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Developing a management plan for oral anticoagulant reversal

WILLIAM E. DAGER

Oral anticoagulants are widely used for several common conditions, and bleeding is a potential complication. Therapy sometimes must be interrupted temporarily for invasive procedures, including surgery, especially when the procedure is associated with a high risk for bleeding. Ideally, the risk of bleeding during oral anticoagulant therapy or when such therapy is interrupted for an invasive procedure is minimized through preventive strategies. These strategies include proper selection of the anticoagulant agent and dosage before, during, and after the procedure; timing of anticoagulant discontinuation before the procedure; careful patient monitoring for early signs and symptoms of bleeding; and laboratory monitoring when applicable. Additional therapeutic considerations include inter-

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 throm-

bin (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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WILLIAM E. DAGER, PHARM.D., BCPS (AQ-Cardiology), FCCP, FCCM, FASHP, is Pharmacist Specialist, University of California (UC) Davis Medical Center, Sacramento; Clinical Professor of Medicine, UC Davis School of Medicine; Clinical Professor of Pharmacy, UC San Francisco School of Pharmacy; and Clinical Professor of Pharmacy, Touros School of Pharmacy, Vallejo, CA.

Address correspondence to Dr. Dager at UC Davis Medical Center, Pharmaceutical Services, 2315 Stockton Boulevard, Sacramento, CA 95817 (william.dager@ucdmc.ucdavis.edu).

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rupting oral anticoagulant therapy for a sufficient amount of time before any invasive procedure takes place to minimize bleeding complications and determining when to reinstitute therapy afterwards. If anticoagulant therapy cannot be discontinued sufficiently early, the patient may be at increased risk for perioperative and postoperative bleeding complications resulting in morbidity and mortality.

Because bleeding may develop during oral anticoagulant therapy or in emergent situations (e.g., an unanticipated invasive procedure or surgery) despite preventive strategies, a comprehensive plan for prompt reversal of the anticoagulant effect may be necessary to minimize associated morbidity and mortality.

Patient evaluation and management plan

Acutely ill patients receiving oral anticoagulants who display signs of anemia or other reasons to suspect bleeding after traumatic events or invasive procedures should be evaluated for the presence of bleeding. Internal bleeding may not be accompanied by overt signs, but complete blood counts can be monitored to detect potential blood loss. When a patient receiving an oral anticoagulant presents with bleeding, the site and risk for complications must be assessed. Accumulation of even small amounts of blood at certain sites (e.g., the spine, ocular region) can cause devastating complications. Accumulation of blood in a closed cavity can be more problematic than accumulation at sites that can be drained or managed with adjunctive interventions, such as the application of pressure, cauterization, or suturing. Blood transfusions may be required to maintain adequate levels of hemoglobin and oxygenation of the blood to support vital physiologic functions.

The level (i.e., intensity) of anticoagulation should be measured as part of the evaluation process for

patients receiving anticoagulation therapy. The laboratory assays used for this purpose depend on the type of anticoagulant and the dosage used. Although routine use of laboratory assays is not routinely needed for target-specific oral anticoagulants (e.g., the direct thrombin inhibitor dabigatran, the factor Xa [FXa] inhibitors rivaroxaban and apixaban), these assays can provide potentially useful information in patients with or at high risk for bleeding.

The possibility that a patient may be receiving agents that inhibit platelet function should be considered, because these agents may increase the risk of a bleeding event in patients receiving oral anticoagulants. Citrate in blood transfusions also can contribute to bleeding because of its anticoagulant effect, underlining the importance of co-administering calcium to counteract the citrate.¹

Various patient characteristics may influence the rate at which the effects of oral anticoagulants decrease when the drug is withheld. The decline in International Normalized Ratio (INR) after warfarin is withheld in patients with elevated values tends to be slower in patients with advanced age, a high initial INR value, decompensated congestive heart failure, active malignancy, or a low weekly maintenance warfarin dose than in patients who are younger with a low initial INR value, high weekly maintenance warfarin dose, and no heart failure or active malignancy.²

Withholding the oral anticoagulant and using mechanical interventions (e.g., sutures) may suffice to resolve bleeding, but mechanical interventions often are not feasible because of the site involved or other factors. Pharmacologic interventions (along with withholding the oral anticoagulant) often are needed instead of or in addition to mechanical interventions. The choice of pharmacologic intervention depends on the oral anticoagulant, measured level of

anticoagulation, time since the last oral anticoagulant dose, and degree of anticoagulation needed after reversal. The goal might be partial or complete reversal of anticoagulation. Complete reversal may be needed to minimize severe bleeding complications. Partial reversal may suffice in patients with less severe bleeding concerns. The overall needs of the patient should be considered in any management plan involving reversal therapies, and the plan should be sufficiently flexible to accommodate acute changes in patient status. Oral anticoagulant therapy may need to be reinitiated if the condition for which anticoagulant use was indicated initially (i.e., risk for thrombosis) persists after bleeding resolves. In surgical patients, the postoperative risk for thrombosis as well as for bleeding should be considered in determining the desired intensity of anticoagulation in the early postoperative period. Short- and long-term risks for thrombosis and bleeding should be continually weighed, with management plans revised accordingly. Controlling bleeding is a priority in the short term, but concerns about thrombosis risk often assume increasing importance in the long term.

