Sticky business: Overview of anticoagulants and antiplatelets

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While a large number of patients receive anticoagulants to prevent thromboembolic events, maintenance anticoagulation therapy is prescribed for a variety of medical diagnoses and conditions, including atrial fibrillation, history of myocardial infarction, mechanical heart valves, myocardial stents, history of thromboembolism, and stroke prevention.

Coagulation function

The major function of the coagulation system is to achieve and maintain hemostasis after an injury. Hemostasis is the stoppage of blood flow and is divided into five stages: vessel spasm, platelet plug formation, blood coagulation, clot retraction, and clot dissolution or lysis. (See Understanding the five stages of hemostasis.)

Anticoagulants

Anticoagulants oppose coagulation by interfering with the coagulation cascade at various points, depending on the drug. Anticoagulants do not lyse clots that already exist, but they can prevent thrombus formation and prevent or slow the extension of an existing clot. Anticoagulants affect the clotting mechanism by targeting specific clotting factors and inhibiting the coagulation cascade.

Drugs inhibiting the coagulation cascade

Warfarin is the most commonly prescribed oral anticoagulant on the market. Additionally, three new oral drugs have recently received FDA approval: dabigatran, rivaroxaban, and apixaban.

Warfarin. Warfarin (Coumadin) is classified as a vitamin K antagonist and acts by inhibiting the synthesis of vitamin K-dependent coagulation factors. With a peak of 72 to 96 hours, warfarin cannot be used in emergencies. After oral administration, warfarin is rapidly absorbed in the gastrointestinal (GI) tract, and its anticoagulant effects persist for 2 to 5 days due to its long half-life after discontinuation. Warfarin has significant disadvantages, including interactions with numerous drugs and foods, a narrow therapeutic index, variable dose response between patients, and lab control that is difficult to standardize. As a result, a baseline prothrombin time and complete blood cell count should be obtained before beginning warfarin, and patients must be closely monitored with international normalized ratio (INR) testing to ensure safe and therapeutic warfarin dosing. According to the American College of Chest Physicians (ACCP) 2012 guidelines, the optimal therapeutic INR range depends on the condition being treated; however, the recommended therapeutic INR range is 2.0 to 3.0 for most patients.

Warfarin interacts with several drugs that will increase the risk of bleeding or decrease the anticoagulant effect. Foods that contain high levels of vitamin K, such as certain leafy green vegetables, can reduce the anticoagulant effects of this medication. Because of these effects, patients taking warfarin should be instructed to maintain a consistent intake of green leafy vegetables from week to week to balance the vitamin K effects of the vegetables and the anticoagulant effects of warfarin. In addition, patients who take warfarin should receive dietary nutritional counseling and should be instructed to avoid over-the-counter drugs and herbal products that may interact with warfarin by increasing the risk of bleeding or decreasing the therapeutic effect of warfarin. Vitamin K is the reversal agent for warfarin. The ACCP does not recommend the routine use of vitamin K for patients taking warfarin with INRs between 4.5 and 10 and no evidence of bleeding. Oral vitamin K should be administered for patients taking warfarin with INRs greater than 10 and no evidence of bleeding. Vitamin K should be given by slow I.V. administration along with four-factor prothrombin complex concentrate in an emergency.
Understanding the five stages of hemostasis

Hemostasis is a process that involves the interaction of enzymes, protein cofactors, and calcium ions that circulate in the blood or are released from platelets and cells in the vessel wall.

1. **Vessel spasm**
Injury to a blood vessel causes vascular smooth muscle in the vessel wall to contract, reducing blood flow.

2. **Formation of the platelet plug**
Seconds after vessel injury, von Willebrand factor, released from the endothelium, binds to platelet receptors, causing platelets to adhere to the exposed collagen fibers. Platelets are activated and release adenosine diphosphate (ADP) and thromboxane A₂ (TXA₂), which attracts more platelets, causing platelet aggregation.

