Review Article

Newer anticoagulants for the prevention of venous thromboembolism

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INTRODUCTION

Anticoagulation is the mainstay of treatment for patients with venous thromboembolism (VTE); this includes patients with both deep vein thrombosis (DVT) and pulmonary embolism (PE).[1]

Heparin (both unfractionated and low molecular weight) and warfarin (along with other coumarin anticoagulants) have been the traditional anticoagulants in use. However, these drugs have many drawbacks,[2] and hence the need for a new and ideal anticoagulant. To be labelled as an 'ideal' anticoagulant, it would have to be highly efficacious and at the same time very safe (i.e. carry a low risk of bleeding), have a fixed dosing schedule and ease of administration, i.e. by the oral route with minimal therapeutic monitoring and a rapid onset of action with potential for rapid reversibility (i.e. have an antidote).[3]

TRADITIONAL ANTICOAGULANTS

Parenteral

As heparin and its analogues have to be administered parenterally, they cannot be called 'ideal' anticoagulants. In addition, because of the inability of heparin to inactivate clot-bound thrombin, reversing thrombosis is not possible.[2] As expectations from the ideal anticoagulant continue to rise, the ability to reverse thrombosis is another feature to be considered.

Oral

Warfarin (the prototype of vitamin K antagonists), though administered orally, has a very narrow therapeutic index. Overdosing can lead to bleeding and underdosing to the risk of recurrent thrombosis.[4] It requires frequent laboratory monitoring during its use. A large number of drug and food interactions and delayed onset of action requiring bridging therapy with heparins are the other major drawbacks of this class of oral anticoagulants.[5]

NEW PARENTERAL ANTICOAGULANTS

Fondaparinux

This is a synthetic pentasaccharide that acts as a selective indirect parenteral factor Xa inhibitor and can be used as an anticoagulant in the initial management of patients with VTE.[1] It is administered subcutaneously and requires only once-daily dosing as it has a half-life of 17 hours.[6] Fondaparinux has been evaluated in many large trials, and the data acquired have supported its use in thromboprophylaxis.

Fondaparinux was initially shown to be as efficacious as enoxaparin, with no increase in the risk of bleeding or death. Of 908 patients on fondaparinux, 37 (4%) were found to have evidence of VTE on day 11 of elective hip replacement surgery versus 85 of 919 (9%) of those on enoxaparin.[7]

In a double-blind study, 2275 consecutive adult patients undergoing elective hip replacement surgery were randomly assigned to receive postoperative subcutaneous injections of either 2.5 mg fondaparinux once daily or 30 mg enoxaparin twice daily. The primary efficacy outcome was VTE on day 11. This was recorded in 48 (6%) of 787 patients on fondaparinux and in 66 (8%) of 797 patients on enoxaparin. The relative reduction in risk was 26.3%. Hence, 2.5 mg fondaparinux once daily was not significantly more effective than 30 mg enoxaparin twice daily in reducing risk of VTE, but was equally effective. Also, there was no increase in clinically relevant bleeding in this study.[8]

In the Matisse DVT trial, 2205 patients were treated with a once-daily subcutaneous dose of fondaparinux (5.0 mg if <50 kg body weight; 7.5 mg if 50–100 kg; 10 mg if >100 kg) or twice-daily subcutaneous low molecular-weight heparin (LMWH; enoxaparin 1 mg/kg) for at least 5 days using a blinded design. There was no difference between the two agents in the occurrence of recurrent VTE at 3 months .[9]

The PEGASUS Investigators demonstrated that postoperative fondaparinux was at least as effective as perioperative dalteparin in patients undergoing high-risk abdominal surgery. The rate of VTE was 4.6% with fondaparinux compared with 6.1% with dalteparin, with no significant increase in the risk of bleeding.[10]

The ARTEMIS Investigators studied the effect of 2.5 mg fondaparinux versus placebo in 849 patients ≥60 years with acute medical illnesses. This study found that there was a relative risk reduction of 46.7% with fondaparinux as compared to placebo, with no increase in the risk of major bleeding.[11]

In summary, fondaparinux was shown to be efficacious in these trials for the prevention and treatment of VTE, with evidence of substantial reduction in the risk of bleeding and mortality.[12] It has been approved by the US Food and Drug Administration (FDA).

