed to find a benefit of adding misoprostol to a standard combination of ergots and oxytocin; however, a general lack of data was acknowledged. These agents are associated with frequent adverse effects such as nausea, vomiting, diarrhea, abdominal pain, hypertension, and fever. One case report also examined the use of tranexamic acid for postpartum hemorrhage, but this does not constitute enough evidence to support its use.

**Phytonadione**

Vitamin K₁ (phytonadione) is a cofactor required for the activation of clotting factors II, VII, IX, and X and is used to treat vitamin K₁ deficiency and to correct coagulopathies related to liver disease and administration of vitamin K₁ antagonists. When given intravenously, the decrease in prothrombin time is more rapid than after oral administration. For reversal of anticoagulation due to administration of vitamin K₁ antagonists in the presence of serious or life-threatening bleeding, the American College of Chest Physicians recommends giving vitamin K₁ 10 mg by slow intravenous infusion, repeated as needed every 12 hours.

Although anaphylactic reactions have been reported with intravenous administration of vitamin K₁, these reactions are considered rare. Subcutaneous administration of vitamin K₁ is not recommended for serious bleeding because of variability in response, and studies show inferiority compared with oral or intravenous administration. Due to the delayed effect of vitamin K₁ on hemostasis, it should not be administered as the sole agent for serious bleeding but may help provide long-term protection against repeat bleeding and, therefore, may be administered at the same time as other hemostatic interventions such as fresh frozen plasma or rFVIIa.

**Recombinant Factor VIIa (rFVIIa)**

This coagulation factor is indicated for the treatment and prevention of acute and surgical bleeding in individuals with hemophilia A or B with inhibitors to clotting factors and acquired hemophilia, and for the treatment of bleeding episodes or prevention of bleeding in surgical procedures in patients with factor VII deficiency.

Mechanistically, rFVIIa forms a complex with tissue factor at the site of injury. This complex is responsible for activating factors IX and X (IXa and Xa), leading to thrombin generation and activation of platelets and other clotting factors (Figure 3). Activation of platelets by this mechanism may increase the rate of clot formation and lead to a “thrombin burst.” An alternate hypothesis suggests that factor Xa can be generated in substantial amounts on the surface of activated platelets in the absence of tissue factor.

**Efficacy**

The off-label use of rFVIIa is common in populations subject to severe bleeding such as in
trauma, neurosurgery, cardiac surgery, and liver transplantation. Recombinant FVIIa has also been used to reverse excessive anticoagulation that occurs with warfarin, analogs of heparin, or with direct thrombin inhibitors. Although published data on these uses of rFVIIa are abundant, many focus on cases or represent observations in limited numbers of patients. Few randomized, well-controlled studies have been performed to support its widespread use. A consensus panel sponsored by the University HealthSystem Consortium (UHC) and the Society for the Advancement of Blood Management reviewed the rFVIIa literature, graded the available evidence, and have offered recommendations to guide its appropriate use. Elsewhere in this supplement, a strategy to develop guidelines to promote safe, effective, and appropriate cost-conscious utilization of pharmacotherapeutic agents that can easily be applied to rFVIIa is provided.

In this article, only several of the more rigorous and recent studies performed with rFVIIa are discussed; others are summarized in Table 1.

Neurocritical Care

Well-designed trials with rFVIIa in patients with intracerebral hemorrhage have shown that rFVIIa effectively reduces hematoma expansion; however, mortality data have been mixed. In one study, patients aged 18 years or older with spontaneous intracerebral hemorrhage documented by computed tomography within 3 hours of symptom onset and a Glasgow Coma Scale (GCS) score of 3–5 were randomly assigned to treatment with rFVIIa 40, 80, or 160 µg/kg, or placebo. Notable exclusion criteria were thrombocytopenia, traumatic or aneurysmal bleeding, history of thrombosis or vascular disease, and patients receiving chronic anticoagulation. A significant reduction (p=0.02) in percent hematoma expansion at 24 hours (primary outcome measure) was noted for patients in the 160-µg/kg group. When combining data from all three dose groups, overall 90-day mortality was lower (18% vs 29%, p=0.02) in rFVIIa-treated patients compared with placebo.

