Pharmacologic interventions for reversing the effects of oral anticoagulants

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The use of oral anticoagulant medications has become quite frequent in clinical practice. Warfarin is the most common oral anticoagulant used. However, newer agents, such as the direct thrombin inhibitor dabigatran and the factor Xa antagonist rivaroxaban, are becoming more commonly used as well. A second factor Xa antagonist, apixaban, became available in December 2012. The anticoagulant effect of warfarin is mediated by inhibition of vitamin K oxide reductase, the enzyme responsible for converting oxidized vitamin K to reduced vitamin K. The latter is vital for hepatic production of active vitamin K-dependent clotting factors II, VII, IX, and X. These clotting factors play key roles in the extrinsic and intrinsic pathways of the clotting cascade (Figure 1), the end result of which is the generation of thrombin (factor IIa), conversion of fibrinogen to fibrin, and clot formation and stabilization. Inhibition of vitamin K oxide reductase by warfarin interferes with clotting by decreasing the availability of vitamin K-dependent clotting factors and thrombin formation. The anticoagulant effect of dabigatran is mediated through direct inhibition of the action of thrombin, and rivaroxaban and apixaban produce anticoagulation through direct inhibition of factor Xa.

Purpose. To describe the pharmacologic agents and strategies used for urgent reversal of warfarin and the target-specific oral anticoagulants dabigatran, rivaroxaban, and apixaban.

Summary. To reverse the anticoagulant effects of warfarin in patients who are bleeding or need surgery, exogenous vitamin K (phytonadione) may be used in combination with another, shorter-acting intervention, such as fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), recombinant factor VIIa, or activated PCC (aPCC). Three-factor PCC contains factors II, IX, and X in an inactivated form, and four-factor PCC also includes factor VII in an inactivated form. No four-factor PCC products are available in the United States, but aPCC, which contains the same four factors with factor VII provided in an activated form, is available. The intervention depends on the International Normalized Ratio, presence of bleeding, and need for and timing of surgery. Research suggests that clotting factor concentrates are more effective than FFP alone for warfarin reversal. These products also may be useful for reversing the effects of target-specific oral anticoagulants, but limited efficacy and safety data are available to support their use. The risks and benefits associated with these products need to be weighed before their use for reversal of dabigatran, rivaroxaban, or apixaban. Additional clinical data are needed to clearly define the role of concentrated clotting factor products in reversal and to determine the optimal clotting factor concentrate product and dose for urgent reversal of oral anticoagulation.

Conclusion. Phytonadione and clotting factor concentrates appear to have a role for reversal of warfarin, and limited evidence suggests that clotting factor concentrates could have a role in reversal of target-specific oral anticoagulants in an emergency situation.


Although these agents are safe and effective, anticoagulant reversal is sometimes required in the setting of bleeding or if an urgent surgical procedure is needed. Reversal can be achieved by interruption of antico-
agulant therapy. Interruption (i.e., withholding) of oral anticoagulant therapy is followed by a gradual reduction in the effects on coagulation with warfarin and a generally more rapid reduction in anticoagulant effects with dabigatran, rivaroxaban, or apixaban. If more rapid reversal of anticoagulant therapy is necessary, pharmacologic intervention in addition to interruption of anticoagulant therapy can be used to hasten the reduction in (i.e., reverse) the effects of oral anticoagulants.

To reverse anticoagulation from warfarin, pharmacologic intervention as a step beyond holding warfarin doses is indicated when the International Normalized Ratio (INR) is greater than 10.2 Intervention is not warranted when the INR is 10 or less unless the patient is bleeding or requires urgent surgery. Reversal is indicated for warfarin-treated patients who are bleeding or require urgent surgery regardless of the INR. Pharmacologic reversal of the newer oral anticoagulants may also be attempted in the setting of active bleeding or need for urgent surgery.

