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Oral Antithrombotic Inhibitors: Dabigatran Etexilate, Meeting an Unmet Need?

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Although effective, vitamin K antagonists (VKAs) are challenging to use because of their slow onset and offset of action, narrow therapeutic window, multiple dietary and drug interactions, and unpredictable anticoagulant effect. Accordingly, it is recognized that there is an unmet need for an oral thrombotic inhibitor that does not require monitoring and has a rapid onset of action. There is also an unmet need in the field of thromboprophylaxis against venous thromboembolism (VTE) in high-risk patients. The topic of this Supplement is the evidence for the use of dabigatran in high-risk orthopedic patients, namely patients with hip and knee athroplasty. An oral therapy with an immediate reliable and predictable anticoagulant effect without the need for coagulation monitoring and without any long-term hepatic or safety concerns will be a major advance in the management of patients with various thrombotic disorders.

Keywords: oral antithrombotic inhibitors; anticoagulants; dabigatran

Unmet Needs in the Field of Thromboembolism

Although effective, vitamin K antagonists (VKAs) are challenging to use because of their slow onset and offset of action, narrow therapeutic window, multiple dietary and drug interactions, and unpredictable anticoagulant effect. Accordingly, it is recognized that there is an unmet need for an oral thrombotic inhibitor that does not require monitoring and has a rapid onset of action. Several new oral anticoagulants or oral inhibitors that target either thrombin or activated factor X (factor Xa) and have the potential to replace VKAs are presently in advanced stages of clinical development. Designed to be given in fixed doses with no coagulation monitoring, these drugs are certainly likely to be more convenient than VKAs.

There is also an unmet need in the field of thromboprophylaxis against venous thromboembolism (VTE) in high-risk patients. Indeed the topic of this Supplement is the evidence for the use of dabigatran in high-risk orthopedic patients, namely patients with hip and knee athroplasty. The use of thromboprophylaxis in patients with hip and knee arthroplasty is high; most patients receive pharmacological thromboprophylaxis against VTE. In North America, VKA prophylaxis is widely used as well as low-molecular-weight heparin (LMWH) prophylaxis.[1] The new oral inhibitors have been compared with LMWH in high-risk orthopedic patients such as patients with hip and knee athroplasty. The future clinical use of the new inhibitors will depend upon the balance of benefit and harm demonstrated by the clinical trials. It is evident that a strong value is placed by orthopedic surgeons on avoiding harm due to bleeding. Accordingly, an oral inhibitor that is effective but safer than LMWH is likely to be preferred. An oral

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inhibitor that is more effective than LMWH but associated with increased bleeding will be less preferred by orthopedic surgeons.

Dabigatran, a New Oral Anticoagulant Without the Requirement for Monitoring

Dabigatran etexilate is an oral reversible direct thrombin inhibitor (DTI). The findings suggest that dabigatran etexilate is a promising new oral anticoagulant that could become an attractive alternative to traditional prophylactic measures of treatments such as LMWH and VKAs and may have a significant impact on the current approach to managing thromboembolic disorders. Dr Stangier and Dr Clemens report that dabigatran etexilate can be administered as a fixed oral dose, once or twice daily.[2] It has a rapid onset of action and provides a predictable and consistent anticoagulant affect without the need for routine coagulation monitoring. In addition, it appears to have a low potential for drug–drug or drug–food interactions. Dabigatran etexilate is not metabolized by cytochrome p450 isoenzymes. Results from phase 2 and phase 3 trials suggest that dabigatran etexilate is an effective anticoagulant. It is being evaluated for the prevention of VTE in patients undergoing major orthopedic surgery (hip or knee replacement), treatment of venous thrombosis (deep vein thrombosis [DVT] and pulmonary embolism [PE]), secondary prevention of venous thrombosis for an extended duration, and prevention of stroke in atrial fibrillation. Primary venous thrombosis prevention studies have been completed in patients undergoing orthopedic surgery, and dabigatran etexilate appears to be a promising alternative to LMWH. The results of ongoing studies in venous thrombosis treatment and stroke prevention in atrial fibrillation will further define the role of dabigatran etexilate in comparison with traditional VKA anticoagulation. In Europe and Canada, dabigatran etexilate is approved for use in the prevention of venous thrombosis in patients undergoing hip and knee replacement surgery.