Preliminary results from a controlled phase III trial, in which 821 patients with intracerebral hemorrhage received rFVIIa 20 or 80 µg/kg or placebo within 4 hours of symptom onset, also demonstrated significant inhibition of hematoma growth, as well as functional improvement at day 15 when treated with rFVIIa. However, neither 90-day mortality nor severe disability (primary end points) were improved by rFVIIa over placebo in this trial. Whether the variance between these and earlier data from the above-mentioned study will impact rFVIIa use for intracerebral hemorrhage in clinical practice remains to be seen.

Trauma

One group published results of two multicenter, double-blind, placebo-controlled trials examining rFVIIa in trauma patients with blunt and penetrating injuries. Patients with severe trauma were included if they had received 6 or more units of red blood cells within 4 hours of admission. Those with gunshot wounds to the head, a GCS score below 8, or severe acidosis (pH < 7.0) were excluded. Treatment was either intravenous rFVIIa 200 µg/kg followed by 100 µg/kg at 1 and 3 hours after the first dose, or placebo. In the blunt trauma group, patients assigned to rFVIIa received, on average, 2.6 fewer units of red blood cells than the placebo group (p=0.02). Massive transfusions, defined in this study as administration of more than 20 units of red blood cells, were also reduced from 33% in the placebo group to 14% in the rFVIIa group, representing a 56% reduction in relative risk (95% CI 9–79%, p=0.03). There were no significant mortality differences in either group of trauma patients compared with the placebo group nor was there a significant difference in the pattern or type of adverse events among

![Figure 3. Schematic representation of normal hemostasis. Generation of activated factor X (Xa) can occur on tissue factor (TF)-bearing cells, as well as on activated platelets. Factor Xa produced on activated platelets may be less susceptible to hydrolysis by plasma proteases such as antithrombin III and tissue factor pathway inhibitor. vWF = von Willebrand factor. (From reference 55 with permission.)](image-url)
Table 1. Summary of Grade I and II Evidence of Off-Label Use of Recombinant Factor VIIa

