Activated Prothrombin Complex Concentrates for the Reversal of Anticoagulant-Associated Coagulopathy

Nadia I. Awad, PharmD; and Craig Cocchio, PharmD, BCPS

ABSTRACT

Objective: Prothrombin complex concentrate (PCC) products are emerging as alternative strategies for reversing anticoagulant pharmacotherapy. **F**actor **e**ight **i**nhibitor **b**ypassing **a**ctivity (FEIBA, or anti-inhibitor coagulant complex) is an activated PCC (aPCC). Although FEIBA is approved by the FDA to control spontaneous bleeding episodes and to prevent bleeding with surgical interventions in hemophilia A and hemophilia B patients with inhibitors to factor VIII, recent data have suggested that the product may be used off-label as an anticoagulant-reversal agent. To evaluate the safety and efficacy of aPCC products in reversing anticoagulant pharmacotherapy, we searched online databases for English-language publications that discussed this topic.

Data Sources: The EMBASE, MEDLINE, and International Pharmaceutical Abstracts databases were used. We evaluated all articles published in the English language identified from the data sources. We included studies conducted in human subjects and in *in vitro* and *in vivo* models in our review.

Results: Current published evidence suggests that the use of an aPCC, compared with fresh-frozen plasma, is associated with a significantly faster correction of supratherapeutic International Normalized Ratios (INRs) secondary to warfarin therapy. Conflicting evidence exists regarding the ability of aPCCs to reverse the prolonged bleeding times caused by the anticoagulant agents dabigatran etexilate (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis), and fondaparinux (Arixtra).

Conclusion: The theoretical risks of thrombosis associated with PCC products must be carefully considered before they are administered to patients who require coagulation therapy. The use of aPCCs to reverse the anticoagulant effects of warfarin, dabigatran, or rivaroxaban should be limited because of the lack of efficacy and safety data in humans. Moreover, the safety of aPCCs in off-label indications has not been adequately assessed.

Key words: FEIBA, activated PCC, hemorrhage, reversal, anticoagulation

INTRODUCTION

The management of life-threatening hemorrhaging in the presence of anticoagulant pharmacotherapy is complex. In the setting of therapy with vitamin K antagonists, the reversal of anticoagulant effects can be achieved by administering vitamin K and fresh-frozen plasma (FFP). However, vitamin K has a delayed onset of action in correcting the International Normalized Ratio (INR) and plays no role in reversing the anticoagulant effects of newer agents, such as the oral direct thrombin inhibitors or the oral direct factor Xa inhibitors.[1–4] Although FFP may be used, several factors make it less than the ideal agent for this purpose. The administration of FFP may be delayed because it must be ABO-matched to the patient's blood and requires time for thawing before it is given. Typically, a large volume of FFP (15 mg/kg) is required for administration, which may lead to transfusion-associated cardiopulmonary overload and other infusion reactions, such as acute lung injury.[5]

Prothrombin complex concentrate (PCC) products are emerging as alternative strategies to FFP for reversing anticoagulant pharmacotherapy. The advantages of PCCs over FFP include no need for ABO matching or plasma thawing; further, a small volume can be given over a short period.[4] In the U.S., three distinct classifications of PCC products are commercially available:[6]

- three-factor PCC products contain three coagulation factors (II, IX, and X)
- four-factor PCC products contain four coagulation factors (II, VII, IX and X)
- activated PCC (aPCC) products contain four coagulation factors (in inactive and activated forms)

Currently, only one aPCC product is available in the U.S.—a freeze-dried sterile human plasma fraction with **f**actor **e**ight (VIII) **i**nhibitor **b**ypassing **a**ctivity (FEIBA). The product is available as FEIBA NF (anti-inhibitor coagulant complex, nanofiltered) and as FEIBA VH (anti-inhibitor coagulant complex, vapor-heated), both made by Baxter.[7] FEIBA NF and VH are considered aPCC products because they contain mostly activated factor VII along with mainly non-activated factors II, IX, and X.

Although FEIBA products are approved to control spontaneous bleeding episodes or to prevent bleeding with surgical interventions in hemophilia A and hemophilia B patients with inhibitors, data from several studies suggest that the product may be used in an off-label fashion as an anticoagulant-reversal agent.[8-13] However, the efficacy and safety of FEIBA in off-label uses remain unsubstantiated.

