Role of Coagulation Factor Concentrates for Reversing Dabigatran-related Anticoagulation

Jerrold H. Levy, M.D., F.A.H.A., F.C.C.M.

THE novel oral anticoagulation agents (NOACs) include dabigatran, a direct thrombin inhibitor, and rivaroxaban, apixaban, and edoxaban, direct Factor Xa inhibitors, indicated for either stroke prevention with nonvalvular atrial fibrillation or thromboprophylaxis.[1,2] The NOACs are administered orally, have predictable onsets within 2 to 4 h, and an offset more rapid than warfarin. Although monitoring is not required, dabigatran's effects can be assessed using standard coagulation assays such as thrombin times and partial thromboplastin times (PTTs), whereas Xa inhibitors require more specialized antifactor-Xa assays. However, managing any anticoagulated critically ill patient is problematic, because all anticoagulation agents can cause bleeding, and patients were anticoagulated for a specific prothrombotic issue. Despite concerns about the NOACs, warfarin and other commonly used anticoagulants including low-molecular-weight heparin are not completely reversible with standard therapies. For acute warfarin reversal, despite the extensive use of plasma, four-component prothrombin complex concentrates (PCCs) are recommended in recent guidelines, and now available in the United States.[3,4] Unlike warfarin, NOACs' anticoagulation effects normalize in approximately 24 to 48 h after discontinuing the drug with normal renal function. However, after trauma, emergency surgery, or major bleeding, acute therapeutic considerations are needed. Current information to help clinicians make decisions about managing bleeding in patients receiving NOACs is based on indirect information derived from multiple sources including *in vitro* data using human blood, animal models, and from volunteers anticoagulated with NOACs.[2]

"… [coagulation factor concentrates] shortened bleeding time in the presence of dabigatran, but standard tests including [partial thromboplastin time] and prothrombin time did not predict this effect."

In this month's Anesthesiology, van Ryn *et al.*[5] evaluated different coagulation factor concentrates (CFCs) to reverse bleeding induced by dabigatran etexilate using a rat tail bleeding model. CFCs available in most countries were compared including three-factor and four-factor PCCs, an activated PCC (factor VIII inhibitor bypassing activity [FEIBA]), and recombinant factor VIIa.[4] They used multiple coagulation tests to evaluate anticoagulation and reversal including PTT, thrombin times, ecarin clotting time, and prothrombin time. They also evaluated thrombin generation using a sensitive fluorometric assay with human plasma spiked with dabigatran at therapeutic and supratherapeutic values. Dabigatran increased bleeding times in the animal model approximately 2.7-fold with supratherapeutic dabigatran levels, and all the CFCs studied significantly reversed this prolonged bleeding time, usually returning to baseline within 5 min. However, the recombinant factor VIIa dose required was 500 μg/kg, a dose approximately five- to six-fold higher than that used for hemophilia with inhibitors, lower doses were ineffective in the model. The standard coagulation tests were prolonged three- to eight-fold over baseline dosing, and despite reducing bleeding, there were minimal changes in coagulation tests, and the assays were not predictive of bleeding reversal. In human blood samples, restoration of thrombin generation was dependent on the dabigatran concentration. Dabigatran reversal occurred at concentrations seen with therapeutic levels, but not at supratherapeutic levels. In summary, in the animal model, CFCs reversed dabigatran-induced bleeding, but routine coagulation assays did not predict this reversal, but there was variability based on the level of anticoagulation.[5]

Novel to clinicians in the United States is the application of PCCs as a therapeutic approach to bleeding. In the current study, higher doses of one four-component PCC (Beriplex/KCENTRA; CSL Behring, Marburg, Germany/King of

Image: M. R. England.

Corresponding article on page 1429.

Accepted for publication December 16, 2013. From the Department of Anesthesiology, Duke University School of Medicine, Durham, North Carolina.

 Anesthesiology 2014; 120:1316-8

Prussia, PA) produced complete hemostasis with formation of stable wound clots that did not reopen. This finding is consistent with different dosing strategies for PCC reversal of warfarin. The variability of CFCs on laboratory tests despite their beneficial effects on bleeding times may be related to heparin in certain CFCs, and the thrombin times and PTT are sensitive to heparin. As the authors note, the PTT is generally insensitive to CFCs, which predominantly affect the prothrombin time/international normalized ratio. In the current study, the lack of effect of dabigatran on anticoagulation reversal based on laboratory testing may also relate to the assays used. The lack of correlation between *in vivo* bleeding and coagulation assay response was also observed in a recent trial comparing four-factor PCC with plasma in patients treated with vitamin K antagonists with major bleeding.[6]

A novel test used in this study is the thrombin-generation assay that we have used in many studies evaluating anticoagulant and procoagulant effects of different agents. This assay is an important way to examine thrombin generation, a sensitive indicator of hemostatic activation, and critical to clot formation. In the current study, dabigatran decreased thrombin generation, whereas most of the CFCs increased thrombin generation except those containing heparin. Thrombin generation was increased in dabigatran-anticoagulated blood with several three- and four-factor PCCs and the activated PCC FEIBA. In plasma with therapeutic dabigatran levels, most CFCs increased thrombin generation but were not effective at supratherapeutic dabigatran concentrations. Of note was recombinant factor VIIa did not restore thrombin generation.