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Evidence Grade</th>
<th>No. of rFVIIa Recipients</th>
<th>Dose Range (µg/kg)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic failure with gastrointestinal bleeding or pending invasive procedure&lt;sup&gt;50&lt;/sup&gt;</td>
<td>I</td>
<td>121</td>
<td>100 (8 doses)</td>
<td>rFVIIa had advantage over standard therapy only in the subgroup of patients with Child-Pugh B and C variceal bleeds, but not in overall population; adverse-event profile was similar to that of placebo</td>
</tr>
<tr>
<td>Prophylaxis before major hepatic resection&lt;sup&gt;51&lt;/sup&gt;</td>
<td>I</td>
<td>132</td>
<td>20 or 80</td>
<td>Hematocrit reduction during surgery was lowest in 80-µg/kg rFVIIa group (p = 0.04), but number of patients requiring transfusion and the volume of blood products administered were not reduced; adverse-event profile was similar to that of placebo</td>
</tr>
<tr>
<td>Nontraumatic intracerebral hemorrhage&lt;sup&gt;62&lt;/sup&gt;</td>
<td>I</td>
<td>303</td>
<td>40, 80, or 160</td>
<td>Comparing all three dosing groups with placebo, rFVIIa administered within 4 hrs of intracerebral hemorrhage onset limited hematoma growth (p = 0.01), improved functional outcomes (p = 0.004), and reduced mortality (p = 0.02); thromboembolic events occurred in 2% and 7% of placebo- and rFVIIa-treated patients, respectively (p = 0.12)</td>
</tr>
<tr>
<td>Prophylaxis in major orthopedic surgery&lt;sup&gt;63&lt;/sup&gt;</td>
<td>I</td>
<td>24</td>
<td>90</td>
<td>No significant differences in the total volume of perioperative blood loss, blood components or fluids infused, number of patients requiring blood components, total operating time, time to reach normal body temperature or time spent in hospital, or acid-base status; no adverse events related to drug administration were reported</td>
</tr>
<tr>
<td>Life-threatening bleeding in children with Dengue-shock syndrome&lt;sup&gt;64&lt;/sup&gt;</td>
<td>I</td>
<td>16</td>
<td>100</td>
<td>Control of bleeding 2 hrs after dosing of rFVIIa was superior to that of placebo; platelet requirement was lower, but requirement for RBCs or plasma was not; no thromboembolic complications were observed</td>
</tr>
<tr>
<td>Salvage therapy for intractable bleeding due to aneurysm, trauma, abdominal surgery&lt;sup&gt;65&lt;/sup&gt;</td>
<td>II-3</td>
<td>10</td>
<td>90–120</td>
<td>Treated patients had already been transfused with ≥ 10 units RBCs; transient cessation of bleeding noted in 60% of rFVIIa-treated patients, but rFVIIa treatment did not rescue patients or affect outcomes</td>
</tr>
<tr>
<td>Reversal of anticoagulant (melagatran constant infusion) in healthy volunteers&lt;sup&gt;66&lt;/sup&gt;</td>
<td>I</td>
<td>20</td>
<td>90</td>
<td>Single doses of rFVIIa did not reverse the anticoagulant effect of a steady-state infusion of direct thrombin inhibitor (melagatran); higher or multiple doses of rFVIIa were not tested; no adverse events reported</td>
</tr>
<tr>
<td>Reversal of excessive anticoagulation with warfarin&lt;sup&gt;67&lt;/sup&gt;</td>
<td>II-3</td>
<td>13</td>
<td>15–90</td>
<td>rFVIIa corrected prolonged INR rapidly and safely</td>
</tr>
<tr>
<td>Emergency reversal of anticoagulation&lt;sup&gt;68&lt;/sup&gt;</td>
<td>II-3</td>
<td>18</td>
<td>20–106</td>
<td>Patients requiring anticoagulant reversal (after failing traditional antidotes and blood products) had been receiving LMWH, unfractionated heparin, coumarin, or warfarin; after rFVIIa given, bleeding stopped in 10, decreased in 3, and slowed in 3 others; blood product and crystalloid or colloid also decreased (p &lt; 0.05) after rFVIIa given. Response observed within 2 hrs of first administration in 12 of 16 patients; no adverse events were attributed to rFVIIa</td>
</tr>
<tr>
<td>Reversal of acute bleeding in warfarin-treated patients&lt;sup&gt;69&lt;/sup&gt;</td>
<td>III</td>
<td>16</td>
<td>11–25</td>
<td>Relatively low dose (mean 16.3 ± 4.1 µg/kg) rFVIIa rapidly corrected prolonged INR, and hemostasis was achieved in 14 of 16 patients; 6 of 16 patients died, one of thrombosis of uncertain relationship to rFVIIa administration</td>
</tr>
<tr>
<td>Blunt trauma&lt;sup&gt;70&lt;/sup&gt;</td>
<td>I</td>
<td>69</td>
<td>200, followed by 2 x 100</td>
<td>rFVIIa administration resulted in fewer RBC transfusions (p = 0.02), fewer massive transfusions (p = 0.03), and trends toward fewer adverse events, lower mortality, and increased ventilator- and ICU-free days; adverse-event profile was similar to that of placebo</td>
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treatment groups. Serious adverse events most commonly reported were acute respiratory distress syndrome, multiple organ failure, and sepsis, as expected for severely injured trauma patients.

