

Anticoagulants: Newer Ones, Mechanisms, and Perioperative Updates

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The ongoing research and development of new anticoagulant/antiplatelet drugs deserves special attention in the evaluation and management of patients presenting for surgery. As part of the development of the ideal anticoagulant, the newer drugs aim to provide safe, effective, and predictable anticoagulant activity with ease of use (ie, oral administration or minimal number of daily injections) and no need for monitoring.¹ Anesthesiologists must be familiar with the newly developed anticoagulants because their use in the perioperative setting will likely increase. Mechanisms of action of these newer anticoagulants warrant consideration as do the risks and benefits of discontinuation or reversal of the drugs before surgery.² Of equal importance are the recommendations by the American Society of Regional Anesthesia and Pain Medicine (ASRA) pertaining to regional anesthesia in patients receiving these new anticoagulants.

The use of herbal medications and certain vitamin supplements has dramatically increased in recent years. Some of these alternative medicines enhance the effects of anticoagulant drugs. Therefore, it is important to elicit a history of use to avoid exaggerated effects, specifically bleeding.³

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NEW ANTICOAGULANTS

The development of newer anticoagulants and their emergence into clinical practice is a result of the demand for more efficacious anticoagulation therapy with a better safety profile than the older anticoagulants, such as heparin and warfarin.⁴ Anticoagulants are the agents of choice for prevention and treatment of venous thromboembolism (VTE). Venous thrombi develop under low shear conditions and are made of fibrin and trapped red cells. These thrombi contain few platelets.^{4,5} Anticoagulants inhibit specific targets in the coagulation pathway (**Fig. 1**). This article focuses on the newer anticoagulants and their mechanisms of action.

Factor Xa Inhibitors

New factor Xa inhibitors block factor Xa either directly or indirectly (**Table 1**). Fondaparinux (Arixtra), an indirect factor Xa inhibitor, is a synthetic pentasaccharide that selectively binds to antithrombin III, potentiating factor Xa neutralization and inhibiting thrombin formation. Fondaparinux, a parenteral agent, is approved for prevention of VTE in high-risk orthopedic surgeries and as a substitute for heparin or low-molecular-weight heparin for the initial treatment of VTE.^{2,5} The plasma half-life of fondaparinux is 21 hours; therefore, it is dosed once a day with the first dose given 6 hours postoperatively.⁶ Compared with unfractionated heparin, fondaparinux has excellent bioavailability and should not cause heparin-induced thrombocytopenia (HIT).

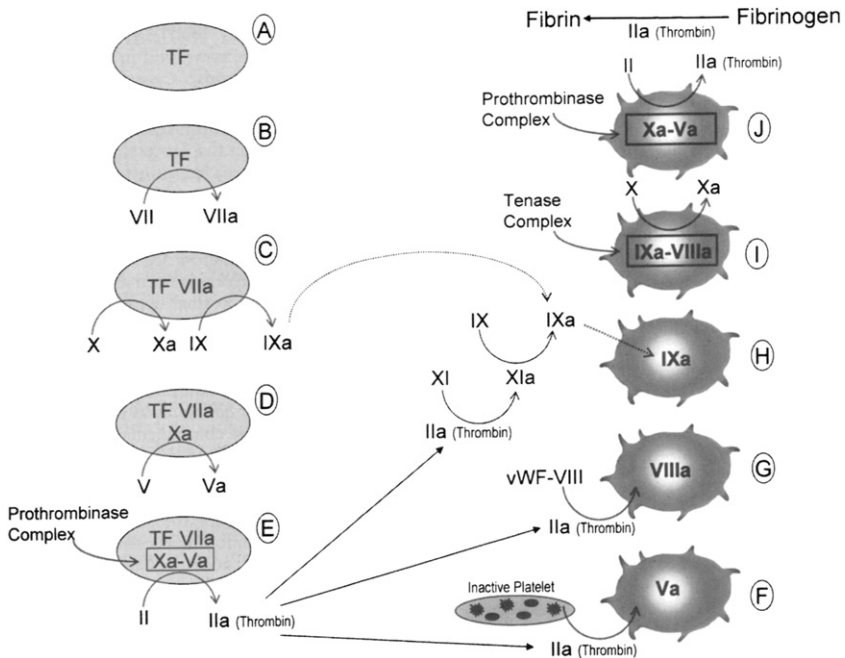


Fig. 1. The coagulation mechanism. A through F represent the complex mechanisms of interaction amongst the factors in the coagulation pathway. TF, membrane-bound tissue factor on an extravascular cell surface; vWF, von Willebrand factor. (From Drummond JC, Petrovitch CT. Hemotherapy and hemostasis. In: Barash PG, Cullen BF, Stoelting RK, editors. Clinical anesthesia. 5th edition. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 223; with permission.)