Reversal of the effects of oral anticoagulants can be achieved by neutralizing or removing the drug or by producing hemostasis independent of direct antagonism of the oral anticoagulant. The duration of the effects of both the anticoagulant and reversal agents should be considered. A rebound anticoagulation effect can occur when the duration of effect of the reversal therapy is shorter than that of the anticoagulant.

The use of clotting factor concentrates for oral anticoagulant reversal may present a challenge because of their prothrombotic effect. The use of long-acting reversal agents also can be problematic because of the risk of thromboembolism as long as the prothrombotic effect persists. Thus, the mechanism of action,

pharmacokinetics, and pharmacodynamics of oral anticoagulant reversal agents are considerations in devising reversal strategies.

The need for replacement of blood loss is a consideration in managing active bleeding from oral anticoagulants. The citrate content of blood products administered and the risk of transfusion reactions are potential concerns. Comorbid conditions that could contribute to coagulopathies and bleeding (e.g., sepsis) should be managed to the extent possible. Administration of calcium may be needed to counteract the anticoagulant effects of citrate in blood products and maintain hemostasis.^{1,3,4} A comprehensive management plan with appropriate follow-up should be devised to address patient needs and concerns associated with the reversal of oral anticoagulants in patients with bleeding. The risk for complications, including continued bleeding or thrombosis, should be addressed in this plan.

Warfarin reversal

Therapeutic options for warfarin reversal include phytonadione, fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), activated PCC (aPCC), and recombinant factor VIIa (rFVIIa). Phytonadione administration promotes hepatic production of vitamin K-dependent clotting factors II, VII, IX, and X, which are depleted by warfarin. Because the onset of effect of phytonadione is not immediate, products containing clotting factors (e.g., PCC, FFP, rFVIIa) are used to expedite hemostasis. PCC products include three-factor PCCs, which primarily contain clotting factors II, IX, and X (with only minimal factor VII) in an inactivated form, and four-factor PCCs, which contain factors II, VII, IX, and X in an inactivated form. Activated PCC contains clotting factor VII in an activated form and clotting factors II, IX, and X primarily in an inactivated form.

Recombinant activated factor VII contains only clotting factor VII. Because these products promote hemostasis independent of the anticoagulant, their use is also associated with a risk for thrombosis; thus, clinicians should use the lowest possible dose to achieve treatment goals.

PCC dosing. The dosing of three- and four-factor PCCs typically is based on patient weight, current INR, and severity of bleeding. The three-factor PCC products currently approved by the Food and Drug Administration (FDA) are indicated for prevention and control of bleeding in patients with factor IX-deficient hemophilia. With the availability of selective factor IX products, PCC product use has shifted to include use for the reversal of vitamin K antagonists such as warfarin. The doses typically used for warfarin reversal (25–50 units of the factor IX component per kilogram of body weight) are lower than those used for patients with hemophilia.^{5,6} Higher doses (i.e., more than 25 units/kg) might be considered in patients with elevated INR values and severe bleeding (i.e., the potential to impair a vital body function). Lower doses (25 units/kg or less) may be considered in patients with a lower INR and a lesser concern or urgency related to bleeding. One example based on the INR alone is to consider a PCC dose of 35 units/kg for an INR value of 4–6 and 50 units/kg if the INR exceeds 6.⁷ It is noteworthy, however, that as the INR climbs, the reduction in the concentration of clotting factors present becomes smaller. Thus, at very high INR values (over 6), a small change in the concentration of clotting factors can lead to a notable reduction in the subsequent INR. Whether to use ideal body weight or total body weight to determine the PCC dose in morbidly obese patients is unclear.

The onset of INR reversal and the induction of hemostasis are rapid, occurring within minutes after infusion of the PCC product, which

allows titrating to response when bleeding sites can be visualized. The vial size is a practical consideration; the dose should be rounded to use the entire vial contents because of the high cost of the products and need to minimize waste in dose preparation.

