Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors

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The new oral anticoagulants dabigatran, rivaroxaban and apixaban have advantages over warfarin which include no need for laboratory monitoring, less drug–drug interactions and less food-drug interactions. However, there is no established antidote for patients who are bleeding or require emergent surgery and there is a paucity of evidence to guide the clinical care during these situations. Members of thrombosis and anticoagulation groups participating in the Thrombosis and Hemostasis Summit of North America formulated expert opinion guidance for reversing the anticoagulant effect of the new oral anticoagulants and suggest: routine supportive care, activated charcoal if drug ingestion was within a couple of hours, and hemodialysis if feasible for dabigatran. Also, the pros and cons of the possible use of four factor prothrombin complex concentrate are discussed. Am. J. Hematol. 87:S141–S145, 2012. © **2012 Wiley Periodicals, Inc.**

INTRODUCTION

Oral anticoagulant alternatives to warfarin are now available for long-term treatment to prevent stroke and short-term treatment to prevent postoperative venous thromboembolism. Currently, the oral direct thrombin inhibitor dabigatran etexilate is approved in the United States for stroke prevention in nonvalvular atrial fibrillation [1] and the oral factor Xa inhibitor rivaroxaban is approved for the prevention of venous thromboembolism after orthopedic surgery and for stroke prevention in atrial fibrillation [2]. Apixaban, another oral factor Xa inhibitor, is currently under review by the FDA for stroke prevention in atrial fibrillation [3] and is approved in Europe for venous thromboembolism prevention in patients undergoing orthopedic surgery. Each of these new oral anticoagulants are also being studied for the secondary prevention of recurrent VTE in patients with deep vein thrombosis or pulmonary embolism and rivaroxaban is approved for this indication in Europe. Moreover, Phase III clinical trials have been recently completed involving rivaroxaban and apixaban for prophylaxis against VTE in medically ill hospitalized patients [4,5] and in patients with acute coronary syndromes [6,7].

These new anticoagulants directly inhibit either thrombin (factor IIa) or factor Xa and, like warfarin and other vitamin K antagonists (VKAs), are associated with an increased risk for major hemorrhage [8]. Unlike VKAs, there are no recognized antidotes to reverse their anticoagulant effect. The traditional approach of replacing multiple clotting factors with fresh frozen plasma (FFP) or prothrombin complex concentrates (PCC) may not make mechanistic sense with these new agents which directly inhibit only a single clotting factor (IIa or Xa). Vitamin K administration has no role in reversing the effect of the new oral anticoagulants.

Although there are no proven antidotes for the new oral anticoagulants, there is a need for practical guidance regarding the clinical approach to patients who (a) have clinically important bleeding or (b) require emergent reversal of their anticoagulant effect because of surgery or an invasive procedure. Representatives from ten organizations that focus on thrombosis and anticoagulation convened a meeting in December 2011 and collaborated to develop pragmatic guidance to help clinicians manage the reversal of these new anticoagulants until more definitive and evidence-based guidelines are available. This meeting had members of the following organizations that belong to the Thrombosis and Hemostasis Summit of North America: Hemostasis and Thrombosis Research Society; Anticoagulation Forum; American Thrombosis and Hemostasis

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Network; North American Specialized Coagulation Laboratory Association; American Heart Association; Association of Hemophilia Clinic Directors of Canada; Foundation for Women & Girls with Blood Disorders; National Blood Clot Alliance; Thrombosis Interest Group of Canada: and National Hemophilia Foundation. The suggestions herein do not necessarily reflect the views of the organizations listed.

BACKGROUND

Although VKAs have been used for over 50 years, uncertainty remains as to the optimal methods to reverse their anticoagulant effect. Guidelines developed by the American College of Chest Physicians for the reversal of warfarin anticoagulation in patients with major bleeding have recently changed and now suggest the use of four factor PCC rather than FFP in conjunction with vitamin K [9]. However, these are Grade 2C recommendations, which means there is uncertainty in the estimates of benefits, risks and burden and the benefits, risk and burden may be closely balanced.