METHODS

To evaluate the safety and efficacy of aPCCs in reversing anticoagulant pharmacotherapy, we searched the databases of EMBASE (1974–June 2012), MEDLINE (1966–June 2012), and

Dr. Awad is Clinical Assistant Professor of Emergency Medicine and an Emergency Medicine Pharmacist at the Ernest Mario School of Pharmacy at Rutgers, The State University of New Jersey, in Piscataway, New Jersey and at Somerset Medical Center in Somerville, New Jersey. At the time of this writing, she was a PGY-2 Emergency Medicine Pharmacy Resident at the university and at Robert Wood Johnson University Hospital, in New Brunswick, New Jersey. Dr. Cocchio is Clinical Assistant Professor of Emergency Medicine and Residency Program Director of Emergency Medicine Pharmacy PGY-2 at the university and at Robert Wood Johnson University Hospital.

Disclosure: The authors report no commercial or financial relationships in regard to this article.

International Pharmaceutical Abstracts (1970–June 2012) for English-language publications that discussed this topic. Search terms included "aPCC," "FEIBA," "aPCC and anticoagulation," "FEIBA and anticoagulation," "aPCC and anticoagulation reversal," and "FEIBA and anticoagulation reversal."

We limited the search to comparative studies of FEIBA and other reversal agents for anticoagulant therapies conducted in both *in vitro* and *in vivo* models. References cited in the identified publications were also reviewed for inclusion.

RESULTS

Activated PCCs Versus Fresh-Frozen Plasma In Warfarin-Induced Hemorrhage

Wojciket et al. conducted a retrospective chart review of 141 patients with life-threatening bleeding episodes associated with warfarin.[8] Two groups of patients were analyzed. The first group included patients who received a standard institutional protocol for FFP (n = 69). Patients in the second group received a fixed-dose regimen of aPCC (FEIBA VH), depending on the INR value at presentation (n = 72). These patients received 500 units of aPCC if the initial INR value was below 5, or 1,000 units if the initial INR value was 5 or above. All patients who received aPCC were treated concomitantly with intravenous (IV) vitamin K 10 mg.

The rates of successful hemostasis (defined as patients who survived the bleeding episode) did not differ significantly between the two treatment arms (77.8% for aPCC/vitamin K vs. 88.2% for FFP; $P = 0.545$). Treatment with aPCC provided faster normalization of the INR to 1.4 or less and provided a lower INR value compared with FFP (50% vs. 33%, respectively; $P = 0.017$). However, there were no significant differences in length of hospital stay; both groups were hospitalized for a median period of 6 days ($P = 0.521$). Five patients in the aPCC group experienced adverse events that were possibly related to treatment, whereas only one adverse event (a mild hypersensitivity reaction) occurred in the FFP group.

Activated PCCs Versus Recombinant Factor VIIa and PCCs

Desmurs-Clavel et al. conducted an *in vitro* study of platelet-rich blood pooled from six healthy volunteers.[9] The blood was treated with fondaparinux (Arixtra, GlaxoSmithKline) at a concentration of 1.5 mcg/mL (equivalent to a therapeutic dose of 7.5 mg). This was followed by the addition of several reversal agents, recombinant factor VIIa (22.4, 45, and 90 mcg/kg); aPCC (10, 20, and 40 U/kg); and a four-factor PCC (Kaskadil, Laboratoire Francais du Fractionnement) (0.25, 0.5, and 1.0 U/mL), to determine their effects on thrombin-generation time, based on the surrogate parameters of lag time, thrombin peak, and endogenous thrombin potential.

Recombinant factor VIIa failed to demonstrate dose-dependent reversal of the prolongation of thrombin-generation time induced by fondaparinux. By contrast, aPCC effectively reversed the prolongation of thrombin-generation time, thereby reversing the anticoagulation effect of fondaparinux, at a dose of 20 IU/kg (lag time, $P = 0.04$; endogenous thrombin potential, $P = 0.0007$).

The effect of PCC on thrombin-generation time could not be determined. The authors speculated that PCC products such as Kaskadil, which contain heparin to reduce the risk of thrombogenicity, result in delayed thrombin generation and thus present difficulty in interpreting thrombin-generation time.