PCC development. Four-factor PCC products, which are recommended for warfarin reversal in current guidelines, are not available in the United States.^{8–10} Recent experience in the United States, including use in patients with intracranial hemorrhage (ICH), has shown limited ability of three-factor PCC products to reverse the INR completely.^{11,12} Several four-factor PCC products are in development; they are either under review by FDA or have received orphan drug status for reversal of vitamin K antagonists such as warfarin.^{13,14}

In abstracts describing a Phase III, randomized, open-label study of 212 warfarin-treated patients with an elevated INR (2 or higher) and acute major bleeding, the hemostatic efficacy of a four-factor PCC product (Beriplex P/N, CSL Behring UK Ltd., Marburg, Germany) designed to reinstate factors specifically reduced by warfarin (25–50 units of the factor IX component per kilogram, depending on the INR) was compared with FFP (10–15 mL/kg based on the INR).^{15–17} The rate of success in achieving hemostasis after 24 hours was similar (72.4% and 65.4%, respectively; difference 7.1%; 95% confidence interval [CI], –5.8–19.9). The four-factor PCC product was more effective than FFP in achieving the target INR within 30 minutes; success rates were 62.2% for four-factor PCC and 9.6% for FFP (difference, 52.6; 95% CI, 39.4–65.9). The risk of fluid overload or similar cardiac events was lower with PCC (4.9%) than with FFP (12.85%).¹⁷ In Phase III studies, this four-factor PCC product was given in combination with phytonadione (orally or by slow intravenous [i.v.] infusion); doses were based on the

INR (25 units/kg for INR of 2 to less than 4, 35 units/kg for INR of 4–6, and 50 units/kg for INR greater than 6).¹⁶ The frequency of treatment-related adverse events was similar with PCC and FFP, although less fluid overload was associated with PCC than with FFP.¹⁸ The relative benefits of weight-based dosing versus fixed dosing of PCC have not been established.

aPCC. Activated PCC has also been explored for reversing the effects of warfarin. A retrospective chart review of patients with warfarin-related life-threatening bleeding showed that target INR values below 1.5 were achieved in approximately half of 72 patients receiving an aPCC product (FEIBA NF, Baxter Healthcare Corporation, Westlake Village, CA) in doses of 500 units for baseline INR values below 5 or 1000 units for INR values of 5 or more, compared with one third of 69 patients receiving FFP (median dose 2 units) ($p = 0.017$).¹⁹ No difference in survival was noted between aPCC and FFP, however. In the 72 patients receiving aPCC, 5 potentially related thromboembolic events were noted.

rFVIIa. The doses of rFVIIa used for lowering the INR during warfarin therapy (53 $\mu\text{g}/\text{kg}$ on average in one retrospective study) are considerably lower than those used for prevention and treatment of bleeding in patients with hemophilia (90 $\mu\text{g}/\text{kg}$), the FDA-approved indications for the drug.^{20,21} Data are available suggesting that rFVIIa doses as low as 1–2 mg (i.e., 14–28 $\mu\text{g}/\text{kg}$ for a 70-kg person) are effective for warfarin reversal using the INR as a surrogate endpoint.^{22–24} The optimal rFVIIa dose and the impact on bleeding complications are uncertain. The onset of effect for reducing both bleeding and the INR appears to be rapid, with the lowest effective dose sought primarily because of concerns about thrombosis.

Phytonadione. Administration of phytonadione promotes hepatic production of the four vitamin

K-dependent clotting factors depleted by warfarin. The route of administration (oral or i.v.) of phytonadione depends on the INR and the presence of bleeding.⁸ Phytonadione should not be given by subcutaneous (s.c.) or intramuscular (i.m.) injection for warfarin reversal, because the oral and i.v. routes have a more rapid and predictable onset of effect.²⁵ Other interventions with a more rapid onset of action on the INR than phytonadione, including three-factor PCC, rFVIIa, FFP, and aPCC, may be added to phytonadione in patients with serious and life-threatening bleeding.

The maximum recommended i.v. infusion rate for phytonadione is 1 mg/min.²⁶ Most infusions are administered over 15–20 minutes. Doses usually are diluted in 50 mL of fluid. Diluting the drug in larger volumes may delay delivery and the onset of action. The drug is sensitive to and must be protected from light.²⁶

Hypersensitivity reactions to phytonadione are rare, but potentially serious adverse effects have been associated with rapid i.v. infusion, with a frequency of 3 per 10,000 i.v. doses, according to a retrospective review of more than 6,000 doses over a five-year period.²⁷ Administering phytonadione by slow i.v. injection reduces the risk of a hypersensitivity reaction.

Up to 10 mg of phytonadione is recommended for reversing the effects of warfarin in patients with life-threatening bleeding.⁸ Because vitamin K is fat soluble and excess amounts can be stored in tissues, the effects of phytonadione on coagulation may be prolonged, which can be a concern once bleeding has resolved and reestablishment of anticoagulation with a vitamin K antagonist is sought. In a retrospective chart review of 114 patients who received i.v. phytonadione alone for warfarin reversal, increasing the i.v. phytonadione dose beyond 2 mg did not influence the rate or extent of INR reduction beyond what was achieved

using 2 mg after 12 hours, 24 hours, or 48 hours.²⁸ Doses as large as 10 mg were used. However, doses larger than 2 mg were associated with a trend toward increased need for and duration of bridging therapy (i.e., dual anticoagulation with another anticoagulant plus warfarin to prevent thrombosis once bleeding resolved) compared with smaller doses, which may reflect warfarin refractoriness (i.e., resistance to the effects of warfarin when the drug was restarted). These findings suggest that large i.v. phytonadione doses do not have an advantage for urgent warfarin reversal over smaller doses in patients without life-threatening bleeding who expect to need to restart warfarin therapy promptly.