Table 1
Summary of factor Xa inhibitors

	Fondaparinux	Rivaroxaban	Apixaban
Action	Inhibits fXa	Inhibits fXa	Inhibits fXa
Route of administration	Subcutaneous	Oral	Oral
Indication	VTE/PE8 prophylaxis	VTE/PE prophylaxis	VTE/PE prophylaxis
Half-life	17–21 hours	5–10 hours	10–14 hours
Elimination	Renal	Renal	Renal
Monitoring	Anti-Xa assay	Anti-Xa assay	Anti-Xa assay

Abbreviation: PE, pulmonary embolism.

A specific anti-Xa assay is needed to measure its anticoagulant effects. Major bleeding complications are less likely to be associated with fondaparinux compared with heparin. Anti-Xa activity of antithrombin from fondaparinux, however, is not reversed with protamine sulfate.⁷ Recombinant factor VIIa can partially reverse the anticoagulant effect of fondaparinux.⁸

A Food and Drug Administration (FDA) black box warning is similar to that of the low-molecular-weight heparin warning of the risk of epidural/spinal hematoma in patients who are or will be anticoagulated with fondaparinux. The ARSA evidence-based guidelines state the actual risk of spinal hematoma with fondaparinux is unknown. Until further clinical experience is available, neuraxial techniques in patients who receive fondaparinux prophylaxis should occur under the strict parameters used in clinical trials (single-needle pass, atraumatic needle placement, and avoidance of indwelling neuraxial catheters). Other forms of prophylaxis may be more feasible.⁶ In patients with severe renal insufficiency, elimination of fondaparinux is prolonged and the risk of bleeding is increased. It is, therefore, contraindicated in this setting.^{5,9}

Direct factor Xa inhibitors bind directly to the active site of Xa and block its interaction with substrates, thereby inhibiting both free and platelet-bound (bound in the prothrombinase complex) factor Xa.⁵ Rivaroxaban (Xarelto) is the first available oral direct factor Xa inhibitor. The drug has completed phase III clinical trials and is reported to have a favorable benefit-to-risk ratio for thromboprophylaxis after elective hip and knee arthroplasty. In patients undergoing major orthopedic surgery, rivaroxaban demonstrated comparable safety and superior efficacy compared with enoxaparin.^{10,11} Rivaroxaban inhibits factor Xa in a concentration-dependant manner and binds rapidly and reversibly.¹² Rivaroxaban's oral bioavailability is 80%; half-life is approximately 9 hours and is cleared by the kidneys and gut.⁵ Maximum inhibitory effect is between 1 and 4 hours after dosing and inhibition is maintained for 12 hours. Once daily dosing is possible because factor Xa activity does not return to normal within 24 hours. Dosing adjustments should be made for patients with renal insufficiency. The drug is contraindicated in patients with severe liver disease. The antithrombotic effect of rivaroxaban may be monitored with prothrombin time, activated partial thromboplastin time (aPTT), and Hepitest. These all show linear dose effects.⁶ Because the accuracy of these laboratory assays to measure the anticoagulant effects of rivaroxaban is uncertain, assessment of these assays continues.¹³ ASRA recommends a "cautious approach" in performing regional anesthesia in light of the lack of information regarding the specifics of block performance during clinical trials and the prolonged half-life of rivaroxaban.⁶

Like rivaroxaban, apixaban is direct inhibitor of factor Xa administered orally. Apixaban has a bioavailability greater than 50% and reaches peak plasma concentration

