Emerging Treatment Options

for the Reversal of Oral Anticoagulant Therapy

EMPOWERING PHARMACISTS THROUGH EDUCATIONAL RESOURCES

Do you come away from educational activities feeling inspired and empowered to make changes in your practice? According to a survey of participants in a live symposium and simultaneous webcast about emerging treatment options in the reversal of oral anticoagulant therapy held during the 47th ASHP Midyear Clinical Meeting and Exhibition in December 2012, others feel the same way. Conducted three months after the symposium, the survey indicated that each of the following practice changes were implemented, improved, or planned by at least 66% of the 97 respondents (range 66-78%):

- ❑ Use objective scores to assess a patient's bleeding risk.
- ❑ Develop algorithms for managing patients receiving oral anticoagulants that are having invasive procedures or require reversal.
- ❑ Develop educational program for colleagues about reversal strategies.
- ❑ Identify patients most likely to benefit from reversal with concentrated blood factors.
- ❑ Ensure correct laboratory tests are used to measure effect of new oral anticoagulants.
- ❑ Consider hemodialysis in patients with renal impairment requiring urgent reversal of dabigatran.

Of the 71 respondents who indicated that they still intend to implement or improve one or more practice changes, 90% are confident in their ability to make these changes in practice. Administrative issues were infrequently reported as barriers to implementing practice changes, indicating that support of health system leadership is a valuable asset to these respondents with regard to following through on planned improvements. Almost a third of respondents indicated that lack of consensus or practice guidelines was a barrier.

Several respondents offered tips about how they overcame barriers when making changes to improve the management of patients requiring reversal in their institutions:

- ❑ Created a P&T subcommittee that included internal medicine, oncology, pathology, laboratory, and pharmacy to review the information and create a strategy.
- ❑ Viewed it as an opportunity for pharmacists to take the lead.
- ❑ Developed plan with input from a hematologist and used scenarios to demonstrate the plan to supervisors.
- ❑ Included discussion and problem solving as a component of education for staff.
- ❑ Provided education for different services over a period of months.
- ❑ Got support from administration.
- ❑ Supported management efforts to search for proper medical billing codes so reimbursement could be obtained.

If you missed the Midyear symposium and these practice changes pique your interest, a free on-demand version of the activity is available. It is approved for 2 hours of continuing pharmacy education, and 82% of the survey respondents indicated they would recommend it for other pharmacists who are interested in learning more about this topic. In addition, a supplement based on the symposium proceedings and approved for 2.5 hours of continuing pharmacy education will be published in the May 15, 2013, issue of the *American Journal of Health-System Pharmacy*.

In this e-newsletter, Initiative Chair Edith A. Nutescu and fellow faculty William E. Dager and James S. Kalus address some frequently asked questions about unresolved issues related to oral anticoagulant reversal that were posed by participants in the Midyear symposium. Additional FAQs were addressed in a previous e-newsletter. The initiative web portal provides access to these and other learning opportunities, such as podcasts of a faculty roundtable discussion. These activities are designed to build on each other, focusing on interventions and practical strategies for reversing oral anticoagulant therapy.

For more information and to access other learning opportunities about this topic, go to the initiative portal. The initiative is supported by an educational grant from CSL Behring. www.ashpadvantage.com/reversal

FREQUENTLY ASKED QUESTIONS

Q How should vitamin K be used for warfarin reversal in patients with life-threatening bleeding? Guidelines recommend intravenous (i.v.) administration, but the package insert for the injectable form of vitamin K recommends using it by the subcutaneous (s.c.) or intramuscular (i.m.) route whenever possible because of severe reactions, including fatalities, after i.v. administration.

A The American College of Chest Physicians (ACCP) recommends 5-10 mg of vitamin K by slow i.v. injection (along with four-factor prothrombin complex concentrate) to reverse the effects of warfarin in patients with major bleeding.[1] It may be feasible to use i.v. vitamin K alone when the need for intervention is not urgent (i.e., not needed within 24 hours) based on the pharmacodynamics of the drug.[2,3] Oral vitamin K is recommended by ACCP for patients with an International Normalized Ratio (INR) exceeding 10 and no evidence of bleeding.