3. **Blood coagulation**
The two coagulation pathways—intrinsic and extrinsic—lead to the activation of factor X, the conversion of prothrombin to thrombin, and conversion of fibrinogen to the insoluble fibrin threads that hold the clot together.

4. **Clot retraction**
Within a few minutes after a clot forms, the fibrin strands are pulled toward the platelets, squeezing serum from the clot and causing it to shrink.

5. **Clot dissolution or lysis**
Clot lysis begins shortly after clot formation with the activation of plasminogen, which converts to plasmin, which digests the fibrin strands and dissolves the clot.

situation for patients with major bleeding. Patients should be monitored during treatment for cardiac dysrhythmias or a type I hypersensitivity reaction.\textsuperscript{2,6}

**Dabigatran.** Dabigatran (Pradaxa) is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, it is also used to treat deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients who were previously treated with parenteral anticoagulants and to reduce the risk of DVT and PE recurrence in previously treated patients.\textsuperscript{7} Dabigatran is administered orally twice a day and does not require routine coagulation monitoring; however, it should be discontinued if active bleeding is evident, and it is not recommended for patients with severe kidney impairment.\textsuperscript{7}

**Rivaroxaban.** Rivaroxaban (Xarelto) is a factor Xa inhibitor administered orally once daily with a rapid onset of action and does not require routine coagulation monitoring.\textsuperscript{8} However, rivaroxaban should be discontinued if active bleeding is evident, and it is not recommended for patients with severe kidney impairment. Rivaroxaban has several indications, including prophylaxis of DVT and PE in orthopedic patients following hip or knee replacement surgery.\textsuperscript{6}

**Apixaban.** Apixaban (Eliquis) is a factor Xa inhibitor administered with maximal plasma concentrations achieved 3 hours after oral administration.\textsuperscript{8} Administered twice daily, it does not require routine coagulation monitoring; however, the drug should be discontinued if active bleeding is evident. Apixaban has several indications, including prophylaxis of DVT and PE in orthopedic patients following hip or knee replacement surgery.\textsuperscript{6}

**Unfractionated heparin.** Unfractionated heparin (UFH) is a rapid-acting anticoagulant derived from the intestines of pigs and lungs of cattle. UFH is administered either I.V. or subcutaneously. UFH acts by binding to antithrombin, an inhibitor of the coagulation cascade preventing growth of the formed thrombus, thus, allowing the patient’s own fibrinolytic system to begin breaking down the clot; UFH also binds to platelets, inhibiting platelet aggregation.\textsuperscript{9} The I.V. route is used when rapid anticoagulation is necessary with a weight-based bolus followed by continuous I.V. infusion. When administered via the I.V. route, UFH’s onset of action is immediate. When administered subcutaneously, onset of action for UFH is approximately 20 to 60 minutes.\textsuperscript{10} On average, the half-life of UFH is 1 to 2 hours.\textsuperscript{10}

Before beginning therapy, the patient’s partial thromboplastin time should be evaluated, as therapeutic range is 1.5 to 2.5 times the mean control value of 20 to 30 seconds.\textsuperscript{10} Contraindications of UFH include hypersensitivity to porcine or bovine and active bleeding. Protamine sulfate may be administered in the event of severe bleeding or if reversal of the effects of UFH is desired and should be administered I.V. slowly to avoid causing bradycardia and hypotension.\textsuperscript{10}

**Low-molecular-weight heparin (LMWH).** Derived from UFH, LMWHs are administered subcutaneously. Examples include enoxaparin (Lovenox), dalteparin (Fragmin), and tinzaparin (Innohep). Advantages of LMWH over UFH include a longer half-life, allowing once-a-day or twice daily administration, and a more predictable anticoagulation response, which for most patients, makes routine coagulation monitoring unnecessary.\textsuperscript{2} It is important to note that protamine sulfate only partially neutralizes the effects, and therefore, should not be considered an antidote in the event of an enoxaparin overdose or uncontrolled bleeding due to enoxaparin.\textsuperscript{5}

