Emergency surgery and trauma in patients treated with the new oral anticoagulants: Dabigatran, rivaroxaban, and apixaban

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Management of anticoagulated patients in the emergency setting changed dramatically in the United States with the introduction of dabigatran etexilate mesylate (Pradaxa, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT) in 2010. This oral direct thrombin inhibitor (DTI) was approved for stroke prevention in nonvalvular atrial fibrillation (NVAF).[1] Its popularity grew rapidly. By 2012, it was being prescribed at more than 18% of office visits for chronic anticoagulation. In addition, a relatively high volume of off-label use for conditions such as coronary artery disease and venous thromboembolism (VTE) have been reported.[2] Since this agent does not require interval monitoring, no method to evaluate the level of anticoagulation was available.[3–5] No reversal agents or strategies were known.[6] We have previously reported on this dilemma and suggested an algorithm for these patients in trauma and acute care surgery (ACS).[7]

The US Food and Drug Administration (FDA) subsequently approved two factor Xa (FXa) inhibitors for similar indications: rivaroxaban for the prevention of stroke in patients with NVAF, prevention of VTE in patients undergoing knee and hip replacement, treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE), and prevention of DVT/PE recurrence;[8] and apixaban for the prevention of stroke and VTE caused by NVAF. In March 2014, apixaban was also approved for VTE prophylaxis following hip or knee replacement surgery.[9] Similar to dabigatran, no laboratory measurement of their effect was available or necessary because of their more predictable pharmacologic profiles. Also like dabigatran, no antidotes were suggested upon the introduction of these drugs to the health care community.[10,11]

The proposed clinical benefit of these agents is clear. When compared with warfarin for the indication of NVAF, a recent meta-analysis confirmed that these new oral anticoagulants reduce stroke, intracranial hemorrhage, and all-cause mortality while slightly raising the risk of gastrointestinal bleeding.[12] This risk is perhaps overstated and likely applies to all anticoagulants if held to the same standards.[13] Still, with no proven antidote or reversal suggestions, bleeding remains a concern especially in trauma and emergency surgery.[14–16]

Acute care surgeons are well adept at reversing warfarin-induced coagulopathy. Warfarin remains the most commonly used anticoagulant in the United States, with more than 30 million prescriptions written each year.[17] Unfortunately, the common methods for quantifying and normalizing the level of anticoagulation resulting from warfarin use are invalid for both DTIs and FXa inhibitors.

The indications for these new medications are highly prevalent in the elderly. In the United States, this population is expected to at least double in the next 30 years.[18] Moreover, it is estimated that by 2050 more than 5 million Americans will have atrial fibrillation, including 10% of those 80 years and older. The growing body of literature highlighting the amount of time patients treated with warfarin are outside the therapeutic window (approximately 33%) or voluntarily discontinue the medication (approximately 26%) adds to the motivation to change to these newer drugs.[19] The total market for oral anticoagulant therapy is well more than $7 billion a year.[18] Dabigatran and rivaroxaban now have sales in excess of $200 million each quarter, while apixaban generated $44 million in the third quarter of 2013.[20–22] The need to develop expertise in dealing with hemorrhage and emergency surgery in this patient population is clear.

The introduction of dabigatran resulted in a several publications describing its pharmacology and safety. Subsequent approval of rivaroxaban and apixaban had similar effect. Only a few have focused on emergency situations such as ACS and trauma where anticoagulation has been shown to lead to poorer outcomes.[17,23–26]

We have successfully applied our previously published approach to dabigatran-induced coagulopathy in an expanding series of patients.[7] In addition, we have now accumulated a series of trauma and ACS patients who presented to our institutions anticoagulated with rivaroxaban. Recently, we have cared for a small number of these patients on apixaban. These experiences have allowed us to modify our dabigatran recommendations and develop similar algorithms for the FXa inhibitors. In this article, we provide a review of these new medications and our care paths for their management in the acutely injured and emergent surgical patient. Additional anticoagulants and antidotes in development are also introduced. Emergence of these drugs into the market is eminent and likely to continue.

