New Oral Anticoagulants for Venous Thromboembolism (VTE) Prophylaxis

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SUMMARY

Venous thromboembolism is a rising concern in Asia especially among patients after surgery where this complication is readily preventable. Despite the availability of several treatment options, the acceptance of prophylaxis and usage of these methods remain low. A possible explanation to this behavior is the limitations attached to the available treatment options: narrow therapeutic window of warfarin and parenteral administration of low molecular weight as well as unfractionated heparins. Newer agents have been researched and introduced to overcome these limitations in the hope of improving the adaptation towards post surgical thromboprophylaxis. Dabigatran and rivaroxaban are two such new agents that are promising in view of efficacy and ease of administration.

KEY WORDS:
Venous thromboembolism, Oral anticoagulant, VTE prophylaxis, dabigatran, Rivaroxaban, Malaysia

INTRODUCTION

Venous thromboembolism (VTE) has been increasingly recognized as a serious complication that afflicts tens of thousands of patients undergoing surgery. This complication is largely preventable by using chemical or mechanical thromboprophylaxis.

Despite the controversy in the actual incidence of VTE in Asia, more data have now emerged suggesting that the incidence could be as high as those in western countries[1, 2]. Meta-analysis of studies in Asia has revealed an incidence of perioperative VTE of 3-28% among general and colorectal surgery and 10-63% in orthopaedic surgery[1]. Increasingly, many hospitals in Asia have witnessed rising rates and have adopted the universally accepted VTE thromboprophylaxis guidelines.

Mechanical methods of thromboprophylaxis include graduated compressive stocking, intermittent pneumatic compression and venous foot pump. There have been few large scale studies of these devices. While they have been shown to decrease the incidence of deep vein thrombosis (DVT), these devices have not been shown to decrease the incidence of pulmonary embolism or death[3, 4].

Subcutaneous low dose unfractionated heparin (LDUH) has been the main chemical modality used in VTE prophylaxis. It has generally been effective but requires a thrice or twice daily injection, with an increased risk of bleeding and rarely heparin induced thrombocytopenia (HIT). Low molecular weight heparin (LMWH) has further reduced the risk of perioperative VTE, with a convenient daily dosing and lower incidence of HIT its acceptance and usage has superseded LDUH. Fondaparinux, a synthetic pentasaccharide, has the advantage of extraction from non-biological source, a longer duration of action affirming its effective single daily dosing but has the disadvantage of increased post-operative bleed unless it is administered six hours post operatively[5].

Warfarin is a coumadin derivative and interferes with synthesis of coagulation factors II, VII, IX and X. It has been used, though uncommonly, as a thromboprophylactic agent in orthopedic surgery. Dosing is convenient as it is taken orally but suffers from delayed onset of action, low bioavailability, unpredictable pharmacokinetics from drug-drug interaction and drug-food interaction[6].

Clearly, the quest for a new anticoagulant that is orally administered, effective, safe, cheap with high bioavailability and predictable pharmacokinetics is ongoing. Recently, a new class of oral anticoagulants that may fulfill the ideals of anticoagulants has emerged.

This paper reviews the clinical studies on the new oral anticoagulants that are available locally, i.e. oral direct factor Xa inhibitor rivaroxaban and oral direct thrombin inhibitor dabigatran.

MECHANISM OF ACTION

The ideal target of anticoagulation would be towards the tail end of the coagulation cascade where prothrombin is converted to thrombin and that a single critical procoagulation complex is inhibited, preferably reversibly. Rivaroxaban inhibits activated factor Xa (Anti-Xa) and dabigatran inhibits thrombin directly (DTI). The mechanism of action of rivaroxaban and dabigatran is shown in Figure 1.

