Wyoming Drug Utilization Review

Oral Anticoagulants

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The Role of Oral Anticoagulation

Oral anticoagulant agents are commonly used to help prevent and treat several different cardiovascular diseases. One of the most common reasons for long-term anticoagulation is stroke prevention in those with atrial fibrillation. Other potential reasons for anticoagulation include deep vein thrombosis (DVT) prophylaxis after orthopedic surgery as well as prophylaxis and treatment of DVT and/or pulmonary embolism (PE). In the past, vitamin K antagonists, such as warfarin, have been the mainstay for long-term anticoagulation.[1] Recently, new oral anticoagulants such as dabigatran (Pradaxa) and rivaroxaban (Xarelto) have come into the picture. These new agents appear to have the potential to be as effective, if not more effective, and just as safe, if not safer, when compared to warfarin.[2]

"Old" Oral Anticoagulants

Currently, warfarin is the most commonly used long-term anticoagulant agent.[3] To produce its anticoagulant effects, warfarin inhibits the synthesis of vitamin K dependent coagulation factors II, VII, IX, and X. It also inhibits the production of anticoagulant proteins C and S, our body's natural anticoagulation defense.[4] Warfarin is a very effective anticoagulant; however, it comes with several different limitations. Limitations include: large variability in patient response, slow onset of action (half-life = 36 hours), routine laboratory monitoring of international normalized ratio (INR), many drug-drug interactions, and dietary restrictions.[2] Because of these limitations, warfarin is widely underused by most physicians. When warfarin is prescribed, it is estimated that patients are out of their desired therapeutic range 30 to 50% of the time.[5]

"New" Oral Anticoagulants

Since there are many limitations to the standard of practice anticoagulation with warfarin, several new oral anticoagulants have been approved by the FDA. While there are several new agents available, this article will focus on dabigatran and rivaroxaban.

Dabigatran was approved by the FDA in 2010 for the prevention of stroke in those with atrial fibrillation. Since then, providers have begun using dabigatran off-label for the prevention of DVT and PE in those who have undergone hip or knee replacement.[4] Dabigatran is an oral, direct thrombin inhibitor that acts on both active (fibrin bound) and inactive (free) thrombin.[1] Thrombin is a logical target for anticoagulation therapy, as it controls the final activation step of blood coagulation.[2]

Rivaroxaban was approved by the FDA in 2011 to reduce the risk of stroke in people with atrial fibrillation and to prevent DVT and PE in those undergoing orthopedic (hip or knee) replacement. In November 2012, rivaroxaban was also FDA approved for treatment of DVT, PE and reduction in the risk of recurrence of DVT and PE. Rivaroxaban is an oral, direct factor Xa (fXa) inhibitor. It works by blocking the active binding site directly without the assistance of a co-factor; therefore, it has the ability to inhibit both free and bound, or active, fXa.[4]

Comparison of Bleeding Risks

While the new agents' safety profiles look to be just as safe as warfarin, the greatest risk and concern with all anticoagulants continues to be bleeds, which can range from minor to life-threatening.[3] Therefore, research has gone to great efforts to compare the bleed risk with

continued on page 3

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P & T Committee Meeting Update

The P&T Committee met for its quarterly business meeting on November 15, 2012. Highlights of this meeting include:

The following prior authorization was approved:

Linzess and Amitiza will be restricted to their labeled indications. Amitiza will be limited to use in women and Linzess will be limited to use in patients aged 18 years and older.

Truvada will be allowed for those with an HIV diagnosis or history of HIV medications on file. In addition, it will be approved for prophylaxis in patients at high risk of contracting HIV. A prior authorization request will be required for this use including documentation of a negative HIV test and negative pregnancy test. A new prior authorization will be required every three months.

Butrans will be allowed following a 14 day trial of tramadol immediate release and 14 day trial of tramadol extended release.

Nucynta will be allowed for use in patients with diabetic peripheral neuropathy and significant gastrointestinal concerns with use of other CII narcotics.

Exalgo will be limited to doses of 16 mg twice daily (32 mg daily).

Xopenex will be allowed for patients with significant tachycardia associated with albuterol use.

The following changes to prior authorization were approved:

Oxycodone immediate release products will be limited to a maximum dose of 180 mg/day. Anything above this amount will require prior authorization.

Modafinil will be allowed for use in patients with ADHD and a history of substance abuse.

Adderall immediate release will be allowed in patients aged 3 years and older.