DABIGATRAN

Pharmacology

Dabigatran etexilate mesylate is an oral, competitive DTI, which is converted in the liver to its active form dabigatran.[27] Dabigatran binds to free and clot-bound thrombin. Its primary mechanism of action is to prevent the conversion of fibrinogen to fibrin. Platelet aggregating effects of thrombin are also reduced.[3,5,6]

Peak concentrations occur in 1 hour to 2 hours.[1] Absorption from the proximal gastrointestinal tract is best in an acidic environment. It is produced as a micropellet around a tartaric acid core to help guarantee this low pH. The now common use of acid reducing medications—proton pump inhibitors, histamine blockers—does not alter the drug's effect, and no dosing adjustments are required.[10,19,28,29]

Clearance of dabigatran is predominantly renal. In patients with normal creatinine clearance (CrCl), the multiple-dose half-life is 14 hours to 17 hours. Renal insufficiency can dramatically prolong clearance. Approximately 20% of the drug is cleared via the liver. Hepatic insufficiency caused by disease or other medications may also affect clearance and dosing.[6,27,29]

Dosing for NVAF is 150 mg given twice a day (BID). With worsening renal insufficiency (CrCl, 15–30 mL/min) the dose is reduced to 75 mg BID. The manufacturer makes no dosing recommendations for CrCl less than 15 mL/min.[1] Multiple drug interactions are problematic. Some result from the prodrug interacting in the liver with P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4). Substances that induce higher P-gp function (e.g., rifampin) may decrease the maximum serum concentration of dabigatran. Alternatively, medications such as amiodarone will suppress P-gp and result in increased levels of dabigatran. Dosing adjustments for these interactions are recommended.[10] Patients with CrCl of 30 mL/min to 50 mL/min and taking medications inhibiting P-gp or CYP3A4 (e.g., amiodarone, ketoconazole) should reduce the dose to 75 mg BID.[1] Concurrent use with antiplatelet agents is to be done with caution because of reported increased bleeding risks.[3,30]

Laboratory Assays

Routine coagulation laboratory values, such as prothrombin time (PT/international normalized ratio [INR]), activated partial thromboplastin time (aPTT), and activated clotting time (ACT), while altered by dabigatran, do not change in such a way that their values can be used to quantify the level of anticoagulation.[4,6,31] PT/INR has an essentially flat dose-response. The aPTT, unlike with intravenous DTIs (e.g., argatroban), changes in a curvilinear fashion, flattening at plasma levels in the therapeutic range. While useful as a screening tool to detect the presence of the drug, it cannot be used to quantify its anticoagulant effect.

Rapid thromboelastography (rTEG) has been reported to consistently show prolonged ACT values in a trauma patient population.[32] Xu et al.[33] compared multiple anticoagulant effects on rTEG and determined that the only dramatic change seen with dabigatran was an increase in LY30 (percent lysis of clot at 30 minutes after maximum amplitude). Other rTEG parameters were shown to be minimally affected and not clinically useful. As was shown by Davis et al,[34] it may be that the trend in values determined with rTEG are of some qualitative use in determining the anticoagulant effect of dabigatran and monitoring its reversal.

Laboratory assays that could have more utility at quantifying dabigatran-induced coagulopathy are much less readily available. Thrombin clotting time (TT) is too sensitive to be used for routine assessment of anticoagulation. However, its profound response to dabigatran makes it a good assay to simply screen for the presence of the medication. If TT is normal, there is essentially no dabigatran in the serum.[3,4] Ecarin clotting time (ECT) has a linear dose-response to dabigatran at serum levels less than approximately 500 ng/mL (twice the typical peak therapeutic value).[4] Unfortunately, TT and ECT are rarely available in most clinical settings.[6,31] The Hemoclot Thrombin Inhibitor assay (Hyphen BioMed, Marseille, France) is accurate at all dabigatran serum concentrations. This makes it useful for quantitative measurement. The use of this assay in the United States is limited to research.[4,6,35]

Reversal of Anticoagulation

Dabigatran has no antidote.[1] The most common reversal strategy is the simple passage of time. In patients with normal renal function, anticoagulation effects will be nearly eliminated 28 hours to 34 hours (i.e., two half-lives) after the last dose.[3,6,29] Our group has proposed a care path for emergent surgical patients.[7] We have had success in patients with CrCl as low as 20 mL/min with delays in surgery of up to 5 days. None of our patients have required active reversal.