DABIGATRAN

Dabigatran is a DTI and reversibly inhibits thrombin. It is similar to ximelagatran which had been proven to be as effective as warfarin and enoxaparin in the treatment and

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Table 1: Comparison of oral anticoagulants

	Warfarin	Dabigatran	Rivaroxaban
Mechanism of action	Vitamin K antagonist	Anti-Thrombin	Anti Factor Xa
Time to peak plasma concentration (hours)	2-8 (anticoagulant effect after 48-72)	2-3	2-4
Drug- food and drug-drug interaction	Yes	No	Yes
Half-life (hours)	20-60	12-17	5-9
Renal clearance (%)	Low	80	66
Need for monitoring	Yes	No	No

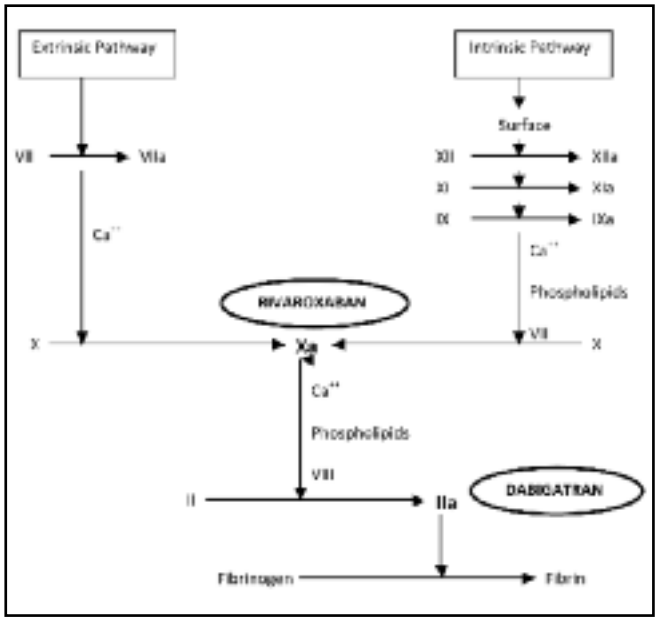

Fig. 1: Mechanism of action of rivaroxaban and dabigatran within the coagulation cascade.

prevention of VTE[7]. Ximelagatran did not gain approval from US FDA and was withdrawn due to the association with liver enzyme elevation and severe liver injury over longer term treatment[8]. Dabigatran however is an improved version and phase III studies have shown no significant increase in liver enzymes as compared to enoxaparin.

Administered orally, Dabigatran reaches peak plasma concentration (Cmax) and anticoagulant effect within 1.5 to 3 hours and has a half life of 12-17 hours and it is eliminated primarily through the kidney[9]. The pharmacokinetics and pharmacodynamics of Dabigatran versus other oral anticoagulants is illustrated in Table 1.

In BISTRO II (Boehringer Ingelheim Study in Thrombosis), dabigatran at doses of 50, 150 or 225 mg twice daily or 300mg daily were compared to subcutaneous enoxaparin 40 mg daily. Increasing doses of dabigatran were shown to decrease VTE rates but at the same time significantly increase major bleeding rates[10].

Dabigatran was found to be not inferior to enoxaparin in the RE-MODEL trial in reducing the incidence of VTE/ all cause mortality after elective total knee (TKR) replacement (36.4%-40.5% vs. 37.7%)[11]. There were no difference in the bleeding rate and the incidence of elevated liver enzymes. RE-NOVATE for total hip replacement (THR) trial and RE-MOBILIZE for TKR trials have again showed non inferiority in terms of VTE and all cause mortality when compared to enoxaparin[12, 13]. The rates of major bleeding were also non-significant.

RIVAROXABAN

Rivaroxaban is a direct factor Xa inhibitor and when administered orally, reaches peak plasma concentration in 2 to 4 hours and has a half life of 5 to 9 hours[14]. It is eliminated mainly by the renal route but a third of the drug is also eliminated by the faecal and biliary route[14].

In ODIXa-OD-HIP (Oral Direct Xa inhibitor given once daily in patients undergoing THR) study, once daily rivaroxaban (5-40mg) had similar efficacy compared to enoxaparin 40mg daily. The study also found that the 10mg regime has the best balance of efficacy and tolerability. The composite DVT, PE and all cause mortality was 10.6% and major post-operative bleeding was 0.7%[15].

In RECORD (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism) -1 and 2, rivaroxaban was shown to reduce the venographically proven VTE events in patients undergoing THR surgery by a significant extent when compared to enoxaparin (1.1% vs. 3.7%, P <0.001). The major bleeding rate was not significant[16, 17]. In RECORD-3 and 4, rivaroxaban has achieved a relative risk reduction rate of 49% and 31% respectively in the composite endpoint of DVT, non fatal PE or death in patients undergoing TKR surgery. The superiority demonstrated in RECORD-4 was in comparison to enoxaparin 30 mg twice daily. Again the incidence of major post operative bleeding was not statistically significant compared to enoxaparin[18, 19].