**Pharyngadione.** Administration of exogenous vitamin K (phytonadione) reverses the anticoagulant effect of warfarin by promoting hepatic production of vitamin K-dependent clotting factors II, VII, IX, and X. The oral route of administration is preferred for phytonadione unless rapid reversal is needed before surgery or because of bleeding. The risk for anaphylaxis is a concern when phytonadione is administered by the intravenous (i.v.) route; however, the i.v. route is preferred in urgent situations because it provides earlier onset of action.3 The intramuscular and subcutaneous routes of phytonadione administration are not recommended in patients requiring warfarin reversal.2

Administrating an excessive phytonadione dose can result in refractoriness to warfarin when warfarin is restarted. Therefore, the lowest possible dose of phytonadione should be used for warfarin reversal.

Administrating phytonadione orally expedites reduction of the INR compared with simply withholding warfarin. Phytonadione given by the i.v. route causes a reduction in the INR within the first six to eight hours after administration.4 However, the reduction in INR achieved after a 24- to 48-hour period is similar with the i.v. and oral routes. Therefore, there is no advantage to using the i.v.
route when the need for reversal is not urgent. If a patient requires surgery within 12–24 hours, however, a higher dose via the i.v. route is preferred because it produces a faster—although incomplete—reduction in INR.

The American College of Chest Physicians (ACCP) recommends against the routine use of phytonadione for reversal of warfarin anticoagulation in patients with an INR of 4.5–10 and no bleeding; clinical studies have demonstrated that there is no advantage to such intervention.² Warfarin should be withheld in these patients until the INR declines. Administering phytonadione 2–2.5 mg orally and withholding warfarin are recommended for patients with an INR greater than 10 and no bleeding. A slow i.v. phytonadione dose of 5–10 mg and withholding warfarin are recommended for patients with bleeding regardless of the INR.

The evidence providing support for most warfarin reversal strategies is weak, because it is based primarily on relatively small observational studies that often evaluate surrogate endpoints (i.e., INR reduction) rather than clinical outcomes (i.e., bleeding) and sometimes do not include a comparator group. In a retrospective analysis of 75 warfarin-treated patients with an INR greater than 10, clinically important bleeding was reported in 3 of 24 patients who had warfarin interrupted but did not receive phytonadione and in 0 of 51 patients who were given single oral 2-mg phytonadione doses.³ In a case series of 107 warfarin-treated patients with an INR greater than 10 who were given oral phytonadione 2.5 mg as a single dose, 16 patients experienced bleeding within the first seven days after administration of the drug, including 1 patient who experienced major bleeding.⁴ Refractoriness to warfarin was not observed in patients treated with low-dose oral phytonadione. These reports suggest that the rates of bleeding are low in warfarin-treated patients with an INR greater than 10 who are given oral phytonadione.

In warfarin-treated patients who are bleeding or require urgent surgery, i.v. phytonadione is a mainstay in reversing anticoagulation. Phytonadione usually is used in combination with another intervention, such as fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), recombinant factor VIIa (rFVIIa), or activated PCC (aPCC, also known as anti-inhibitor factor complex and factor VIII inhibitor bypassing activity). The duration of action of i.v. phytonadione is longer than that of these other short-acting interventions, with the target INR achieved 24–36 hours after an i.v. phytonadione dose.⁵ These short-acting agents have a faster onset of action than i.v. phytonadione because of the time required for formation of vitamin K-dependent clotting factors with phytonadione.

Fresh frozen plasma. FFP is obtained from human blood and contains all of the clotting factors found in plasma. Dosing of FFP is based on patient weight and expressed as the volume or number of units of the product. Each unit of FFP contains approximately 200–250 mL. A dosage of 10–20 mL/kg produces a 20–30% increase in plasma levels of clotting factors.⁶ In clinical practice, 2 units of FFP is a commonly prescribed fixed dose, although this dose could be inadequate for a patient with a large body weight. Potential disadvantages of FFP include the large volume of fluid administered (often 400 mL or more), which can present a problem for patients with heart failure or other comorbid conditions that are aggravated by excessive fluid.⁷ The need for thawing can delay therapy and present a problem when the need for treatment is urgent. Because human blood is the source of FFP, there is a risk for transmission of infectious diseases, although this risk is low as a result of stringent screening of blood donors and blood testing technology. Transfusion reactions (e.g., transfusion-related acute lung injury, hemolytic reactions due to a blood type mismatch, hypersensitivity) also are associated with FFP.