Protein binding of dabigatran is approximately 35%, which has allowed hemodialysis (HD) to be used successfully.[10,36] Its large volume of distribution may lead to a rebound in plasma concentration after short-cycle HD.[37,38] The patient who presents in extremis will not likely tolerate HD, and logistics in these situations makes its use difficult.[32] We have yet to encounter a situation where it has been considered. Despite this, HD remains an option in emergency situations.

Review of our previous recommendations and subsequent data indicates that prothrombin complex concentrate (PCC) alone has not been shown to be effective at reversing dabigatran-induced anticoagulation in humans. This is true for both three-factor and four-factor PCC.[39,40] Rat tail data were referenced in abstract form, but the antidote in questions was actually not PCC but rather an activated PCC (discussed later).[41] No human data indicating success of PCC are available.[42,43] Many case reports exist in the literature documenting its failure.[44–46] For these reasons, we no longer consider PCC an option for reversing dabigatran.

The use of recombinant factor VIIa (rFVIIa) remains unproven in these situations.[39] Again, only animal studies show success.[18,43,47] Several published case studies have documented failure.[45,47,48] It should remain only a rescue therapy as we previously reported.[5]

An activated form of PCC, commonly referred to as FEIBA (Factor Eight Inhibitor Bypass Activity or, more accurately, Anti-Inhibitor Coagulant Complex; Baxter Healthcare Co., Deerfield, IL), is a human plasma derivative that contains factors II, VII, IX, and X. The factor VII component is primarily in the active form, while the others are predominantly inactive. FEIBA is used to control spontaneous or perioperative bleeding in patients with hemophilia. Its use for reversing a drug effect is off-label.[18] Bleeding has been described as reduced in animal studies.[41] Human data are promising but in very small cohorts and case reports. In eight patients described as stable on dabigatran, spiking their plasma with FEIBA (0, 50, 75, and 100 units/kg) resulted in a significant increase in thrombin generation. This beneficial effect was not compared with the thrombotic complications at these varying doses.[49] There are no data that determines the risk of this complication when reversing patients emergently. Thrombotic events have been shown in hemophilia patients when given more than 200 U/kg per day.[50]

The use of tranexamic acid (TXA) in trauma has been well described.[51] Recent emergency medicine literature advocates for its use in patients with any major bleeding complicated by dabigatran.[26] Definitive data to support the use of TXA to reverse dabigatran do not yet exist.

RIVAROXABAN

Pharmacology

Rivaroxaban (Xarelto, Janssen Pharmaceuticals, Inc., Titusville, NJ) is an oral medication that reversibly binds to the active site of FXa. This competitively inhibits both free and clot-associated FXa, which, in turn, interrupts the formation of thrombin. It is rapidly absorbed and reaches its peak plasma level in 2 hours to 4 hours.[8,10,11]

Clearance is approximately 66% renal and 33% hepatic via CYP3A4. In healthy adults, the half-life of rivaroxaban is 5 hours to 9 hours. In those older than 65 year, the half-life is extended to 11 hours to 13 hours. This is likely not a purely age-induced effect but rather a result of lower CrCl.[8,10,11,52]

Plasma concentration of rivaroxaban will be elevated in patients with renal insufficiency. Kubitza et al.[52] demonstrated up to a 64% increase in the area under the curve (AUC, plasma concentration over time) with severe renal impairment. Interestingly, this corresponded to only a 1-hour increase in the average half-life of the drug (9.5 hours vs. 8.3 hours in healthy

adult). It seems that the time to clear the drug and return the blood to normal coagulation is minimally affected by renal failure.