3 to 4 hours after dosing. With repeated dosing, the terminal half-life of apixaban is 10 to 14 hours. The drug is partially metabolized in the liver and is cleared via the renal and fecal route. At present, it is undetermined if apixaban can safely be used in patients with mild to moderate hepatic or renal impairment.¹⁴ Trials evaluating apixaban for the prevention of VTE are ongoing. When compared with enoxaparin for thromboprophylaxis after knee replacement, apixaban was associated with lower rates of clinically relevant bleeding. It did not meet the prespecified statistical criteria for non-inferiority, however.¹⁵ The Apixaban Versus Acetylsalicylic Acid to Prevent Strokes (AVERROES) trial compared the safety and effectiveness of apixaban and aspirin in patients with atrial fibrillation. Recently, the trial was stopped early due to reports of clear evidence of a clinically important reduction in stroke and systemic embolism.

Direct Thrombin Inhibitors

Thrombin converts fibrinogen to fibrin and can be inhibited directly or indirectly (**Table 2**). The direct inhibitors of thrombin work by binding to thrombin and blocking its interaction with substrates. Currently, there are three parenteral direct thrombin inhibitors and one oral direct thrombin inhibitor licensed in North America for limited indications. Hirudin and argatroban are used for treatment of HIT. Bivalirudin is approved for use as an alternative to heparin in percutaneous coronary intervention (PCI) patients with or without HIT.⁵ Hirudin is a natural anticoagulant originally isolated from the salivary gland of the medicinal leech. Hirudin, bivalirudin, and lepirudin exhibit bivalent binding. Hirudin and its recombinant analogs block the substrate recognition and the catalytic site on thrombin responsible for fibrinogen cleavage. Hirudin acts only on thrombin and has no effect on other components of the clotting pathway.¹⁶ Desirudin (Iprivask) for injection is a new direct thrombin inhibitor similar in structure to hirudin. Approved for use by the FDA in 2003, but not immediately marketed, it is indicated for use in preventing deep vein thrombosis in patients undergoing elective hip arthroplasty. Desirudin is a selective inhibitor of free circulating and clot-bound thrombin. Peak plasma concentrations occur between 1 and 3 hours after subcutaneous injection. Terminal elimination half-life of desirudin is 2 to 3 hours. The drug is primarily eliminated and metabolized by the kidney. Patients with moderate to severe renal impairment require dose reductions and monitoring of daily aPTT and serum

	Dabigatran	Hirudin	Bivalirudin	Argatroban	Desirudin
Action	Inhibits thrombin	Inhibits thrombin	Inhibits thrombin	Inhibits thrombin	Inhibits thrombin
Route of administration	Oral	IV	IV	IV	Subcutaneous
Indication	Not yet approved ^a	HIT	PCI	HIT	VTE/PE prophylaxis
Half-life	14–17 hours	1–2 hours	25 minutes	40–50 minutes	2–3 hours
Elimination	Renal	Proteolysis and renal	Plasma/renal	Hepatic and biliary	Renal
Monitoring	None	aPTT	aPTT	aPTT/ACT	aPTT

Abbreviations: ACT, activated clotting time; IV, intravenous; PE, pulmonary embolism.

^a Completed clinical trials for stroke prevention and nonvalvular atrial fibrillation and treatment of acute VTE; currently in clinical trials for treatment and prevention of secondary VTE.

creatinine. Desirudin carries a black box warning like that of the other thrombin inhibitors. There is an increased risk of epidural or spinal hematoma when neuraxial anesthesia is performed on patients who are anticoagulated or scheduled to be anticoagulated with thrombin inhibitors, such as desirudin. The risk may be increased with indwelling catheters or by concomitant use of other medications altering hemostasis, such as nonsteroidal anti-inflammatory medications, platelet inhibitors, or other anticoagulants. Risk of spinal or epidural hematoma formation is further increased by traumatic or repeated epidural or spinal puncture.¹⁷ The ASRA states that there are no case reports of spinal hematoma related to neuraxial anesthesia among patients receiving direct thrombin inhibitors but spontaneous intracranial bleeding has occurred. In general, patients on direct thrombin inhibitors are not good candidates for neuraxial anesthesia due to underlying conditions requiring anticoagulation. ASRA makes no statement regarding risk assessment and patient management in these patients except to recommend identification of cardiac and surgical risk factors associated with bleeding after invasive procedures.⁶