Clotting factor concentrates. Concentrated clotting factor products containing one or more clotting factors are available for use as alternatives to FFP for reversal of warfarin and other oral anticoagulants. There are four major types of products:⁸⁻¹⁰

- rFVIIa (NovoSeven RT, Novo Nordisk Inc., Princeton, NJ);
- Three-factor PCC, which contains factors II, IX, and X in an inactivated form (Bebulin, Baxter Healthcare Corporation, Westlake Village, CA, and Profilnine SD, Grifols Biologicals, Inc., Los Angeles, CA);
- Four-factor PCC, which contains factor VII as well as factors II, IX, and X in an inactivated form (Beriplex P/N, CSL Behring UK Ltd., Marburg, Germany; Cofact, Sanquin Blood Supply, Amsterdam; Kanokad, LFB-Biomedicaments, Paris; Octaplex, Octapharma AG, Vienna, Austria); and
- Activated PCC, which contains factor VII in an activated form and factors II, IX, and X primarily in an inactivated form (FEIBA NF, Baxter Healthcare Corporation, Westlake Village, CA).

The main difference between four-factor PCC products and three-factor PCC products is the presence of factor VII in the former. Bebulin and Profilnine SD are considered three-factor PCC products because they contain a much smaller amount of factor VII than four-factor PCC products. Recombinant factor VIIa and aPCC both contain activated factor VII, but all three-factor PCC products and other four-factor PCC products contain inactivated clotting factors. The inactivated four-factor PCC products are not available in the United States, but aPCC, which contains the same four vitamin K-dependent clotting factors, is available in the United States.
The concentrations of clotting factors vary among three- and four-factor PCC products, depending on the manufacturer and lot (Table 1). Dosages are expressed as units of the factor IX component. The use of fixed doses (e.g., 4000 units regardless of body weight) and the use of weight-based doses (e.g., 25 or 50 units/kg) have been reported in the literature. Extrapolating results reported in the literature from one product to another is problematic because the content of factors II, VII, and X differs among products when the same amount of factor IX is used.

The prothrombotic potential of clotting factor concentrates, especially activated products (i.e., rFVIIa, aPCC), is a concern. The anticipated benefit must outweigh the prothrombotic risk when these products are used.

**Urgent warfarin reversal**

Several clinical studies have addressed the safety and efficacy of options for reversing warfarin in an urgent situation.

**Three-factor PCC.** The efficacy of 25 units/kg and 50 units/kg of a three-factor PCC product (Profilnine SD) for reversing warfarin anticoagulation in 40 patients was compared with that of FFP (approximately 2 units at the discretion of the prescriber) in 42 historical control patients. All patients had an INR greater than 3 and bleeding or a high risk for bleeding at baseline. Patients with intracranial hemorrhage (ICH) were excluded. Phytonadione was administered to 71% of the patients (median dose, 5 mg; range 1–10 mg).

The baseline INR was similar in the three treatment groups, and the target INR was less than 3 within 24 hours after the initial INR measurement. After PCC alone, the mean INR declined from 9.0 at baseline to 4.6 in the low-dose group and from 8.6 at baseline to 4.7 in the high-dose group. When supplemental FFP was given after PCC, the mean INR decreased further to 2.1 and 2.0 in the low- and high-dose group, respectively. In the historical control group treated with FFP alone, the mean INR declined from 9.4 at baseline to 2.3, and 62% of patients achieved an INR less than 3. A similar percentage of patients treated with low- and high-dose PCC (55% and 43%, respectively) achieved the target INR within approximately 24 hours. The addition of FFP to the low- and high-dose PCC groups significantly increased these percentages achieving the target INR to 89% (p = 0.01) and 93% (p < 0.01), respectively, compared with PCC alone. The percentage of historical control patients treated with FFP alone who achieved the target INR (62%) was significantly lower than the percentage of patients treated with PCC (either dose) plus FFP (p ≤ 0.01).