The prescribing information for phytonadione (injectable vitamin K) contains a boxed warning about the risk for severe reactions resembling hypersensitivity or anaphylaxis, including shock and cardiac or respiratory arrest, but the incidence of anaphylaxis is low (1 in 3500 doses).[4,5] The i.v. route is preferred over the s.c. and i.m. routes of administration for vitamin K when reversing warfarin in patients with life-threatening bleeding because it has a more rapid and predictable onset of effect.[6,7]

The results of a retrospective analysis of the use of vitamin K for warfarin reversal in 135 patients, including 42 patients with acute bleeding, were recently published.[8] Eighty-one patients received the drug orally (including 19 patients with acute bleeding) and 54 patients received it by the i.v. route (23 of whom had acute bleeding). Other patients required reversal before an invasive procedure or for correction of a supratherapeutic INR value. The median INR before vitamin K administration was similar for patients receiving the drug by the oral route (5.8) and the i.v. route (5.0), although a wide range of pretreatment INRs was observed in both the oral and i.v. groups. The percentage of patients achieving an INR of 2.0 or less within 12 hours after vitamin K administration was significantly higher with the i.v. route (44%) than the oral route (14%, $p<0.01$), which is consistent with the more rapid onset of effect by the i.v. route. There was no significant difference between the two groups in the percentage of patients with an INR of 1.5 or less within 24 hours after vitamin K administration ($p=0.87$).

The dose administered, time elapsed between availability of INR test results and vitamin K administration, and time of blood sample collection after vitamin K administration for INR measurement were similar for the oral and i.v. groups. The pretreatment INR and time after vitamin K administration were independent variables affecting the post-administration INR, but the dose administered did not correlate with the post-administration INR. Doses ranging from 1 mg to 10 mg were used by both routes, but there was no indication that doses exceeding 1 mg affected the magnitude of the INR reduction by either route.

In another recently published retrospective chart review of 400 patients who received vitamin K for warfarin reversal, including 233 patients who received the drug by the i.v. route, the dose, route of administration, and pretreatment INR influenced subsequent INR values.[2] Half of the patients received fresh frozen plasma, but patients who received a clotting factor concentrate were excluded. Ninety-two of the 400 patients had major bleeding, and 60 of these patients received the drug by the i.v. route. Up to 10 mg of i.v. vitamin K was administered, but increasing the dose beyond 2 mg did not increase the rate or extent of INR reduction beyond what was achieved using 2 mg after 12 hours, 24 hours, or 48 hours. Larger doses were associated with a need for bridging therapy with another anticoagulant plus warfarin to prevent

Faculty

Edith A. Nutescu, Pharm.D., FCCP
Initiative Chair
Clinical Professor
Center for Pharmacoepidemiology and Pharmacoeconomic Research
The University of Illinois at Chicago College of Pharmacy
Director, Antithrombosis Center
Co-Director, Pharmacogenomics Service
The University of Illinois Hospital and Health Sciences System
Chicago, Illinois

William E. Dager, Pharm.D., BCPS (AQ-Cardiology)
Pharmacist Specialist, University of California (UC) Davis Medical Center
Clinical Professor of Medicine, UC Davis School of Medicine
Sacramento, California
Clinical Professor of Pharmacy, UC San Francisco School of Pharmacy
San Francisco, California
Clinical Professor of Pharmacy, Touro School of Pharmacy
Vallejo, California

James S. Kalus, Pharm.D., BCPS (AQ-Cardiology)
Senior Manager, Patient Care Services
Department of Pharmacy Services
Henry Ford Hospital
Detroit, Michigan

thrombosis once bleeding had resolved. These results may reflect the storage of excess vitamin K in adipose tissues and warfarin refractoriness (i.e., resistance to the effects of warfarin when therapy is resumed).

The findings of these two retrospective analyses suggest that smaller i.v. vitamin K doses than those recommended by ACCP may suffice for warfarin reversal in patients with bleeding. The use of such doses may avoid warfarin refractoriness, which is helpful if resumption of anticoagulation therapy is planned in the near future. Patients whose oral anticoagulant therapy has been reversed often remain at risk for thromboembolism and require resumption of anticoagulation therapy.

Q Should dosing of clotting factor concentrates be based on ideal body weight or actual body weight in obese patients?