Trial and failure of both preferred triptans will be required before approval of non-preferred medications.

All proposed prior authorization criteria will be posted for public comment at www.uwyo.edu/DUR. In addition, the draft 2013 Preferred Drug List (PDL) is posted on the DUR Program website for review. This PDL will be effective January 1, 2013. 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 December 15, 2012.

The next P&T Committee meeting will be held March 7, 2013 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

Correction

In September 2012, a letter was sent to several providers in Wyoming regarding medications used for migraine prevention. Topiramate was inadvertently left off of the Level A medications (those with established efficacy). We apologize for any confusion this may have caused.

2013 P&T Committee Meeting Dates

March 7, 2013
May 16, 2013
August 22, 2013
November 21, 2013

All meetings are on Thursday.

Meetings are held in Cheyenne at Laramie County Community College from 9 am - 1 pm.

Please visit our website at *www.uwyo.edu/DUR* for meeting information.

warfarin to that of the new agents. Many different factors can affect one's risk of developing a bleed; however, the most important aspect to consider is the degree of anticoagulation. Studies have shown that once the measured INR is greater than 3, the occurrence of major bleeds doubles.[3]

A meta-analysis done by Miller et al. looked at the long-term efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, and apixaban) compared to warfarin in patients with atrial fibrillation. When looking at the risk for major bleeds, the data was inconclusive and favored neither therapy. However, when comparing intracranial bleeds, the new agents were associated with less risk when compared to warfarin. Finally, the analysis showed that the risk for developing a gastrointestinal bleed is actually greater when using the new agents.[5]

Komòcsi et al. recently published a meta-analysis that reviewed the use of new oral anticoagulants in patients receiving concurrent anti-platelet therapy in acute coronary syndrome (ACS). Current standard of practice does not recommend the use of warfarin therapy on top of dual anti-platelet therapy in ACS due to the substantial increase risk of bleeds when used together. This review found that the same is also true with new oral anticoagulants. When new agents were used concurrently with dual anti-platelet therapy, the incidence of major bleeds increased two to three times.[6]

When comparing bleeding risk between anticoagulant agents, one must consider other factors that can increase the risk for developing a bleed, such as elderly age, renal or hepatic function, and underlying blood disorders. We must remember that the patients involved in clinical trials typically misrepresent the real-life clinical population that receives these drugs; therefore, the event rates that are reported by the trials may be underestimated.[3]

So Which Anticoagulant Should Be Used?

When selecting an oral anticoagulant, it is important to take into consideration the needs of each individual patient. What is right for one patient is not necessarily the best treatment for the next patient. There are advantages and disadvantages to both warfarin and the new oral agents.

One of the greatest concerns for the new anticoagulants is the lack of a reversal agent. In an emergent situation, for example a severe bleed or need for an emergency surgery, anticoagulation effects need to be reversed quickly. When on warfarin, a patient can be given vitamin K; however, with the new agents, no established reversal agent is available and only supportive care and fresh frozen plasma can be used.[3] The new agents have a shorter half-life (7-17 hours), so their effects will be naturally reversed quicker than warfarin. However, this is only useful in non-life threatening situations.[2]

When comparing dosing, warfarin may be favored. Compliance is often an issue for many patients, and warfarin only requires once daily dosing, where dabigatran requires twice daily doing. Both dabigatran and rivaroxaban require dose adjustments based on renal function, where warfarin does not. If the dose is not adjusted for renal impairment, one could potentially be at an increased risk for a bleed due to accumulation.[4]

While the continuous monitoring of warfarin can become burdensome, it may actually be beneficial, as it tells the extent to which anticoagulation is occurring.[1] Monitoring shows if the patient is therapeutic, and it can also help detect bleed risk before a major bleed occurs. With the new agents, one can only presume the patient is therapeutic. Furthermore, dabigatran has a high rate of dyspepsia, which leads to patient intolerance and discontinuation without the provider's knowledge.[2]

The new oral anticoagulant agents at this point serve as an acceptable alternative to warfarin therapy, not a replacement.[5] One of the best ways to improve the use of warfarin therapy, a drug that is currently well understood, is proper patient and provider education. If everyone involved in warfarin therapy recognizes the signs of bleeding, the importance of monitoring INR, the need for a consistent diet, and the potential for drug-drug interactions, then the use of warfarin may be sufficient until the new agents are better understood.

References

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December 2012

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In This Issue

Oral Anticoagulants
P & T Committee Meeting Update
2013 P & T Committee Meeting Dates

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