Orthopedic surgery can be a life changing event for people suffering from knee and hip pain. Knee and hip replacements have made vast improvements in the past 20 years; no longer are patients experiencing months of rehabilitation and discomfort. New techniques allow for rapid recovery times and less pain. However, the risk of forming a venous thromboembolism (VTE) is still a very real threat. VTE is a major cause of orthopedic surgery morbidity and mortality.¹ VTEs, more specifically deep vein thrombosis (DVT), are the leading cause of pulmonary embolism (PE) which can be fatal.²

Preventing DVTs from forming is the best method to prevent complications of orthopedic surgery.¹ Without prophylaxis, it is estimated that a DVT will form in 40-60% of patients undergoing a total hip arthroplasty (THA). Of these patients, about 2-5% will be symptomatic. For patients undergoing a total knee arthroplasty (TKA), an estimated 85% will form some type of VTE, if not prophylactically treated with anticoagulants.¹

**Novel Oral Anticoagulants**

Options for prophylactic anticoagulation therapy are continuing to increase. There are multiple options for oral anticoagulation therapy on the market; and many of them are expanding their indications.

An ideal anticoagulant should be inexpensive, orally administered, not require monitoring, and have few drug-drug and drug-food interactions.¹ Novel oral anticoagulants (NOACs) either inhibit thrombin or factor Xa, which play a central role in the coagulation cascade. Three NOACs will be discussed in this article; rivaroxaban (Xarelto), apixaban (Eliquis), and dabigatran (Pradaxa).

**Rivaroxaban (Xarelto)**

Rivaroxaban is a direct, reversible, selective inhibitor of free and prothrombin bound factor Xa.¹ Its original indication was for the prevention of DVT in patients undergoing THA and TKA, and for stroke and systemic embolism prophylaxis in patients with nonvalvular atrial fibrillation.³ Rivaroxaban was later approved for the treatment of DVT and PE, and the prevention of recurrent DVT and PE.³ Monitoring the anticoagulant effect of rivaroxaban is not easily obtained with standard laboratory testing, however calibrated chromogenic factor Xa inhibition assays can be used if necessary.¹,³ Currently there is no approved antidote for rivaroxaban.¹,³

The dose of rivaroxaban in adults to prophylaxis against DVT after orthopedic surgery is 10 mg orally daily for 12 days after TKA and 35 days after THA.³ The initial dose should be given 6-10 hours after surgery and hemodynamic stability achieved. The half-life of rivaroxaban is 5-9 hours.¹ Bioavailability is not affected by food at the 10 mg dose, nor does patients’ weight affect dose. Because rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and P-glycoproteins, inhibitors and inducers of these enzymes can affect drug levels.¹,³

The RECORD trials compared rivaroxaban with enoxaparin in four randomized, double blind, Phase III trials including more than 12,500 patients. This series of trials showed rivaroxaban to be superior to enoxaparin prophylaxis after TKA and THA with a similar safety profile.¹

**Apixaban (Eliquis)**

Apixaban is a selective factor Xa inhibitor.³ Apixaban is approved for DVT prophylaxis post TKA and THA, and stroke and systemic embolism prevention in patients with nonvalvular atrial fibrillation. Routine monitoring is not required for apixaban. An antidote to apixaban has not yet been approved.³

The adult dose for post-surgical prophylaxis is 2.5 mg PO twice daily for 12 days post TKA and 35 days post THA.¹,³ Apixaban should be initiated 12-24 hours after

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P & T Committee Meeting Update

The P&T Committee met for its quarterly business meeting on August 14, 2014.

Highlights of this meeting include:

The Pharmacy Program is working to revise the reimbursement structure used for outpatient drugs, removing the federal upper limit (FUL) from the reimbursement methodology.

The new American Academy of Pediatrics guidelines for use of Synagis were reviewed. No changes were made to the prior authorization for the upcoming season. The guidelines will be reviewed annually.

Oralair, Ragwitek and Grastek will be limited to their approved indications as well as to those patients who are not receiving additional allergy shots.

Zontivity will be limited to its approved indication.

Sivextro will be approved following trial and failure of two other antibiotics with methicillin-resistant staphylococcus aureus coverage or a culture indicating resistance to other available agents.

All proposed prior authorization criteria will be posted for public comment at www.uwyo.edu/DUR. Comments may be sent by email to alewis13@uwyo.edu or by mail to: Wyoming Drug Utilization Review Board, Dept. 3375, 1000 E. University Avenue, Laramie, WY 82071. Comments should be received prior to September 30, 2014.