Four factor PCCs, which contain similar relative concentrations of nonactivated factors II, VII, IX, and X (Beriplex, Octaplex) are currently not available in the United States. In the United States, the three factor PCCs Profilnine SD and Bebulin VH have relatively similar concentration of non-activated Factors II, IX, and X but relatively low concentrations of non-activated factor VII [10]. There is an "activated" 4-factor PCC available in the United States (FEIBA NF) which contains relatively similar concentrations of non-activated Factors II, IX, and X and activated factor VII [10,11]. In the United States, in theory, another way to give all 4 prothrombin complex factors in an "activated" state (aside from FEIBA) is to give one of the 3-factor PCCs plus recombinant activated factor VII (rVIIa), however, this is not commonly done in clinical practice in the authors' experience due to the thrombosis risk. There are concerns that 3-factor PCCs are not as effective as 4-factor PCCs for the reversal of VKA anticoagulation [9,10] and activated PCCs may be more thrombogenic than nonactivated PCCs [9].

FFP has the disadvantages of longer preparation time (thawing) and volume of administration compared with PCCs [9]. PCCs have been dosed at approximately 25–50 units/kg body weight in patients with VKA related bleeding [10] and an 80 kg patient would require approximately 2,000–4,000 units of a 4-factor PCC. This would equate to approximately 2,000–4,000 ml of FFP [12] which is approximately 8–16 units. Therefore, when applying these or other suggestions for administration of plasma products for the reversal of the new oral anticoagulants; speed and volume of administration, number of factors available in the PCC and the activated state of the factors must be taken into consideration.

Several organizations have developed guidelines for the reversal of dabigatran, the first of the new oral anticoagulants to be approved for use in many countries. The Italian Federation of Thrombosis Centers has published questions and answers to the use of dabigatran in patients with atrial fibrillation and offers suggestions for the treatment of major or life-threatening bleeding [13]. The American Society of Hematology has also developed a pocket guide to anticoagulant dosing and management of anticoagulation associated bleeding complications and discusses reversal guidance for warfarin, low-molecular-weight heparin, fondaparinux, and dabigatran [14], and the New Zealand Pharmaceutical Management Agency has developed a one page guideline for management of bleeding with dabigatran [15]. Suggestions for the management of dabigatran-related bleeding is also offered on a number of websites of various medical centers or academic organizations.

TABLE I. Pharmacodynamic Properties of New Oral Anticoagulants [16–19]

	Apixaban	Dabigatran	Rivaroxaban
Direct factor inhibition	Xa	IIa	Xa
Bioavailability (F_{rel})	80%	6%	80%
Peak action (t_{max})	1–3 hr	1–3 hr	1–3 hr
Protein binding	84%	35%	92–95%
Renal clearance	25%	80%	33%
Elimination half life with creatinine clearance $>$ 80 ml/min	15.1 hr	13.8 hr	8.3 hr
Elimination half life with creatinine clearance 50–79 ml/min	14.6 hr	16.6 hr	8.7 hr
Elimination half life with creatinine clearance 30–49 ml/min	17.6 hr	18.7 hr	9.0 hr
Elimination half life with creatinine clearance $<$ 30 ml/min	17.3 hr	27.5 hr	9.5 hr

One of the advantages of the new anticoagulants is that they all have a considerably shorter half-life than warfarin (7–17 hr vs. 38–42 hr). After warfarin is stopped, it takes 4–5 days for its anticoagulant effect to be eliminated during which time clotting factors are being replenished. With the new anticoagulants, which have half-lives of 12–17 hr (dabigatran), 7–11 hr (rivaroxaban), and 9–14 hr (apixaban), their anticoagulant effect dissipates much faster than with warfarin [16]. Each of these new medications is eliminated by the kidneys to varying degrees, and in the presence of renal impairment their half-lives will be prolonged. The key pharmacologic properties of these agents are summarized in Table I [16–19].

Data on Reversal of New Oral Anticoagulants

General measures for anticoagulated patients who present with bleeding include fluid resuscitation, red blood cell transfusion, diagnostic and therapeutic procedures to identify the source of bleeding and to apply local hemostatic measures [20]. These recommendations apply to all patients, regardless whether they are anticoagulated or not. In addition, patients with an anticoagulant overdose may be candidates for standard therapy applied to any drug overdose, such as gastric lavage and administration of activated charcoal if these interventions can be done within a few hours of drug ingestion so as to effectively prevent further drug absorption. Hemodialysis or hemoperfusion are general measures used to remove drugs in urgent clinical situations and medications that are not highly protein-bound are potential candidates' for hemodialysis. Pragmatic issues, however, in relation to how quickly hemodialysis or hemoperfusion can be started, how long it should continue and obtaining vascular access in an anticoagulated patient are barriers to use of these therapies.