These findings and those from other studies suggest that while the percentage of patients achieving the endpoint of INR less than 3 was similar for FFP and three-factor PCC when used alone, the use of three-factor PCC in addition to FFP can provide even greater INR reduction than either agent alone. Conclusions that can be drawn from these studies are limited, however, because of their observational nature and the lack of standardization of the time after PCC administration until measurement of the INR. In most studies of three-factor PCC for warfarin reversal, PCC was used in addition to FFP, which could reduce FFP dosing requirements. Reducing the FFP dosing requirement would be advantageous for patients with heart failure or other conditions in which volume restriction is needed. The dose of three-factor PCC used in most studies was 25–50 units/kg, which reflects the factor IX content, not the content of factor II or factor X. The variable content of products

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**Table 1. Approximate Clotting Factor Content* of Selected Prothrombin Complex Concentrate Products**

<table>
<thead>
<tr>
<th>Product</th>
<th>Factor II</th>
<th>Factor VII</th>
<th>Factor IX</th>
<th>Factor X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three-Factor PCCs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Profilnine SD</td>
<td>24–38 units/mL</td>
<td>&lt;5 units/mL</td>
<td>24–38 units/mL</td>
<td>24–38 units/mL</td>
</tr>
<tr>
<td></td>
<td>NMT 150 units/100 factor IX units</td>
<td>NMT 35 units/100 factor IX units</td>
<td>100 units</td>
<td>NMT 100 units/100 factor IX units</td>
</tr>
<tr>
<td>Four-Factor PCCs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beriplex P/N</td>
<td>20–48 units/mL</td>
<td>10–25 units/mL</td>
<td>20–31 units/mL</td>
<td>22–60 units/mL</td>
</tr>
<tr>
<td>Cofact</td>
<td>14–35 units/mL</td>
<td>7–20 units/mL</td>
<td>25 units/mL</td>
<td>14–35 units/mL</td>
</tr>
<tr>
<td>Kanokad</td>
<td>14–35 units/mL</td>
<td>7–20 units/mL</td>
<td>25 units/mL</td>
<td>14–35 units/mL</td>
</tr>
<tr>
<td>Octaplex</td>
<td>14–38 units/mL</td>
<td>9–24 units/mL</td>
<td>25 units/mL</td>
<td>18–30 units/mL</td>
</tr>
<tr>
<td>aPCC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEIBA NF</td>
<td>1.3 units/FEIBA unit</td>
<td>0.9 unit/FEIBA unit</td>
<td>1.4 units/FEIBA unit</td>
<td>1.1 units/FEIBA unit</td>
</tr>
</tbody>
</table>

*All concentrations are approximate and vary from one lot to another.

*aPCC = activated prothrombin complex concentrate, NMT = not more than, PCC = prothrombin complex concentrate.
from different manufacturers and different lots from the same manufacturer makes comparison and extrapolation of results from studies of different products difficult. Another shortcoming of the studies is the lack of clinical outcomes data, particularly for bleeding. The INR was used as a surrogate endpoint that may or may not reflect bleeding risk.

**Four-factor PCC.** In a case series of 82 warfarin-treated patients who received 85 doses of a four-factor PCC product (Octaplex) with or without phytonadione for immediate reversal, the mean ± S.D. INR was significantly reduced from 5.08 ± 5.39 before reversal to 1.43 ± 0.42 ($p < 0.0001$). The mean ± S.D. PCC and phytonadione doses were 1792 ± 601 units and 4.9 ± 5.5 mg, respectively. None of the patients received FFP. Seven deaths (4 of 40 patients requiring reversal before surgery and 3 of 36 patients requiring reversal for bleeding) were reported, and thrombosis occurred in three patients. The thrombosis observed in this study highlights the potential risks associated with use of four-factor PCC for warfarin reversal.

Outcomes from use of a four-factor PCC product (Beriplex P/N) were assessed in a randomized, open-label study of 212 patients who required reversal of warfarin therapy because of bleeding. The mean baseline INR was similar in the two treatment groups. The INR was corrected within 30 minutes in more patients receiving PCC (62.2%) than receiving FFP (9.6%), and the frequency of fluid overload was lower in the PCC group (5.0%) than in the FFP group (13.2%).