Unfortunately, there is no laboratory test available that can monitor the therapeutic efficacy of this drug and it does not have a specific antidote. Cessation of therapy and transfusion of fresh frozen plasma are the measures to be taken in the event of bleeding. Recombinant factor VIIa may reverse the bleeding

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caused by this drug, but needs further evaluation in this setting.[13] There is a biotinylated version of the pentasaccharide class of anticoagulants whose action is easily reversible by the egg white protein avidin.[14] However, there is not much evidence from large randomized controlled trials yet to support its use.

The American College of Chest Physicians recommends thromboprophylaxis with a LMWH, low-dose unfractionated heparin (LDUH) or fondaparinux for patients undergoing major surgery. It is recommended that patients undergoing elective hip or knee arthroplasty be on anticoagulation with an LMWH, fondaparinux or a vitamin K antagonist, maintaining an international normalized ratio (INR) of 2–3.[15]

NEWER ORAL ANTICOAGULANTS

Despite the promise of parenteral fondaparinux, the need and search for the 'ideal' (oral and reversible) anticoagulant continues. In the process, newer drugs have been developed.

Dabigatran etexilate (an oral thrombin inhibitor), rivaroxaban and apixaban (oral anti-factor Xa inhibitors) are three agents that are in advanced stages of development as well as clinical use as oral anticoagulants.[4] These compounds have the potential to complement the action of heparins and fondaparinux for short-term anticoagulation, and/or to replace vitamin K antagonists for long-term anticoagulation in most patients.[16]

The first direct oral thrombin inhibitor to complete phase 3 trials was ximelagatran, but further development was dropped due to hepatotoxicity.[17] The drug that has progressed further in its development is dabigatran etexilate.

Major orthopaedic surgery, such as total knee replacement, hip replacement and hip fracture repair, puts patients at the highest risk for VTE. PE is the main cause of death in these patients.[18] Hence, these newer anticoagulants have been studied in major orthopaedic trials, with the aim of finding an ideal drug for thromboprophylaxis in the postoperative period.

Dabigatran

Dabigatran etexilate is an oral prodrug, which is rapidly converted by serum esterases to dabigatran, a competitive direct thrombin inhibitor. Its bioavailability is 6.5%, and it has a 2-hour onset of action, and a 12–18-hour half-life.[4] It is administered once or twice daily. Eighty per cent of the drug is excreted through the kidney. Direct thrombin inhibitors (excluding argatroban) are mainly excreted by the kidneys, and hence their doses require adjustment in cases of renal impairment.[19] It is not recommended for patients with a creatinine clearance <30 ml/hour. It prolongs the activated partial thromboplastin time (APTT), has a negligible effect on the prothrombin time (PT), but has the maximum effect on prolonging the Ecarin clotting time.[4]

The major trials in orthopaedic thromboprophylaxis with dabigatran include the RENOVATE trial, which was a double-blind study including 3494 patients who had undergone total hip replacement. In this trial, two different doses of dabigatran (220 mg once daily versus 150 mg once daily) were compared with enoxaparin in a prophylactic dose, and dabigatran was found to be as efficacious as enoxaparin. The risk of VTE and bleeding with either of these agents at both the doses was the same.[20]

The REMODEL trial included 2076 patients undergoing total knee replacement. Two different doses of dabigatran (220 mg once daily and 150 mg once daily) were compared with enoxaparin prophylaxis. It was found that dabigatran was not inferior to enoxaparin for the prophylaxis of VTE, and the risk of bleeding with both these agents (even at different doses) was the same.[21]

The British National Institute of Clinical Excellence (NICE) has reviewed the data from these major trials and concluded that dabigatran etexilate is comparable to LMWH in preventing VTE events and in terms of short-term adverse effects. However, dabigatran etexilate does not have an antidote, while LMWH and warfarin do.[22]

Dabigatran is approved in Europe and Canada for thromboprophylaxis following total hip and total knee replacement surgeries, and is under consideration in many countries for the prevention of stroke in atrial fibrillation.