When evaluating the use of clotting factors such as FFP, PCC (activated or inactivated), or rVIIa in animal models, it is important to note that human clotting factors likely behave differently in other mammalian species and generalization to patient care requires considerable caution. The use of rVIIa has been associated with an increased risk of arterial thrombosis [21] and this risk must be taken into account when considering the use of this agent. PCCs consist of either 3-factor concentrates (II, IX, and X) or 4-factor concentrates (II, VII, IX, and X), with the later available in activated or non-activated clotting factor formulations. Most PCC formulations also contain small amounts of endogenous anticoagulants, protein C and S. Both 3- and 4-factor PCC preparations have been associated with thrombotic events and should be used cautiously [22].

Initial evaluation of a patient on anticoagulant therapy who needs emergent/urgent reversal should include sending laboratory coagulation studies to help assess the anticoagulant effect. However, for emergent situations, therapeutic

intervention or administration of procoagulants may proceed before such laboratory studies are completed. These coagulation tests may help interpret why the patient bled and may help guide subsequent management. A more detailed discussion of the laboratory tests that might be useful in these situations is beyond the scope of this article.

Dabigatran

Oral activated charcoal

In an in vitro model, dabigatran etexilate was suspended in highly acidic water (pH $\sim$ 2.5), mimicking gastric pH, and the concentration of the drug was measured by high pressure liquid chromatography. After the addition of activated charcoal, $>$99.9% of the drug was adsorbed, suggesting that oral activated charcoal may effectively absorb dabigatran after recent ingestion [23]. This may be particularly helpful in the case of a recent overdose.

Hemodialysis or hemoperfusion

Six volunteers who were receiving hemodialysis for end-stage renal disease were given a single 50 mg dose of dabigatran etexilate (the inactive prodrug of dabigatran) and the mean fraction of (active) dabigatran that was removed with dialysis was 62% at 2 hr and 68% at 4 hr [18]. In an in vitro model, dabigatran was added to human plasma and the addition of activated charcoal reduced the level of dabigatran to close or below the limit of the assay suggesting that hemoperfusion with activated charcoal may be effective method to eliminate dabigatran [23].

Fresh frozen plasma

In a mouse model, intracranial hemorrhage was induced and mice that received 4.5 mg/kg or 9.0 mg/kg of dabigatran had larger hematoma expansion than a control group of mice that received saline. Murine FFP significantly reduced the intracranial hemorrhage volume in mice receiving the high dose but not the low dose of dabigatran. Mortality was higher in mice receiving high-dose dabigatran etexilate compared to controls, and murine FFP did not reduce mortality [24]. These data suggest that FFP may be effective in limiting dabigatran-associated serious bleeding in mice, but how these results correlate with use in humans or what dose of FFP would be used requires further study.

Recombinant activated factor VII

In the above mentioned intracranial hemorrhage mouse model [24], human rVIIa failed to prevent hematoma expansion in mice receiving either high or low dose dabigatran etexilate. In a rat model, intravenous dabigatran at clinically relevant doses was infused and increased the bleeding time, using a standard tail incision, from 125 sec in controls (saline) to 1,455 sec. Administering human rVIIa (Novoseven) at a dose of 0.1 mg/kg or 0.5 mg/kg intravenously significantly reduced the bleeding time to 186 sec, and 135 sec, respectively. This animal model suggests that rVIIa may be effective in reversing the anticoagulation effect of dabigatran [25].

In a follow up animal experiment whereby laboratory rats were given supratherapeutic doses of dabigatran, corresponding to plasma levels of 800–1,000 ng/ml (3–10 times human peak plasma levels) [26], 0.5 mg/kg of intravenous human rVIIa (Novoseven) corrected the prolonged bleeding time. Of note, although the bleeding time was completely corrected, the thrombin time, aPTT and ecarin clotting time did not normalize. Only the PT returned to normal after infusion of rVIIa [27].