Activated PCCs and New Oral Anticoagulant Therapies

By supplementing activated coagulation factor II (prothrombin) and factor VIIa, aPCC products might be expected to overcome the competitive inhibition of thrombin by dabigatran (Pradaxa, Boehringer Ingelheim). Consistent with this theory, the hemostatic effects of aPCC are associated with its factor X and prothrombin content rather than with its factor VIIa activity.[10] Few clinical trials, however, have tested this theory in human subjects.

In a mouse model, van Ryn et al. induced bleeding by administering high-dose dabigatran (1 µmol/kg bolus, followed by an 0.5-µmol/kg/hour infusion for 25 minutes).[11] Recombinant factor VIIa (0.1 and 0.5 mg/kg) and aPCC (50 and 100 U/kg) were administered as reversal agents 20 minutes after the infusion was started.

Blood was sampled for activated partial thromboplastin time (aPTT) and bleeding time at the completion of the infusion. After dabigatran was given, aPTT and bleeding time increased to 58 ± 8 seconds and 1,455 ± 352 seconds, respectively. The effect of dabigatran on bleeding time was reduced to 186 ± 49 seconds and 135 ± 13 seconds after administration of 0.1 mg/kg or 0.5 mg/kg of recombinant factor VIIa, respectively.

Similarly, aPCC reduced bleeding time to 146 ± 11 seconds after administration of 50 U/kg, but it did not achieve the same reduction in bleeding time after a higher dose was given (i.e., 174 ± 18 seconds after 100 U/kg was administered).

aPTT was reversed by recombinant factor VIIa in a dose-dependent manner to 31 ± 1.9 seconds and 27 ± 2 seconds after administration of 0.1 mg/kg or 0.5 mg/kg, respectively. van Rhyn et al. commented that the dose-dependent effect on aPTT was not seen after administration; however, data were not provided.[11]

Perzborn et al. investigated the effects of reversal of rivaroxaban (Xarelto, Janssen) using aPCC (FEIBA), four-factor PCC (Beriplex, CSL Behring), and recombinant factor VIIa (NovoSeven, Novo Nordisk) in anesthetized rats and primates.[12] After IV rivaroxaban 2 mg/kg was administered to anesthetized rats, one of the three reversal agents was administered: aPCC (50 or 100 U/kg), PCC (25 or 50 U/kg), or recombinant factor VIIa (100 or 400 mcg/kg).

A loading dose of 0.6 mg/kg of IV rivaroxaban was administered to primates, followed by a continuous infusion of 0.6 mg/kg/hour for 1 hour. One of two reversal agents was then given: aPCC (50 U/kg) or recombinant factor VIIa (210 U/kg). In the rat model, administration of high doses of these reversal agents significantly reduced bleeding times. Prolongation of prothrombin time (PT) was reduced after all three agents were given, but the effects were more pronounced with recombinant factor VIIa than with the other agents.

Both high-dose aPCC and PCC significantly reversed inhibition of thrombin generation in the rat model, but this was not observed with recombinant factor VIIa. In the primate model, administration of aPCC shortened the PT and effectively reversed inhibition of thrombin generation. However, although bleeding time did normalize at the completion of the infusion of aPCC, bleeding time increased relative to baseline 20 minutes after the infusion was completed. Recombinant factor VIIa reduced both bleeding time and PT, but it had no significant effects on reversing the inhibition of thrombin generation.

Marlu et al. conducted a study in 10 healthy volunteers who

were randomly assigned to receive dabigatran (150 mg) or rivaroxaban (20 mg), followed by a 2-week washout period.[13] At that point, the volunteers received the alternative anticoagulant. Peak concentrations of both agents were evaluated 2 hours after administration. The investigators analyzed anticoagulation reversal with recombinant factor VIIa, aPCC, and four-factor PCC (Kanokad, LFB-Biomedicaments), given at varying doses. The coagulation parameters included ETP, lag time, and time to peak concentration of thrombin.