DISCUSSION

With the rising incidence of perioperative VTE, prophylactic anticoagulation usage should increase proportionately. LMWH has been widely accepted as the standard chemoprophylaxis method. However, the need for parenteral administration and the relative high cost of LMWH has been a disadvantage. The emerging oral anticoagulants have proven their efficacy and safety in Phase III studies and has the potential to replace the parenteral anticoagulants and warfarin in the future.

There are caveats, however, when extrapolating the clinical trial results to real life scenarios. The exclusion criteria are stringent in clinical trials and this would preclude a substantial number of patients from using the medication. These include patients with renal impairment, elevated liver

enzymes and morbid obesity. Oral medication also poses problems when a patient is unable to take orally or is vomiting; not an uncommon occurrence in general surgical patients.

With a prolonged half life and lack of antidote, the usage of regional anaesthesia is a serious issue. The American Society of Regional Anaesthesia and Pain Medicine guidelines state that – the administration of these medications in combination with neuraxial anaesthesia must be carefully considered[20]. Due to the lack of data, no statement regarding risk assessment and patient management can be made.

The question of hepatotoxicity could be the Achilles heel for the new oral anticoagulants after the ximelagatran fiasco. The current newer oral anticoagulants have been shown to be safe in phase III trials. In particular, the serum bilirubin and liver enzyme elevation has been studied extensively. While the long term effects are still unknown, most medication in VTE prophylaxis is used only for a short period, diminishing the concern on liver safety.

CONCLUSION

The results of phase III studies on dabigatran and rivaroxaban have proven the efficacy and safety of the two molecules in preventing perioperative VTE in patients undergoing knee or hip arthroplasty. Dabigatran was non-inferior to enoxaparin and rivaroxaban was superior to enoxaparin across a range of orthopedic patients with no significant adverse effect on the liver profile and no significant increase in post-operative bleeding. The predictable pharmacokinetic and pharmacodynamic profiles make monitoring unnecessary. With the ease of oral administration, safety and efficacy, these molecules provide an efficacious alternative to the conventional agents for perioperative VTE prevention and hopefully would promote adherence to VTE prophylaxis as well as increase acceptance in its usage.

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Oral Anticoagulant CME questions

1. Regarding perioperative VTE

a. The incidence is low in Asia so routine thromboprophylaxis is not recommended
b. There are no Clinical Practice Guidelines in Malaysia on VTE prophylaxis
c. Pulmonary embolism is now the major cause of maternal deaths in Malaysia
d. After a total hip or total knee replacement, the incidence of VTE is between 40-80%
e. Inferior vena caval filter is recommended for prevention of PE in high risk surgery

2. Regarding the mechanical methods of thromboprophylaxis:

a. Graduated compressive stocking is an acceptable method of prophylaxis in low risk surgery
b. Mechanical methods have been shown to reduce post-operative deaths from VTE
c. Intermittent pneumatic compression is recommended in spinal surgery
d. The pressure in the stocking should exceed 25mmHg
e. Combined chemical and mechanical prophylaxis is recommended in very high risk surgery

3. The following drugs are recommended for chemoprophylaxis in latest ACCP guidelines:

a. Clopidogrel
b. Unfractionated Heparin
c. Low Molecular Weight Heparin
d. Rivaroxaban
e. Fondaparinux

4. Dabigatran

a. is non inferior to Enoxaparin in reducing the incidence of VTE after total knee replacement
b. is biologically similar to Ximelagatran
c. should be stopped a day prior to epidural anaesthesia
d. interacts with Vit K containing food
e. shows excessive bleeding when compared to enoxaparin

5. Rivaroxaban

a. is shown to be superior to Enoxaparin in reducing VTE after Total Hip Replacement
b. is not affected by food
c. requires regular monitoring with INR to achieve therapeutic range
d. is recommended for VTE prophylaxis in knee replacement surgery
e. is safe in patients with renal impairment