Clinical Science

Antiplatelet and anticoagulation medications and the surgical patient

Brian K. Yorkgitis, D.O. a,*, Christina Ruggia-Check, Pharm.D., B.C.P.S. b, Jay E. Dujon, M.D. c

a Department of Surgery, b Division of Surgical Critical Care and Trauma, Temple University Hospital, 3401 North Broad Street, Suite 450, Philadelphia, PA 19140, USA; c Department of Pharmacy, Temple University Hospital, Philadelphia, PA, USA

KEYWORDS: Antiplatelet; Anticoagulation; Bleeding; Thrombosis; Novel oral anticoagulants

Abstract

BACKGROUND: Acute coronary syndrome affects more than 750,000 Americans per year, and antiplatelet agents are the cornerstones of treatment. Atrial fibrillation affects 2.4 million patients in the United States, and venous thromboembolism occurs in 1 to 2 per 1,000 adults per year. Anticoagulants are commonly prescribed to affected patients. Surgeons are commonly called upon to care for patients taking medications that affect normal coagulation. It is important that the surgical community has a fundamental understanding of these agents’ pharmacology, which may impact patients’ clinical course.

METHODS: A review of recent literature on pharmacologic agents that affect coagulation was performed.

RESULTS: A number of medications that alter normal coagulation were reviewed in this article including their pharmacologic properties and reversal strategies.

CONCLUSIONS: There are a variety of medications that affect a patient’s coagulation ability, including many newer agents on the market. This review provides surgeons with the knowledge needed to assist in caring for individuals receiving these drugs.

© 2014 Elsevier Inc. All rights reserved.

Medications that alter normal coagulation are commonly prescribed for a variety of conditions. These medications present a challenge for a surgeon when called on for a patient receiving these agents who sustains an illness or injury or requires an invasive procedure. There have been many advances with new drugs during recent years, particularly the novel oral anticoagulants (NOACs). The surgeon needs to be aware of these drugs along with their basic pharmacology, including half-lives and reversal strategies.

The surgeon must determine whether to continue or discontinue the drug(s) along with timing the resumption of the medication(s) when discontinued. Although many have attempted to create algorithms for this situation, it must be based on the drug’s pharmacologic profile along with an individualized care strategy for each patient. This care strategy should include risk stratification of both the patient-specific risk of thrombosis and the procedure-specific risk of bleeding. Often this strategy includes a preoperative discussion with the patient’s provider or discipline who prescribes the agent(s) and possibly anesthesiology. Some of these agents present difficulties when neuraxial anesthesia is being considered (Table 1).
**Table 1** Neuraxial anesthesia considerations

<table>
<thead>
<tr>
<th>Agent</th>
<th>Timing of discontinuation for neuraxial anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticlopidine</td>
<td>14 d before procedure</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>7 d before procedure</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitors</td>
<td>8–48 h before procedure</td>
</tr>
<tr>
<td>Warfarin subcutaneously</td>
<td>Normal INR before procedure, INR &lt;1.5 for catheter removal</td>
</tr>
<tr>
<td>UFH intravenously</td>
<td>Twice daily dose total &lt;10,000 units/d no need to discontinue</td>
</tr>
<tr>
<td>LMWH</td>
<td>Therapeutic dose 24 h, prophylactic dose 10–12 h before procedure</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Heparinize 1 h after neuraxial procedure, remove catheter 2–4 h after last dose</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Catheter removal 10–12 h after last dose, after removal dose withheld for at least 2 h</td>
</tr>
<tr>
<td>Fondaparinux catheters</td>
<td>Avoid indwelling catheters</td>
</tr>
<tr>
<td>Fondaparinux catheters</td>
<td>Catheter removal &gt;18 h after last dose, resume &gt;6 h after catheter removal, hold for &gt;24 h if traumatic puncture</td>
</tr>
<tr>
<td>Fondaparinux catheters</td>
<td>Insufficient information, suggest avoiding neuraxial procedures</td>
</tr>
</tbody>
</table>

