ANESTHESIOLOGY™2014
OCTOBER 11-15 | NEW ORLEANS, LA

Session: L050
Session: L174

Perioperative Management of the Patient on Anticoagulant Therapy: A Fresh Look at an Old Problem

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Disclosures: This presenter has no financial relationships with commercial interests

Stem Case and Key Questions Content

An 83 y.o. female 160 cm 74 kg presents to the emergency room with right hip pain after a fall at home. BP 170/90, HR 92, RR 24, T 37.3C and SpO2 95% breathing room air. She has a history of atrial fibrillation and takes warfarin for cardioembolic stroke prevention. Her INR is 2.2 and serum creatinine 1.3 mg/dL. She is found to have a right intertrochanteric hip fracture and is scheduled for non-elective right hemiarthroplasty the next day (estimated time late morning or early afternoon). You evaluate her and recommend a spinal anesthetic (after her hemostatic capacity has been restored).

What is the data supporting prophylactic anticoagulation therapy for patients with atrial fibrillation? What is the mechanism of action of warfarin and how can its effects be reversed for an urgent or emergent surgical procedure? Is the management any different in a patient for whom a central neuraxial regional anesthetic is planned? Would the management be different if the patient had a prosthetic cardiac valve in addition to atrial fibrillation? What new, oral anti-coagulant drugs are available to prevent the cardioembolic complications associated with atrial fibrillation? What is the mechanism of action and clinically important pharmacologic properties of these drugs? Given a similar case scenario, how would you optimize hemostatic reserve prior to surgery? Is a regional technique still an option for a patient taking these newer anticoagulant medications?

Surgery under spinal anesthesia is completed and the patient returns to the hospital ward. The surgeons would like to begin anti-coagulant therapy to prevent deep venous thrombosis in the postoperative period. The surgeons ask when the first dosage of anticoagulation can be given, in light of her recent spinal block placement, and how to manage the postoperative anticoagulant therapy in light of this patient's renal disease.

Is this patient at risk for deep venous thrombosis? What is the data supporting anticoagulant therapy for the prevention of deep venous thrombosis following hip surgery? Following a medical or surgical procedure, when is it safe to begin anticoagulant therapy? When is it safe to begin postoperative anticoagulant therapy following a neuraxial anesthetic? If an epidural catheter remains in place for postoperative analgesia, would the timing for the initiation of postoperative anticoagulant therapy change? What drug options are available for the prevention of postoperative venous thromboembolism, and what are their pharmacokinetic and pharmacodynamic characteristics? What is the extent of her renal insufficiency? What is the

effect of renal insufficiency upon each pharmacologic option? What anticoagulant would you choose for this indication? Is dosage adjustment of anticoagulant therapy necessary for this patient? Should adjustment be made to the loading dose, the maintenance dosage, or both? How are the effects of therapy monitored?

The patient's anti-coagulant therapy is changed to the low-molecular weight heparin (LMWH) enoxaparin 30 mg subcutaneously every 24 hours. By day seven, she is progressively more mobile. However, her platelet count has decreased markedly and heparin-induced thrombocytopenia is suspected.

What is the pathophysiology associated with heparin-induced thrombocytopenia (HIT)? Is it possible to develop HIT during therapy with low-molecular weight heparins such as enoxaparin? How is HIT diagnosed? How is HIT treated? Does the patient still require anti-coagulation therapy? What are the pharmacologic options? How does renal insufficiency affect the choice of therapy?

Argatroban therapy is initiated. Two days later, she begins to complain of right upper quadrant pain and acute cholecystitis is diagnosed. The general surgeons would like to take her to the operating room tomorrow for a cholecystectomy.

What is the mechanism of action of argatroban? What are its clinically significant pharmacologic properties? How is the effect of argatroban monitored? In preparation for surgery, how will her argatroban therapy be managed so that the effects are reversed by the time of surgery (0800 hours)? Would you resume anti-coagulant therapy in the postoperative period? What are the options for therapy?

Model Discussion Content

Patients on long-term anticoagulant therapy occasionally present for elective or urgent/emergent surgical procedures. Anticoagulant therapy may have one or more of the following indications (listed from most common to least common):

1) To prevent cardioembolic stroke associated with atrial fibrillation, valvular heart disease (e.g., rheumatic heart disease), and/or a prosthetic heart valve;

2) To prevent adverse cardiac events associated with acute coronary syndrome or post-percutaneous coronary intervention;

3) To prevent venous thromboembolism following surgery, recent trauma, or associated with hypercoagulable states, and to prevent recurrence after deep venous thrombosis (DVT) has been treated;

4) To prevent non-cardioembolic stroke after transient ischemic attacks (e.g., associated with carotid artery plaque rupture).

These are just a few of the indications for which patients receive anticoagulant therapy.