Reversal of Anticoagulation

The clotting factor most affected by vitamin K antagonists is FVIIa. The potential for rFVIIa to correct excessive warfarin-related coagulopathy has been examined, mostly in the form of case reports or descriptive studies. Although no well-controlled trial has been performed, three studies provide an intermediate grade of evidence that rFVIIa is effective in this setting. In one, rFVIIa corrected critically prolonged international normalized ratios (INRs) and reversed bleeding associated with excessive warfarin. In another, bleeding was controlled in patients who had received anticoagulation with warfarin, coumarin, low-molecular-weight heparin, or heparin. A third observational study reported that low-dose rFVIIa (mean ± SD dose 16.3 ± 4.1 µg/kg [range 11–25 µg/kg]) rapidly corrected INR to normal in warfarin-treated patients.

Postpartum Hemorrhage

A recent audit of a registry of patients with postpartum hemorrhage analyzed rFVIIa usage as primary treatment or salvage therapy. The median dose administered was 32.2 µg/kg with 20 of 25 patients receiving only one dose. Although bleeding decreased in all but one patient and rFVIIa reduced the amount of blood products used, no statistical analysis was performed. No thrombotic events were reported; however, conclusions regarding the safety and efficacy of rFVIIa cannot be made for its use in postpartum hemorrhage due to the lack of grade II or higher evidence.

Safety and Factors Affecting rFVIIa Efficacy

Given the variety of populations who have received rFVIIa and diversity of risk factors present in those patients, the risk for thrombosis associated with rFVIIa is not precisely known. According to postmarketing data, the thrombotic risk has been low, on the order of 0.02%. In one study, 5% of patients receiving rFVIIa for intracerebral hemorrhage experienced arterial thrombosis (myocardial or cerebral infarction) versus 0% in the placebo group, with the highest frequency reported in the 160-µg/kg group, suggesting a possible dose-related effect. Another study examining voluntary reporting of adverse events to the FDA's MedWatch program identified 185 adverse thromboembolic events.

### Table 1. Summary of Grade I and II Evidence of Off-Label Use of Recombinant Factor VIIa (continued)

<table>
<thead>
<tr>
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<th>Evidence Gradea</th>
<th>No. of rFVIIa Recipients</th>
<th>Dose Range (µg/kg)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penetrating trauma</td>
<td>I</td>
<td>70</td>
<td>200, followed by 2 x 100</td>
<td>rFVIIa administration resulted in nonsignificant trends toward fewer RBC transfusions, fewer massive transfusions, fewer adverse events, increased ventilator- and ICU-free days, and lower mortality; adverse-event profile was similar to that of placebo</td>
</tr>
<tr>
<td>Partial hepatectomy in patients with cirrhosis</td>
<td>I</td>
<td>71</td>
<td>50 and 100 (50 µg/kg)</td>
<td>rFVIIa had no significant effect on proportion of patients receiving RBC transfusions nor on the amount of RBCs transfused; adverse-event profile at both doses of rFVIIa was similar to that of placebo</td>
</tr>
<tr>
<td>Complex noncoronary cardiac surgery requiring CPBb</td>
<td>I (pilot study)</td>
<td>10</td>
<td>90</td>
<td>rFVIIa significantly reduced the need for RBC transfusions; adverse-event profile similar to that of placebo</td>
</tr>
</tbody>
</table>

rFVIIa = recombinant factor VIIa; RBC = red blood cell; INR = international normalized ratio; CPB = cardiopulmonary bypass; LMWH = low-molecular-weight heparin; ICU = intensive care unit.