**DTIs** = direct thrombin inhibitors; **LMWH** = low-molecular-weight heparin; **UFH** = unfractionated heparin.

**Risk assessment**

Risk assessment begins with a thorough history of each patient including the type and dose of the coagulation-affected drug, personal characteristics of the patient (age, comorbidities, weight, and concomitant medications), and length of time in which the agent(s) had been prescribed (particularly in the setting of a coronary stent, heart valve replacement, and venous thromboembolism). Current appropriate laboratory values are important to obtain. When using anticoagulant medication for prophylaxis of venous thromboembolism (VTE), it is important to review the individual’s risk factors for an event. Additionally, the risk of hemorrhage from the proposed procedure or the disease entity the patient may face needs to be taken into consideration before continuing, discontinuing, or resuming medications that alter coagulation.2–6

**Antiplatelet Agents**

Aspirin is one of the oldest agents that affect the coagulation cascade. The pharmacologic effect on platelets is through irreversible acetylation and the inhibition of platelet cyclooxygenase-1, a critical enzyme involved in the production of thromboxane A2. The release of thromboxane A2 stimulates the recruitment and activation of further platelets and increases platelet aggregation.7

Ticlopidine (Ticlid; Roche, San Francisco, CA) and clopidogrel (Plavix; Bristol-Meyers Squibb, New York, NY) belong to a class of thienopyridines, drugs that block P2Y12, a receptor on platelets for adenosine diphosphate (ADP). These drugs irreversibly inhibit ADP-induced platelet aggregation.7 Because clopidogrel is a prodrug that must be metabolized by hepatic conversion, its effectiveness on platelet inhibition correlates with the metabolic activity of several cytochrome P450 enzymes. Thus, there is a variable degree of antiplatelet activity based on the individual patient. This variability launched the search for more reliable drugs.8

Two newer ADP receptor antagonists used in acute coronary syndrome have been developed. Prasugrel (Effient; Eli Lilly, Indianapolis, IN), an irreversible inhibitor, and ticagrelor (Brilinta; AstraZeneca, Wilmington, DE), a reversible inhibitor, have a faster onset of action and stronger, more reliable antiplatelet activity than clopidogrel. They are more potent P2Y12 receptor inhibitors; however, with their benefits of increased potency come risks.8

When compared with clopidogrel, prasugrel had increased bleeding events including vascular access site and coronary artery bypass graft (CABG)-related bleeding. CABG bleeding complications were 4-fold higher than those treated with clopidogrel. Also, major bleeding events were higher (ie, 2.4% compared with 1.8% in patients receiving clopidogrel). The bleeding risk was higher in patients greater than 75 years and less than 60 kg. There was a reduction in cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke in patients receiving prasugrel.9 The dose for prasugrel is 10 mg/d and 5 mg/d if patients are less than 60 kg. The loading dose, if indicated, is 60 mg.10

Ticagrelor showed a decreased rate of myocardial infarction, stroke, and cardiovascular death. There was not a dramatic increase in all major bleeding events in the ticagrelor patients when compared with clopidogrel (ie, 11.6% vs 11.2%, respectively). However, there was a statistical increase in intracranial bleeding and non–CABG-related bleeding. There is no need for dose reduction in renally impaired patients.11 The dose for ticagrelor is 90 mg/d with a loading dose of 180 mg. It is not recommended for patients with severe hepatic impairment, and it must be used with caution in patients with moderate hepatic impairment.12

Both agents show an overall increased risk of bleeding compared with clopidogrel, and the bleeding risk increases with the duration of therapy. In the pivotal studies of these drugs, one of the most common etiologies of bleeding was gastrointestinal. Thus, the liberal use of gastrointestinal acid suppression should be considered.8