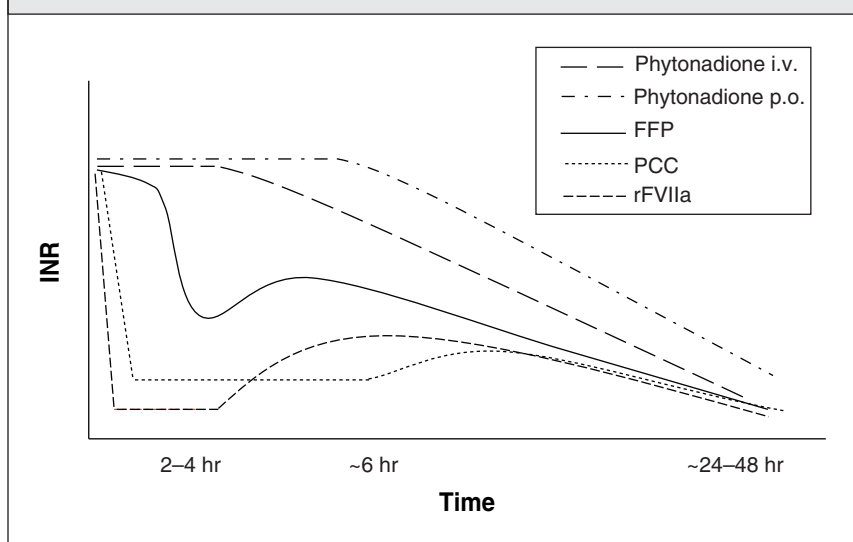
Pharmacodynamics. There is a delay before the INR decreases in response to i.v. or oral phytonadione administration in warfarin-treated patients with an elevated INR because of the lag time needed for production of vitamin K-dependent clotting factors, although the INR decrease occurs sooner after i.v. administration than after oral administration (Figure 1).²³ Administering a clotting factor concentrate, such as a PCC product or rFVIIa, to a warfarin-treated patient with an elevated INR provides an immediate drop in INR, but this drop is followed several hours later by a rebound increase due to the short elimination half-life of factor VII. Because the other clotting factors in PCC products (i.e., factors II, IX, and X) have longer half-lives than factor VII, the rebound increase in INR occurs later than after rFVIIa administration.²⁹ The onset of action of FFP is delayed because of the time required for thawing and administration of the product, which involves infusion of a large volume. Warfarin reversal by FFP is only partial, and a rebound increase in INR begins shortly after the end of the infusion. Combination therapies (e.g., phytonadione plus either PCC or rFVIIa or all

three agents) may be used to avoid rebound increases in INR.

Role of surgery and pharmacologic intervention. Questions have arisen about the role of pharmacologic interventions in improving clinical outcomes in patients with warfarin-related ICH. In 141 such patients, the INR was reduced from a median of 2.6 to less than 1.5 (i.e., normalized) within one hour after administration of a four-factor PCC product (Octaplex, Octapharma AG, Vienna, Austria) in 79.5% of the patients.³⁰ However, the in-hospital mortality rate was high (42.3%), substantial hematoma expansion occurred in nearly half the patients (45.5%), and the median modified Rankin scale was 5, reflecting severe disability. In a review of a protocol using a three-factor PCC product (Profilnine, Grifols Biologicals, Inc., Los Angeles, CA; mean dose, 47 units/kg) in 70 patients for urgent reversal of warfarin in the setting of ICH, correction of the INR (target <1.4) was incomplete (the mean INR was reduced from 3.36 to 1.96), and PCC-related serious adverse events occurred in 10% of patients.¹²

Pharmacologic intervention may play an important role in prompt reduction of the INR to a value considered safe enough for surgical intervention. In an analysis of seven patients with warfarin-related ICH, administration of a three-factor PCC product (Profilnine) halted hematoma expansion and expedited surgical intervention.³¹ The effects of PCC and rFVIIa on INR reported in retrospective studies were prompt, although the times to measurement of INR were not standardized to allow comparison among products.³² In the Surgical Trial in Intracerebral Haemorrhage (STICH), which compared early surgical intervention with initial conservative treatment of spontaneous supratentorial intracerebral hematomas ($n = 1033$), no benefit from early surgery was noted.³³ In the 80 patients receiving

Figure 1. Onset and duration of effect on International Normalized Ratio (INR) of various warfarin reversal therapies. FFP = fresh frozen plasma, PCC = prothrombin complex concentrate, rFVIIa = recombinant factor VIIa. Adapted from reference 23.



an oral anticoagulant, there was a nonsignificant trend toward fewer unfavorable outcomes; the trial used a prognosis-based outcome that incorporated a Glasgow outcome score at six months with early surgery (fixed OR, 0.51; 95% CI, 0.17–1.46)].