In these and other studies of four-factor PCC for warfarin reversal, the INR was promptly normalized within minutes or hours. In contrast to three-factor PCC products, four-factor PCC products were effective for reducing the INR when used without FFP. The effect of four-factor PCC products on bleeding was similar to that of FFP. Fixed doses (typically 25–50 units/kg) and dosing based on the INR both have been used. The potential for thromboembolic complications during four-factor PCC treatment should be considered, although thromboembolic events have been reported infrequently. As with the three-factor PCC products, most available data for four-factor PCC products evaluate surrogate endpoints (i.e., INR) instead of clinical outcomes (i.e., bleeding). However, the one study of four-factor PCC products that did evaluate clinical outcomes suggested similar efficacy of PCC and FFP and greater tolerability of PCC.

**Recombinant factor VIIa.** In a retrospective, nonrandomized study of 40 warfarin-treated adults with traumatic ICH and an INR greater than 1.3, the effectiveness of rFVIIa (mean dose, 17.7 ± 6.2 µg/kg) plus standard treatment for warfarin reversal (FFP with or without phytonadione) was compared with standard treatment alone. All participants received other supportive measures or surgical interventions as needed.

The mean baseline INR was similar in the rFVIIa group (2.87) and the standard treatment group (2.51, $p > 0.05$). The time to an INR less than 1.3 (i.e., normalization) was significantly shorter in the rFVIIa group than the standard treatment group (4.8 hours versus 17.5 hours, respectively, $p < 0.001$). The time to surgery, which may reflect the time until the INR is reduced to a safe level, was lower in the rFVIIa group (5.6 hours; range, 2.1–9.2 hours) than the standard treatment group (74.6 hours; range, 70.5–219.7 hours), although the difference was not significant ($p = 0.30$). There was no difference between the two treatment groups in in-hospital mortality (35% for both groups, $p = 1.0$). The frequency of thromboembolism was higher with rFVIIa than with standard treatment alone (20.0% versus 5.0%, respectively), although the difference was not significant ($p = 0.15$).

In a retrospective cohort study of 24 adults with warfarin-related ICH, rFVIIa was compared with three-factor PCC (Bebulin). Fifteen patients received rFVIIa (mean dose, 53.4 µg/kg; range, 15–78 µg/kg), and nine patients received the PCC product (mean dose, 27.8 units/kg; range, 7.6–58 units/kg). The INR decreased from 6.1 to 1.1 after one hour in patients receiving rFVIIa and from 2.3 to 1.48 after one hour in patients receiving PCC. The success rate in achieving an INR of 1.3 or less within one hour was 83% with rFVIIa and 20% with PCC. After six hours, the success rate was 93% with rFVIIa and 50% with PCC.

**Building a four-factor PCC.** Because four-factor PCC products other than aPCC are not available in the United States, a combination of three-factor PCC plus rFVIIa has been used in an effort to build a four-factor PCC that provides the same clotting factors. In a retrospective analysis of 46 patients with warfarin-related ICH and INR values of 1.6 or higher, the efficacy of a reversal strategy involving three-factor PCC (4000 units Profilnine SD) plus rFVIIa 1 mg (as well as phytonadione 5 mg by slow i.v. injection) was compared with that of FFP in 12 historical control patients. Three of the historical control patients received FFP alone, and the other nine historical control patients received a three-factor PCC plus FFP. In the PCC plus rFVIIa group, the mean INR was 3.4 at baseline, 1.0 at the end of the infusion, and 1.2 after 24 hours. In the FFP alone group, the mean INR was 2.6 at baseline and 1.6 both at the end of the infusion and after 24 hours. In the PCC plus rFVIIa group, the mean INR was 3.3 at baseline, 1.4 at the end of the infusion, and 1.3 after 24 hours. The reductions in INR with
PCC plus rFVIIa at end of infusion and at 24 hours were significantly greater than the INR reduction in the FFP alone group ($p = 0.0036$ and $p = 0.0056$, respectively) and in the FFP plus PCC group ($p = 0.0019$ and $p = 0.025$, respectively). Two patients developed thrombotic complications (non-ST segment elevation myocardial infarction) eight hours and three days after treatment with PCC plus a higher dose (2.4 mg) of rFVIIa. Subsequently, the rFVIIa dose was altered to include only low dose.