Prothrombin complex concentrate

In a follow-up to the above mentioned study with rVIIa [27],rats that were given oral dabigatran etexilate to achieve supratherapeutic plasma levels of dabigatran (800–1,000 ng/ml) were also treated with different commercially available 4-factor prothrombin complex concentrates: nonactivated PCCs (Beriplex, Octaplex), and activated PCC (FEIBA). Similar to rVIIa, all of these PCCs corrected dabigatran's increase in rat tail bleeding time but did not reverse the prolongations in the aPTT, thrombin time, dilute thrombin time, or ecarin clotting time. Only the PT was shortened. This animal model suggests that changes in clotting times and bleeding complications may not be related when attempts are made to reverse the effect of dabigatran. Of note, dabigatran at usual therapeutic plasma levels does not induce an increase in bleeding time in humans, thereby limiting this type of experiment in healthy volunteers (unpublished data, personal communication with Joanne Van Ryn, 12-11-11).

In the mouse intracranial hemorrhage model [24] study, 100 U/kg of intravenous nonactivated PCC (Beriplex P/N 500) prevented hematoma expansion with low and high dose dabigatran etexilate.

In a randomized, double-blind, placebo controlled trial, 12 healthy male volunteers received dabigatran etexilate 150 mg twice-daily or rivaroxaban 20 mg twice-daily in random order [28]. The study subjects were switched from one anticoagulant to the other after an 11-day washout period. After 2 1/2 days of treatment with the anticoagulant, the volunteers were given either intravenous saline or 50 IU/kg of nonactivated 4-factor PCC (Cofact). The aPTT increased from 33.6 ± 3.3 to 59.4 ± 15.8 sec after dabigatran etexilate was given but there was no effect on the prolonged aPTT by subsequent administration of PCC (70.3 ± 15.1 [$P = 0.21$]) or saline (57.9 ± 10.3 [$P = 0.64$]). Similarly, dabigatran significantly prolonged the thrombin time and ecarin clotting time, which were not reversed with PCCs. Although this first trial in humans did not measure bleeding times, it did demonstrate that at least one of the nonactivated 4-factor PCCs does not reverse the anticoagulant effect of dabigatran as measured with currently available laboratory tests. Whether such treatment will reverse the bleeding tendency in patients on dabigatran is unknown.

Rivaroxaban

Oral activated charcoal

We were unable to find any data regarding the use of oral activated charcoal in animal or human studies with rivaroxaban.

Hemodialysis or hemoperfusion

Rivaroxaban is highly protein-bound and it is unlikely that it can be removed by hemodialysis [29]

Fresh frozen plasma

We were unable to find any data regarding rivaroxaban and the use of FFP in animal or human studies.

Recombinant activated factor VIIa (rVIIa)

In a rat model, 2 mg/kg of intravenous rivaroxaban increased mesenteric bleeding times 3.6-fold and this increase in bleeding time was decreased to 1.7-fold prolongation compared to baseline, when rVIIa was administered 1 min after induction of bleeding. There was no effect of rVIIa on rivaroxaban induced inhibition of factor Xa activity. This animal model suggests that rVIIa may reduce bleeding even though it does not appear to affect rivaroxaban's inhibition of factor Xa [30].

In a baboon model, 0.6 mg/kg of rivaroxaban increased the template bleeding time by 2.5-fold, 30 min after an intravenous bolus. This was reduced to 1.7-fold the baseline, 5 min after treatment with 210 μg/kg rVIIa (Novoseven), while the bleeding time was 2.0-fold higher 30 min after rVIIa administration. These results in a primate model

TABLE II. Types of Studies Evaluating Reversal of New Oral Anticoagulants

	Apixaban	Dabigatran	Rivaroxaban
Oral activated charcoal	No data	In vitro	No data
Hemodialysis	No data	Human volunteers	No data
Hemoperfusion with activated charcoal	No data	In vitro	No data
Fresh frozen plasma	No data	Mouse model	No data
Activated factor VIIa	No data	Rat model	Rat and baboon model
3-factor PCC	No data	No data	No data
4-factor PCC	No data	Human volunteers and rat model	Human volunteers

TABLE III. Suggestions for Reversal of New Oral Anticoagulants

	Apixaban	Dabigatran	Rivaroxaban
Oral activated charcoal	Yes	Yes	Yes
Hemodialysis	No	Yes	No
Hemoperfusion with activated charcoal	Possible	Yes	Possible
Fresh frozen plasma	No	No	No
Activated factor VIIa	Unclear	Unclear	Unclear
3-factor PCC	Unclear	Unclear	Unclear
4-factor PCC	Possible	Possible	Possible

suggest only a modest effect in reversing bleeding with high doses of rVIIa [31].

