

Reversal of New Oral Anticoagulants

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Although the options for therapeutic modalities such as chemotherapy and antibiotics have flourished, anticoagulant management has remained stagnant since the first agents were developed during World War II. Traditional anticoagulants widely used to treat thromboembolic disease include heparin-based drugs and warfarin. These drugs are cumbersome to administer. They have a narrow therapeutic window to achieve adequate anticoagulation without bleeding, and they exhibit interactions with food and other drugs that led to the requirement for frequent monitoring by laboratory testing. Until recently, few other options remained for antithrombotic therapy. Recently, however, there has been an influx of new anticoagulants poised to enter the market, providing more therapeutic options for patients. They promise to be better than current agents because they achieve similar, if not better, efficacy with less bleeding and fewer interactions with food and drugs and without the need for frequent monitoring.

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These new agents work by targeting specific components of the coagulation cascade, such as thrombin itself or its precursor, factor Xa. Dabigatran etexilate is a direct inhibitor of both free and clot-associated thrombin. It is a prodrug that is converted to its active compound, dabigatran, with a peak plasma concentration achieved 1.5 hours after ingestion, and it has a half-life of 14 to 17 hours. Unlike warfarin, it is not metabolized by cytochrome p450, so there are few drug interactions. It does, however, interact with the efflux transporter P-glycoprotein, leading to concern about alterations in efficacy when used with P-glycoprotein inhibitors or inducers such as rifampin, quinidine, ketoconazole, and verapamil. A number of studies have proved its efficacy as an anticoagulant for the prevention and treatment of venous and arterial thromboembolic events, including prevention after total knee or hip arthroplasty, treatment of acute venous thromboembolic events, and prevention of stroke associated with atrial fibrillation.¹⁻⁶ Because it has predictable pharmacokinetics, regular monitoring is not required. Laboratory assessments of anticoagulant effect can be monitored by the activated prothrombin time and thrombin time, although they do not

provide an accurate quantitative measure of anticoagulant level. The ecarin clotting time has been established as the best means of assessing bleeding risk.^{7,8} Another new agent, rivaroxaban, is a direct Xa inhibitor with maxima plasma levels achieved just 3 hours after ingestion and a half-life of 4 to 9 hours. This drug is an attractive agent because it has very few drug-drug interactions and because food does not interfere with its absorption or bioavailability. A number of phase 3 clinical trials have proven the efficacy of rivaroxaban in the prevention and treatment of venous thromboembolic events in patients undergoing orthopedic procedures.⁹⁻¹³ Both dabigatran and rivaroxaban are associated with an improved bleeding profile with decreased rates of major bleeding compared with warfarin. Despite the clinical benefits of these drugs, bleeding remains a feared complication because there are limited strategies for reversal of the anticoagulant effects of these agents, especially in emergent cases when immediate reversal is necessary.

In this issue of *Circulation*, Eerenberg and colleagues¹⁴ evaluate the use of prothrombin complex concentrates (PCCs) as an antidote to reverse the unwanted anticoagulant effects of rivaroxaban and dabigatran. In this randomized, double-blind, placebo-controlled study, 12 volunteers received either rivaroxaban 20 mg or dabigatran 150 mg twice daily for 2.5 days. This was followed by administration of 50 IU/kg PCC or saline in the control group. The groups were then reversed after a washout period. Measurements of standard laboratory markers of anticoagulation were used as evidence of reversal. In this study, the use of PCCs was shown to effectively reverse the anticoagulant effects of rivaroxaban but not dabigatran. Rivaroxaban prolonged the activated prothrombin time to 15.8 ± 1.3 seconds compared with baseline levels of 12.3 ± 0.7 seconds ($P < 0.001$). PCCs were able to immediately reverse this prolongation to 12.8 ± 1.0 seconds at significant levels. Similar results were seen when the endogenous thrombin potential was used as a measure of anticoagulant effect, with rivaroxaban decreasing the thrombin potential to $51 \pm 22\%$ (baseline, $92 \pm 22\%$; $P = 0.002$) and PCCs normalizing this inhibition ($114 \pm 26\%$; $P < 0.001$). In the case of dabigatran, however, similar rates of reversal were not seen, implying that PCCs are not effective at reversing its anticoagulant effects. The authors conclude that PCC is a viable option for reversing the anticoagulant effects of rivaroxaban in healthy subjects but has no role in the reversal of dabigatran.

Several questions remain unanswered by this study. The activated prothrombin time and thrombin time are not particularly good means of monitoring anticoagulant levels in patients on these agents, although the ability to normalize these tests supports some reversal of anticoagulant effect. However, this underscores the need for further study of the effect of these agents in the setting of acute bleeding to

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determine whether the normalization of clotting times correlates with better hemostatic response. In addition, the role of reversal by PCCs in situations in which patients may metabolize the drug differently as a result of renal failure is not addressed. Another question relates to the type and dose of PCCs used and their specific abilities to act as reversal agents because different formulations are variably available.

