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A Review of Rivaroxaban, an Oral Anticoagulant

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Background
In post-operative patients, limited mobility can lead to increased morbidity and mortality due to venous thromboembolism (VTE), which is a life-threatening complication consisting of either deep vein thrombosis (DVT) or pulmonary embolism (PE). Prophylaxis with anticoagulants is often recommended for this patient group for this reason. In general surgery patients without prophylaxis, DVT incidence is approximately 25 percent. Patients undergoing more mobility-limiting procedures, such as total hip or knee replacement surgery or hip fracture surgery, DVT rates are at rates of up to 35-60 percent. With regard to PE, prevalence varies greatly depending on the site of surgery but overall is an important consideration due to the high potential for patient harm. Without prophylaxis, general surgery patients have a PE incidence of 1.6 percent, with 0.9 percent fatality. With an increase in procedure complexity, PE incidence can go as high as 3.6-12.9 percent, such as in hip fracture surgery.

The effectiveness of anticoagulation prophylaxis often is weighed against the safety risks and administration issues of available treatments, and these issues can leave physicians looking for better options. As addressed in the previous issue of The Pharmacy and Wellness Review, development of new anticoagulation agents for prophylaxis of VTE has been underway as drug companies aim to create orally available agents that target the clotting cascade in specific ways to avoid undesired coagulation while minimizing patient bleeding risk. The goal of these new therapeutic agents is to ease patient administration and increase tolerability while being as effective or better than currently available agents in prevention of VTE. Specific targets for therapy include Factors IIa and Xa. Select anticoagulants showing promise in the pipeline include dabigatran, a direct thrombin (Factor IIa) inhibitor, which was discussed in a previous issue of The Pharmacy and Wellness Review (May 2010), and rivaroxaban, a direct Factor Xa inhibitor. Dabigatran was recently given approval by the Food and Drug Administration (FDA). Rivaroxaban has been granted approval for use in both the European Union and Canada since September 2008. Rivaroxaban was submitted in July 2008 for U.S. FDA approval. It was approved by the FDA advisory committee but was denied by the FDA with a need for more information, which the manufacturer, Bayer, is preparing.

Rivaroxaban is a competitive, selective and reversible Factor Xa inhibitor. The bioavailability is greater than 80 percent and is not affected by food, leading to a half-life of approximately nine hours, which may be prolonged in the elderly. Renal excretion accounts for two-thirds of elimination, while the rest is eliminated in the feces via P-glycoprotein and some hepatic metabolism by the CYP450 enzyme system. It is possible that inhibition of CYP3A4 could cause an increase in plasma levels. Rivaroxaban has a contraindication in renal failure (CrCl <30 ml/ min) due to lack of evidence. Early dose-finding studies in hip or knee replacement found rivaroxaban did not have a true dose-response relationship with regards to efficacy, but bleeding risk did increase proportionally with increases in dosage. The optimal dose was found to be between 5 and 20 mg, and rivaroxaban is available as a 10 mg tablet in countries where it is approved.

Efficacy
Several trials concluded efficacy exists for regular clinical use of rivaroxaban in patients. The RECORD 1 and 4 trials had a primary efficacy composite outcome of any DVT (proximal or distal), confirmed non-fatal PE, and all cause mortality during treatment. The RECORD 4 trial had 366 patients eligible for the efficacy analysis with symptomatic DVT during follow-up confirmed by venography or ultra-sound. Using the composite data, 44.3 percent of patients on enoxaparin 40 mg daily had some complication included in the composite endpoint. The 10 mg twice-daily dose of rivaroxaban did considerably better, with only 23.3 percent of patients having a complication (p=0.29). The 5 mg twice-daily rivaroxaban dose had similar efficacy to enoxaparin, with 40.4 percent having complications. Major VTE occurred in patients ranging from rates of 0-6.7 percent with various doses of rivaroxaban versus 4.3 percent with enoxaparin. All rivaroxaban dose-range groups investigated had efficacy similar to twice-daily enoxaparin beginning the day after surgery.

Alternatively, RECORD 1 compared 10 mg rivaroxaban to 40 mg enoxaparin in patients receiving VTE prophylaxis after hip arthroplasty and found rivaroxaban to be more efficacious than enoxaparin. At the end of the trial, 69 percent of 4,541 patients were included in the superiority analysis, with venography required for inclusion. The primary composite endpoint of complications occurred in 1.1 percent in the rivaroxaban group and 3.7 percent in the enoxaparin group (p <0.001), with major VTE occurring in 0.2 percent of the rivaroxaban group contrasted with 2 percent of enoxaparin patients. Major bleeding was observed in 0.3 percent of the rivaroxaban group versus 0.1 percent with enoxaparin.