Proof of Principle, Pharmacokinetic, and Phase 2 Data

Dahl reports the findings of phase 2 trial data for dabigatran.[3] He identifies venous thrombosis as a well-recognized serious risk after major orthopedic surgery. The use of LMWH is the standard of care for thromboprophylaxis after major orthopedic surgery in Europe and in many centers in North America. Although LMWH is effective, subcutaneous injection is required, making it inconvenient for extended prophylaxis in the outpatient setting. Thrombin is a key enzyme in the blood coagulation cascade and a major factor in the initiation and propagation of thrombosis. Thrombin inhibition therefore represents a therapeutic target for numerous thromboembolism-related disorders, such as VTE and arterial thrombosis. Dabigatran etexilate, a DTI, is a promising agent. It is anticipated that dabigatran etexilate will overcome the limitations of current thromboprophylaxis by providing effective oral thromboprophylaxis after elective surgical procedures such as total hip replacement or total knee replacement. Furthermore, dabigatran etexilate has a predictable pharmacological profile.

Dr Dahl reports the findings of BISTRO 1, a proof of principle study. This was primarily a safety study with dose escalation based on clinical and pharmacokinetic data. This study demonstrated that approximately 20% of patients had low plasma concentrations after the first dose with high interindividual variability in the pharmacokinetic parameters. In view of this high interindividual variability with a trial tablet used, a capsule formulation with an improved pharmacokinetic profile was developed.

BISTRO 1b was a small single dose (150 mg) study evaluating a new capsule formulation of dabigatran etexilate with improved pharmacokinetic properties compared to the tablet used in BISTRO 1. This study showed that the new dabigatran etexilate capsule administered 1 to 3 hours following surgery was effective with prompt absorption and peak plasma concentrations of dabigatran occurring 6 hours after administration. Peak plasma concentrations and systemic exposure of dabigatran using this new capsule formulation were approximately 85% of those seen in healthy volunteers at steady state using the tablet formulation. These characteristics confirmed its suitability for use in future clinical trials.

Dr Dahl then goes on to report the findings of the phase 2b dose-ranging studies. BISTRO 2 was a large randomized, multicenter, parallel-group, double-blind study conducted to determine the efficacy and bleeding dose-response relationship of different dabigatran etexilate–dosing regimens (50, 150, and 225 mg twice daily, as well as 300 mg once daily) for the prevention of VTE after hip and knee replacement surgery. A secondary outcome was to compare the efficacy and safety of the different dabigatran

etexilate–dosing regimens with enoxaparin 40 mg subcutaneously once daily. Dabigatran etexilate was administered 1 to 4 hours after surgery, and enoxaparin was administered subcutaneously the evening before surgery. Treatment was continued for 6 to 10 days, and patients were followed for 4 to 6 weeks after surgery. The primary efficacy outcome was the occurrence of VTE (ie, composite occurrence of venographically documented DVT and symptomatic DVT or PE) during the treatment period. The primary safety outcome was the frequency of major bleeding that also included major bleeding at the operative wound site.

Importantly, the trial demonstrated a significant dose-dependent decrease in total VTE with higher doses of dabigatran etexilate. Based on the same total daily dose, once-daily dosing of dabigatran etexilate was equally as effective compared with twice-daily dosing with comparable rates of bleeding. Furthermore, Dr Dahl reports that dabigatran etexilate was well tolerated in these phase 2 studies with a similar safety profile to enoxaparin. Fixed doses of dabigatran etexilate were given to all patients. After short-term use in the postsurgical setting, there was no evidence of compromised liver safety. Dabigatran etexilate had no effect on laboratory parameters (except clotting test), and a low incidence of nausea and vomiting with early postoperative dabigatran administration was reported.

Dose Selection for Use in the Phase 3 Trial Program

Dose selection for use in the phase 3 trial program based on the phase 2 data resulted in determination of the optimal doses to be evaluated in the phase 3 trials. These were determined to be 150 and 220 mg once daily, with initial doses of 75 and 110 mg on the day of surgery.

Phase 3 Findings

Drs Eriksson and Friedman report the findings of 3 large clinical prophylaxis phase 3 studies that have been completed and reported.[4] These were also prospective, double-blind, randomized trials comparing the antithrombotic efficacy and safety of 2 doses of dabigatran etexilate (150 and 220 mg once daily) with the approved enoxaparin regimen for that region: either enoxaparin 40 mg once daily or 30 mg twice daily in patients undergoing total hip athroplasty or total knee athroplasty.