Rivaroxaban dosing is dependent on indication and renal function. Doses of 15 mg or greater are taken with a meal. Lower doses can be taken with or without food. Stroke prevention in NVAF is accomplished with 20 mg daily with the evening meal. Patients with CrCl of 15 mL/min to 50 mL/min should take only 15 mg. Rivaroxaban should be avoided for this indication with a CrCl of less than 15 mL/min.[8]

Treatment of DVT or PE is performed with 15 mg BID for 21 days followed by 20 mg once daily for the remainder of the therapy. VTE prophylaxis after hip or knee replacement requires only 10 mg daily. This is started 6 hours to 10 hours after surgery and continued for 12 days or 35 days for knee or hip replacement, respectively. Use of rivaroxaban for VTE-associated indications is not recommended with CrCl less than 30 mL/min.[8]

Patients with moderate-to-severe hepatic dysfunction (Childs-Pugh B or C) or those taking medications that strongly inhibit CYP3A4 should avoid rivaroxaban. Medications such as the azole antifungals and human immunodeficiency virus protease inhibitors fall into this category, and their interaction with rivaroxaban may cause bleeding complications. Less significant CYP3A4 inhibitors such as the macrolide antimicrobials have a less profound effect on anticoagulation when mixed with rivaroxaban. A lesser bleeding risk is expected. Drugs that inhibit or induce the P-gp pathway should also be used with caution.[8,10,11]

Laboratory Assays

A routine laboratory assay to determine the serum concentration of rivaroxaban is not available. PT is prolonged, and it demonstrates a linear dose-response. Unfortunately, it does so in a highly variable fashion, is invalid at low plasma concentrations, and shows substantial variation between individual reagents.[53–55] The INR, a mathematical conversion accounting for variability in thromboplastin reagents used in the PT assay, cannot be similarly calibrated for FXa inhibitors.[53]

Measurements of aPTT do not correlate with rivaroxaban concentrations or anticoagulant effect. The response is nonlinear, flattens at higher concentrations, and is minimally affected at trough concentrations.[54,56,57] Rivaroxaban's effect on aPTT is more modest than on PT and is, again, highly variable, depending on reagents used in individual laboratories.[53,57]

Anti–factor Xa (aFXa) chromogenic assays are used to determine plasma concentrations and effectiveness of unfractionated and low molecular weight heparin. Recent reports indicate that they may also be quantitative for rivaroxaban if appropriately calibrated.[53,57] Molenaar et al. comment that aFXa is linear up to a plasma concentration of 400 ng/mL but imprecise beyond. Multiple variants of aFXa assays are available, although perhaps not in all settings, and show promise in accurately quantifying rivaroxaban plasma levels. Standardized calibrators and assays are being developed.[10,53,56]

The use of rTEG to measure rivaroxaban-induced anticoagulation has shown promising results. Rapid TEG consistently showed prolonged *R* and *K* times in laboratory studies. Results and discussion on the utility of rTEG vary from useful to useless. It remains to be seen if these values can be used clinically.[57]

Reversal of Anticoagulation

Rivaroxaban has no verified reversal agent.[8] It is highly protein bound (92–95%), making dialysis impractical.[58] As with dabigatran, typical antidotes (fresh frozen plasma, protamine, cryoprecipitate, vitamin K) are ineffective, and the most common strategy for eliminating the anticoagulant effect is simply allowing the drug to be cleared from the body over time.