Risks to consider. The potential for INR rebound after administration of PCC or rFVIIa to patients with warfarin-related ICH needs to be considered. Administering i.v. phytonadione with these agents may prevent or delay INR rebound, and early phytonadione administration is needed because of the lag time before clotting factors are replenished by vitamin K. The INR needs to be closely monitored, and adjunctive therapies (e.g., PCC or rFVIIa) may be needed if rebound occurs.

The risk for thromboembolism is a serious concern with the administration of clotting factor concentrates. The administration of these products when endothelial damage, tissue factor expression, or underlying disease processes (e.g., coronary artery disease) are present may increase the risk for thrombosis, including acute coronary syndrome and sudden death from pulmonary

embolism.^{12,29} In a retrospective analysis of 69 patients who received rFVIIa for various off-label uses (i.e., non-hemophilia patients), 36 possible thromboembolic adverse events were identified in 29 patients, including 12 patients with events judged related to rFVIIa.³⁴ The mean rFVIIa dose was 8.2 mg (i.e., 117 $\mu\text{g}/\text{kg}$ for a 70-kg person). On average, the events were identified 8.8 days after exposure to the drug. None of the 48 physicians who cared for these patients and later completed questionnaires about the care provided were aware of the thromboembolic events, perhaps because the patient moved to a different care setting before the event occurred. These findings suggest that such events may be underreported in patients receiving rFVIIa (especially at higher doses) for off-label uses, and clinicians need to be aware of the risk for thromboembolism, especially while anticoagulation therapy is being withheld.

In warfarin-treated patients with elevated INR values requiring reversal because of bleeding or an urgent need for surgery, the frequency of thromboembolism after use of three-factor PCC products (0.7%) was low-

er than after use of four-factor PCC products (approximately 1.8%).³⁵ However, rates of thromboembolism higher than these reported values for both three-factor PCC and four-factor PCC products have recently been observed.³⁶⁻³⁸

Adding rFVIIa to three-factor PCC (Profilnine) has been proposed for warfarin-treated patients with INR values exceeding 4.5 to enhance the INR reduction.³⁹ In one assessment of combining a three-factor PCC and low-dose rFVIIa in 46 patients, two cases of thromboembolism were observed.⁴⁰ In another study of 70 patients with warfarin-related ICH, adding FFP either before or concomitant with a three-factor PCC product (Profilnine) did not appear to improve the INR correction, compared with three-factor PCC alone.¹² Additional concerns associated with the use of PCC products include the presence of unfractionated heparin (UFH) in some three- and four-factor PCC products. These PCC products should not be given to patients with heparin-induced thrombocytopenia (HIT), an immune-mediated effect of heparin therapy that increases the risk for thrombosis.

Patients with antithrombin III deficiency, a rare hereditary disorder that results in a hypercoagulable state, should not receive PCC products because these products may increase the risk for thrombosis.³⁹

Low levels of the natural regulatory anticoagulant protein C and protein S are present in some warfarin-treated patients who require reversal. Some four-factor PCC products (e.g., Beriplex P/N; Octaplex; Cofact, Sanquin Blood Supply, Amsterdam) contain these proteins, and administering these four-factor PCC products (an approach referred to as balanced PCC therapy) could in theory reduce the risk for thromboembolic complications.^{34,41}

Interpreting laboratory test results. The reliability of laboratory

tests used to monitor warfarin therapy should be considered in interpreting test results, because of the risk of inappropriate clinical conclusions. Isolated values or a series of rapidly rising or falling values that are inconsistent with prior trends and expectations based on warfarin dosing should be questioned. Clinicians should understand the implications of a change in the INR. There is little difference in the concentration of clotting factors present between an INR of 6 and an INR of 12, but a much larger difference between an INR of 1 and an INR of 2.⁴²

The method by which the blood sample is obtained also can affect the reliability of the results. If the sample is obtained from a venous site too close to the site where i.v. fluids are administered or withdrawn from a recently flushed i.v. line, the results may reflect hemodilution. Hemodilution can result in falsely elevated INR and activated partial thromboplastin time (aPTT) values and a low hematocrit value, misleading clinicians to suspect internal bleeding. Falsely elevated aPTT values also may occur if a syringe is used to obtain the blood sample and there is a delay in transferring the sample to a collection tube containing citrate.