Anticoagulant Therapy to Prevent Cardioembolic Stroke
Elderly patients consistently fear stroke more than cancer, heart attack, diabetes, and even death. Atrial fibrillation increases the risk of embolic stroke by a factor of five. Most patients who receive anti-coagulants to prevent cardioembolic stroke associated with atrial fibrillation are treated with warfarin. Dabigatran, a direct thrombin inhibitor, and rivaroxaban, a selective Factor Xa inhibitor, have recently been approved in the US (Oct 2010 for dabigatran and July 2011 for rivaroxaban) to prevent stroke in patients with atrial fibrillation not associated with cardiac valve pathology.

Warfarin is a Vitamin K antagonist that inhibits the hepatic synthesis of coagulation Factors X, IX, VII, and II. Specifically, it prevents the carboxlation of these serine proteases, thereby making them ineffective when activated during tissue injury.[1]

Warfarin, a coumarin, it is extensively metabolized by the hepatic CYP enzyme system (specifically CYP2C9). The half-life is highly variable (36-42 hours). Although the liver primarily metabolizes warfarin, chronic renal failure can significantly alter its pharmacokinetics by affecting protein binding, volume of distribution, and bioavailability.

The onset of warfarin's effect upon the prothrombin time (PT) is dependent upon the half-life of the circulating vitamin-K dependent coagulation factors (VII - 6-8 hours; IX - 24 hours; X - 25-60 hours; II - 50-80 hours). Warfarin's *clinical* effect is associated with a reduction in the concentration of the factors with the longest half-lives - Factors II and X.[1,2]

Treatment with Vitamin K 1-10 mg intravenously may normalize the PT within 6 hours (depending upon the dosage of Vitamin K and the patient's liver function).[3] However, normalization of the PT primarily reflects restoration of plasma concentrations of Factor VII. An INR of 1.5 is associated with a Factor VII activity of 40% baseline. Although the PT is sensitive to changes in Factor VII concentrations, concurrent plasma concentrations of Factors II and X may still be below the level necessary for normal clinical hemostatic capacity.[1,2]

In the patient who requires emergent intervention or urgent intervention that cannot wait several hours, plasma coagulation factors may be restored with the administration of fresh frozen plasma (FFP) or plasma complex concentrate (PCC). Importantly, the coagulation factors in FFP and PCC have a limited half-life (4-6 hours), and, unless Vitamin K is administered in addition to fresh frozen plasma, the warfarin-induced coagulopathy will recrudesce in about 12-18 hours.[4]

Recently, plasma complex concentrate (PCC) has become available for the reversal of warfarin's effects. PCC's contain high concentrations of Factors II, VII, IX, and X as well as Protein S and Protein C. The INR is normalized over a period of 30-60 minutes, and the volume of one PCC bottle is 100 milliliters.

In patients for elective surgery who are at high or medium risk for stroke when warfarin therapy is discontinued, bridging therapy should be considered during the time warfarin therapy is interrupted. Low molecular weight heparin (LMWH - discussed in detail later) subcutaneously or intravenous unfractionated heparin (UFH) are two common "bridging" medications. These medications must be discontinued for an appropriate period prior to regional block placement

and/or surgical or medical intervention, and resumed after waiting for an appropriate interval of time following the end of the procedure.

Dabigatran etexilate is an orally administered direct, reversible thrombin inhibitor that is rapidly metabolized to dabigatran, its active form. Dabigatran's peak effect occurs within 0.5-2 hours of ingestion and its half-life is 12-17 hours. The drug is almost exclusively renally cleared, and accumulation can occur with severe renal impairment (e.g., creatinine clearance less than 30 mL/min). Residual drug levels of dabigatran considered safe for surgery are presently unknown, and no laboratory test has been correlated with bleeding risk. The prothrombin (PT) and ecarin clotting time may be useful in assessing the effects of dabigatran because dabigatran prolongs the test result in a dose-dependent manner. At present, these tests must be interpreted with caution because test result does not provide an indication of bleeding risk, and patient can have abnormal bleeding despite a normal test result.[5,6]

Rivaroxaban is an orally administered direct, reversible inhibitor of Factor Xa, both free and clot-bound. Rivaroxaban's peak clinical effect is seen within 3-4 hours, and its half-life is 5-9 hours. Rivaroxaban prolongs the PT in a dose-dependent manner and its effects are evident in testing for anti-Factor Xa activity. However, these tests are not currently recommended for monitoring the clinical effect of rivaroxaban.[5,6]