Dabigatran, an oral direct thrombin inhibitor, is being studied for various clinical indications. Dabigatran, like argatroban, is a synthetic small-molecule hirudin analog. It exhibits univalent binding to only one of the two key thrombin sites.¹⁶ Dabigatran etexilate is the prodrug of dabigatran, a reversible inhibitor of the active site of thrombin. The prodrug is rapidly converted to dabigatran after oral ingestion and hepatic processing. Peak plasma concentrations occur approximately 1.5 hours after oral administration. After reaching steady state, dabigatran's half-life is 14 to 17 hours. Bioavailability of dabigatran is 7.2% and it is primarily excreted in feces. Up to 80% of the drug is eliminated by the kidney. Recommendations from countries where dabigatran is already approved suggest renal dosing considerations in patients with moderate renal dysfunction and recommend against its use in patients with severe renal impairment.¹⁴ Dabigatran has been compared with warfarin for stroke prevention in patients with nonvalvular atrial fibrillation and treatment of acute venous thromboembolism.^{18,19} Implications of the results of these clinical trials are expected in the near future. Ongoing phase III clinical trials are looking at dabigatran in treatment and prevention of secondary VTE in postoperative orthopedic patients and long-term prophylaxis in acute coronary syndrome. Dabigatran's predictable pharmacokinetic profile would allow for a fixed-dose regimen without the need for routine coagulation monitoring. If an assessment of dabigatran's anticoagulation status were necessary, there is no best method established at present. If available, however, thrombin clotting time and ecarin clotting time determined by thrombin inhibitor assay are reported to be sensitive tests to evaluate dabigatran's anticoagulant effects. Less sensitive but more accessible qualitative methods of anticoagulant effects are aPTT and thrombin clotting time. No antidote is currently available to antagonize dabigatran. It has been suggested that in cases of life-threatening bleeding, recombinant factor activated VII and prothrombin complex concentrate may be considered.²⁰

NEW ANTIPLATELET AGENTS

Drugs that block platelet function are vital in the prevention of arterial thrombogenesis. Forming under high shear conditions, arterial thrombi consist of mainly platelet aggregates held together by small amounts of fibrin. Clopidogrel (Plavix) and ticlopidine (Ticlid) are structurally related thienopyridines that inhibit platelet aggregation by selectively and irreversibly inhibiting the adenosine diphosphate (ADP) stimulation of the P2Y₁₂ receptor. New antiplatelet drugs include the thromboxane receptor antagonist, PAR-1 antagonists (targets thrombin receptors on platelets), and P2Y₁₂ antagonists.⁵

ADP Receptor Antagonists

Of the new antiplatelet agents, the ADP receptor antagonist, prasugrel (Effient), is the only drug currently available in United States. It is indicated to reduce the rate of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with PCI. These include patients with unstable angina or non-ST-elevation myocardial infarction and patients with ST-elevation myocardial infarction when managed with primary or delayed PCI. Prasugrel is rapidly absorbed from the gastrointestinal tract with mean time to peak plasma concentration of approximately 30 minutes. Prasugrel is a prodrug requiring hepatic conversion to express its antiplatelet activity. Hepatic metabolism results in an active metabolite that irreversibly inhibits the P2Y₁₂ receptor. Plasma half-life of the active metabolite is approximately 4 hours and steady state is reached in 3 days. Prasugrel is excreted primarily in the urine.²¹ Platelet inhibition is more rapid with prasugrel than with clopidogrel, but both drugs have a delayed offset of action due to the irreversible inhibition of their target receptor.²² Prasugrel has been shown to have more potent antiplatelet effects, lower interindividual variability in platelet response, and faster onset of activity than clopidogrel. Furthermore, prasugrel is more efficacious in preventing ischemic events in patients with acute coronary syndrome undergoing PCI. Although prasugrel provides more rapid and consistent platelet inhibition than clopidogrel, it also increases the risk of bleeding.^{23–25} The manufacturer warns of bleeding risk and recommends discontinuation at least 7 days before any surgery. Although there is no generally accepted test to guide antiplatelet therapy, careful preoperative assessment focusing on alterations in health that might contribute to bleeding is important. Examples include history of easy bruising and/or excessive bleeding, female sex, and increased age. ASRA recommends discontinuation of thienopyridine therapy for 7 days for clopidogrel and 14 days for ticlodipine. Neuraxial techniques should be avoided until platelet function has been recovered.⁶ Although not specifically addressed in the ASRA guidelines at this time, the manufacturer recommends stopping prasugrel at least 7 days before planned surgery. Currently, there is no specific reversal agent available for prasugrel. The manufacturer is conducting an open-label trial of ex vivo reversal of platelet inhibition by exogenous platelets at this time.