*aLevels of evidence for references 60–67 are for studies reviewed and graded in a previous study. Those studies published since (references 68–72) were graded by the current author. Definitions of evidence grades are as follows: type I: randomized, controlled trial; type II-1: well-designed controlled trial without randomization; type II-2: well-designed cohort or case-controlled analytic study, preferably from more than one center; type II-3: multiple time series with or without the intervention, and dramatic results in noncontrolled setting could be included; type III: opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.
that occurred in 168 patients. Of these, 54% were identified as arterial (non–intracerebral hemorrhage cerebrovascular accident, acute myocardial infarction, or other arterial site), 40% were venous (deep vein or other venous thrombosis or pulmonary embolism), and 6% were due to device occlusion. Because reporting by this method is voluntary, it is difficult to establish a causal relationship between rFVIIa administration and thrombosis.

In another review of safety data obtained from 13 manufacturer-sponsored clinical trials in various populations, thrombotic adverse events were reported in 5.3% of patients receiving placebo versus 6.0% of actively treated patients (p=0.57). Finally, another group compared thrombosis occurrence with rFVIIa and a factor VIII inhibitor bypass agent and found that in both cases, events were rare at 67 and 16 events/100,000 infusions, respectively. It is noteworthy that all of these estimates are based on spontaneous reports (which are notoriously underreported) or are derived from clinical studies in which at-risk patients are generally excluded. Thus, the potential risk for thrombosis with rFVIIa may be somewhat higher, especially in patients with underlying risk factors.

For patients in whom rFVIIa is being considered, platelets and blood pH should be assessed. Recombinant FVIIa is reportedly ineffective in patients with platelet counts below 50 x 10^3/mm^3 because of the inability to form a stable clot. Efficacy of rFVIIa may also be dependent on blood pH. In one study, rFVIIa activity was reduced by 90% at a pH of 7.0 versus 7.4. Hypothermia has not been shown to decrease the activity of rFVIIa, but it is a factor that may adversely affect coagulation and should be corrected before rFVIIa administration.

In patients with thrombosis risk who require treatment with an anticoagulant, extreme caution should be exercised when administering rFVIIa. Further study is warranted to determine rFVIIa safety in this population, as well as in patients with antithrombin III deficiency, factor V leiden, and protein C and/or S deficiency or other factors that increase thrombosis risk.

Two recent studies addressed risk factors for futility of rFVIIa administration. In the first, in patients who received rFVIIa for acute hemorrhage, a poor hemostatic response was predicted by elevated lactate level, revised trauma score less than 4.09, and baseline prothrombin time 17.6 seconds or greater (p=0.05 for each). The authors concluded that coagulopathy, profound acidosis, and depth of hemorrhagic shock as assessed by the revised trauma score should be considered as potential contraindications for rFVIIa administration. A second study provided data consistent with these recommendations, suggesting that acidosis and a high volume of red blood cells administered contribute to a poor response to rFVIIa.

Dosing of rFVIIa varies with clinical use and is summarized in Table 1. Administration of rFVIIa should be by slow intravenous bolus over 2–5 minutes. The half-life of rFVIIa varies from 1.7–3.1 hours. Because of the limited stability (3 hrs after reconstitution) and high cost of rFVIIa, many centers advocate rounding the calculated dose up or down to the nearest vial size to avoid waste. The appropriate dosage of rFVIIa, whether dosing should be based on ideal or actual body weight, as well as questions about safety, efficacy, and impact on outcomes, remain unanswered.

**Conjugated Estrogens**

Estrogens have been shown to decrease circulating levels of antithrombin III and protein S and to increase factors VII, VIII, IX, X, and prothrombin. Platelet counts may be quantitatively and qualitatively increased with estrogen use. In a study of patients with chronic renal insufficiency and receiving hemodialysis, six patients with uremic bleeding received intravenous conjugated estrogens 0.6 mg/kg/day. Bleeding times decreased in all patients within 6 hours after the first infusion, with maximum effects being achieved in 5–7 days and persisting for 14 days.

In patients undergoing renal transplantation with preoperative bleeding times greater than 10 minutes, conjugated estrogens 50 mg or 2 units of fresh frozen plasma were administered after induction of anesthesia and compared with placebo in patients with only mildly elevated bleeding times. In both groups, bleeding times were significantly decreased by the end of surgery. Adverse events were not reported in this trial.