Recombinant factor VIIa and aPCC corrected the altered lag time following dabigatran administration; however, four-factor PCC and aPCC increased ETP in a concentration-dependent manner. After rivaroxaban administration, higher doses of PCC had a more profound effect on endogenous thrombin potential compared with recombinant factor VIIa. aPCC corrected all coagulation parameters related to thrombin generation, even at its lowest dose. The lower doses of aPCC, one-quarter to one-half of a typical dose, appeared to have coagulation effects similar to that of the highest dose (80 U/kg). This suggests that lower doses of aPCC might be effective for the reversal of anticoagulant agents, with the potential added benefit of a reduced risk of thrombosis; however, more studies are needed to evaluate this possibility.

To date, no published studies or case reports have evaluated the use of aPCC for the reversal of life-threatening hemorrhage secondary to apixaban (Eliquis, Pfizer/Bristol-Myers Squibb), approved December 2012. Similarly, no data are available comparing aPCC with Kcentra (CSL Behring), a four-factor PCC product approved by the FDA in April 2013.

DISCUSSION

Safety

Thrombotic complications, such as venous thromboembolism, disseminated intravascular coagulation, myocardial infarction (MI), and pulmonary embolism, pose concerns and have been reported when PCC products are administered for anticoagulant reversal.[14–21] When used for its FDA-approved indication (hemophilia), aPCC therapy is associated with from four to nine thrombotic events for every 100,000 infusions.[21]

aPCC and other PCC products are not intended to be used off-label as reversal agents for warfarin or dabigatran, nor have they been adequately assessed for appropriate dosing, efficacy, and safety in off-label situations. The off-label use of PCC products may be associated with an increased incidence of thrombotic events similar to that observed with recombinant factor VIIa.[22–24] Further research is needed to determine whether the benefit of using these products to stop potentially life-threatening bleeding outweighs the risk of thrombosis.

Because all patients taking oral anticoagulant medications have underlying risk factors for thrombosis, reversing the action of these agents may place the patient at risk for thromboembolic adverse events. A history of liver disease and high doses of a given PCC product have been associated with the greatest risk of thromboembolic adverse events.[25] Moreover, the PCC products themselves carry an inherent risk of thrombosis. The prothrombin content of a given PCC product is a major determinant of its potential to generate excessive thrombin.[26] Repeated dosing may increase the risks of bleeding because of accumulation of prothrombin and thrombin resulting from their prolonged half-life, compared with other coagulation factors. It has been theorized that because aPCC has a high content of both prothrombin and thrombin compared with other PCC products, it might therefore pose a higher risk of thrombosis.[27]

In addition, the balance between procoagulant and anticoagulant activity plays a large part in the potential for thrombosis with PCC products. Heparin or a combination of proteins C, S, and Z is found in FFP, as well as in some three-factor and four-factor PCC products, but not in aPCC.

Costs

Although the balance between therapeutic efficacy and safety are critical components in evaluating the use of these products, cost considerations cannot be overlooked. Based on the varied dosing strategies for recombinant factor VIIa, PCC, and aPCC products, it is difficult to estimate a typical cost per dose. However, evaluating the costs per unit, or per microgram in the case of recombinant factor VIIa, can help in evaluating therapeutic and cost comparisons based on individualized institutional protocols.

Table 1 lists the average wholesale price (AWP) for available recombinant factor VIIa, PCC, and aPCC products in the U.S.[28]

BALANCING RISKS AND BENEFITS OF ANTICOAGULANT REVERSAL

Therapeutic anticoagulation must strike a fine balance between reducing hemorrhage and avoiding thrombosis. Emergent reversal of the antithrombotic effects of anticoagulant drugs is necessary when life-threatening hemorrhage occurs. However, no pharmacological agent has been developed that specifically reverses the anticoagulant effects of dabigatran and rivaroxaban. Therefore, agents traditionally used for the treatment of hemophilia A and B, including PCC products, have been recruited for this purpose.

Limited clinical data are available regarding the efficacy and safety of PCC products for reversing anticoagulant pharmacotherapy in human subjects. As reviewed in this article, the use of an activated PCC (aPCC) product (FEIBA) was associated with a significantly faster correction of supratherapeutic INRs

Table 1 Average Wholesale Prices of Available PCCs, Activated PCCs, and Recombinant Factor VIIa in the U.S.