Another study, RECORD 2, looked at an extended duration of rivaroxaban versus short-term enoxaparin use for prevention of VTE after hip arthroplasty. This study used a modified intention-to-treatment analysis for the primary efficacy of 864 patients in the rivaroxaban group and 869 patients in the enoxaparin group. The primary endpoint occurred in 2 percent of the rivaroxaban group and 9.3 percent in the enoxaparin group. The incidence of bleeding was similar in both groups (6.6 percent for rivaroxaban versus 5.5 percent with enoxaparin). Extended thromboprophylaxis was concluded to be more effective with rivaroxaban than short-term enoxaparin.

A trial independent of the RECORD series, known as the Einstein Study, was a randomized, dose-ranging, double-blind, open-labeled study that compared rivaroxaban to low molecular weight heparin (LMWH) and vitamin K antagonist (VKAs) therapy per hospital protocol until an INR of 2-3 was reached in patients with acute symptomatic DVTs. Of the 543 patients in the study, 449 were eligible to be included in the per-protocol...
analysis. With a primary efficacy composite outcome of symptomatic recurrent DVT, symptomatic fatal/nonfatal PE and asymptomatic deterioration in negative thrombotic effects, rivaroxaban was found to be more efficacious than LMWH/VKA. The LMWH/VKA group had 9 percent of patients experience the primary efficacy endpoint compared to 5.4-6.6 percent of rivaroxaban patients. With the 5-20 mg rivaroxaban range deemed to be efficacious, the 20 mg dose was found to be most effective in preventing DVT recurrences.

Safety

The phase II ATLAS trial was a double-blind, open-label, with block randomization of 1:1:1 placebo: rivaroxaban (doses 5-20 mg) once daily: rivaroxaban (2.5-10 mg) twice daily with at least 225 patients per tier. The study called for liver function tests to take place once a month during the study. The safety endpoint consisted of clinically significant bleeding requiring assistance, such as lab tests or surgery. Liver function tests revealed no significant difference in the rate of alanine aminotransferase greater than three times the upper limit of normal in patients given rivaroxaban compared with placebo (3.7 percent versus 4.5 percent, respectively). Clinically significant bleeding occurred in a dose-dependent manner compared to placebo. Rivaroxaban was compared to enoxaparin in a randomized, double-blind/dummy study, active-comparator-controlled, multi-national study in 873 patients undergoing hip replacement surgery that received prophylaxis of VTE between six and eight hours post-operation. The primary safety outcome was the incidence of major bleeding, which ranged from 0.7 percent with the 10 mg rivaroxaban dose to 5.1 percent with the 40 mg dose. The study determined no significant difference in incidence of major post-operation bleeding between rivaroxaban and enoxaparin. A total of 845 patients was used in the safety population data, which determined a significant dose-response relationship (p=0.0391).13

In RECORD 1 when dosing rivaroxaban, the occurrence of major VTE decreased while the risk of major bleeding increased compared to enoxaparin, suggesting the patient's status should be considered when selecting therapy. A challenge in the approval process for rivaroxaban is the lack of power for safety outcomes in the studies. Post-marketing pharmacovigilance should provide more data on the safety of rivaroxaban.

Place in therapy

Based on safety and efficacy data, rivaroxaban has evidence that it could be an effective treatment in VTE prophylaxis in post-surgical patients. Further studies, including post-marketing surveillance, could help to reinforce this evidence. There are no currently published studies looking into efficacy and safety of rivaroxaban in comparison to warfarin in VTE. The ROCKET-AF trial looking at rivaroxaban in atrial fibrillation versus warfarin is currently ongoing, and results will help to further determine rivaroxaban’s usefulness long-term. Although rivaroxaban has been shown to be clinically useful in patients, some concern was raised over the degree of benefit over enoxaparin in the RECORD trial series results due to inherent trial/design issues. Specifically, Van Thiel raised awareness in an editorial that enoxaparin dosing was inconsistent with recommendations in the United States and that less-than-optimium duration and dosing prevented maximum enoxaparin benefit in comparison to rivaroxaban. Lack of power for differences in major bleeding, as well as some questionable safety evaluations compared to current recommendations, also weakened the findings of this extensive study. While these points are justified, the trial program did demonstrate promising results for rivaroxaban as an alternative agent for VTE prophylaxis. With varying international standards for prophylaxis and new CHEST guidelines, which were published after the trials had been conducted, the issues do not seem to limit rivaroxaban therapy for consideration. Slated to finish in fall 2010, the ROCKET-AF trial will provide results detailing the clinical comparison of rivaroxaban to warfarin. The FDA Advisory Panel has requested more data of Bayer, rivaroxaban’s manufacturer, which is not likely to be submitted until late 2010 or early 2011, meaning FDA approval will be delayed until 2011 at the earliest.

References:

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