When Anticoagulants Become a Bloody Mess

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ANNALS CASE

Imagine just another busy day in your emergency department (ED) when an elderly gentleman presents with a simple, straightforward mechanical fall. Sounds easy. Subsequent head computed tomography shows a traumatic subdural hemorrhage and now his care is a little more complicated. Then you discover his history of atrial fibrillation and, as recommended by his CHA_2DS_2-VASc score,[1] he is in fact receiving an oral anticoagulant. Of course he has no previous records or medication list on hand and cannot recall the name of his mystery anticoagulant. Now this simple case is very, very complicated. Anticoagulation reversal for his unknown anticoagulant is needed…and fast. Could he be receiving a non–vitamin K oral anticoagulant (NOAC)? How do we reverse these agents?

WARFARIN VERSUS NOACs

Good old warfarin (Coumadin), a vitamin K antagonist, was the criterion standard for treating and preventing venous thromboembolism. However, its use is complicated by multiple drug interactions, dietary restrictions, and a narrow, less reliable therapeutic index requiring frequent laboratory monitoring and dose adjustments.[2] Thankfully (go, science!), we now have other options. Dabigatran (Pradaxa) is a direct thrombin-competitive (factor II), reversible inhibitor, whereas "xabans" (ie, rivaroxaban, apixaban, edoxaban, and betrixaban) are direct factor Xa inhibitors. More recently, NOACs have replaced warfarin as the first-line agents in treating and preventing venous thromboembolism.[3]

So why use NOACs over our old standard, warfarin? In short, NOACs are easier to use. They have more straightforward dosing, minimal food and drug interactions, and no need for anticoagulation bridging or laboratory monitoring.[2,4,5] Compared with warfarin, NOACs have decreased major bleeding risk and intracranial bleeding while yielding noninferior efficacy in patients with nonvalvular atrial fibrillation.[2-6] Still, warfarin does have 2 big advantages over NOACs. First, its anticoagulation effect is easily measured with the international normalized ratio (INR) of prothrombin time. Second, warfarin reversal with vitamin K and fresh frozen plasma or 4-factor prothrombin complex concentrates (PCCs) is relative easy and well studied. Reversing NOACs, on the other hand, might be a bit more complicated….

CAN LABORATORY TESTS HELP YOU WITH NOACs?

Although the INR and activated partial thromboplastin time help quantify warfarin and heparin effects, respectively, measuring supratherapeutic or therapeutic levels of NOACs is far more challenging for us emergency physicians. Thrombin time, dilute thrombin time, and ecarin clotting time quantify dabigatran effect, whereas apixaban and rivaroxaban are best followed by the anti–factor Xa chromogenic assay. Unfortunately, these assays are not typically available in the ED, nor will they provide results quickly.[6,7]

As for our ED tests prothrombin time, INR, and activated partial thromboplastin time, these may be helpful to measure NOAC effect. With dabigatran, if the activated partial thromboplastin time is elevated, it is suggestive of active dabigatran on board. The elevated level, however, does not correlate with dabigatran effect. Similarly, for factor Xa inhibitors, an elevated INR is suggestive of active rivaroxaban, although it will not clue you in about its clinical effect. Unfortunately, normal values do not exclude clinically relevant plasma levels of NOACs.[6,7] In the end, asking patients when they last took a NOAC is often the

most practical method for quickly assessing residual anticoagulant activity because most of the effects of the NOAC will wane after 3 to 5 half-lives (Table).[8] That's right: talking to our patients may be more helpful than ordering a test!

WHAT TO DO IN BLEEDING WITH NOACs

When approaching the anticoagulated patient with a life-threatening bleeding event (eg, intracranial hemorrhage, massive gastrointestinal bleeding), always start with the basics. Step 1 remains assess and maintain the ABCs, obtain 2 large-bore intravenous lines, use a monitor for the patient, and start transfusing RBCs as indicated. Next, hold direct pressure on the source of bleeding, if possible, and call in any specialty services that may be helpful in fixing it. As discussed above, although the laboratory results may be suggestive of a NOAC effect, a more practical measure is the time since the last NOAC dose.

For our patient with subdural bleeding, direct pressure isn't really an option, and last dose is unknown. After ABCs, intravenous lines, and monitor, neurosurgery consultation may be helpful.