Dipyridamole (Persantine; Boehringer-Ingelheim, Ridgefield, CT) is a weak antiplatelet agent. It inhibits
phosphodiesterase, which impedes the breakdown of cyclic adenosine monophosphate, causing a reduction of intracellular calcium and inhibiting platelet activation.7 Cilostazol (Pletal; Otuska America Pharmaceutical, Rockville, MD) causes reversible inhibition of platelet aggregation via the inhibition of phosphodiesterase III. It is recommended to discontinue therapy 4 days before surgery.13

The platelet effect of these drugs continues through the life of the platelet (5 to 9 days). The current drug label recommendations are to stop clopidogrel, ticagrelor, and prasugrel 5 to 7 days before surgery. There is no specific reversal agent for the antiplatelet effect of these drugs. In theory, their effect can be overcome by the transfusion of nonaffected platelets. A bleeding time may be used to monitor the effect of these agents on platelet function.7,14

**Glycoprotein IIb/IIIa receptor antagonists**

The glycoprotein IIb/IIIa receptor is pivotal in platelet aggregation. Cross-linking of platelets occurs through the binding of fibrinogen to 2 of these receptors on 2 separate platelets. Agents in this class commonly used in revascularization procedures include abciximab (ReoPro; Eli Lilly, Indianapolis, IN), epifibatide (Integrilin; Millennium Pharmaceuticals, Cambridge, MA); and tirofiban (Aggrastat; Medice Inc, Somerset, NJ). Reversing the agent’s effect can be achieved by discontinuation and allowing time for clearance. Abciximab has an approximate 12-hour pharmacologic effective half-life. The other agents are much shorter (ie, 2 to 4 hours). The transfusion of unaffected platelets can overcome the antiplatelet effect of a glycoprotein IIb/IIIa receptor antagonist.14,15

**Vitamin K Antagonist**

Warfarin (Coumadin; Bristol-Meyers Squibb, New York, NY) is the oldest of the oral anticoagulants. It produces its effect through interference with the cyclic interconversion of vitamin K to its 2,3 epoxide. This affects the carboxylation of glutamate residues in vitamin K-dependent proteins, including factors II, VII, IX, and X. Thus, these factors have reduced procoagulant properties. In addition, vitamin K antagonists inhibit carboxylation of the anticoagulant proteins C and S, reducing their anticoagulant effect. The prothrombin time and international normalized ratio (INR) are used to monitor its effect.16

There exists a range of desirable INR values for specific conditions requiring anticoagulation. Warfarin half-life is 36 to 42 hours. Withholding administration can take 3 to 5 days for complete reversal. Coagulopathy can be corrected with the administration of vitamin K. Intravenous (IV) administration is more rapid, decreasing the INR within 2 hours and complete normalization within 12 to 16 hours. There exists the rare event of anaphylactic reaction with IV administration because of polysorbate 80, an excipient carrier that acts as an emulsifier contained in the preparation. Oral administration can take up to 24 hours to achieve a normal INR.17

Fresh frozen plasma (FFP) contains vitamin K–dependent coagulation factors that can be used. Varying amounts of coagulation factors in FFP may result in a partial or insufficient reversal of INR.18

Recombinant factor VIIa has been used to correct alterations of vitamin K coagulopathy. Prothrombin complex concentrate (PCC) contains high doses of coagulation factors with varying amounts of each factor, which is product specific. In the United States, only 3-factor PCC (Bebulin VH; Baxter, Deerfield, IL and Profilnine SD; Grifols, Los Angeles, CA) containing factors II, IX, and X is available. An activated PCC product known as FEIBA NF (Baxter, Deerfield, IL) contains mainly nonactivated factors II, IX, and X along with mainly activated factor VII. These agents do carry the risk of thrombotic events, including an increased risk for cerebrovascular thrombosis.18,19

**Heparin-based Drugs**

Unfractionated heparin acts through the activation of antithrombin III. It induces a conformational change that accelerates the rate at which antithrombin III inhibits factor Xa. Additionally, it inactivates several coagulation enzymes; thrombin factor (IIa); and factors IXa, Xa, Xla, and XIIa. The anticoagulant effect has a half-life that is dose dependent in the order of 30 to 150 minutes. The effect can be measured by activated partial thromboplastin time (aPTT) or activated clotting time. Protamine derived from fish sperm is a cationic protein that binds to the anionic heparin and blocks heparin’s effect.20