**Activated PCC.** In a retrospective analysis of patients requiring warfarin reversal because of life-threatening bleeding, 72 patients receiving phytonadione 10 mg by slow i.v. injection plus aPCC (500 units for INR less than 5 or 1000 units for INR of 5 or more) were compared with 69 historical control patients who were treated with FFP (approximately 2 units at the discretion of the prescriber). Administration of aPCC produced lower INR values than did FFP. The median time to an INR of 1.4 or lower (i.e., INR normalization) was significantly shorter with aPCC (2.0 hours) than FFP (25.2 hours, $p = 0.006$). Three of the 72 patients treated with aPCC developed possible cardiac ischemia, and one aPCC-treated patient developed deep vein thrombosis.

**Table 2. Comparative Acquisition Costs of Concentrated Clotting Factor Products for Urgent Warfarin Reversal**

<table>
<thead>
<tr>
<th>Agent (dose)</th>
<th>Regimen</th>
<th>FFP + Three-Factor PCC</th>
<th>Three-Factor PCC + rFVIIa</th>
<th>aPCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP (15 mL/kg)</td>
<td>$300</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Three-factor PCC (25 units/kg)</td>
<td>$1932</td>
<td>$1932</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>rFVIIa (20 µg/kg)</td>
<td>N/A</td>
<td>$2820</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>aPCC (1000 units)</td>
<td>N/A</td>
<td>N/A</td>
<td>$1800</td>
<td></td>
</tr>
<tr>
<td>Total cost of regimen</td>
<td>$2232</td>
<td>$4752</td>
<td>$1800</td>
<td></td>
</tr>
</tbody>
</table>

**Therapeutic strategy.** In warfarin-treated patients with bleeding, phytonadione 5–10 mg by slow i.v. injection plus a four-factor PCC is recommended for urgent warfarin reversal by ACCP, although no four-factor PCC products currently are available in the United States. In warfarin-treated patients who require surgery within 24 hours, a two-drug combination of phytonadione 5–10 mg slow i.v. injection plus (1) four-factor PCC, (2) rFVIIa, or (3) aPCC will likely be effective for lowering the INR, according to the published literature. If surgery is needed but can be delayed for more than 24 hours, oral phytonadione alone may suffice for warfarin reversal based on the pharmacodynamics of vitamin K. Because four-factor PCC products currently are not available in the United States, another strategy must be devised to provide the four vitamin K-dependent clotting factors. FFP can be used in combination with three-factor PCC or rFVIIa in patients who can tolerate the fluid volume associated with FFP. Alternatively, three-factor PCC plus rFVIIa can be used to build a four-factor PCC. Another option would be to use aPCC.

The high cost of clotting factor concentrates is a concern for health-system pharmacists and administrators responsible for managing the drug budget, although the cost for concentrated clotting factor regimens used for anticoagulant reversal is much lower than when these products are used to treat hemorrhage. Consideration of the acquisition costs of concentrated clotting factor products (Table 2) may influence the choice among the therapeutic regimens for urgent warfarin reversal.

**Reversal of target-specific oral anticoagulants**

Strategies for reversing the effects of the target-specific anticoagulants dabigatran, a direct thrombin (factor IIa) inhibitor, and rivaroxaban and apixaban, direct factor Xa (FXa) inhibitors, currently are largely theoretical and based on limited data obtained primarily from animal models, although some studies in healthy human volunteers and case reports are available. In theory, exogenous administration of the clotting factors that these novel anticoagulants inhibit could overcome (i.e., reverse) the effects of the anticoagulant.

**Animal data.** Animal models have explored the impact of reversal attempts on both laboratory measures of coagulation and actual bleeding. Animal data suggest that four-factor PCC products may reduce bleeding with dabigatran.
but not rivaroxaban.\textsuperscript{36,37} Laboratory indices were improved when four-factor PCC products were used to counteract rivaroxaban; however, bleeding was not improved.\textsuperscript{37} The effects of three-factor PCC products on dabigatran and rivaroxaban are unknown, because data are not available. Data from animals are conflicting regarding the usefulness of rFVIIa for reversing dabigatran and rivaroxaban.\textsuperscript{36-39} The effects of both dabigatran and rivaroxaban appear to be reversed by aPCC.\textsuperscript{38,39} FFP does not appear useful for reversing dabigatran, and data are not available on the use of FFP for reversing the effects of rivaroxaban. To the author’s knowledge, there are no published data from animal studies of the reversal of apixaban; however, in vitro data suggest that apixaban may be only partially reversed by aPCC.\textsuperscript{40}