STEP 2: STOP OR SLOW BLEEDING

Now on to the complicated part: NOAC reversal. There are few data on the ideal strategy, although therapies can be categorized as such:

1. Reduce absorption or remove the drug from circulation: activated charcoal and hemodialysis
2. Antifibrinolytic agents: tranexamic acid and Ɛ-aminocaproic acid
3. Plasma factor reversal: PCC, fresh frozen plasma, and cryoprecipitate
4. Specific antidote reversal: idarucizumab

As for the reversal, what evidence do we have for these strategies? In general, not a lot. Limited data suggest that charcoal within 2 to 3 hours of ingestion may be useful in decreasing the levels of dabigatran and apixaban absorbed, presuming safe per os intake by an awake cooperative patient, or by gastric tube in an intubated patient.[9,10] Hemodialysis is a possible treatment for dabigatran reversal because it can remove approximately 50% to 60% of the drug in 4 hours.[11] However, hemodialysis remains challenging in cases of major bleeding and hemodynamic instability.[12,13] In regard to antifibrinolytic agents, such as tranexamic acid, their efficacy in cases of NOAC-associated bleeding has not yet been studied. Nonetheless, their pathophysiology indicates they may be safe and helpful to give.[12]

The mainstay of NOAC reversal in life-threatening bleeding events is PCC and specific antidotes. To briefly review, PCC comes in 3-factor (factors II, IX, and X) and 4-factor (factors II, VII, IX, and X) flavors, both with proteins C and S. Activated PCC, also known as factor VII inhibitor bypassing activity, contains mostly activated factor VII and nonactivated factors II, IX, and X. Limited data from both animal studies and healthy human volunteers have demonstrated an attenuation of anticoagulation parameters and bleeding across the NOACs, with a recommended dosage of PCC or activated prothrombin complex concentrates (aPCC) at 50 U/kg for NOAC in patients with a severe life-threatening bleeding event.[8-10,12] PCC is often now preferred over fresh frozen plasma for NOAC– and warfarin-related bleeding according to the American College of Emergency Physicians, Chest guidelines, the Neurocritical Care Society, and Society of Critical Care Medicine.[4,8,14] PCC contains a higher concentration of factors and lower overall volume, particularly pertinent for individuals at risk for fluid overload or harm from more fluids.

As for specific NOAC antidotes, idarucizumab (Praxbind) is the only Food and Drug Administration–approved agent available at this time…and it's only for dabigatran. Preliminary data have demonstrated that idarucizumab reverses the anticoagulant

Table. Comparison of NOACs and their reversal agents.

Name	Elimination $t^{1/2}$,* Hours	Elimination 3–5 $t^{1/2}$,* Hours	Removed by HD	Treatment	Antidote
Dabigatran (Pradaxa)	14–17	42–85	Yes	Activated charcoal† Consider PCC/aPCC	Idarucizumab (Praxbind)
Rivaroxaban (Xarelto)	5–9	15–45	No	Activated charcoal† Consider PCC/aPCC	None
Apixaban (Eliquis)	8–15	24–75	No	Activated charcoal† Consider PCC/aPCC	None
Edoxaban (Savaysa)	10–14	40–70	Partial	Activated charcoal† Consider PCC/aPCC	None

*Longer in renal impairment.
†Within 2 hours of ingestion.