One of the main benefits of the use of dabigatran and rivaroxaban is their beneficial bleeding profile. This partly reflects the fact that both drugs have very short half-lives and therefore clear quickly. A number of studies have tried to estimate the bleeding risk associated with the use of dabigatran and found it to be similar to that of warfarin. Data from many phase III clinical trials of dabigatran involving 8135 patients showed the bleeding rate to be 1.4%, which was the same for the low-molecular-weight heparin enoxaparin used at prophylactic dosing.¹⁵ In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study, which involved >18 000 patients with atrial fibrillation who were treated with dabigatran, the major bleeding risk was comparable to the risk of bleeding from warfarin (3.1%/y versus 3.4%/y; $P=0.31$).¹⁶ When specific sites of bleeding were evaluated, there was a striking decrease in the incidence of intracranial bleeding with the use of dabigatran compared with warfarin. Many patients who take anticoagulant medication concomitantly use other agents that increase their risk of bleeding. The use of dabigatran with nonsteroidal antiinflammatory drugs and aspirin did not appear to increase the risk of major bleeding.¹⁷ In the Prevention of Embolic and Thrombotic Events in Patients With Persistent Atrial Fibrillation (PETRO) study, however, in patients taking dabigatran to prevent stroke associated with AF, the use of aspirin did significantly increase the risk of bleeding. For this reason, concomitant use of antiplatelet agents and antiinflammatory agents may increase the risk of having serious bleeding sequelae in the setting of dabigatran use. For rivaroxaban, similar reduced rates of bleeding have been observed with no significant bleeding differences seen when rivaroxaban was compared with standard low-molecular-weight heparin regimens.¹⁷ Pooled data from the Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism (RECORD) 1 to 4 trials, which looked at venous thromboembolic event rates in orthopedic surgery patients, compared major bleeding events between rivaroxaban regimens and enoxaparin regimens. This study demonstrated no statistically significant different rates of major bleeding between the 2 groups (2.85% versus 2.45%; $P=0.186$) but slightly higher levels of nonmajor bleeding with rivaroxaban (3.19% versus 2.55%; $P=0.039$).

The question that remains, however, is, What means are available to reverse emergent bleeding when immediate reversal is clinically necessary? Supportive strategies are the mainstay of treatment with discontinuation of the drug, mechanical compression, surgical hemostasis measures, and administration of transfusional support. If a recent overdose of the medication is suspected, activated charcoal can also be used. Because the half-life of these agents is short, one hopes that time will offer the best hope for gaining control of bleeding. Another option is recombinant activated factor VII,

which achieves hemostasis by directly activating thrombin on the surface of platelets.¹⁸ This drug has been suggested to be effective in life-threatening bleeding owing to a number of different anticoagulants. The use of recombinant activated factor VII, however, has had inconsistent results in clinical settings with other direct thrombin inhibitors, suggesting that its use in the emergent setting is not clearly established.⁷ The last option available for reversal is dialysis. In an open-label study, dabigatran was given to 6 patients with end-stage renal failure on hemodialysis, and it was estimated that 62% of the drug could be removed by dialysis within 2 hours of administration.¹⁹ However, because 95% of rivaroxaban is bound to protein, dialysis is not an option for elimination of the drug.

If all supportive measures fail, then what reversal agents are available to initiate hemostasis? This study by Eerenberg and colleagues has provided evidence that PCCs may be effective, at least for reversal of rivaroxaban. PCCs exist in both activated and inactivated formulations. These drugs were historically used in the treatment of hemophilia because they provide substantial amounts of vitamin K-dependent clotting factors. They also have been shown to reverse the effects of warfarin quickly and efficiently. Results from animal models have provided the impetus for the use of PCCs in major bleeding events.²⁰ There are 2 types of products: 3-factor formulations that contain factors II, IX, and X and 4-factor formulations that contain these factors plus factor VII. There have been no studies comparing the efficacy of 3- and 4-factor concentrates, and it remains unclear whether there is a significant difference in terms of overall bleeding suppression between the 2 agents. In this clinical trial by Eerenberg et al, a 4-factor PCC was used. In vivo data suggest that PCCs may be a useful means of reversing the effects of anticoagulation because they contain large amounts of thrombin, which can overwhelm the thrombin inhibition induced by direct thrombin inhibitors. Similarly, these drugs are thought to work for direct Xa inhibitors by providing a large dose of factor X, which can then overwhelm the inhibitory effect of the drug. The use of these formulations is not without risk, however, especially in patients requiring therapeutic anticoagulation, because there is an association between PCC use and increased thrombotic risk.

In reality, it is assumed that very few patients using these drugs routinely will require an antidote to reverse the anticoagulant effects. However, when supportive measures fail and control of hemostasis is needed emergently, the use of PCCs may be a viable option, at least for the reversal of rivaroxaban. Until data are collected regarding the cumulative use of PCCs in times of emergent major bleeding episodes, their utility is based on laboratory evidence alone. Rivaroxaban and dabigatran represent major advances in our ability to manage thromboembolic events, and their use is sure to rise as a result of their ease of administration. Balancing the risk of clotting and the risk of bleeding, however, still weighs heavily on the minds of clinicians. Knowing that readily available antidotes exist to quickly control hemostasis will certainly tip the scale in their favor.

Disclosures

None.

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