Cangrelor, an ATP analog, is a direct competitive inhibitor of P2Y₁₂ that, unlike prasugrel and clopidogrel, does not require hepatic conversion to an active metabolite. Cangrelor has a short half-life of 3 to 5 minutes and recovery of platelet function occurs within 60 minutes of cessation.⁵ Phase III testing of cangrelor in patients undergoing PCI was discontinued by the manufacturer due to evidence that the drug would fail to show a meaningful clinical difference. Cangrelor is currently being evaluated as a bridge therapy for patients who need to discontinue clopidogrel before cardiac surgery.

Glycoprotein IIb/IIIa Antagonists

Although they are not new antiplatelet agents, the use of parenteral glycoprotein IIb/IIIa (GPIIb/IIIa) antagonists is fairly commonplace in preventing thrombotic complications after PCI and in patients with acute coronary syndrome. The GPIIb/IIIa receptor on the platelet surface serves as a base for fibrin cross-linking responsible for platelet aggregation. Platelet antagonists, abciximab (ReoPro), eptifibatide (Integrilin), and tirofiban (Aggrastat), directly block the fibrinogen receptor on platelets, thereby preventing ligand binding and aggregation.^{26,27} Based on the success of these parenteral agents, oral GPIIb/IIIa receptor inhibitors were developed for chronic use in patients at high risk for arterial thrombotic events.²⁸ Results of the first large clinical trials

with oral GPIIb/IIIa receptor inhibitors were unfavorable. Oral agents failed to reduce major cardiovascular events and showed a small but significant increase in mortality in patients with acute coronary syndromes.^{28,29} Although disappointing, information gleaned for the trials involving the first generation of oral GPIIb/IIIa receptor blockers will perhaps result in another generation's success.

The ASRA guidelines address the GPIIb/IIIa receptor inhibitors by asserting that they have a profound effect on platelet aggregation. Neuraxial techniques should be avoided until platelet function is recovered. After administration of abciximab, time to normal platelet aggregation is 24 to 48 hours. Eptifibatide and tirofiban administration requires 4 to 8 hours for return of normal platelet aggregation. Furthermore, GPIIb/IIIa antagonists are contraindicated within 4 weeks of surgery. ASRA guidelines recommend careful monitoring of neurologic function should one of the GPIIb/IIIa inhibitors be administered in the postoperative period after a neuraxial technique.⁶

HERBAL MEDICATIONS AND DIETARY SUPPLEMENTS

Widespread use of herbal medications and vitamin supplements in the presurgical population necessitates a familiarity with the implications of patient use of alternative medications. Current US regulatory mechanisms for commercial herbal preparations sold in this country do not provide protection against unpredictable effects. Herbal medications and vitamin supplements may pose a concern in the perioperative period by contributing to cardiovascular instability and hypoglycemia, potentiating commonly used anesthetics sedative effects, and altering metabolism of anesthetic drugs.³⁰ In addition, some of these alternative medications may result in increased bleeding in the perioperative period, especially in conjunction with other anticoagulants (**Table 3**).