Low–molecular-weight heparins (LMWH) include enoxaparin (Lovenox; Sanofi-Aventis, Bridgewater, NJ), dalteparin (Fragmin; Eïsai Inc, Woodcliff, NJ), and tinzaparin (Innohep; Celgene, Summit, NJ). They are derived from heparin through depolymerization, yielding a molecular weight approximately one third of the original molecule. These agents catalyze the inactivation of factor Xa through antithrombin III. Laboratory monitoring is usually not necessary with these drugs. When needed, anti-Xa testing can be done by select laboratories via a chromogenic anti-Xa assay. The onset of activity peaks around 3 to 5 hours after subcutaneous injection. The half-life of LMWH is around 6 hours and is not dose dependent. LMWHs are excreted primarily through the renal route. Thus, renal insufficiency prolongs their effect. Reversal of the anti-Xa activity of LMWH can be incompletely (60%) achieved with protamine.20 Because of their long half-lives, repeated dosing may be needed.21 Heparin-induced thrombocytopenia (HIT) can occur with either unfractionated heparin or LMWH.20

**Factor Xa Inhibitors**

The class of NOAC includes rivaroxaban (Xarelto; Janssen Pharmaceuticals, Titusville, NJ) and apixaban
(Eliquis; Bristol-Meyers Squibb, New York, NY). They are synthetic, direct factor Xa inhibitors that act through reversible binding to the active site of both free and bound molecules. They do not require antithrombin III as a cofactor. Both agents are approved for use in nonvalvular atrial fibrillation (NVAF).24,25 Rivaroxaban has additional approval for VTE prophylaxis in patients undergoing hip or knee arthroplasty and for the treatment of VTE.22

The ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial provided clinical data that proved non-inferiority in the prevention of stroke or systemic emboli comparing rivaroxaban with warfarin.24 The ARISTOTLE (Apixaban for Reduction In Stroke and Other Thromboembolic Events) trial provided similar outcomes for apixaban.25 In both trials, patients receiving these factor Xa inhibitors had a statistically significant reduced incidence of fatal bleeding and intracranial bleeding.24,25 The REgulation of Coagulation in ORThopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism (RECORD) studies compared enoxaparin with rivaroxaban for hip and knee arthroplasty. Rivaroxaban showed improved VTE prevention with a similar rate of major bleeding.26,27

The oral administration of rivaroxaban results in predictable and dose-proportional anticoagulation without the need for dose adjustment or routine coagulation monitoring.28 Although it prolongs both prothrombin time (with greater sensitivity) and aPTT, the prolongation of clotting time varies depending on the reagent used; the reactivity of rivaroxaban in clotting assays are influenced by the composition of the reagents. Therefore, these tests are not useful for measuring its pharmacodynamic effects.29 Its onset is about 2 to 4 hours, and its half-life ranges between 7 and 11 hours. It has a dual elimination pathway, renal and hepatic. Dosage should be adjusted for impairments in these systems.28 The dose when used for NVAF is 20 mg in patients with a creatinine clearance (CrCl) greater than 50 mL/min and 15 mg for patients with a CrCl of 15 to 50 mL/min daily. For VTE prophylaxis, 10 mg is taken daily. It should be avoided in patients with a CrCl less than 15 mL/min or moderate to severe (Childs-Pugh B or C) hepatic insufficiency or associated coagulopathy.22

The dose for VTE treatment is 15 mg twice per day for 21 days followed by 20 mg/d for the remainder of treatment. It is not recommended for VTE treatment in patients with a CrCl less than 30 mL/min, and it should be used with caution if a patient’s CrCl is between 30 and 50 mL/min.22