Studies investigating active correction of rivaroxaban-induced anticoagulation have focused on PCC, FEIBA, and rFVIIa. Eerenberg et al.[40] determined four-factor PCC to be effective at reversing rivaroxaban in 12 healthy males. These subjects were given the medication and then reversed with PCC. They were not actual emergent patients and had none of the comorbid conditions typical of the anticoagulated patient. Other investigators have found PCC to be ineffective alone and favored activated PCC or FEIBA. Those authors report normalized coagulation parameters in healthy volunteers given rivaroxaban followed by FEIBA. Animal data from multiple studies are offered as support for these findings.[39] The thrombotic risk of PCC versus FEIBA are unknown, and it is important to remember that no data have been obtained in actual bleeding humans.[16]

TXA has been shown to stabilize clot lysis in vitro in blood samples treated with FXa inhibitors.[59] Small studies have reported less perioperative blood loss when giving TXA to patients on rivaroxaban for VTE postoperative prophylaxis.[60] Further clinical data are needed to consider TXA a viable option in this context.

As with dabigatran, data supporting the use of rFVIIa to reverse the effects of rivaroxaban do not exist. There is growing comfort with off-label use of rFVIIa in bleeding emergencies in multiple specialties.[61] Its use cannot be recommended for anything other than salvage situations associated with rivaroxaban.[18,39,43]

APIXABAN

Pharmacology

Apixaban (Eliquis, Bristol-Myers Squibb Co., Princeton, NJ) is another oral, direct, reversible, competitive inhibitor of FXa. It acts via a mechanism identical to rivaroxaban. It is rapidly absorbed in the gut and reaches its maximum effect in approximately 3 hours to 4 hours. Unlike rivaroxaban, its interaction with food has no effect on its absorption, and no such cautions are found in its dosing instructions.[9] Half of the dose of apixaban is passed into the feces unchanged. The remaining systemic portion of the drug is then cleared by the hepatobiliary and renal systems. Overall, of the systemically available dose, half is cleared via the kidney and half via the liver. Those with nominal hepatic and renal function will eliminate the drug in 8 hours to 15 hours.[62] Severe renal insufficiency (CrCl < 30 mL/min) prolongs the half-life to only 17.3 hours but increases the AUC by approximately 50%. Because of its similar hepatic metabolism, apixaban has the same drug interaction issues as rivaroxaban. Any alteration of CYP3A4 or P-gp will affect clearance.[9,10]

Dosing of apixaban is 5 mg BID for NVAF. This dose is cut in half (2.5 mg BID) if taken with strong inhibitors of CYP3A4 and P-gp or if two of the following criteria are met: weight of 60 kg or less, age of 80 years or older, serum

TABLE 1. Pharmacology of New Oral Anticoagulants

	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)
Mechanism	Direct thrombin (factor IIa) inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Indications and Dosing	NVAF 150 mg BID 75 mg BID if CrCl 15–30 mL/min 75 mg BID if CrCl 30–50 mL/min and taking medication inhibiting P-gp or P450 systems No dosing recommendation for CrCl < 15 mL/min	NVAF 20 mg daily 15 mg daily if CrCl < 50 mL/min VTE prophylaxis 10 mg daily VTE treatment 15 mg BID × 21 d, then 20 mg daily	NVAF 5 mg BID 2.3 mg BID if two of the following: Weight ≤ 60 kg, age ≥ 80 y, creatinine ≤ 1.5 mg/dL 2.5 mg BID if concomitant use with strong inhibitor of P450/CYP and P-gp
T_{max}	1–2 h	2–4 h	3–4 h
Clearance	Renal 80%, bile 20%	Hepatic 66%, renal 33%	Hepatic 75%, renal 25%
$T_{1/2}$	14–17 h	5–9 h (11–13 h in age > 65 y) $T_{1/2}$ minimally effected by low CrCl	8–15 h (17 h if CrCl < 30 mL/min)
Laboratory assays	PT/INR—min/flat response; not useful. aPTT—curvilinear response; qualitative only. ACT—similar to aPTT. ECT—linear response; sensitive but not useful in overdose (>470 ng/mL). TT, HTI—linear response; sensitive but not readily available. rTEG—unknown response and utility	PT—variable linear response; qualitative only. aPTT—curvilinear response; not useful. anti-Xa—must be calibrated; linear response. HepTest—similar to anti-Xa assay. rTEG—unknown response and utility	Expect similar results as those listed for rivaroxaban.
Drug interactions	Increased bleeding risk with antiplatelet drugs. P450, P-gp.	Clearance prolonged with CYP3A4 inhibitors (macrolides, ketaconazole, protease inhibitors)	Clearance prolonged with CYP3A4 inhibitors (macrolides, ketaconazole, protease inhibitors).
Notes/cautions	No dosing guidance for CrCl < 15 mL/min.	Not used for NVAF if CrCl < 15 mL/min. Not used for VTE if CrCl < 30 mL/min. Avoid if Childs-Pugh B or C Avoid with strong inhibitors of P450/CYP3A4. Higher doses (≥15 mg) taken with food.	No dose adjustment needed in mild hepatic insufficiency. Avoid with strong inhibitors of CYP3A4 and P-gp.