Garlic, ginkgo, and ginseng are three herbal medications that may be commonly encountered in the perioperative setting. Extensive research involving garlic shows the herbal may reduce blood pressure and thrombus formation, thereby modifying risk of atherosclerosis.³⁰ Also, garlic may lower serum lipid and cholesterol levels.³¹ Garlic seem to irreversibly inhibit platelet aggregation in dose-dependant fashion and may potentiate the effect of other platelet inhibitors, such as prostacyclin, indomethacin, and dipyridamole.³⁰ There is one case report of a spontaneous epidural hematoma attributed to heavy garlic use.^{30,32} Insufficient

Table 3
Some commonly used herbal medications and supplements and their anesthetic considerations

Herbal Medication	Adverse Effects	Anesthetic Considerations
Garlic	Prolongation of bleeding time, hypotension	Increased risk of bleeding and hemodynamic instability
Ginger	Prolongation of bleeding time	Increased risk of bleeding and hemodynamic instability
Ginkgo biloba	Platelet dysfunction	Increased risk of bleeding
Kava kava	Platelet dysfunction, hepatotoxicity	Increased risk of bleeding
Fish oil	Platelet dysfunction	Increased risk of bleeding
Vitamin E	Platelet dysfunction	Increased risk of bleeding, may enhance hypertension

pharmacokinetic data preclude development of absolute recommendations regarding discontinuation of garlic before surgery. It has been suggested, however, that given the potential for irreversible inhibition of platelet function, cessation of garlic use 7 days before surgery is warranted.³⁰ Ginkgo is derived from the leaf of ginkgo biloba. Its common uses include stabilization and/or improvement of cognitive defects in disorders, such as Alzheimer disease and multi-infarct dementia. Ginkgo is also used in patients with peripheral vascular disease, macular degeneration, vertigo, tinnitus, motion sickness, and erectile dysfunction. Terpenoids and flavonoids are the compounds believed to produce its pharmacologic effects. Ginkgo may act as an antioxidant, alter vasoregulation, and modulate neurotransmitter and receptor activity. In addition, ginkgo may inhibit platelet-activating factor and alter platelet function. Study of pharmacokinetic data and bleeding risk suggests that patients should stop taking ginkgo at least 36 hours before surgery.³⁰ Ginseng, both Asian and American types, is commonly used as an adaptogen, protecting the body from stress and restoring homeostasis. Other uses include lowering postprandial glucose in patients with type 2 diabetes mellitus and without diabetes. Although not completely understood, the underlying pharmacologic mechanism seems similar to that of steroid hormones. Ginsenosides inhibit platelet aggregation in vitro and prolong coagulation time of thrombin and activated partial thromboplastin in laboratory rats. Findings await confirmation in humans. Because platelet inhibition seems irreversible, it is suggested that patients discontinue use of ginseng at least 7 days before surgery.³⁰ ASRA guidelines state that there does not seem to be a clinically significant increase in surgical bleeding or spinal hematoma overall in patients taking herbal medications. Because the use of herbal medications alone does not create a level of risk that interferes with neuraxial blockade, ASRA recommends against mandatory discontinuation of herbal medications or avoidance of regional anesthetic techniques in these patients. There is a lack of data, however, pertaining to patients taking herbal medications with other forms of anticoagulation. Concurrent use of medications, such as oral anticoagulants or heparin, may increase the risk of bleeding in patients taking herbal medications.⁶

Other herbal medications may increase bleeding, especially in patients already taking drugs and/or other herbs or supplements that affect normal clotting function. These include feverfew, ginger, kava kava, clove, and white willow bark. The American Society of Anesthesiologists suggests that patients should be encouraged to discontinue these products 2 weeks before surgery, which is the estimated time for the compounds to be fully metabolized.³³

Dietary supplements are taken regularly by all patient populations for various reasons. Vitamins E and A have been implicated in increasing risk of bleeding in combination with prescribed anticoagulants. Vitamin E is popular because it is thought to have antioxidant properties, provide protection against environmental pollution, and slow the aging process. Vitamin E supplementation may increase the effects of anticoagulants and antiplatelet drugs, thereby increasing the risk of bleeding perioperatively. Vitamin A is found in two major forms of foods, including retinol and carotenes. Of concern is the risk of increased bleeding in patients taking vitamin A and warfarin. Vitamin A may increase the anticoagulant effects of warfarin. Informing patients of these potential effects may help to avoid perioperative complications. Another dietary supplement with potential to increase the risk of bleeding is fish oil. Evidence suggests that the components of fish oil, docosahexaenoic acid and eicosapentaenoic acid, lower triglycerides, and reduce the risk of death, heart attack, arrhythmias, and stroke in people with known heart disease. At

high doses, however, harmful effects, such as increased risk of bleeding, may occur.³⁴