The summary of product characteristics states that dabigatran etexilate should be started within 1–4 hours of surgery at a dose of 110 mg. Thereafter, treatment is continued with a standard dose of 220 mg once daily for 10 days after knee replacement, and for 28–35 days after hip replacement. For special patient populations (including patients with moderate renal impairment, those >75 years and those receiving amiodarone), a reduced dose of 150 mg (75 mg starting dose, 150 mg continuing dose) once daily is recommended.[23]

In summary, dabigatran is as effective as warfarin for the treatment of acute VTE and has a safety profile that is similar to that of warfarin, does not require laboratory monitoring[24] and has a more predictable response.[25] As this drug has fewer drug interactions than warfarin, it is likely to have a better compliance as well.[26]

Argatroban

This is a direct thrombin inhibitor and is indicated for the treatment and prophylaxis of thrombosis in patients with heparin-induced thrombocytopenia and in those with heparin-induced thrombocytopenia undergoing percutaneous coronary intervention.

Two prospective multicentre, non-randomized, open-label studies (ARG-911 and ARG-915) evaluated the efficacy and safety of argatroban as an anticoagulant in patients with heparin-induced thrombocytopenia.[27,28] Both studies showed that the incidence of the primary efficacy end-point (a composite of all-cause death, all-cause amputation or new thrombosis) was reduced in argatroban-treated patients versus control subjects. In both studies, bleeding rates were similar between the groups. Argatroban has also been evaluated in three prospective, multicentre, open-label studies (ARG-216, ARG-310 and ARG-311) in patients with heparin-induced thrombocytopenia who underwent percutaneous coronary intervention.[29] A pooled analysis of these studies showed that most (≥95%) patients achieved a satisfactory outcome from the procedure and were adequately anticoagulated.[30]

A single-centre retrospective study on 138 patients compared the effectiveness of bivalirudin and argatroban in achieving the goals of anticoagulation. It also assessed the safety and efficacy in patients with known or suspected heparin-induced thrombocytopenia. Ninety-two patients were on bivalirudin and 46 on argatroban. New thromboembolic events occurred in 7 patients (8%) receiving bivalirudin and 2 (4%) receiving argatroban (p=0.718). Bleeding events occurred at similar rates in both the groups (9% for bivalirudin *v.* 11% for argatroban). Hence, bivalirudin and argatroban were similar in achieving and maintaining therapeutic anticoagulation goals, clinical outcomes and safety.[31]

Argatroban is given parenterally. For continuous anticoagulation, argatroban 0.75 μg/kg/minute (0.2 μg/kg/minute in hepatic impairment) is used. The dose is adjusted to achieve a therapeutic activated partial thromboplastin time (APTT). A multicentre, single-arm, open-label study of 18 children requiring non-heparin

anticoagulation, and hence on agatroban, found that it rapidly provides adequate levels of anticoagulation and is generally well tolerated.[32]

The drug requires dose modification in hepatic and renal dysfunction. Total serum bilirubin >1.5 mg/dl or combined hepatic and renal dysfunction are indications for decreasing the dose. The dose can be titrated by monitoring the APTT values such that they are 1.5–3-times the control.[33]

There is no specific antidote for argatroban overdose. If life-threatening bleeding occurs or excessive plasma concentrations of argatroban are suspected, therapy should be discontinued immediately and symptomatic therapy provided to the patient.[34]

Rivaroxaban

Rivaroxaban is a potent and selective oral factor Xa inhibitor with a bioavailability of nearly 80%. Its plasma levels peak after 3–4 hours, and it has a mean half-life ranging from 5 to 9 hours in young individuals, and from 11 to 13 hours in the elderly. It is excreted mainly by the kidneys but also by the faecal and biliary routes. Rivaroxaban can be administered at a fixed dose to any patient and does not need laboratory monitoring.[1]

The major trials in orthopaedic thromboprophylaxis with rivaroxaban include the RECORD1, RECORD2 and RECORD3 trials which compared rivaroxaban with enoxaparin prophylaxis in total hip and knee replacement. They showed that rivaroxaban was superior in preventing VTE.