The perioperative management of patients treated with these new, oral anticoagulant drugs has been reviewed in several recent papers.[7-12] The recommendations are generally based upon the pharmacokinetics of each drug. At least two to three half-lives (about 36-52 hours for dabigatran and 24-36 hours for rivaroxaban) are required to return the patient to near-normal hemostatic capacity. The time required may be significantly longer for the elderly patients and patients with abnormal renal function. If the effects must be reversed sooner, then there are no specific agents for reversal. Hemodialysis has been effective for reversal of dabigatran's effects, but application may be limited in most clinical scenarios.[13] PCC and activated Factor VII have been used with limited success. In the absence of evidence-based recommendations, the clinician must "individually assess⋯ [each situation] ⋯according to the institutional transfusion guideline and the available consensus."[7]

In 2010, the American Society of Regional Anesthesia and Pain Management (ASRA) recommended against the use of regional anesthesia in patients who are receiving dabigatran or rivaroxaban therapy.[14] In 2011, Horlocker[2] recommended waiting at least 7 days after the last dosage of dabigatran to perform a neuraxial technique. If earlier block placement is clinically indicated, then assessment of the thrombin time (TT) may be useful to demonstrate the absence of dabigatran effect.

According to the European guidelines[15], a wait of at least 22-26 hours after the last dosage of rivaroxaban is recommended prior to neuraxial blockade. This is based on a recommendation from Rosencher and colleagues[16], who suggested waiting at least two half-lives after discontinuation of an anticoagulant before considering a neuraxial block. In elderly patients and those with renal insufficiency or other conditions that affect drug clearance, the wait may need to be prolonged.

Anticoagulants to Prevent Venous Thromboembolism
Without thromboembolic prophylaxis, 46-60% of patients will develop deep venous thrombosis

within 7-14 days following hip fracture.[17-19] In untreated patients, the incidence of fatal pulmonary embolism within three months of hip fracture surgery is 1.5-7.5%.[17-19] In a population-based study of 581 patients who died following hip fracture from 1953 to 1992, pulmonary embolism was the fourth leading cause of mortality, accounting for 14% of deaths. [7-19] Thromboprophylaxis effectively prevents symptomatic deep vein thrombosis and pulmonary embolism. [17-19]

The American College of Chest Physicians recommends (evidence Grade 1A) that all patients undergoing hip fracture surgery receive venous thromboembolism (VTE) prophylaxis.[17] Currently available pharmacologic therapies for VTE prophylaxis in patients undergoing hip fracture surgery include unfractionated heparin (UFH), low-molecular-weight heparins (LMWH), fondaparinux, a synthetic pentasaccharide that has effects similar to LMWH, and warfarin. **Unfractionated heparin (UFH)** is a heterogenous mixture of negatively charged glycosaminoglycans derived primarily from bovine lung and porcine gut mucosa. Its molecular weight ranges from 3000 to 30,000 daltons, with a mean of 15,000 daltons. Its action is a reflection of its ability to amplify the effect of anti-thrombin; it enables anti-thrombin to more effectively inhibit the actions of factors XIIa, XIa, IXa, and IIa. It also binds to tissue-factor-pathway inhibitor (TFPI), which inhibits the effect of the tissue factor VIIa when bound to tissue factor.

UFH is highly and variably bound to plasma proteins, and this largely accounts for its variable anticoagulant effect between patients. Clearance of UFH is via both the reticuloendothelial and the renal systems. The half-life is dose-dependent, ranging from 30-150 minutes. At dosages up to 100 units/kg, UFH is largely eliminated by the reticuloendothelial system; at larger dosages, the renal system participates in its elimination. The half-life is prolonged by a factor of about 1.5 in patients with chronic renal failure (eGFR less than 30 mL/min/1.73m^2).

When used for VTE prophylaxis, UFH is administered subcutaneously in a dosage of 5000 units. This is termed “low-dose” or “mini-dose” heparin, and is typically administered every eight to twelve hours. UFH equally inhibits Factors Xa and IIa. However, low-dose UFH does not alter the activated partial thromboplastin time (aPTT) or anti-Xa activity; therefore, coagulation studies such as these are not used to monitor heparin therapy or confirm the absence of its effect.

There are a two recommendations regarding regional anesthesia during low-dose UFH therapy administered twice daily. The most conservative management recommends that prophylactic UFH be held at least 4-6 hours prior to a central neuraxial block.[15] ASRA indicates that neuraxial blocks are generally safe during UFH therapy given twice daily subcutaneously. However, if the next dosage of subcutaneous UFH is due, hold this dosage until at least one hour after block placement.[14] In a retrospective review of a small sample of patients with indwelling thoracic epidural catheters, there were no spinal epidural hematoma incidences during thrice daily UFH heparin therapy.[20]

Low molecular weight heparin (LMWH) is produced by chemical or enzymatic degradation of unfractionated heparin (UFH). The resulting molecular weight is between 1000 and 10,000 daltons, and the mean molecular weight is about one-third that of UFH. LMWH exerts its effect upon factors Xa and IIa by amplifying the effect of anti-thrombin. LMWH inhibits Xa more so than IIa by a factor ranging from 2 to 4. Its bioavailability is 90% after subcutaneous injection, by

virtue of the fact that it has far less affinity for plasma proteins than UFH. It also binds less to platelets; consequently, the incidence of heparin-induced thrombocytopenia is less than that associated with UFH.