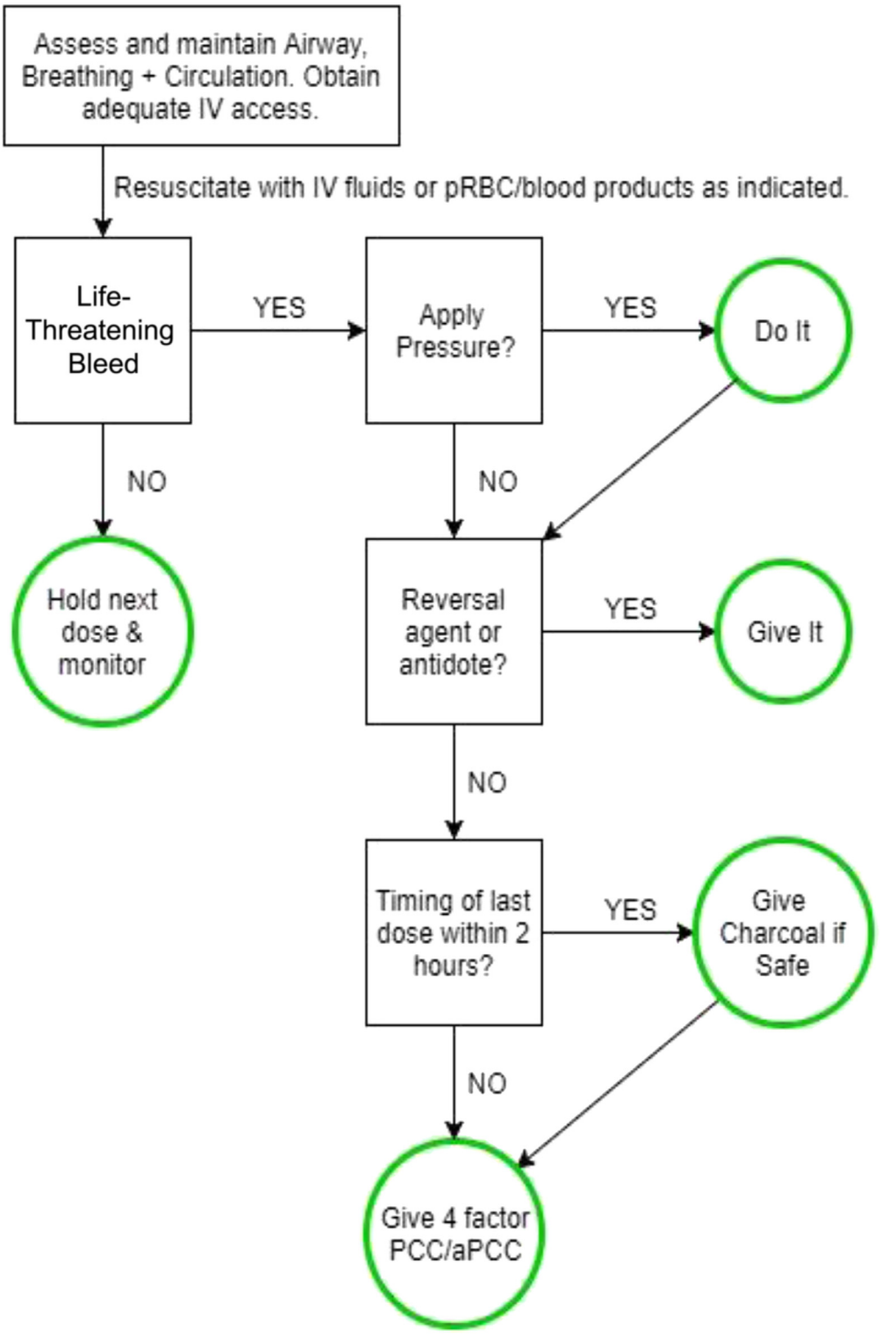

Figure. Proposed algorithm in approaching life-threatening, NOAC-associated hemorrhage. *FFP*, Fresh frozen plasma; *TXA*, tranexamic acid.

effects of dabigatran spectacularly…according to laboratory values.[15,16] Actually, one study showed a median maximum dabigatran reversal of either diluted thrombin time or ecarin clotting time of—wait for it—100% (95% confidence interval 100% to 100%)![16] Hemostasis during a periprocedural assessment was deemed normal in 93.4% of patients as well.[16] Although this evidence is certainly tantalizing, randomized controlled trials are lacking.

Two other antidotes under study have not yet been Food and Drug Administration approved. The first, andexanet alpha, is a factor Xa decoy protein that is proposed to reverse the xabans. It has been shown to reverse xaban effect in the laboratory and seems to have had clinical benefit in a cohort study.[17,18] The second, ciraparantag, noncovalently binds and neutralizes dabigatran, rivaroxaban, apixaban, and edoxaban![18] The efficacy of both of these drugs has yet to be fully elucidated, but keep an eye out for them in the near future.

CASE CONCLUSION

Take 1: Fortunately for us and our patient, a family member shows up and reports he last took his dabigatran 6 hours ago. You cleverly order idarucizumab, and a concerned neurosurgeon takes the patient up to the ICU. After giving yourself a hearty and deserved pat on the back, on to the next patient!

Take 2: But what if this family member reported rivaroxaban taken 7 hours ago instead? Well, we are outside the 2-hour last ingestion window for activated charcoal, rivaroxaban does not currently have an antidote available, and it is not dialyzable. Here, you cleverly order PCC or aPCC and consider tranexamic acid, after which a concerned neurosurgeon takes the patient up to the ICU. Time for another hearty and deserved pat on the back, and on to the next patient!

BOTTOM LINE

NOACs offer a convenient and effective means of anticoagulation compared with warfarin. In the case of a life-threatening or massive hemorrhage, such as intracranial hemorrhage or massive gastrointestinal bleeding, aggressive supportive care combined with PCC and specific antidotes when available may help decrease the time to cessation of bleeding. See our handy-dandy algorithm (Figure) for a simple step-by-step guide.

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