NEW ANTICOAGULANTS AND REGIONAL ANESTHESIA

Anticoagulant, antiplatelet, and thrombolytic drugs are commonly used in the prevention and treatment of thromboembolism. In addition, increasingly more potent antithrombotic medications have raised concerns regarding the risk of increased neuraxial bleeding. The incidence of spinal hematoma is estimated to be less than 1 in 220,000. Although the risk of epidural hematoma is estimated to be 1 in 150,000, the risk is increased 15-fold in patients on anticoagulant therapy.³⁵ Risk factors for clinically significant bleeding increase with age, associated abnormalities of the spinal cord and vertebral column, underlying coagulopathy, difficult needle placement, and indwelling neuraxial catheter during sustained anticoagulation. To optimize neurologic outcome in the face of a complication, it is imperative to promptly diagnose and intervene.⁶ The ARSA published its practice advisory in 2009 addressing patient safety issues and the concerns listed previously. The consensus statements represent opinions of recognized experts in the field of neuraxial anesthesia and anticoagulation. The guidelines are based on case reports, clinical series, pharmacology, hematology, and risk factors for surgical bleeding.

European groups have proposed guidelines to improve safety of neuraxial techniques in patients receiving newer anticoagulants. Proposed recommendations suggest the risk-to-benefit ratio needs to be individualized for each patient depending on type and dose of anticoagulant, the type of regional anesthesia, and patient risk factors.

In addition, neuraxial anesthetic management strategies may be based on pharmacokinetic properties of the anticoagulant drug, including time required to reach maximal concentration, half-life, and dose regimen. The time elapsed from the last injection of anticoagulant to performance of a central neuraxial block should be at least two half-lives of the drug. The same amount of time should elapse before removal of an epidural catheter. Renal function plays a role in half-life. After removal of an epidural catheter, timing of the next dose of anticoagulant should be based on time required for the drug to meet maximum activity. Furthermore, both the American and European societies agree that vigilance in monitoring is crucial to allow for early evaluation of neurologic dysfunction and prompt intervention.⁴

Risk of bleeding after peripheral nerve blockade and plexus nerve blockade in the anticoagulated patient is undefined.⁶ There are few investigations examining the frequency and severity of hemorrhagic complications from peripheral nerve blockade and plexus nerve blockade in this patient population. Serious complications have been reported after neurovascular sheath cannulation for surgical, radiologic, and cardiac procedures. ASRA states there are insufficient data to make definitive recommendations regarding performing these blocks in anticoagulated patients. The ASRA suggests, however, that significant blood loss, rather than neural defects, may be the most serious complication of non-neuraxial regional techniques. Hemorrhage after deep plexus/peripheral techniques, such as lumbar sympathetic/plexus and paravertebral blocks, in the presence of antithrombotic activity is a serious complication.⁶ Therefore, the ASRA states the same recommendations regarding neuraxial techniques be observed for patients undergoing deep plexus or peripheral nerve block.

Interventional pain management procedures carry a minimal, but potentially hazardous, risk of bleeding. Risk is difficult to assess based on available source

data. Anesthesiologists must assess bleeding risk based on existing literature and judgment. Most interventional pain procedures are elective; therefore, bleeding risks should be weighed against potential benefits.³⁶ The ASRA has adapted guidelines that are reflective of the guidelines for neuraxial anesthesia in patients on anticoagulation therapy. Clopidogrel should be withheld for 7 days before a neuraxial procedure. Thienopyridine derivatives have been implicated in bleeding after lumbar sympathetic blockade and cervical steroid injections.³⁶ GPIIb/IIIa receptor inhibitors should be discontinued 4 weeks before neuraxial blockade. Neuraxial blockade is contraindicated in patients on oral anticoagulants. Bleeding risk factors associated with technique may influence the risk and consequences of bleeding. Assessment and understanding of the above subject matter improves patient safety during interventional pain procedures.³⁶