**Human data.** Human data for reversal of newer anticoagulants are extremely limited. The usefulness of four-factor PCC (Cofact) for reversing the anticoagulant effects of dabigatran and rivaroxaban was evaluated in a randomized, double-blind, placebo-controlled study of 12 healthy male volunteers.\textsuperscript{41} Dabigatran 150 mg twice daily or rivaroxaban 20 mg twice daily was provided for 2½ days before 50 units/kg of PCC or a similar volume of saline placebo was administered. After an 11-day washout period, subjects were crossed over to receive 2½ days of treatment with the other anticoagulant. Dabigatran reversal was assessed using 24-hour serial laboratory monitoring of the activated partial thromboplastin time, ecarin clotting time, and thrombin time. Administration of four-factor PCC had no effect on any of these measures of coagulation in dabigatran-treated subjects. Rivaroxaban reversal was assessed using 24-hour serial laboratory monitoring of prothrombin time (PT) and endogenous thrombin potential (ETP). Administration of four-factor PCC normalized both the PT and ETP within 15 minutes in rivaroxaban-treated subjects. The fact that laboratory indices were improved for subjects receiving rivaroxaban is consistent with animal data. Findings with dabigatran are less consistent with animal data and might be attributed to use of laboratory tests that are not optimal for monitoring coagulation or to differences in the clotting factor content or dose of four-factor PCC product used. It is also important to note that it is unclear whether correction of laboratory indices, observed with rivaroxaban in this study, will translate to arrest of bleeding in a patient.

An ex vivo study was conducted to evaluate the use of four-factor PCC (Kanokad), rFVIIa, and aPCC in reversing dabigatran and rivaroxaban in humans.\textsuperscript{42} Venous blood samples were obtained from 10 healthy white male volunteers immediately before and two hours after they received a single 150-mg dose of dabigatran or a 20-mg dose of rivaroxaban. After a two-week washout period, subjects were crossed over to receive the other anticoagulant, and the blood sampling procedure was repeated. Measures of thrombin generation, including ETP, peak thrombin generation, lag time, and time to peak thrombin, were used to assess reversal of the anticoagulants after the blood samples were exposed to several concentrations of four-factor PCC, rFVIIa, and aPCC. The contribution of hemodialysis to a successful outcome in these case reports is supported by the results of an open-label pharmacokinetic study in which hemodialysis removed 62% of a single 50-mg dabigatran dose over a two-hour period and 68% of this dose over a four-hour period in six patients with end-stage renal disease.\textsuperscript{46} The case report of the 79-year-old man illustrates the importance of considering renal function as well as the type of surgery (i.e., risk for bleeding) in planning surgery for patients receiving dabigatran, because of the importance of the kidneys in eliminating the drug.\textsuperscript{47} As renal function deteriorates (i.e., creatinine clearance decreases), the half-life of
dabigatran increases, and the time interval needed between the last dose of dabigatran and the surgery to prevent perioperative bleeding also increases. In addition, the time elapsed between the last dose of dabigatran and surgery should be longer for surgeries associated with a high risk for bleeding than surgeries associated with a lower risk for bleeding. Therefore, discontinuation of dabigatran therapy four days before the 79-year-old man’s aortic valve replacement and coronary artery bypass surgery may have been more appropriate, given his age, high bleeding risk associated with the surgery, and underlying renal function.

Perioperative management of patients with renal impairment may be less problematic when rivaroxaban is used instead of dabigatran, because renal filtration plays a smaller role in elimination of rivaroxaban. Decreases in creatinine clearance prolong the half-life of rivaroxaban to a lesser extent than with dabigatran. Nonrenal routes (i.e., hepatic metabolism, fecal elimination) and renal secretion contribute to the elimination of rivaroxaban, and the drug is highly protein bound.48,49 Although apixaban has a slightly longer apparent half-life than rivaroxaban, apixaban also has other routes of clearance beyond renal clearance. Therefore, perioperative management issues may be similar for rivaroxaban and apixaban.