A Both fixed and weight-based doses of clotting factor concentrates have been used to reverse oral anticoagulants. In patients with hemophilia, dosing of clotting factor replacement therapy usually is based on actual body weight. However, ideal body weight is increasingly used instead of actual body weight for dosing in obese patients with hemophilia because ideal body weight correlates more closely with the blood volume in these patients.[9] Whether ideal body weight is a more appropriate basis for dosing clotting factor concentrates than actual body weight for reversal of oral anticoagulants in obese patients without hemophilia remains to be determined.

Vial size may be a consideration in dosing clotting factor concentrates because of the high cost of these products. Rounding off the calculated dose to the nearest vial size can minimize waste.

Q When oral anticoagulant therapy is reversed, how do you determine whether and when to restart anticoagulation?

A Patients whose oral anticoagulant therapy has been reversed often remain at risk for thromboembolism. Questions about whether and when to restart anticoagulation, the agent and dosage to use, and how best to monitor such patients can be difficult to answer. Clinical judgment is needed in weighing the risks for thromboembolism and bleeding.

In a retrospective cohort study of 442 patients with gastrointestinal (GI) bleeding during warfarin therapy, restarting warfarin therapy was associated with a lower risk for thrombosis and death over a 90-day period, without

NEWS UPDATE

New Product Approved by FDA for Warfarin Reversal

At the end of April 2013, a new four-factor prothrombin complex concentrate (PCC) product was approved by the Food and Drug Administration (FDA) for the urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (e.g., warfarin) therapy in adults with acute major bleeding.

The product (Kcentra, CSL Behring LLC, Kankakee, IL) contains the vitamin K-dependent clotting factors II, VII, IX, and X in an inactivated form. Activated PCC (also known as anti-inhibitor factor complex, factor VIII inhibitor bypassing activity, or FEIBA), which contains clotting factor VII in an activated form and clotting factors II, IX, and X primarily in an inactivated form, has been available in the United States since 2011. Kcentra is the first inactivated four-factor PCC product approved in the United States. It also contains the antithrombotic proteins C and S, antithrombin III, and heparin.

Known heparin-induced thrombocytopenia is a contraindication to use of the new four-factor PCC product because of its heparin content. It is not approved for use in patients without acute major bleeding. See the prescribing information for dosing considerations and the boxed warning related to thromboembolic complications.

Kcentra (prothrombin complex concentrate, human) prescribing information. Kankakee, IL: CSL Behring LLC; 2013 Apr. http://www.kcentra.com/docs/Kcentra_Prescribing_Information.pdf (accessed 2013 May 1).

U.S. Food and Drug Administration. FDA approves Kcentra for the urgent reversal of anticoagulation in adults with major bleeding. April 29, 2013. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm350026.htm (accessed 2013 May 1).

Practical Guide from European Society Addresses Novel Oral Anticoagulants

Recognizing the need for clinicians to be able to use the novel oral anticoagulants dabigatran, rivaroxaban, and apixaban safely and effectively as an alternative to warfarin to prevent stroke in patients with atrial fibrillation, the European Health Rhythm Association (EHRA) recently published a practical guide. The guide is centered around 15 clinical scenarios, including measurement of anticoagulation effect and management of bleeding complications.

EHRA developed a website to accompany the guide that provides useful resources for clinicians, such as downloadable patient cards. The website will also contain updates to the practical guide as new information becomes available.

Heidbuchel H, Verhamme P, Alings M et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *Europace*. 2013 Apr 26. [Epub ahead of print]

European Society of Cardiology. Novel oral anticoagulants for atrial fibrillation: practical guide documents. www.NOACforAF.eu (accessed 2013 May 1).

increasing the risk for recurrent GI bleeding compared with not resuming warfarin therapy.[10] The investigators concluded that the benefits of restarting anticoagulant therapy outweigh the risks for many patients.