Conjugated estrogens have also been studied for reducing the amount of blood products given to patients undergoing orthotopic liver transplantation. Thirty hypocoagulable patients, as determined by thromboelastography, were randomly assigned to receive intravenous conjugated estrogen 100 mg or placebo at the beginning of surgery and after graft reperfusion. Patients in the estrogen group required fewer units of intraoperative red blood cells (p=0.05),
fresh frozen plasma (p=0.001), and platelets (p=0.05). However, no significant difference was seen in the amount of blood products required during the first 24 hours after surgery. The potential for thrombotic adverse events was not assessed.

Because of their delayed onset of action, estrogens may not be useful when control of bleeding is considered urgent. However, anticoagulant effects may be prolonged for several days, which may be useful in cases of persistent, nonemergent bleeding. The safety of estrogen use for hemostasis has not been adequately assessed. Studies are needed, especially since a high dose of estrogen is typically required to control bleeding and previous studies have noted an increase in thrombotic risk with estrogen use.89, 90

Topical Hemostatic Agents

Used as adjunctive therapy to augment hemostasis in surgical procedures or in trauma-associated bleeding, a variety of topical agents (Table 2)91–104 may be applied as solutions, gels, granules, or sprays, or used with absorbable gelatin sponges or powders (e.g., Surgifoam), collagen, or cellulose preparations (e.g., Surgicel, oxidized regenerated cellulose). Thrombin is a plasma protein that enzymatically converts fibrinogen, another plasma protein, to fibrin. At sites of tissue injury induced by trauma or surgery, local thrombin and fibrinogen concentrations determine the rate of clot formation. When fibrin is incorporated into a blood clot, the clot strengthens and degradation of the formed clot by fibrinolytic enzymes is

<table>
<thead>
<tr>
<th>Table 2. Topical Hemostatic Agents</th>
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<tbody>
<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td>Bovine thrombin</td>
</tr>
<tr>
<td>Recombinant human thrombin</td>
</tr>
<tr>
<td>FloSeal hemostatic matrix: bovine gelatin granules and human thrombin</td>
</tr>
<tr>
<td>Fibrin sealants (Tisseel VH): fibrinogen, fibrinolysis inhibitor (bovine), aprotinin, and human thrombin</td>
</tr>
<tr>
<td>Virally inactivated aprotinin-free fibrin sealant (Crosseal): thrombin and fibrinogen (human)</td>
</tr>
<tr>
<td>CoStasis: microfibrillar collagen-fibrin (bovine)</td>
</tr>
<tr>
<td>CoSeal Surgical Sealant: two synthetic polyethylene glycols</td>
</tr>
<tr>
<td>Aprotinin and tranexamic acid</td>
</tr>
<tr>
<td>Chitosan hemostatic bandage</td>
</tr>
<tr>
<td>Zeolite</td>
</tr>
</tbody>
</table>

9Phase III clinical trials completed; application submitted to U.S. Food and Drug Administration and decision is pending, according to public information released by ZymoGenetics, Seattle, WA.
PHARMACOTHERAPY FOR CRITICAL BLEEDING

Voils

Thrombin also facilitates coagulation by direct activation of platelets and other coagulation enzymes,91 and stimulates cellular signaling through interactions with adhesive receptors (e.g., glycoprotein Ib-V-IX) present on the surface of circulating platelets.105 Because of these mechanisms, topical thrombin, purified from human or bovine plasma, has been used to stop diffuse bleeding during major surgical procedures. Bovine thrombin, however, has been associated with safety concerns due to impurities and immunologic risks. Antibodies formed against host thrombin, prothrombin, factor V, and cardiolipin can lead to severe bleeding and/or clotting disorders.106