**Therapeutic strategy.** Currently available evidence on the effects of clotting factor concentrates in reversing the anticoagulant effects of dabigatran and rivaroxaban in animals and humans is limited, but animal data, ex vivo data, and a case report suggest a possible role for aPCC. The combination of three-factor PCC and rFVIIa, which provides the same four clotting factors as aPCC (in different quantities), might be an alternative. Evidence to support the use of four-factor PCC for reversal of these target-specific oral anticoagulants is conflicting, and the limited available data suggest that a four-factor PCC may be ineffective for reversal of dabigatran. Data related to the impact of reversal agents on apixaban are even sparser than for dabigatran and rivaroxaban; however, it may be reasonable to expect that apixaban would respond to reversal agents in a manner similar to rivaroxaban, given that both are factor Xa inhibitors.

Larger doses of concentrated clotting factor products often are needed for reversal of the target-specific oral anticoagulants than for warfarin reversal. Determining what dose to use for reversal is difficult, and it may not be possible to extrapolate animal dosing data to humans.

The impact of concentrated clotting factor products may be enhanced by using them in combination with other modalities (e.g., hemodialysis for dabigatran reversal). Administering oral activated charcoal after recent ingestion (<2 hours) of the target-specific oral anticoagulants may be beneficial, as well.47,50,51

The lack of evidence of a clear benefit from clotting factor concentrates in patients requiring reversal of target-specific oral anticoagulant therapy suggests that the risks and benefits of these products must be weighed before use for this purpose. Data on the use of clotting factor concentrates to reverse the effects of warfarin suggest that thrombosis is a risk, and one may assume that a prothrombotic risk would also be present if these agents were used for reversal of dabigatran, rivaroxaban, or apixaban. The mostly unproven positive impact of concentrated clotting factor products on bleeding risk may not outweigh the risk of thrombosis, especially in patients in whom thrombosis could be catastrophic (e.g., patients with mechanical valves or left-ventricular assist devices). As such, proper patient selection is vital to optimizing the use of these therapies and patient outcomes.

**Conclusion**

Phytonadione and clotting factor concentrates appear to have a role for reversal of warfarin, and limited evidence suggests that clotting factor concentrates could have a role in reversal of target-specific oral anticoagulants in an emergency situation.

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Developing a management plan for oral anticoagulant reversal

WILLIAM E. DAGER

Purpose. To describe a process for prompt evaluation and management— including reversal of the effects of warfarin and target-specific oral anticoagulants—of patients with or at high risk for bleeding during oral anticoagulant therapy or when such therapy is interrupted for an urgent invasive procedure or surgery.

Summary. The use of pharmacologic interventions for anticoagulant reversal may depend on the measured level of anticoagulation, time since the last anticoagulant dose, target level of coagulation, reliability of laboratory tests of coagulation, severity of or risk for bleeding, the agents’ mechanism of action and pharmacokinetics, and pharmacodynamics of the reversal agent. The patient’s age, weight, renal function, comorbid conditions, and other drug therapy, as well as the risk for thromboembolism and other adverse effects of the reversal therapies, also enter into therapeutic decisions. Hemodialysis may be used to remove the direct thrombin (factor IIa) inhibitor dabigatran and reverse its anticoagulant effects. Limited experience with clotting factor concentrates suggests that activated prothrombin complex concentrate may be useful for reversing the anticoagulant effects of dabigatran. The activity of oral factor Xa inhibitors (i.e., rivaroxaban and apixaban) is higher up the common pathway of the coagulation cascade and thus may be easier to reverse than that of direct thrombin inhibitors. Additional clinical experience is needed to identify the optimal reversal agents, dosage, and impact on thrombosis or bleeding outcomes for both classes of agents.

Conclusion. A comprehensive plan individualized to each agent should be developed to promptly reverse the effects of oral anticoagulants and optimize outcomes in patients with bleeding or an urgent need for surgery.


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SYMPOSIUM Developing a management plan