The INR may not be a reliable measure of the degree of anticoagulation during the initial days of warfarin therapy.^{42,43} A rising INR during this period primarily reflects the depletion of factor VII before depletion of the more potent factor II. Therefore, the INR during early warfarin therapy exaggerates the degree of anticoagulation.

Similarly, the declining INR is not a reliable measure of anticoagulation when warfarin therapy is withheld, because levels of factor VII recover before factor II levels do. A falling INR in the early days after warfarin discontinuation may suggest a greater degree of anticoagulation due to the lag time for hepatic production of factor II.

Interpretation of changing INR values requires consideration of the context. A person with a falling INR of 1.8 shortly after warfarin is withheld might have a greater degree of anticoagulation than a person with a rapidly rising INR of 2.2 during initial warfarin therapy.

Warfarin therapy sometimes overlaps treatment with UFH or the target-specific oral anticoagulants, and these agents can independently elevate the INR. Some laboratories neutralize the UFH to avoid test interference. The INR accurately reflects the effect of warfarin only after the direct thrombin inhibitor has been discontinued and effects (measured by aPTT) have dissipated, which requires hours to days.⁴⁴ Patients who have reduced dabigatran, rivaroxaban, or apixaban daily dosing requirements for a given indication to maintain desired anticoagulation may have a low rate of drug clearance; thus, interference with the INR test can persist for a longer period after drug discontinuation than in patients with normal clearance.

Reversal of target-specific oral anticoagulants

Although antidotes are in development for both dabigatran and the direct FXa inhibitors rivaroxaban and apixaban, no such antidotes currently are available.^{45,46}

In patients with normal renal function, the anticoagulant effect of dabigatran, rivaroxaban, and apixaban diminishes within a day or two after stopping the drug.⁴⁷ The elimination half-life and anticoagulant effect of all three agents are prolonged in patients with kidney dysfunction. The greatest effect of renal impairment is observed with dabigatran because the kidneys have a greater role in its elimination, compared with the FXa inhibitors. Age-related decreases in renal function may be responsible for the prolonged elimination half-life of these agents in the elderly.⁴⁸

Role of hemodialysis. Hemodialysis can be used to remove dabigatran because of low protein binding.⁴⁴ Hemodialysis is not expected to remove rivaroxaban or apixaban because the drugs are highly protein bound (92–95% and 87%, respectively).^{48,49} In six patients with stage V chronic kidney disease (i.e., end-stage renal disease), approximately two thirds of a single 50-mg oral dabigatran dose was removed by hemodialysis over a two-hour period.⁵⁰ These observations should be interpreted with caution because they reflect the use of single 50-mg doses instead of the multiple 150-mg doses typically used in practice, and the measured plasma concentrations in these six patients do not reflect the distribution of the drug into tissues in patients with renal impairment receiving multiple 150-mg doses. The plasma drug concentration measured after a first dose may reflect initial drug distribution from the plasma to the tissues, suggesting a higher clearance rate than that seen after equilibrium between plasma and tissues has been established.⁵¹

In a case report, hemodialysis was used to reverse the effects of dabigatran 150 mg orally twice daily in a 59-year-old woman with moderate renal impairment (creatinine clearance, 40 mL/min) who was planning to undergo heart transplantation.⁵² Her thrombin time (TT, a measure of thrombin activity in plasma) was elevated (90.6 seconds) before hemodialysis. After 2.5 hours of hemodialysis using a blood flow rate of 500 mL/hr, which is considered robust to promote the adequacy of hemodialysis, the TT was only marginally reduced to 60.2 seconds, an elevated level that suggests that appreciable amounts of the drug remained after hemodialysis.

In another case report, a 94-year-old man with normal renal function who was receiving dabigatran 150 mg orally twice daily developed a life-threatening ICH after a fall.⁵³ After a brief delay, hemodialysis was initiated

to reverse the anticoagulant effect. The plasma dabigatran concentration decreased substantially during the three-hour hemodialysis session, but a marked increase in concentration was observed after hemodialysis ended. This rebound probably reflects redistribution of the drug from tissues to plasma. These observations suggest that a longer period of hemodialysis may be needed to provide a sustained reduction in plasma concentrations of dabigatran and reverse its anticoagulant effect.

Coagulation tests. The results of many common coagulation tests used as quantitative estimates of the intensity (i.e., level) of anticoagulation can vary among the target-specific oral anticoagulants for multiple reasons, including differences in the agents' site of action.⁴¹ The TT is often used as a very sensitive qualitative test to detect the presence of dabigatran.^{28,54} Quantitative assays (e.g., chromogenic ecarin clotting time [ECT], dilute prothrombin time) under development may be useful for monitoring coagulation during dabigatran therapy. Chromogenic anti-FXa assays can be used to provide qualitative and quantitative information about rivaroxaban and apixaban.⁴¹ The ECT and TT are not useful for monitoring coagulation during treatment with the FXa inhibitors.