CoSeal, FloSeal, and FloSeal Matrix are topical agents classified as fibrin sealants. CoSeal is a synthetic hydrogel mixture of polyethylene glycols that forms a mechanical seal and has no associated risk of infectious disease transmission. Aprotinin and tranexamic acid have been used topically in cardiopulmonary bypass surgery with limited success.102 Other topical products used to arrest blood loss in extreme emergency settings (i.e., primarily in combat settings) include chitosan bandages103 and zeolite powder. Zeolite induces a hypothermic reaction that helps to cauterize wounds, but it may cause damage to tissues.104

Pharmacotherapy for Disseminated Intravascular Coagulation

In patients who develop disseminated intravascular coagulation (DIC), platelets, fresh frozen plasma, and/or cryoprecipitate are used first line to treat or prevent bleeding.104, 107 Because DIC can manifest acutely with hypercoagulability, heparin has been evaluated experimentally with good results, but controlled clinical trials have failed to show benefit.108 The potential also exists for bleeding and lack of efficacy due to decreased levels of antithrombin seen in DIC. Treating the underlying disorder that triggered DIC (i.e., sepsis) to restore physiologic anticoagulant pathways provides a rationale for administration of activated protein C to manage DIC.108, 109 As reviewed elsewhere,110 activated protein C has had beneficial effects on 28-day mortality in patients with severe sepsis or septic shock. The risk of bleeding was also increased, however, and activated protein C should, thus, be reserved for patients with minimal bleeding risk and whose platelet count is greater than 30 x 10^9/mm^3.

Products in Clinical Development

Several new pharmaceutical agents are in development that may change the face of management of critical bleeding and severe acute blood loss (Table 3).48, 111–115 Most of the blood substitutes (now referred to as artificial oxygen carriers) that had promise in previous decades were compromised by safety issues arising during clinical investigations.116–119 As a result, none of these products has met regulatory approval for use in humans. One new fourth-generation polyethylene glycol conjugate of hemoglobin is being evaluated in a phase III clinical trial for elective surgery.111 Thus, the current list of pharmacotherapies in various stages of preclinical or clinical development is largely composed of human plasma proteins (factor XIII,112, 120 monomeric113 and dimerized albumin,114 and thrombin121) that were synthesized and manufactured with use of recombinant technology. One formulation containing both recombinant prothrombin (recombinant factor II) with activated recombinant factor X is said to mimic the active components of plasma-derived prothrombin complex concentrates, but with no risk of viral transmission and less thrombogenic potential.115, 122 Should any of these products meet FDA criteria for safety and efficacy, clinicians will have more options to treat patients with critical bleeding pharmacologically, rather than with blood products.

Guidelines for Pharmacotherapeutic Management of Bleeding

Several useful guidelines concerning pharmacotherapy for management of bleeding associated with a variety of clinical scenarios have been published. The clinical context, sponsoring agencies, and citations where these guidelines may be found are listed in Table 4.52, 123–131

Conclusion

Pharmacists, particularly those who practice in the hospital setting, need to be familiar with each of the various hemostatic agents and keep abreast of their dosing, efficacy, and associated safety concerns. Whether aprotinin will continue to be recommended for cardiac surgery in light of emerging data remains to be seen. Many questions remain about the use of rFVIIa, and well-controlled studies are needed to understand the risk of thrombosis in various patient populations, as well as its effect on outcomes. Similarly,
agents in clinical development will need further study to establish their respective places in the management of bleeding. Judicious patient selection, above all, is the key to increasing the likelihood that the benefit of using any particular hemostatic agent exceeds the risk.