The results of a post-hoc analysis of data from the ROCKET-AF study in which rivaroxaban was judged non-inferior to warfarin for stroke prevention in patients with atrial fibrillation (AF) were recently published.[11] In the post-hoc analysis, the incidence of stroke and non-central nervous system (CNS) embolism after temporary discontinuation of anticoagulation in moderate- to high-risk patients with AF was similar with rivaroxaban and warfarin (6.20 vs. 5.05 per 100 patient-years, respectively). Temporary discontinuation was defined as an interruption in therapy of more than 3 days, and the median duration of temporary interruption in therapy was 6 days. Clinical events occurring 3 days after temporary interruption of therapy to 3 days after resumption of therapy were included in the analysis. The most common reasons for temporary discontinuation were bleeding and non-bleeding adverse events (40%) and need for surgical or invasive procedure (38%).

The incidence of stroke and non-CNS systemic embolism was high and similar 3 to 30 days after early permanent discontinuation of rivaroxaban and warfarin (25.6 vs. 23.3 per 100 patient-years, respectively). Bleeding and non-bleeding adverse events were the most common reason (39%) for early permanent discontinuation.

At the end of the study, when patients transitioned to open-label warfarin therapy, a significantly higher incidence of stroke and non-CNS embolism within 30 days was observed in the group that had received rivaroxaban compared with the group that had received warfarin (6.42 vs. 1.73 per 100 patient-years, respectively, p=0.0044). The incidence of all thrombotic events (stroke, non-CNS embolism, myocardial infarction, and vascular death) within 30 days after any discontinuation of or interruption in therapy was high and similar in the two groups (27.0 per 100 patient-years for rivaroxaban vs. 27.0 per 100 patient-years for warfarin, p=0.85). These findings underscore the importance of minimizing the need for and duration of interruptions in anticoagulant therapy and suggest the need for bridging anticoagulation therapy when making the transition between agents in high-risk patients. The prescribing information for rivaroxaban includes a boxed warning about the increased risk of thrombotic events in patients with AF discontinuing the drug and the need to consider administering another anticoagulant if rivaroxaban therapy must be discontinued for a reason other than pathological bleeding.[12]

Q What is the role of oral activated charcoal in the reversal of the new oral anticoagulants?

A *In vitro* data suggest that oral administration of activated charcoal can reduce dabigatran absorption if the charcoal is administered within 2 hours after the anticoagulant.[13] Data are not available for the use of oral charcoal after rivaroxaban or apixaban administration, but charcoal administration is warranted if a short time has elapsed since the last dose of the anticoagulant because of the minimal adverse effects associated with charcoal administration.[14]

Q What is the role of antifibrinolytic agents in promoting hemostasis in patients with bleeding during oral anticoagulant therapy?

A The antifibrinolytic agents tranexamic acid and epsilon aminocaproic acid have been used to promote hemostasis and reduce blood loss in trauma patients and patients undergoing surgery.[15,16] These lysine analogs exert their antifibrinolytic activity by blocking the lysine binding site on plasminogen and interfering with the activation of plasminogen to plasmin, which ordinarily degrades fibrin.[15] An i.v. bolus dose of 10-20 mg/kg or approximately 2.5 g, followed by 2-40 mg/kg/hr has been used for tranexamic acid.[15] An i.v. bolus dose of 80-150 mg/kg or 5-10 g, followed by 2.5-30 mg/kg/hr or 1-2.5 g/hr has been used for epsilon aminocaproic acid.[15] Tranexamic acid is more effective than epsilon aminocaproic acid for reducing the need for blood transfusion in surgical patients.[16] In a large, randomized, placebo-controlled study of patients with serious bleeding due to trauma, tranexamic acid significantly reduced the risk of death from bleeding and all-cause mortality.[17]

Unwanted clotting is a potential complication of antifibrinolytic agents, however, and, although the mechanism is not yet clear, accumulation of tranexamic acid may occur in patients with renal insufficiency.[18] A recent retrospective analysis showing that high doses of tranexamic acid were associated with a risk of convulsive seizures underscores the need to carefully evaluate how antifibrinolytic agents are used.[19]

Additional ASHP Advantage Educational Activities

Visit the ASHP Advantage website to browse listings of convenient on-demand continuing education (CE) activities, as well as publications, podcasts, and live webinars. More than 30 hours of free on-demand CE programming are available. Learn more and find a full listing of topics and activities at http://www.ashpadvantage.com.

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For complete information about educational activities that are part of this initiative, visit www.ashpadvantage.com/reversal. There is no charge for the activities, and ASHP membership is not required.

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