Apixaban is rapidly absorbed with a peak plasma level within 1 to 3 hours and a 10- to 14-hour half-life.25 A dose of 5 mg is given twice per day for NVAF. It is reduced to 2.5 mg twice per day if the patient has 2 or more of the following: age of 80 years or older, weight of 60 kg or less, or serum creatinine of 1.5 mg/dL or greater. The drug should be avoided in patients with a CrCl less than 15 mL/min or on dialysis because it is partially renally excreted (25%).23

Recently, the Food and Drug Administration required the manufacturers to inform prescribers about the increased risk of stroke when apixaban or rivaroxaban is discontinued in NVAF patients without adequate alternative anticoagulation. They recommend if the drug is discontinued for reasons other than pathologic bleeding that an alternative anticoagulant be administered. This is important if the surgeon is planning a procedure that requires cessation.22,23

Fondaparinux (Arixtra) is a synthetic indirect (through antithrombin III) factor Xa inhibitor used for VTE prophylaxis and treatment. It is given subcutaneously and reaches its peak steady state within 3 hours with a half-life around 21 hours. It is excreted renally. Rarely has it been found as a causative agent in HIT with thrombosis. The drug should be given 6 hours after an operation because of the risk of bleeding.14,30

Because of the lack of reliable and readily available monitoring of these agents’ anticoagulation effect, they present challenges to the surgeon when faced with bleeding. FFP has not been shown to be an effective reversal agent. No specific reversal agent exists for the anticoagulant effect of the factor Xa inhibitors. Several procoagulant agents have been used in severe/life-threatening bleeding, but the literature is lacking in a large body of evidenced-based recommendations. These include PCC and recombinant factor VIIa.24,31

The clinician must weigh the risk and benefits of administering these agents because they are not currently approved for the specific reversal of these medications and carry a risk of thrombosis when given. Because of the short half-lives of these agents, observation and supportive care may be all that are needed. An approach to bleeding (Fig. 1) developed through limited clinical data may assist the surgeon when faced with a hemorrhagic event in a patient receiving these agents. The practitioner must use, as indicated, the standard treatments such as intensive monitoring, aggressive resuscitation, mechanical/surgical/procedural bleeding control, mechanical ventilation, and vasopressor support that they would in any bleeding patient.19,21,31

Direct Thrombin Inhibitors

Direct thrombin inhibitors (DTIs) work through the direct inhibition of thrombin, both free and clot bound. They act very predictably because of their direct action. They require no binding to plasma proteins and cofactors such as antithrombin III and heparin cofactor II and are not neutralized by platelet factor 4. Additionally, these drugs do not induce immune-mediated thrombocytopenia. Through DTI’s mechanism, the clinician must be observant for signs of bleeding because thrombin is paramount to the coagulation cascade. Most of the parenterally administered drugs have an increased risk of bleeding compared with heparin.32,33

Parenteral agents

Argatroban is a DTI that reversibly binds to the active thrombin site. It is administered via a continuous IV
infusion and monitored by aPTT with a goal of 1.5 to 3 times the patient’s baseline aPTT. The drug requires dose adjustments in patients with hepatic impairment, severe anasarca, heart failure, post-cardiac surgery, or critical illness. The clinician must use caution when monitoring warfarin therapy with INR because argatroban can falsely elevate the INR. Thus, the patient may not be adequately anticoagulated based off an INR drawn while receiving argatroban and warfarin concomitantly.

Bivalirudin (Angiomax) is a reversible DTI that binds to both circulating and clot-bound thrombin. The drug is administered via continuous IV infusion and predominantly eliminated by blood proteases with a minor (20%) degree of renal clearance. Monitoring of this drug is done through aPTT with a goal of 1.5 to 2.5 times the patient’s baseline aPTT. In patients receiving this drug for percutaneous coronary procedures with or without HIT and cardiac surgery, the activated clotting time is commonly used. It causes an intermediate increase in INR compared with argatroban. Anticoagulant effects reverse rapidly with a return to baseline within 1 to 2 hours after stopping the infusion.