Table 3. Products in Clinical Development for Management of Critical Bleeding

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Potential Uses</th>
<th>Potential Risks</th>
<th>Development Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemospan</td>
<td>Polyethylene glycol conjugated hemoglobin; provides oxygen-carrying capacity with high oxygen affinity, which limits excessive vasoactivity</td>
<td>Substitute for RBCs in elective surgery</td>
<td>Hypotension, but generally safe in studies thus far</td>
<td>Phase III clinical trial</td>
</tr>
<tr>
<td>ZL-HbBv</td>
<td>“Zero-link” technology polymerizes bovine hemoglobin; provides oxygen-carrying capacity with high oxygen affinity</td>
<td>Sepsis</td>
<td>Tendency to extravasate in animals</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Recombinant human factor XIII</td>
<td>Thrombin-activated protransglutaminase responsible for fibrin clot stabilization and longevity</td>
<td>Replacement in congenital factor XIII deficiency for prevention and treatment of bleeding complications and abnormalities in tissue repair; factor XIII inhibitor development; factor XIII deficiency due to blood loss or chronic coagulation system activation</td>
<td>Occlusive coagulopathy due to high-molecular-weight stable complex formation Anti-recombinant factor XIII antibody development</td>
<td>Phase I clinical trials</td>
</tr>
<tr>
<td>Recombinant human serum albumin</td>
<td>Plasma protein provides osmotic support to circulation</td>
<td>Vascular volume expander</td>
<td>Vascular leakage and tissue edema in critically ill burn patients and if hypoalbuminemia is present; minor skin-related allergic reactions when administered intramuscularly</td>
<td>Phase I clinical studies</td>
</tr>
<tr>
<td>Dimerized recombinant human serum</td>
<td>Dimerized plasma protein has higher retention in circulation and prevents vascular leakage and excessive tissue edema</td>
<td>Vascular volume expander possibly superior to nondimerized albumin</td>
<td>Unknown</td>
<td>Animal (rat) studies</td>
</tr>
<tr>
<td>Recombinant partial prothrombin inhibitor complex</td>
<td>Recombinant prothrombin (recombinant factor II) combined with recombinant activated factor X are active components used to bypass factor VIII activity</td>
<td>Patients with inhibitors to factor VIII</td>
<td>Similar to prothrombin complexes but with potentially less thrombogenicity</td>
<td>Animal (rabbit) studies</td>
</tr>
<tr>
<td>Terlipressin</td>
<td>Vasopressin analog with more potent vasoconstricting activity than vasopressin or desmopressin</td>
<td>Management of esophageal varices alone or in combination with sclerotherapy</td>
<td>May decrease cardiac index and oxygen consumption; use with caution in patients with pulmonary or cardiac dysfunction</td>
<td>Pending FDA decision after phase III trial</td>
</tr>
</tbody>
</table>

RBC = red blood cell; FDA = U.S. Food and Drug Administration.

References

Table 4.  Current Guidelines for Pharmacotherapy to Manage Critical Bleeding

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Guideline Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracerebral hemorrhage in patients receiving oral anticoagulant therapy</td>
<td>Several existing guidelines summarized; not standardized</td>
</tr>
<tr>
<td>Postpartum hemorrhage</td>
<td>American College of Obstetrics and Gynecology</td>
</tr>
<tr>
<td>Perioperative bleeding</td>
<td>American Society of Anesthesiologists</td>
</tr>
<tr>
<td>Inhibitors to factors VII and IX</td>
<td>United Kingdom Haemophilia Centre Doctors Organisation</td>
</tr>
<tr>
<td>Warfarin reversal</td>
<td>American College of Chest Physicians</td>
</tr>
<tr>
<td>Nonvariceal upper gastrointestinal bleeding</td>
<td>Australasian Society of Thrombosis and Haemostasis</td>
</tr>
<tr>
<td>Hemorrhagic shock</td>
<td>Society of Obstetricians and Gynaecologists of Canada</td>
</tr>
<tr>
<td>Major trauma</td>
<td>European Society of Anesthesiologists, European Society of Intensive Care Medicine, European Shock Society, European Trauma Society, and European Society for Emergency Medicine</td>
</tr>
</tbody>
</table>

*Only guidelines recommending the use of some pharmacotherapy to manage critical bleeding that have been issued in the last 5 years are included.*

21:35–44.


