Reversal of New Oral Anticoagulants

Elisabeth M. Battinelli, MD, PhD

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, including dabigatran, rivaroxaban, and apixaban. These drugs are anticoagulants widely used to treat thromboembolic disease, 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. 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. 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. 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 colleagues 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±22% (baseline, 92±22%; P=0.002) and PCCs normalizing this inhibition (114±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
Battinelli  Reversal of New Oral Anticoagulants  1509
determine whether the normalization of clotting times corre-
lates with better hemostatic response. In addition, the role of
reversal by PCCs in situations in which patients may metabo-
Iolize 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 dabiga-
tran 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. 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 compa-
ritable to that of bleeding from warfarin (3.1%/y versus
3.4%/y; P=0.31). 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 medica-
tion concomitantly use other agents that increase their risk
of bleeding. The use of dabigatran with nonsteroidal anti-
flammatory drugs and aspirin did not appear to increase the
risk of major bleeding. In the Prevention of Embolic and
Thrombotic Events in Patients With Persistent Atrial Fibril-
ulation(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 regi-
mens. 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 rivaroxa-
ban regimens and enoxaparin regimens. This study demon-
strated 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. 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. The
last option available for reversal is dialysis. In a 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 admin-
istration. 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. 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-actor 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 throm-
bin, 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 antico-
agulation, 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 antico-
agulant 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 rivaroxa-
ban. 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.
References


Key Words: Editorials ■ anticoagulants
Reversal of New Oral Anticoagulants
Elisabeth M. Battinelli

Circulation. 2011;124:1508-1510
doi: 10.1161/CIRCULATIONAHA.111.054510

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/124/14/1508

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/