Brand Name	Product Content Type	Average Wholesale Price
Novoseven	Recombinant factor VIIa	$1.64/mcg
Novoseven RT	Recombinant factor VIIa	$2.06/mcg
FEIBA VH	aPCC	$2.17/IU
FEIBA NF	aPCC	$2.17/IU
Bebulin VH	Three-factor PCC	$1.14/IU
Profilnine SD	Three-factor PCC	$1.19/IU
Kcentra	Four-factor PCC	$2.17/IU

aPCC = activated prothrombin complex concentrate; FEIBA NF = factor eight inhibitor bypassing activity, nanofiltered; FEIBA VH = factor eight inhibitor bypassing activity, vapor-heated; PCC = prothrombin complex concentrate; RT = recombinant; SD = solvent detergent.

Data from *Red Book,* June 14, 2013.[28]

secondary to warfarin therapy compared with fresh-frozen plasma (FFP).[8] Although no difference was found in mortality or hospital length of stay, five patients who were treated with aPCC experienced adverse events compared with none of the patients treated with FFP.

Although Wojcik et al. determined that none of the adverse events in the aPCC group were treatment-related, four out of five of these events were associated with thrombosis.[8] However, the INR is a measure of factor deficiencies in the extrinsic and common coagulation pathways, encompassing factors II, V, VII and X rather than a measure of generation of prothrombin and thrombin. The INR is therefore sensitive to changes in concentration of these factors, but it is particularly sensitive to factor VIIa concentrations.[29] Thus, the INR is subject to change if factors are supplemented, as shown by a decrease in the INR, even though a correction of coagulopathy might not be achieved. It is therefore important to recognize that INR correction with any reversal agent is a surrogate marker, and future studies should focus on measuring thrombin generation and clinical outcomes such as in-hospital morbidity and mortality rates.

Marlu et al. raised the question of whether the traditional dose of an aPCC product in reversing anticoagulation might be reduced without potentially increasing the risk of thrombosis.[13] The presence of prothrombin and activated coagulation factors in these agents and the absence of an anticoagulant warrant further evaluation of the safety of aPCC products for reversing the effects of anticoagulant agents.

CONCLUSION

The use of aPCC products for reversing the anticoagulant effects of dabigatran, rivaroxaban, and fondaparinux remains subject to further investigation. Conflicting preclinical evidence exists regarding the ability of aPCC products to shorten bleeding times that are prolonged by anticoagulant agents. Furthermore, the safety of aPCC products for use in off-label indications has not been adequately assessed in human subjects. Both the potential benefits, as well as the theoretical risks of thrombosis in human subjects, and the cost of these products themselves must be carefully considered.

Although conventional therapies to reverse the anticoagulant effects of warfarin are still used, novel agents will be needed as anticoagulant pharmacotherapy continues to evolve.