T_{max}, time to maximum concentration; $T_{1/2}$, half-life.

TABLE 2. Perioperative Recommendations for New Oral Anticoagulants

	Routine, Nonemergent Surgery; Minor Trauma	Major Surgery; High-Risk Bleeding Sites	Life-Threatening Hemorrhage; Major Trauma; Emergency Surgery
Dabigatran			
CrCl > 80 mL/min	Wait 24 h	Wait 48 h	Options (regardless of CrCl)
CrCl 50–80 mL/min	Wait 1–2 d	Wait 2–4 d	■ Direct hemorrhage control (surgery, embolization).
CrCl 30–50 mL/min	Wait 2–4 d	Wait 4+ d	■ Immediate HD
CrCl 15–30 mL/min	Wait 4+ d	Wait 5+ d	■ TXA, FEIBA
CrCl < 15 mL/min	Consider HD	Consider HD	■ rFVIIa as a last resort/salvage
Rivaroxaban			
CrCl > 50 mL/min	Wait 24 h	Wait 48 h	Options (regardless of CrCl)
CrCl 30–50 mL/min	Wait 48 h	Wait 2–3 d	■ Direct hemorrhage control (surgery, embolization).
CrCl 15–30 mL/min	Wait 2–3 d	Wait 3+ d	■ TXA
CrCl < 15 mL/min	Wait 3+ d	Wait 3+ d	■ PCC or FEIBA
Strong P450/P-gp inhibitor	Wait 48 h	Wait 2–3 d	■ rFVIIa as a last resort/salvage
Apixaban			
CrCl > 50 mL/min	Wait 24 hour	Wait 48 h	Options (regardless of CrCl)
CrCl 30–50 mL/min	Wait 48 h	Wait 2–3 d	■ Direct hemorrhage control (surgery, embolization).
CrCl 15–30 mL/min	Wait 2–3 d	Wait 3+ d	■ TXA
CrCl < 15 mL/min	Wait 3+ d	Wait 3+ d	■ PCC or FEIBA
Strong P450/P-gp inhibitor	Wait 48 h	Wait 2–3 d	■ rFVIIa as a last resort/salvage

TXA dosing: 1 g in 100 mL 0.9 normal saline intravenously (IV)/10 minutes, then 1 g in 100 mL 0.9 NS IV/8 hours. (First dose must be given within 3 hours of injury.)
PCC dosing: 25 U/kg to 50 U/kg IV.
FEIBA dosing: 50 U/kg to 100 U/kg IV (maximum, 200 U/kg/d).
rFVIIa dosing: 100 μg/kg, may repeat every 20 minutes.
Physicians should be familiar with these agents and local policies governing their off-label use outside clinical trials.

creatinine of 1.5 mg/dL or greater. For VTE prophylaxis, 2.5 mg BID starting 12 hours to 24 hours after surgery is recommended. This dose is taken for 12 days or 35 days for knee or hip replacement, respectively. In patients already taking 2.5 mg BID, concomitant use with strong inhibitors of CYP3A4 and P-gp should be avoided.[9]

Laboratory Assays

As is seen with the other novel oral anticoagulants, while there are elevations in the typical anticoagulation laboratory values (PT, aPTT, INR), these changes may be small and variable. They are unusable for quantifying the anticoagulant effect or serum concentration of apixaban. Data on the use of ACT, ECT, rTEG, or aFXa assays are insufficient to comment on their clinical utility.[57,63] It is likely that all FXa inhibitors will show similar laboratory results, but this has yet to be confirmed.