LMWH has little effect upon the aPTT in therapeutic dosages, and can be monitored by assay of anti-Xa activity. LMWH effect is only partially inhibited by protamine, and there is no other antidote available. Excretion is primarily by the renal route; monitoring for activity is usually not indicated except in patients with renal impairment. In patients whose creatinine clearance is below 30 mL/min, anti-Xa assay is suggested 4-6 hours after subcutaneous administration, and the dosage adjusted accordingly with the result.

The clinical effects of LMWH are maximal 3-4 hours after administration, and the clinical effects are maintained for up to 12 hours. The terminal elimination half-life in patients with normal renal function is 4-6 hours. LMWH only inhibits Factor Xa. Of the currently available LMWH drugs (enoxaparin, dalteparin, tinzaparin), no one drug is recommended over the other.
Block placement should be delayed at least 10-12 hours following the administration of prophylactic LMWH.[14] If therapeutic dosages of LMWH are used (e.g., for a patient with a prosthetic heart valve for whom LMWH is administered as “bridge” therapy after stopping warfarin prior to surgery), then 24 hours should elapse before block placement.[14] LMWH for prevention of venous thromboembolism is usually initiated at least 12 hours after wound closure.[17]

Fondaparinux is a synthetic pentasaccharide with a high affinity for anti-thrombin. The drug accelerates the selective anti-Xa activity of anti-thrombin and there is no antidote to its effects. It is administered subcutaneously, usually in a dosage of 2.5 mg. Up to 80% is excreted unchanged in the urine. The half-life is 17.2 hours in normal volunteers and 20.7 hours in the elderly. Activity is monitored by assay for anti-Xa; the activated partial thromboplastin time (aPTT) and prothrombin time (PT and INR) do not monitor the activity of this drug. In patients over 75 years, the clearance was 25% less than that of patients under 65 years. The effect of renal insufficiency was marked; in patients with moderate renal impairment (eGFR 30-59 mL/min/1.73m^2), the clearance was decreased by 40%.[8]

Fondaparinux, when used to prevent postoperative venous thromboembolism, is administered 6-8 hours after surgery. Gogarten et al.[15] recommend an interval of at least 36-42 hours post drug administration before performing neuraxial techniques. Horlocker et al.[14] recommend against using an indwelling epidural catheter if fondaparinux will be administered postoperatively; however, a single-shot regional anesthesia technique is acceptable.

Heparin-Induced Thrombocytopenia
Heparin induced thrombocytopenia (HIT) is an immune-mediated platelet aggregation reaction. An unexpected drop of 50% or more in the baseline platelet count during heparin therapy (without another apparent cause for thrombocytopenia) is considered a presumptive diagnostic criterion for HIT. The presence of a heparin-associated antibody is confirmatory, and a normal platelet count should return once heparin exposure is discontinued. HIT can occur within 4-5 days of beginning therapy with either UFH or LMWH. The incidence of HIT in association with UFH therapy is 1-5% and 0.1-1.3% in association with LMWH. Although HIT is ten times more likely in association with UFH as compared to LMWH therapy, once HIT has been diagnosed, it

is not appropriate to switch treatment from UFH to LMWH as cross-reactivity occurs in 90% of cases.

Patients can develop both venous and arterial platelet thromboembolic complications from HIT. Treatment with direct thrombin inhibitors has been recommended in these scenarios because these drugs are not polysaccharides and have no structural similarities to UFH or LMWH.[16] Patients with HIT treated with warfarin can experience progression of VTE leading to complications such as venous limb gangrene and warfarin-associated skin necrosis. To minimize the risk for these complications, warfarin should not be initiated until the platelet count substantially recovers.[16] At this point, warfarin therapy, if indicated, can be cautiously begun. **Argatroban** is a direct thrombin inhibitor. Derived from L-arginine, it is almost exclusively metabolized by the liver. Argatroban is also administered by infusion. The clinical effect of this drug can be monitored by the aPTT and/or activated clotting time (ACT). Therapeutic effect is achieved when the aPTT or ACT is 1.5 to 3.0 times normal. Argatroban has no antidote to its biological effects, but has a relatively short half-life, and clinical anticoagulant effects dissipate within 2-4 hours in the patient with normal hepatic function. Surgery may be acceptable in the patient with normal hepatic function 3-4 hours after argatroban's discontinuation; the resolution of its clinical effects should be confirmed by a normal aPTT or ACT result.[8] If the patient is still believed to be suffering from acute HIT, then the discontinuation of the argatroban infusion (and the timing of surgery) should be discussed with a hematologist and the surgeon.

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