For the target-specific oral anticoagulants, assay sensitivity may depend on the class of agents. The prothrombin time (PT) is a more sensitive test than aPTT for the FXa inhibitors, whereas the aPTT is a more sensitive test than PT for the direct thrombin inhibitors.^{54,55} The INR is derived from the PT, and point-of-care INR test results during dabigatran therapy tend to be higher than those obtained from clinical laboratories.⁵⁶ Therefore, the use of point-of-care INR tests to measure coagulation in patients receiving dabigatran is not recommended. The INR is not an easily used method for

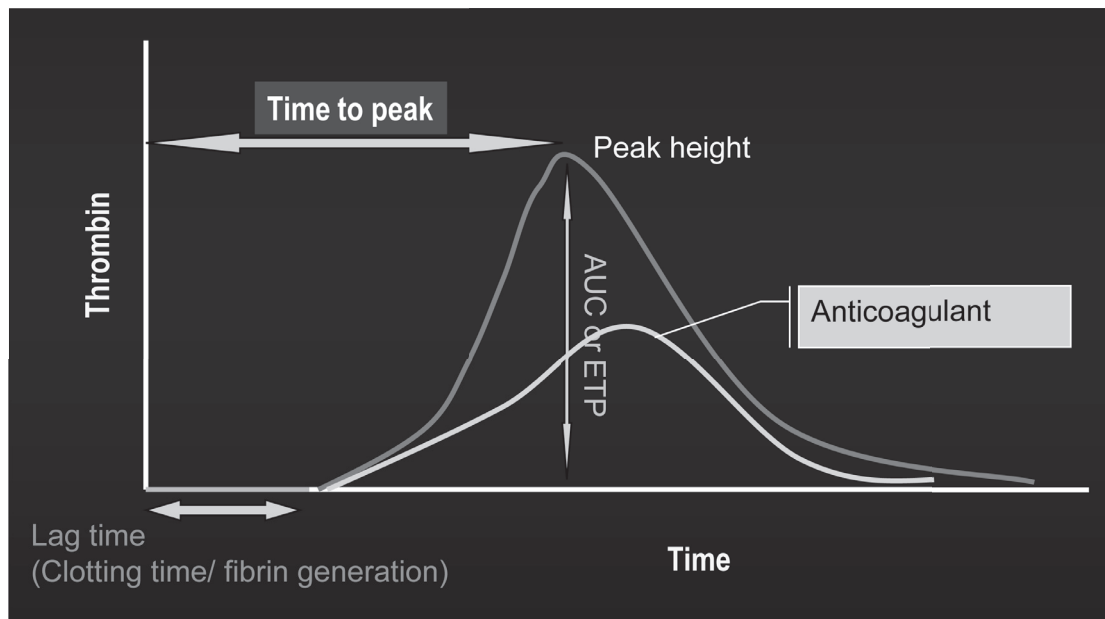
monitoring coagulation during treatment with FXa inhibitors because the assay would need to be calibrated for the specific agent being measured, and differences in the international sensitivity index and available assays may further influence values.^{41,57}

The implications of abnormal coagulation assay results are unclear. Normal values may not indicate loss of anticoagulant effects, and elevated values may occur for multiple reasons, making it difficult to quantify the degree of anticoagulation. When excessively high coagulation test values are observed in the absence of other explanations, clinicians should consider potential causes of the excessive effects, such as acute organ dysfunction or drug interactions that reduce elimination of the anticoagulant. Elevated INR values from sources other than warfarin (e.g., a target-specific oral anticoagulant or liver disease) may make transitioning to warfarin problematic, since it may be difficult to know when the target INR value solely attributed to warfarin has been achieved.

Thrombin generation tests reflect the inhibition of thrombin (factor IIa) production by an anticoagulant, the administration of which leads to a delay before thrombin production is detected (i.e., lag time), delay in the peak thrombin generation (i.e., increase in the time to peak thrombin activity), and reduction in the peak thrombin activity (Figure 2). The area under the plasma thrombin concentration–time curve (AUC) is diminished by anticoagulants. The endogenous thrombin potential (ETP) reflects this AUC and is one test that is being explored for assessment of the ability of various reversal agents to reduce anticoagulant activity. The test, however, has not been validated in controlled trials with bleeding patients receiving reversal agents.

In making decisions about oral anticoagulant dosages and invasive procedures or surgery, coagulation

Figure 2. Thrombin generation. AUC = area under the concentration–time curve, ETP = endogenous thrombin potential.



test results should be interpreted in the context of the clinical status of the patient. Test results indicating when changes in anticoagulant dosages are needed or when invasive procedures or surgery are safe have not been defined.

Clotting factor concentrates. Various clotting factor concentrates have been used to reverse target-specific oral anticoagulants. Limited data are available on the use of these products in humans.