Oral agents

Dabigatran (Pradaxa), an oral DTI and NOAC, works through direct, competitive inhibition of thrombin. In the

<table>
<thead>
<tr>
<th>Drug</th>
<th>Affect</th>
<th>Onset</th>
<th>Half-life</th>
<th>Reversal agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasugrel</td>
<td>Antiplatelet</td>
<td>30 min</td>
<td>2–7 h</td>
<td>Transfusion of nonaffected platelets</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>Antiplatelet</td>
<td>2–4 h</td>
<td>7–8.5 h</td>
<td>Transfusion of nonaffected platelets</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Factor Xa inhibitor</td>
<td>2–4 h</td>
<td>12–14 h</td>
<td>No specific agent</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Factor Xa inhibitor</td>
<td>1–3 h</td>
<td>10–14 h</td>
<td>No specific agent</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>DTI</td>
<td>2–3 h</td>
<td>12–14 h</td>
<td>No specific agent</td>
</tr>
</tbody>
</table>

DTI = direct thrombin inhibitor.
United States, it is indicated for the prevention of embolism in NVAF, and in Canada it has additional indications for VTE prophylaxis in hip or knee arthroplasty.\(^3\)

The drug was compared with warfarin in a noninferiority trial for embolic events in patients with NVAF. The results yielded a 1.11% versus a 1.69% per year embolic event rate in patients taking dabigatran 150 mg twice a day compared with warfarin, respectively. In comparison to warfarin, dabigatran at 150 mg twice daily had lower rates of serious bleeding (3.36% vs 3.11%). Most notable was a rate of hemorrhagic stroke of .30% per year in the warfarin group compared with .10% per year in the dabigatran group. The rate of gastrointestinal hemorrhage was higher in the dabigatran group.\(^3\)

The drug possesses a predictable pharmacokinetic profile that does not require routine monitoring using blood tests as warfarin does. It reaches its peak anticoagulant effect 2 to 3 hours after ingestion, and its half-life is between 12 to 14 hours with normal renal function.\(^3\) The drug is metabolized by the liver cytochrome P450 system and excreted through the kidneys.\(^3\) Thus, the dosage of dabigatran is 150 mg twice daily in patients with a CrCl greater than 30 mL/min and 75 mg twice daily with a CrCl of 15 to 30 mL/min; there is no dosing recommendation for patients on dialysis or with a CrCl less than 15 mL/min.\(^3\)

When discontinuation of dabigatran is needed, it should be discontinued 1 to 2 days preoperatively in patients with a CrCl greater than 50 mL/min. Patients with a CrCl less than 50 mL/min should discontinue the drug 3 to 5 days preoperatively. If the patient requires conversion to a parenteral anticoagulant, it is ideal to wait 12 hours (CrCl >30 mL/min) or 24 hours with impaired renal function after the last dose of dabigatran before starting the parenteral agent.\(^3\) No specific reversal agent exists for dabigatran, but the algorithm in Fig. 1 may assist the surgeon with a bleeding patient along with standard supportive measures.\(^21,31,35\) There is a monoclonal antibody against dabigatran in development.\(^3\)

Conclusions

It is not an uncommon situation that surgeons are called to evaluate illnesses and injury that may require invasive intervention or bleeding complications that may arise in patients who are receiving pharmacologic agents that affect coagulation. A review of the newer agents that affect coagulation can be found in Table 2. NOACs present a challenge to the surgeon because of their lack of a specific reversal agent. Often, the surgeon needs to plan for an invasive procedure(s) that carries a risk for bleeding. The individual patient, risk of bleeding and conversely the risk of thrombosis, proposed procedure needed, the drug’s affect on the coagulation system, and indication(s) for the drug need to be considered before discontinuing or restarting the agent(s). It is important not to hesitate to use a multidisciplinary approach in the care of these complicated patients for optimal outcomes. This review provides the surgical community a base of knowledge regarding some of the most common agents patients may be receiving in the United States.

References