Reversal of Anticoagulation

Virtually, no data exist specifically assessing the reversal of apixaban.[43] Its relatively recent approval in the United States and its similarity to rivaroxaban likely have resulted in the assumption that study of specific reversal algorithms are of low yield. The manufacturer's prescribing information notes that no reversal agents are available, but if given within 2 hours of ingestion, activated charcoal has been shown to reduce the mean apixaban AUC by 50%.[9]

NEW MEDICATIONS IN DEVELOPMENT

Anticoagulants

Edoxaban is an oral direct inhibitor of FXa not yet approved in the United States. Recent reports indicate a path similar to its predecessors en route to FDA approval.[64] Also rapidly absorbed and with no food interactions, it reaches maximum plasma concentration in 1 hour to 2 hours.[65] It has a 60% bioavailability and is cleared both renally (35%) and hepatically with a half-life of 6 hours to 11 hours.[58] There is only partial activity with the CYP3A4 pathway in the liver, and this alters potential drug interaction difficulties when compared with other anticoagulants in this class. Alterations in hepatic P-gp may increase the AUC. Interactions with medications typically used for atrial fibrillation, such as amiodarone or digoxin, may be problematic.

A recent study demonstrated noninferiority to warfarin in the treatment of VTE. These patients, initially treated with heparin, received 60 mg of edoxaban daily (30 mg daily if CrCl is 30–50 mL/min or weight is <60 kg).[65] Similar dosing was used in the ENGAGE AF-TIME 48 trial with similar encouraging results.[66]

Limited information is available regarding the reversal of edoxaban. In vitro human plasma studies as well as animal models indicate that PCC, FEIBA, or rFVIIa may be viable reversal agents. These data show normalization of coagulation laboratory values and not actual bleeding cessation.[67]

Numerous new anticoagulants are mentioned in the literature. A recent review of clinical trials listed numerous drugs in development (e.g., betrixaban, darexaban, edoxaban). Predicting their FDA approval is not yet possible, but it seems clear that the current options will be expanding in the near future.[68]

Antidotes

The search for an antidote for the new oral anticoagulants is ongoing. Current results are focused on agents that bind the drug by acting as a decoy for their preferred target.[16] A rat model has shown the ability to reverse dabigatran with this mechanism.[6] Data have also been reported in 145 healthy human subjects receiving dabigatran followed by varying doses of an antibody fragment decoy.[67,69] Ongoing trials are currently recruiting patients and expected to be completed soon.[70,71]

Study data were recently reported regarding an antidote for FXa inhibitors. A modified, recombinant human FXa molecule, andexanet alfa, binds the drug and eliminates its effect. The mechanism has been shown with both rivaroxaban and apixaban.[72] Additional studies are planned with each of the new oral anticoagulants.

In determining the safety and efficacy of any reversal agent, one must keep in mind that much of this work is reported in animal studies. This is also true of work conducted to determine the optimal laboratory strategy to asses the anticoagulant effect of these new medications. Kaatz et al.[43] very wisely caution against generalizing these results to humans.

DISCUSSION

Patients who enter an emergency department with a history of anticoagulant use will almost certainly have PT, aPTT, and INR included in their initial laboratory workup in an effort to quantify their present state of anticoagulation. If the anticoagulant is one of the new oral medications, this measurement becomes problematic. If the serum concentration of any of these drugs is high enough to cause clinically significant anticoagulation, these routine laboratory values should be elevated. While they will not reach therapeutic levels used for heparin or warfarin therapy, they will likely be above normal, and this should prompt physicians to consider the patient fully anticoagulated.