The next P&T Committee meeting will be held November 13, 2014 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

Introducing UW TelePain

Rural states like Wyoming lack access to pain specialists and other resources in pain management. UW TelePain, created by the University of Washington, is a new program that provides access to pain specialists in rural areas. The UW TelePain program consists of weekly sessions that begin with a half hour didactic lecture regarding various aspects of pain management and are followed by case presentations by community practitioners. These presentations are interactive consultations with a panel of specialists in pain management, anesthesiology, psychiatry, rehab medicine, addiction medicine and a nurse care coordinator. The weekly sessions are offered Wednesdays at 1 pm Mountain time and Thursdays at 8 am Mountain time.

Additional benefits of UW TelePain include the following:

- The ability to present your difficult patients to the panel of specialists.
- A study funded by NIH which includes reimbursement to providers and patients who participate.
- Continuing medical education credits for each session attended (up to 1.5 hours per session).

The UW TelePain team has offered to speak directly with Wyoming providers. If you have any questions or would like additional information, please contact Aimee Lewis, DUR Manager, at alewis13@uwyo.edu or (307) 766-6750, or visit the following website.

Anticoagulants for Orthopedic Surgery, continued

Surgery. The half-life of apixaban is 12 hours. Apixaban is a substrate of P-glycoproteins and is mainly metabolized by CYP3A4, leading to the possibility of drug interactions.

Phase III clinical trials comparing the efficacy of apixaban to enoxaparin include the ADVANCE trials. These 3 trials found apixaban to be non-inferior to enoxaparin in preventing DVT.

Dabigatran (Pradaxa)
Dabigatran is a prodrug that is rapidly converted to an active direct thrombin inhibitor. Since thrombin plays a role in platelet aggregation, depending on the dose, dabigatran can be used for prophylaxis against arterial thrombus, which tend to be high in platelets. Dabigatran is indicated and approved to treat and reduce recurrence of DVT and PE. While not indicated for surgical VTE prophylaxis in the US, dabigatran is approved in Canada and Europe for surgical prophylaxis in patients undergoing THA and TKA. Routine monitoring is not required, however if monitoring needs to be accomplished the Hemoclot thrombin inhibitor test is the most sensitive for dabigatran plasma levels. Similar to other NOACs, an antidote for dabigatran is not yet approved.

The adult dose for DVT prophylaxis post THA and TKA used in Canada is 220 mg PO daily for 10 days post TKA or 28-35 days post THA. An initial dose of 110 mg should be administered 1-4 hours after surgery. The half-life of dabigatran is 12-17 hours. Dabigatran is renally excreted, dose adjustments based on renal function may be necessary. Canadian labeling suggests a dose adjustment for patients with CrCl 30 to 50 mL/min of a reduced initial dose of 75 mg dabigatran, followed by a maintenance dose of 150 mg orally daily. For patients with CrCl<30 mL/min, dabigatran is contraindicated for use as post-surgical VTE prophylaxis.

Phase III trials comparing dabigatran to enoxaparin include RE-NOVATE, RE-NOVATE II, RE-MODEL, and RE-MOBILIZE. A meta-analysis of these trials concluded there is no significant difference between dabigatran and enoxaparin in preventing post-surgical VTE events.

Orthopedic VTE Prophylaxis Guideline Recommendations
The 2012 ACCP (CHEST) guidelines pertaining to VTE prevention in orthopedic surgery patients provides detailed recommendations for therapy in multiple situations. For patients undergoing THA and TKA, a minimum of 10-14 days of either LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, heparin, warfarin, aspirin, or a graduated compression device should be used. For hip fracture surgery (HFS) NOACs are not recommended for VTE prophylaxis.

LMWH is still the preferred drug for VTE prophylaxis for patients undergoing a THA, HFS or TKA, regardless of length of treatment or use of graduated compression devices. LMWH are preferred due to possible increased bleeding, decreased efficacy, and lack of long term safety data of other therapies. Patients may choose an alternate therapy if averse to daily injections or have other personal preferences. Apixaban or dabigatran are the preferred alternate agents, followed by rivaroxaban and warfarin, if patients are opposed to LMWH.

For major orthopedic surgery, thromboprophylaxis should be extended up to 35 days. Dual therapy of graduated compression devices and an antithrombotic agent should be used in these patients. For patients with increased risk of bleeding, a graduated compression device alone should be used as monotherapy or no therapy should be given.

In patients with an increased risk of bleeding or contraindications to pharmacologic and mechanical therapy, IVC filters are not recommended. For these patients not treating with prophylactic therapy is the preferred option. Doppler ultrasound screening for DVT is also not recommended before discharge.

For patients with an isolated leg injury below the knee requiring immobilization, no thromboprophylaxis is recommended rather than pharmacologic therapy. In patient undergoing knee arthroscopy with no history of VTE, no thromboprophylaxis is recommended.

References:
Wyoming Drug Utilization Review
University of Wyoming
School of Pharmacy
Dept. 3375
1000 E. University Avenue
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Non-Profit Organization
US Postage
Paid
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