Anticoagulation, the thinning of the blood to treat abnormal clotting, is used by physicians to treat existing clots and to prevent new clots. The inherent problem with anticoagulation is that it not only prevents abnormal clotting but also interferes with normal clotting. This was evident with the anticoagulant warfarin (Coumadin), with which, even with carefully monitored anticoagulation, serious bleeding complications sometimes occur. Warfarin, also known as a vitamin K antagonist, thins the blood by preventing the body from synthesizing several clotting factors required for normal coagulation. Those clotting factors all require vitamin K for their production.

When warfarin-related bleeding complications occur, physicians reverse the warfarin anticoagulation, that is, return “thinned” blood to a more normal clotting condition, by following protocols that are in turn guided by the measured anticoagulation effect that warfarin induces. That measurement is done with a blood test called the international normalized ratio, which is readily available in hospital and outpatient laboratories. The international normalized ratio provides physicians with laboratory information that can help them decide whether to give extra vitamin K or to administer concentrated doses of the clotting factors to treat patients who are bleeding because of the warfarin.

Over the past 5 years, 4 new (novel) drugs have come to market that also cause thinning of the blood, but in a more precise way than warfarin. Collectively called novel oral anticoagulants (NOACs), dabigatran (PRADAXA), apixaban (ELIQUIS), edoxaban (SAVAYSA), and rivaroxaban (XARELTO) are at least as effective as warfarin, even though they only inhibit 1 clotting protein instead of several. The action of NOACs is not related to vitamin K. Importantly, these drugs are in many ways safer than warfarin in that all 4 NOACs have a lower risk than warfarin of the most feared complication of anticoagulation: bleeding into or around the brain. Collectively, the NOACs are associated with a greater than 50% reduction in that risk (Table). Still, bleeding complications occasionally occur in patients being treated with NOACs and are viewed by many physicians as more problematic than warfarin-associated bleeding because there is no rapidly available quantitative measurement test for the extent of blood thinning with NOACs, like the international normalized ratio for warfarin, and because the treatment of NOAC-related bleeding is not as straightforward as simply replacing depleted clotting factors.

Reversal of Anticoagulation

In warfarin-treated patients, the necessary proteins (clotting factors) are missing, so replacing them makes sense. In NOAC-treated patients, only 1 clotting factor is not working, although it is actually present at normal levels. NOACs work by preventing the specific protein they target from participating in clotting. Therefore, giving more of those clotting factors does not necessarily resolve the “thinned blood problem” in bleeding NOAC-treated patients. Giving vitamin K has no impact.

Even if there is no active bleeding, NOAC-treated patients may require urgent or emergent surgery, made more dangerous by the ongoing anticoagulation. There is great interest in developing reversal agents for NOACs to remove the effect of anticoagulation and to allow the clotting process to return to normal. In critical situations such as life-threatening hemorrhage,
bleeding into or around the brain, or the need for lifesaving surgery in a NOAC-treated patient, reversal agents could be very useful. The US Food and Drug Administration has granted 2 potential reversal agents—idarucizumab for dabigatran and andexanet alfa for apixaban, edoxaban, and rivaroxaban—special status that could hasten their approval. Both of these drugs are being tested in actual NOAC-treated bleeding patients, and in mid-2015, initial results for idarucizumab were published.1

Promising Results

Idarucizumab is an antibody that binds to dabigatran exclusively and tightly (Figure, A and B). Initial tests in dabigatran-treated animals and human volunteers showed that after intravenous dosing, idarucizumab effectively removed all anticoagulant effects of dabigatran without causing any clotting or other safety concerns. The Reversal of Dabigatran Anticoagulant Effect With Idarucizumab (RE-VERSE AD) study is expanding that work into dabigatran-treated patients with severe bleeding or a need for urgent or emergent procedures. The study will eventually enroll 500 patients worldwide in more than 400 hospitals (an indication of the rarity of such extreme events), but there are data published now on the first 90 patients (51 with bleeding, 39 before the procedure). In the study, idarucizumab worked as effectively as it did in preliminary animal and human volunteer studies. It removed the anticoagulant effect of dabigatran completely, durably, and safely. One cannot say from the RE-VERSE AD data that idarucizumab saved lives. However, idarucizumab removed thinned blood from the priority list of problems requiring immediate management by the emergency physician taking care of the patient. This is a ground-breaking advance in contemporary anticoagulation therapy because the use of idarucizumab further strengthens the safety profile of dabigatran by providing a precisely targeted, rapid, and safe response in rare but dire clinical situations. One fixed dose of idarucizumab was effective for almost all treated patients.

Andexanet alfa is currently being studied in patients who are bleeding while taking one of the other NOACs.4 Its development will add further safety and security to the use of NOACs for anticoagulation.

Summary

Oral anticoagulation with medications other than warfarin (NOACs) offers advantages of convenience and safety to patients. One worry some patients and physicians have had about using NOACs has been the lack of a specific approach to bleeding that may occur while taking them. The development of safe, potent, and reliable antidotes is addressing that concern.

Disclosures

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Charles V. Pollack, Jr.

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