In a randomized, double-blind, placebo-controlled, crossover study of 12 healthy male volunteers, dabigatran 150 mg twice daily for 2½ days increased the aPTT, ECT, and TT.⁵⁸ A four-factor PCC (Cofact) given in a dose of 50 units/kg did not fully reverse these anticoagulant effects. However, when the volunteers were crossed over to receive rivaroxaban 20 mg twice daily for 2½ days (an 11-day washout period between anticoagulants was provided), four-factor PCC normalized the ETP and PT. The ETP was 92% of the normal value at baseline, 51% of the normal

value after rivaroxaban treatment, and 114% of the normal value after PCC treatment (i.e., 14% higher than normal, possibly reflecting a hypercoagulable state). Reversal of the PT was immediate and was sustained for 24 hours. The degree of hemostasis and the dose necessary to manage active bleeding have not been established.

The effects of four-factor PCC (Kanokad, LFB-Biomedicaments, Paris), rFVIIa, and aPCC in reversing dabigatran and rivaroxaban were evaluated in an ex vivo, crossover study of blood samples obtained immediately before and two hours after a single 150-mg dose of dabigatran or 20-mg dose of rivaroxaban in 10 healthy white male volunteers.⁵⁹ A two-week washout period was provided between anticoagulant doses. Measures of thrombin generation, including ETP, peak thrombin generation, lag time, and time to peak thrombin, were used to assess reversal of the anticoagulant effects after the addition of a concentrated clotting factor product. Both rFVIIa

and aPCC (but not four-factor PCC) corrected the dabigatran-induced prolongation of the lag time.⁵⁹ Four-factor PCC increased (i.e., corrected) the ETP in dabigatran-treated blood to a greater extent than rFVIIa, suggesting a greater antagonist effect. Four-factor PCC strongly corrected the rivaroxaban-induced reduction in ETP, but rFVIIa did not (although rFVIIa corrected the lag time). By contrast, aPCC corrected all measures of thrombin generation in rivaroxaban-treated blood. These results should be interpreted with caution because the doses of reversal agents used were high, especially for aPCC, and the tests were performed ex vivo, not in vivo. The investigators expressed interest in the potential usefulness of low-dose aPCC.

Case reports provide additional insight into the use of clotting factor concentrates for reversal of target-specific oral anticoagulants. Large doses of rFVIIa (three 2.4-mg doses and two 7.2-mg doses) and six hours of hemodialysis were required to manage massive postoperative

bleeding in a 79-year-old man with renal impairment who was receiving dabigatran 150 mg twice daily and underwent coronary artery bypass graft surgery.⁶⁰ Dabigatran therapy had been withheld for two days before surgery. This case report demonstrates the need for early discontinuation of dabigatran before surgery, especially in patients with renal impairment, and the limited usefulness of rFVIIa for urgent reversal of the drug. In another case report of a patient receiving dabigatran with acute kidney injury and gastrointestinal bleeding, FFP, rFVIIa (30 µg/kg), and cryoprecipitate provided no apparent benefit.⁶¹ As noted in two other case reports, a three-factor PCC (Profilnine) had little effect on measured coagulation parameters.^{62,63} In each of these cases, hemodialysis was part of the management plan.

In another case report, a 67-year-old man receiving dabigatran 150 mg twice daily for atrial fibrillation experienced life-threatening bleeding during a cardiac ablation procedure.⁶⁴ His last dabigatran dose was administered seven hours before the procedure. Transseptal perforation occurred, and blood losses exceeded 3 L through the pericardial window. Administration of FFP, protamine, and packed red blood cells failed to reduce the bleeding. Low-dose aPCC (3159 units, which is 26 units/kg actual body weight) therapy was administered over 15 minutes. Hemostasis was noted within minutes after initiation of the infusion, with cessation of bleeding observed at the time administration was complete. A limited impact on TT, ECT, INR, and aPTT was observed, suggesting that aPCC produced hemostasis through a mechanism independent of dabigatran reversal. This case report suggests that low doses of aPCC may be effective for urgent reversal of dabigatran, although such therapy should be used with caution because experience with this approach is limited to this single case report.

Institutional system support

Institutions should establish a plan for managing patients who require oral anticoagulant reversal because of life-threatening bleeding or an urgent need for an invasive procedure or surgery. The management plan should include guidelines for laboratory testing, clinical assessment of coagulation, use of hemodialysis, and selection among the available pharmacologic agents for reversal, with appropriate dosing strategies for each oral anticoagulant. The institutional system should facilitate rapid guideline implementation and order entry. The guidelines should be updated as additional clinical data become available. Policies and procedures should be established to provide for swift administration of reversal agents and transfer of patients requiring hemodialysis to a setting where it is available. The management plan should be readily available around the clock to facilitate prompt implementation and avoid delays.

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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