**Fondaparinux.** Fondaparinux (Arixtra) is a factor Xa inhibitor. Fondaparinux is a synthetic pentasaccharide and achieves its effect by factor Xa inhibition.\textsuperscript{9} Used for the prevention of DVT and also for treatment of acute DVT and PE along with warfarin therapy. Fondaparinux should be discontinued if active bleeding is evident, and it is not recommended for patients with severe kidney impairment. It is given subcutaneously once a day and has no direct effect on thrombin, as does UFH and LMWH.\textsuperscript{9}

**Bridging**

Many patients undergoing surgery are on maintenance anticoagulation therapy before surgery and may require anticoagulation because of an acute situation. The term bridging is often used when patients need treatment with enoxaparin or heparin pending adequate anticoagulation with warfarin. The term can also be used when a patient needs to be “bridged” when he or she is taking warfarin and needs surgery.\textsuperscript{11} Current guidelines recommend discontinuation of warfarin 5 days before surgery, as this regimen tends to allow for normal or near-normal hemostasis.\textsuperscript{12} Resuming warfarin after surgery is feasible and safe for most patients on the evening of or the morning after surgery. This practice is supported by several prospective cohort studies, totaling more than 2,500 patients who had perioperative management (typically with heparin bridging), in which warfarin was
resumed within 24 hours of surgery.12 The need for heparin bridging during warfarin interruption is driven largely by patient’s estimated risk for perioperative thromboembolism, which, in turn, is determined by the indication for warfarin and, to a lesser extent, by the type of surgery.11

**Drugs inhibiting platelet activity**

**Aspirin and clopidogrel.** Aspirin and clopidogrel are two commonly used antplatelet drugs. Antplatelet drugs affect the action of platelets. Aspirin has long been utilized as an antplatelet agent because of its effect of inhibiting platelet cyclooxygenase by irreversible acetylation, thereby preventing the formation of thromboxane A$_2$, which is a powerful stimulant of platelet aggregation.13 Clopidogrel, a thienopyridine, acts by inhibiting adenosine receptors, which inhibits the early step of platelet activation. Clopidogrel has been found to be more effective than aspirin in the management of all ischemic events.13 The normal life span of a platelet is short, ranging from 7 to 10 days. Because clopidogrel irreversibly affects platelets, current guidelines recommend discontinuation of this medication at least 7 days before surgery.13

**Perioperative implications**

Patients who receive anticoagulants or antplatelet drugs carry certain perioperative implications. A thorough medication history for all preoperative patients is a priority. Depending upon the reason for the anticoagulant or antplatelet, the surgeon may decrease or discontinue the medication prior to surgery. With this knowledge, it is important to verify this with the patient in the pre-operative setting. The reasons behind the continuation may be the delicate balance between reducing the risk of thromboembolism and the prevention of major bleeding during the operative procedure. The continuation, tapering, or discontinuation of the drug is individualized to the patient and their disease processes and should be verified. Restarting is also specific to the patient, disease processes, and the surgical procedure and will vary depending upon these factors.

**Complications**

Bleeding is the number one complication, with GI bleed being the main source. Additional risks may include hematomas resulting from epidural and spinal procedures. It is important to be alert for back or abdominal pain, black, tarry stools, bruising, nosebleeds, and petechiae on the skin, blood in the urine, and bleeding gums. Patient teaching is important and should include the use of an electric shaver, soft tooth brush, taking medication as directed, regular lab monitoring if indicated, diet modifications, and the importance of notifying the healthcare provider if they experience any of the aforementioned signs indicating a complication.

**Stick to it!**

Several resources, such as those from The Joint Commission, the National Patient Safety Agency, the Institute for Safe Medication Practices, and the Institute for Healthcare Improvement (www.ismp.org), among others, can be used to learn more about the uses and some of the risks of these medications in the OR and other perioperative settings. The use of anticoagulants and antplatelets can be life saving for a patient who requires them, and perioperative clinicians must be familiar with them when monitoring for adverse reactions.11

**REFERENCES**


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