More sophisticated laboratories may use TT or ECT for dabigatran. Likewise, appropriately calibrated anti-Xa assays may be used for the FXa inhibitors. These laboratory values are not always available and are therefore difficult to include in a universal best-practice recommendation. Direct measurement of drug concentration is possible, but results may not be quickly available. These assays are more appropriate to confirm compliance than assess anticoagulation effect. Local resources will drive local laboratory protocols to screen for the effect of these new anticoagulants. Regardless, present level of anticoagulation is likely best estimated by knowing the time since the last dose and the patient's ability to clear the drug (i.e., CrCl and other medication use).

Several changes have been made to our previously published dabigatran management algorithm.[7] The use of PCC has been eliminated. In its place, FEIBA can be used in emergent, life-threatening bleeding. Appropriately timed use of TXA may be effective. The use of TXA is broadening beyond the military and, in some settings, may already be part of the treatment algorithm for hemorrhagic trauma. Its use has been validated only in trauma patients requiring blood product resuscitation—many requiring massive transfusion—and must be initiated within 3 hours of injury. Delays have been associated with worse

outcome. TXA should not be used for subarachnoid hemorrhage control. Data to support its use in traumatic brain injury are equivocal. Finally, TXA in combination with activated PCC or FEIBA may increase thrombotic complications.[73]

While each of the FXa inhibitors behaves slightly different, they can be managed similarly in the emergent setting. The half-lives vary, but routine, nonemergent procedures can be performed safely 24 hours after the last dose. Several caveats must be understood for age, lower CrCl, concomitant medication use, and high-risk surgery. Moreover, the appropriate doses for these patients should be confirmed. Individualized judgment is necessary for patients whose dose does not match their present condition (e.g., acute kidney injury).

Patients older than 65 years or with CrCl less than 50 mL/min should likely delay routine surgery a second day. Procedures with high bleeding risk should likewise be delayed a second day.[8,9] There are no data to determine necessary delay with worsening renal insufficiency. These times are best estimated by using four to five half-lives (i.e., complete drug clearance) in these extreme situations. HD is not an option with FXa inhibitors.

Life-threatening bleeding and procedures that must be performed emergently require either direct hemorrhage control or rapid active pharmacologic reversal of anticoagulation. Data support four-factor PCC or FEIBA as reasonable first-line therapy. As with dabigatran, TXA may be used in trauma patients requiring blood transfusion.

The use of rFVIIa to reverse any of these four drugs is unproven. The risks of its use associated with acute reversal of a DTI or FXa inhibitor are unknown. The use of rFVIIa for active correction should be reserved to refractory situations as a last resort where its risks are obviously less than the imminent death of the patient.

CONCLUSION

The indications, safety, and dosing of apixaban, dabigatran, and rivaroxaban are well established. The use of these medications—and various similar versions yet to be FDA approved—is certain to increase and perhaps nearly eliminate the use of warfarin. The editorial critique of our group's review of dabigatran very astutely confirms the global lack of knowledge regarding the optimum method of its reversal.[7] This statement is true for all of these new drugs. The best method for dealing with them urgently remains undetermined. Trauma and acute care surgeons are becoming more knowledgeable about these medications and more comfortable working around them in emergent situations. Still, the discussions that ensue when they are encountered confirm the need for further study and the development of evidence-based guidelines. Tables 1 and 2 summarize our understanding and management plans for trauma and emergency surgery in patients treated with these new medications.

AUTHORSHIP

J.E.N. conducted the literature search and review, wrote the institutional review board request, wrote the original manuscript, and participated in editing and revision. K.L.S. conducted the literature review, performed critical review and editing of pharmacologic principles, and participated in editing and revision. M.L.M. established the guidelines for the article and study design, performed critical review and major revision of original manuscript, and edited the final manuscript.

DISCLOSURE

The authors declare no conflicts of interest.

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