RE-NOVATE was performed in patients with total hip athroplasty, and 40 mg once daily of enoxaparin was used for comparison. Both prophylactic regimens were given for a total duration of 28 to 35 days (long term). Because the long-term prophylaxis is not recommended after total knee arthroplasty, RE-MODEL and RE-MOBILIZE were performed in total knee athroplasty patients with short-term duration (6 to 14 days) in both treatments. In RE-MODEL, once-daily dabigatran doses started 1 to 4 hours after surgery were compared with 40 mg of enoxaparin started in the evening before surgery, whereas in RE-MOBILIZE, enoxaparin 30 mg twice daily started 12 to 24 hours after surgery was used in the comparator arm.

Importantly, in all 3 trials the first dose of dabigatran etexilate was given as a half dose on the day of surgery. This half-dose regimen was used to address the high rate of major bleeding that occurred on the first day of treatment in BISTRO 2. If the patient was hemodynamically unstable after surgery, the first dose of dabigatran etexilate was administered the day after surgery as a full dose followed by a second dose 12 hours later. The primary efficacy end point in all 3 trials was a composite of total VTE events including venographic or symptomatic proximal and distal DVT or PE, plus all-cause mortality. Bilateral venography was performed within 24 hours of the last dose. The primary safety end point at all trials was the occurrence of major bleeding events during treatment (including those at the surgical site).

The RE-NOVATE trial showed that oral dabigatran etexilate 220 and 150 mg once daily each were noninferior to an enoxaparin subcutaneously 40 mg once daily in reducing the frequency of VTE and all-cause mortality when given for VTE prophylaxis in patients undergoing total hip athroplasty. Major bleeding was similar to that seen with enoxaparin.

The low frequency of hepatic dysfunction during administration may also support the use of dabigatran etexilate for the suggested prolonged time period.

The RE-MODEL trial, which evaluated patients undergoing total knee replacement, demonstrated that dabigatran etexilate 220 mg and 150 mg orally once daily were each noninferior to enoxaparin 40 mg subcutaneously once daily for the prevention of VTE in patients who have undergone total knee

replacement. There was no significant difference in the frequency of major bleeding or overall rate of adverse events between either dose of dabigatran etexilate and enoxaparin.

The RE-MOBILIZE trial, performed predominantly in North America in patients undergoing total knee replacement, compared dabigatran etexilate against the North American regimen of enoxaparin, which was 30 mg twice daily started 12 to 24 hours postsurgery. Treatment was continued for 12 to 15 days in accordance with contemporary US practice. Overall, the REMOBILIZE trial demonstrated that dabigatran etexilate was not as effective as twice-daily enoxaparin in preventing total VTE and mortality. Differences in study design have been postulated to explain these findings compared with the findings observed in RE-MODEL. The high comparative dose (enoxaparin 60 mg) and the later time to first dose orally may have provided the lower effectiveness.

Based on the results of the phase 3 studies described above, a new study (RE-NOVATE II) has been initiated in North America comparing 220 mg of dabigatran etexilate (commenced 1 to 4 hours after surgery) with enoxaparin (40 mg once daily, approved for long-term use in North America) for an extended treatment period of 28 to 35 days in patients undergoing total hip replacement. The trial is expected to complete recruitment in late 2009.

In conclusion, 2 studies conducted in Europe (RE-MODEL and RE-NOVATE) showed dabigatran etexilate 150 and 220 mg once daily to be noninferior to enoxaparin (40 mg once daily, presurgery) for the prevention of the composite of total VTE and all-cause mortality after total knee replacement or total hip replacement. In both studies, the efficacy results in the 220-mg dose group were numerically slightly better than in the 150-mg group. The rates of major bleeding (which included surgical site bleeding) were low (1.3%-2.0%) and similar between the treatment groups in both studies. On the basis of these 2 trials, dabigatran etexilate is approved in Europe and Canada for the prophylaxis of venous thrombosis in patients undergoing hip and knee replacement surgery.

Future Directions in Anticoagulant Treatment

Drs Schulman and Reilly discuss the role of dabigatran for the secondary prevention of VTE (treatment) and for stroke prevention in nonvalvular atrial fibrillation.[5] Preliminary data from 1 study for stroke prevention in patients with nonvalvular atrial fibrillation suggest that dabigatran etexilate may be a reasonable alternative to warfarin, with relatively low rates of bleeding.

Ongoing phase 3 trials are now evaluating the longer term use of dabigatran etexilate for treatment and secondary prevention of VTE and for the prevention of stroke in patients with atrial fibrillation as a replacement for VKAs.

An oral therapy with an immediate reliable and predictable anticoagulant effect without the need for coagulation monitoring and without any long-term hepatic or safety concerns will be a major advance in the management of patients with various thrombotic disorders.

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