NEW ANTICOAGULANTS: MONITORING, REVERSAL, AND CONTINUATION THROUGH THE PERIOPERATIVE PERIOD

Approved new anticoagulants and those still in clinical trials offer many benefits and advantages when compared with the older vitamin K antagonists and heparin. Oral administration, more predictable pharmacokinetics, and no need for laboratory monitoring of anticoagulant effects are a few of the advantages. Investigations into monitoring capabilities of the anticoagulation effects of direct factor Xa inhibitors and direct thrombin inhibitors thus far have yielded no standard measure of the of these two new drug classes. Lack of standardization and significant variability of results depending on the reagent or test method make currently available tests of anticoagulant effects unreliable in the case of direct factor Xa and direct thrombin inhibitors.¹⁶

Specific tests to measure platelet inhibitory effects of clopidogrel are available, including ADP-stimulated aggregometry. The time required to perform this test restricts its usefulness during surgery. Currently, there are two platelet function assays commercially available that measure platelet inhibition by the ADP antagonist clopidogrel. Also, accurate measuring of receptor inhibition by GPIIb/IIIa inhibitors in patients undergoing invasive cardiology procedures has been documented. Platelet inhibition measured by a point-of-care monitor, *Ultegra*, correlates inversely with adverse outcomes after PCI.²⁶ Whether or not such monitoring devices will become useful in the perioperative setting is uncertain.

Reversal of the anticoagulant effects of new anticoagulants poses potential problems in managing surgical patients. Traditional agents used to reverse bleeding or older anticoagulants include antifibrinolytics, protamine, desmopressin, fibrinogen, purified protein concentrates, and recombinant factor VIIa.³⁷ Only one of the new anticoagulants, fondaparinux, is partially reversed by one of these agents, recombinant factor VIIa.⁸ Transfusion of fresh platelets can effectively reverse the antiplatelet effects of clopidogrel, but circulating platelets already bound with the drug remain inhibited.²⁶ Transfusion therapies are often used, but data supporting their efficacy are needed.³⁷

Recommendations regarding discontinuation of anticoagulants/antiplatelet medications are discussed previously. In certain patient populations, it is strongly advised that anticoagulation or antiplatelet therapy continue throughout the perioperative period. It is recommended that in patients at high risk for development of VTE, such as cancer patients, thromboprophylaxis be started preoperatively. Fondaparinux is an option for these patients. Trauma patients are also at high risk for development of VTE and sudden fatal pulmonary embolism. In these patients, thromboprophylaxis with enoxaparin should be started as soon as it is considered safe to do so.³⁸

Perioperative management of patients with coronary artery stents is one of the most important topics involving anticoagulation and surgery. Perioperative stent thrombosis is life threatening and can occur with both bare-metal and drug-eluting stents. Noncardiac surgery increases risk of stent thrombosis, myocardial infarction, and death. These risks are increased if surgery occurs early after stent implantation and if antiplatelet therapy is discontinued preoperatively.³⁹ Thienopyridine therapy in combination with aspirin is the treatment strategy used to prevent stent thrombosis. Elective procedures with significant risk of perioperative bleeding should be deferred until patients have completed an appropriate course of thienopyridine therapy. Patients with drug-eluting stents who are not at high risk of bleeding require 12 months of dual antiplatelet therapy after stent implantation. Patients with bare-metal stents require a minimum of 1 month of therapy after stent implantation.⁴⁰ If surgery cannot be deferred and thienopyridine therapy must be interrupted in patients with new coronary stents, aspirin should be continued if possible and the thienopyridine restarted as soon as possible. In patients with drug-eluting stents and high risk of stent thrombosis, dual antiplatelet therapy with aspirin and the thienopyridine should be considered perioperatively even if the time since implantation is beyond the initial 12 months. After the thienopyridine has been discontinued, serious consideration should be given to continuing perioperative aspirin antiplatelet therapy in any patient with drug-eluting stents.⁴¹

SUMMARY

With a growing number of new anticoagulant/antiplatelet agents being developed, it is likely that an increasing number of patients taking these drugs will present for surgery and other procedures. A familiarity with mechanisms of action and drug interactions helps to maintain optimal patient safety in the perioperative period. Furthermore, it is crucial for anesthesiologists to remain current on recommendations regarding discontinuation or need to continue the newer anticoagulants/antiplatelet drugs in patients presenting for surgery and/or regional anesthesia. Further studies are needed for monitoring of many of these newer agents and to identify antidotes.

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