Prothrombin complex concentrate

In the randomized trial discussed above involving 12 healthy volunteers, rivaroxaban increased the PT from a baseline of 12.3 ± 0.7 sec to 15.8 ± 1.3 sec ($P < 0.001$); subsequent administration of nonactivated 4-factor PCC (Cofact 50 IU/kg IV) normalized the PT (12.8 ± 1.0 [$P < 0.001$)], which persisted for 24 hr [28]. Saline infusion had no effect on prolonged PT. This trial showed that a nonactivated 4-factor PCC can reverse rivaroxaban's prolongation of the PT, but how this relates to actually reversing the bleeding tendency in patients on rivaroxaban remains to be studied.

Apixaban

We were unable to find any information regarding use of activated charcoal, hemodialysis, hemoperfusion, FFP, rVIIa, nonactivated or activated PCCs for the reversal of the anticoagulant effect of apixaban.

Suggestions for Emergent Reversal of the New Oral Anticoagulants

At the present time at least one of the new oral anticoagulants are approved in various countries for prophylaxis of venous thromboembolic disease in major orthopedic surgery; treatment of deep vein thrombosis and/or for stroke prevention in atrial fibrillation. Reports of patients presenting with a need for urgent anticoagulation reversal are appearing in the literature [32,33] and several countries have issued warnings about major bleeding with at least one of these agents [34–36]. When clinicians are faced with a patient who requires emergent reversal of anticoagulation and a lack of adequate scientific evidence to make an informed decision on best treatment, management decisions are based largely on clinical judgment, which can be supported by expert opinion. On the basis of personal experience and the meager (Table II) evidence from the peer-reviewed literature, we offer these suggestions (Table III):

1. Supportive care: Patients treated with apixaban, dabigatran, or rivaroxaban who present with significant bleeding or the need for emergent surgery should receive routine usual supportive care including fluid resuscitation, red blood cell transfusions, maintenance of renal function, identification of bleeding source, and surgical intervention as needed.
2. Discontinuation of drug: Given the relatively short half-lives of the new oral anticoagulants, withholding further doses and supportive care is likely to be sufficient for many patients. In patients with normal renal function, most of the anticoagulant effect of the new medications should dissipate within a day or two.
3. Activated charcoal: If oral drug intake was within a couple hours of presentation, oral activated charcoal offers a low side effect treatment option.
4. Hemodialysis and hemoperfusion: The pragmatic barriers to initiating emergent dialysis often impedes the practicality of this therapy and likely will remove 2/3 of dabigatran within a couple of hours. It should be considered, especially in patients with impaired renal function who will require more time to clear the drug. Use of dialysis is not likely to be effective for apixaban or rivaroxaban, as they are highly protein bound.
5. FFP: In our opinion, FFP is not likely to be helpful for emergent reversal of the new oral anticoagulants. The use of FFP has only been evaluated for dabigatran using a mouse model using species-specific plasma. The use of human FFP in patients has not been studied. Additionally, reversal of the new anticoagulants with FFP would require overwhelming the direct effect of the drugs either on factor IIa or Xa, not merely replacing depleted factor concentration as in the case of reversal of VKAs.
6. The use of factor VIIa in nonhemophiliac patients is associated with an increase in arterial thrombosis [21]. Human rVIIa decreases the bleeding time in rats that have been given dabigatran or rivaroxaban, however, it does not reverse the anticoagulation effect as measured by most laboratory tests in this model. There have been no human studies to date and it is unclear if this therapy will be useful for emergent anticoagulation reversal.
7. PCC: The use of either 3-factor or 4-factor PCCs have the potential to increase the risk of thrombosis [22]. One nonactivated 4-factor PCC has been shown to normalize the PT in human volunteers that received rivaroxaban, but did not normalize the aPTT or thrombin time in subjects who received dabigatran. There have been no studies evaluating the effect of PCCs on bleeding in humans receiving the new oral anticoagulants. Whether use of PCCs will be effective to stop critical bleeding or reverse the anticoagulant effects of the new agents enough to safely proceed with emergent surgery is not established but seems, given the current state of information, to be a reasonable approach in dire clinical situations in the opinion of several of the authors. Importantly, however, consensus was not reached regarding PCC, as two authors felt that PCC cannot be recommended at this time due to absence of data. All authors agreed that an equally justifiable approach, based on the current level of information, is to continue with supportive care and local measures to arrest bleeding.

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