There are several important insights to consider from this study. This report is the first to compare all available CFCs on dabigatran-related bleeding. The "clinical end point" in this model was bleeding as measured by prolongation of bleeding times and noted that CFCs shortened bleeding time in the presence of dabigatran, but standard tests including PTT and prothrombin time did not predict this effect. This observation is consistent with the problems of using coagulation testing as predictors of bleeding and the lack of correlation between laboratory tests and clinical bleeding. As an example, in a factor XII–deficient patient, the baseline PTT is greatly prolonged, but patients have no clinically relevant bleeding issues. Also, coagulation tests can be corrected without correcting the underlying hemostatic defect as we have reported where recombinant factor VIIa corrects the international normalized ratio of warfarin-treated patients, but only PCCs actually restore thrombin generation.[7] One explanation for stopping bleeding without restoration of *in vitro* coagulation tests may be explained by prohemostatic effects at the site of vascular injury where tissue factor is expressed, thrombin generation can be intensified, and CFCs produce localized rather than systemic effects.

Another important aspect of the study by van Ryn is that it reports the potential for PCCs to mitigate the effects of dabigatran *in vivo*, even though these effects cannot be observed by standard coagulation testing. Also, this study gives clinicians some hope that PCCs might be helpful when treating dabigatran-related bleeding in patients as previous experiments provided minimal hope for benefit from PCCs, but it does not guarantee successful treatment of NOAC-related bleeding in humans by PCCs. Perhaps, the most interesting point that comes from this study is that exogenously added PCCs can enhance thrombin generation to the point where this "extra" thrombin has the potential to potentially "overcome" the anticoagulant effect of dabigatran. However, this effect is dependent on the NOAC concentration, and whether PCCs will stop bleeding in patients following overdosage, particularly when NOAC concentrations are high, remains to be determined.

What are the take-home messages for clinicians? As we described in our recent review in Anesthesiology, CFCs represent part of an important multimodal therapeutic plan in treating bleeding with NOACs, and initial measures should include hemodynamic and hemostatic resuscitation with volume and vasoactive support, identification of the bleeding source, and attempts at local hemostatic control.[2] For dabigatran, hemodialysis or hemoperfusion may be potential options but may not be feasible in emergencies or patients in shock.[8] As part of a multimodal approach, the off label use of PCCs including FEIBA represents a logical approach to treating bleeding when it occurs in dabigatran-treated patients. Overall, therapy of bleeding should be multimodal, with repletion and normalization of hemostasis with CFCs and transfusion factors.[2]

Despite concerns about NOACs and bleeding, a recent report compared the management and prognosis of major bleeding from randomized clinical trials of dabigatran or warfarin.[9] From 27,419 patients treated for 6 to 36 months, 1,034 patients had 1,121 major bleeds. The 30-day mortality after the first major bleed was 9.1% in the dabigatran group compared with 13.0% in the warfarin group, and dabigatran-treated patients required a shorter intensive care unit stay compared with that in warfarin-treated patients.[9] As I initially stated, managing any anticoagulated critically ill patient is problematic, because all anticoagulation agents can cause bleeding, and patients were anticoagulated for a specific prothrombotic issue. Despite the relative safety of NOACs compared with warfarin, additional clinical studies are needed to best determine the optimal therapy for bleeding when it occurs. Of note is a specific reversal agent currently under development for dabigatran, using an immunospecific Fab fragment (BI 655075).[10] This novel therapeutic approach is currently in early clinical testing and will soon enter into clinical trials.

Competing Interests

Dr. Levy serves on Steering Committees for Boehringer-Ingelheim (Ingelheim, Germany), CSL Behring (King of Prussia, Pennsylvania), J&J (Raritan, New Jersey), and Grifols (Research Triangle Park, North Carolina).

Correspondence

Address correspondence to Dr. Levy: jerrold.levy@duke.edu

References

1. Levy JH, Key NS, Azran MS: Novel oral anticoagulants: Implications in the perioperative setting. Anesthesiology 2010; 113:726–45
2. Levy JH, Faraoni D, Spring JL, Douketis JD, Samama CM: Managing new oral anticoagulants in the perioperative and intensive care unit setting. Anesthesiology 2013; 118:1466–74
3. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, Dunn AS, Kunz R: Perioperative management of antithrombotic therapy: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141:e326S–50S
4. Levy JH, Tanaka KA, Dietrich W: Perioperative hemostatic management of patients treated with vitamin K antagonists. Anesthesiology 2008; 109:918–26
5. van Ryn J, Schurer J, Kink-Eiband M, Clemens A: Reversal of dabigatran-induced bleeding by coagulation factor concentrates in a rat-tail bleeding model and lack of effect on assays of coagulation. Anesthesiology 2014; 120:1429–40
6. Sarode R, Milling TJ Jr, Refaai MA, Mangione A, Schneider A, Durn BL, Goldstein JN: Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: A randomized, plasma-controlled, phase IIIb study. Circulation 2013; 128:1234–43
7. Tanaka KA, Szlam F, Dickneite G, Levy JH: Effects of prothrombin complex concentrate and recombinant activated factor VII on vitamin K antagonist induced anticoagulation. Thromb Res 2008; 122:117–23
8. Khadzhynov D, Wagner F, Formella S, Wiegert E, Moschetti V, Slowinski T, Neumayer HH, Liesenfeld KH, Lehr T, Härtter S, Friedman J, Peters H, Clemens A: Effective elimination of dabigatran by haemodialysis. A phase I single-centre study in patients with end-stage renal disease. Thromb Haemost 2013; 109:596–605
9. Majeed A, Hwang HG, Connolly SJ, Eikelboom JW, Ezekowitz MD, Wallentin L, Brueckmann M, Fraessdorf M, Yusuf S, Schulman S: Management and outcomes of major bleeding during treatment with dabigatran or warfarin. Circulation 2013; 128:2325–32
10. Schiele F, van Ryn J, Canada K, Newsome C, Sepulveda E, Park J, Nar H, Litzenburger T: A specific antidote for dabigatran: Functional and structural characterization. Blood 2013; 121:3554–62