REFERENCES

1. Lubetsky A, Yonath H, Olchovsky D, et al. Comparison of oral vs. intravenous phytonadione (vitamin K1) in patients with excessive anticoagulation: A prospective randomized controlled study. *Arch Intern Med* 2003;163(20):2469–2473.
2. Crowther MA, Douketis JD, Schnurr T, et al. Oral vitamin K lowers the international normalized ratio more rapidly than subcutaneous vitamin K in the treatment of warfarin-associated coagulopathy: A randomized, controlled trial. *Ann Intern Med* 2002;137(4):251–254.
3. Raj G, Kumar R, McKinney WP. Time course of reversal of anticoagulant effect of warfarin by intravenous and subcutaneous phytonadione. *Arch Intern Med* 1999;159(22):2721–2724.
4. Ageno W, Gallus AS, Wittkowsky A, et al. Oral Anticoagulant Therapy-Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2)(Suppl):e44S–e88S.
5. Popovsky MA. Transfusion-related acute lung injury: Incidence, pathogenesis, and the role of multicomponent apheresis in its prevention. *Transfus Med Hemother* 2008;35(2):76–79.
6. Hellstern P. Production and composition of prothrombin complex concentrates: Correlation between composition and therapeutic efficiency. *Thrombosis Res* 1999;95(4 Suppl 1):S7–S12.
7. FEIBA NF, prescribing information. Westlake Village, Calif.: Baxter Healthcare Corp.; 2011.
8. Wojcik C, Schymik ML, Cure EG. Activated prothrombin complex concentrate factor VIII inhibitor bypassing activity (FEIBA) for the reversal of warfarin-induced coagulopathy. *Int J Emerg Med* 2009;2:217–225.
9. Desmurs-Clavel H, Huchon C, Chatard B, et al. Reversal of the inhibitory effect of fondaparinux on thrombin generation by rFVIIa, aPCC, and PCC. *Thrombosis Res* 2009;123:796–798.
10. Turecek PL, Váradi K, Gritsch H, Schwarz HP. FEIBA: Mode of action. *Haemophilia* 2004;10(Suppl 2):3–9.
11. van Ryn J, Ruehl D, Priepke H, et al. Reversibility of the anticoagulant effect of high doses of the direct thrombin inhibitor dabigatran by recombinant factor VIIa or activated prothrombin complex concentrate. *Haematologica* 2008;93(Suppl 1):148.
12. Perzborn E, Gruber A, Tinel H, et al. Reversal of rivaroxaban anticoagulation by haemostatic agents in rats and primates. *Thromb Haemost* 2013;110 (online).
13. Marlu R, Hodaj E, Paris A, et al. Effect of non-specific reversal of agents on anticoagulant activity of dabigatran and rivaroxaban. *J Thrombosis Haemost* 2012;108:217–224.
14. Lankiewicz MW, Hays J, Friedman KD, et al. Urgent reversal of warfarin with prothrombin complex concentrate. *J Thromb Haemost* 2006,4:967–970.
15. van Aart L, Eijkhout HW, Kamphuis JS, et al. Individualized dosing regimen for prothrombin complex concentrate more effective than standard treatment in the reversal of oral anticoagulant therapy: An open, prospective randomized controlled trial. *Thromb Res* 2006;118:313–320.
16. Preston FE, Laidlaw ST, Sampson B, Kitchen S. Rapid reversal of oral anticoagulation with warfarin by a prothrombin complex concentrate (Beriplex): Efficacy and safety in 42 patients. *Br J Haematol* 2002;116:619–624.
17. Pabinger-Fasching I: Warfarin-reversal: Results of a phase III study with pasteurised, nanofiltrated prothrombin complex concentrate. *Thromb Res* 2008;122(Suppl 2):S19–S22.
18. Bagot CN, Cregg R, Patel RK, et al. Perioperative myocardial infarction in a patient receiving low-dose prothrombin complex concentrates. *Thromb Haemost* 2007;98:1141–1142.
19. Warren O, Simon B. Massive, fatal, intracardiac thrombosis associated with prothrombin complex concentrate. *Ann Emerg Med* 2009;53:758–761.
20. Kohler M, Hellstern P, Lechler E, et al. Thromboembolic complications associated with the use of prothrombin complex and factor IX concentrates. *Thromb Haemost* 1998;80:399–402.
21. Pabinger I, Tiede A, Kalina U, et al. Impact of infusion speed on the safety and effectiveness of prothrombin complex concentrate: A prospective clinical trial of emergency anticoagulation reversal. *Ann Hematol* 2010;89:309–316.
22. Aledort LM. Factor VIII inhibitor bypassing activity (FEIBA): Addressing safety issues. *Haemophilia* 2008;14:39–43.
23. O'Connell KA, Wood JJ, Wise RP, et al. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA* 2006;295:293–298.
24. Yank V, Tuohy V, Logan AC, et al. Effectiveness of off-label use of recombinant factor VIIa. *Ann Intern Med* 2011;154:529–540.
25. Levi M, Levy JH, Andersen HF, Truloff D. Safety of recombinant activated factor VII in randomized clinical trials. *N Engl J Med* 2010;363:1791–1800.
26. Kohler M. Thrombogenicity of prothrombin complex concentrates. *Thromb Res* 1999;95:S13–S17.
27. Gallistl S, Cvirn G, Leschnik B, Muntean W. Respective roles of factors II, VII, IX, and X in the procoagulant activity of FEIBA. *Blood Coagul Fibrinol* 2002;13:653–655.
28. *Red Book.* Greenwood Village, Colo.: Thomson Reuters (Healthcare) Inc.; June 14, 2013.
29. Sakata T, Kario K, Matsuo T, et al. Suppression of plasma-activated factor VII levels by warfarin therapy. *Arterioscler Thromb Vasc Biol* 1995;15:241–246. ■