The RECORD1 study included 3153 patients and concluded that a once-daily 10 mg oral dose of rivaroxaban was significantly more effective for extended thromboprophylaxis than a once-daily 40 mg subcutaneous dose of enoxaparin in patients undergoing elective total hip arthroplasty. Both drugs had a similar safety profile.[35]

In the RECORD2 trial, 2509 patients scheduled to undergo elective total hip arthroplasty were randomly assigned to oral rivaroxaban 10 mg once daily for 31–39 days (with placebo for 10–14 days) or enoxaparin 40 mg once daily subcutaneously for 10–14 days (with placebo for 31–39 days). The primary efficacy outcome was the composite of DVT, non-fatal PE and all-cause mortality up to day 30–42. The results showed that extended thromboprophylaxis with rivaroxaban was significantly more effective than short-term enoxaparin and placebo for the prevention of VTE.[36]

The RECORD3 trial was done on 2531 patients and revealed that rivaroxaban was superior to enoxaparin for thrombo-prophylaxis after total knee arthroplasty, with similar rates of bleeding.[37]

In the RECORD4 trial, 3148 patients undergoing knee arthroplasty received either oral rivaroxaban 10 mg once daily beginning 6–8 hours after surgery, or subcutaneous enoxaparin 30 mg every 12 hours, starting 12–24 hours after surgery. The results showed that oral rivaroxaban for 10–14 days was significantly superior to subcutaneous enoxaparin for the prevention of VTE.[38]

The Einstein-DVT Dose Ranging Study has shown the need for further trials to evaluate the most appropriate dose for rivaroxaban.[39] The British NICE recommended rivaroxaban as an option for the prevention of VTE in adults undergoing elective total hip or knee replacement surgeries.[40]

The summary of product characteristics for rivaroxaban states that it should be taken orally once daily at a dose of 10 mg per day. The initial dose should be taken 6–10 hours after surgery. The duration of treatment depends on the individual risk of the patient for VTE, which is determined by the type of orthopaedic surgery. The recommended duration of treatment is 5 weeks for patients undergoing major hip surgery and 2 weeks for patients undergoing major knee surgery. According to the document, approximately 14% of treated patients across the phase 3 studies experienced adverse reactions. Bleeding was noticed in 3.3% and anaemia in approximately 1%. Other common adverse reactions were nausea and an increase in transaminases.[41]

Rivaroxaban is now approved in Canada and Europe for thromboprophylaxis after major orthopaedic surgery. However, the US FDA decided not to approve it due to the concern that it 'could lead to bleeding events in significantly more patients than enoxaparin'. The FDA has requested more safety data and the possibility of approval at a later date remains.[42]

Apixaban

Apixaban is a selective direct factor Xa inhibitor given orally in a dose of 2.5 mg twice daily. It has a 3-hour onset of action and a half-life of 8–15 hours. It is well tolerated by patients with hepatic and renal disease. Potent CYP 34A inhibitors decrease the absorption of apixaban.[43] When added to dual antiplatelet therapy with aspirin and clopidogrel, apixaban resulted in unacceptably high rates of major bleeding.[44]

The major trials in orthopaedic thromboprophylaxis with apixaban include the ADVANCE2 trial. It included 3057 patients and showed that apixaban 2.5 mg twice daily commenced on the morning after total knee replacement is a convenient and more effective oral alternative to enoxaparin 40 mg per day. It is not accompanied by increased bleeding.[45]

The double-blind ADVANCE3 trial conducted on 5407 patients found that among patients undergoing hip replacement, thromboprophylaxis with apixaban, as compared with enoxaparin, was associated with lower rates of VTE without increased bleeding.[46]

CONCLUSION

In addition to prophylaxis for VTE, newer anticoagulants are also being tested for use in patients with atrial fibrillation, prosthetic heart valves and coronary artery disease.[4]

The main limitations of these new anticoagulants are their high cost and the lack of specific antidotes.[47] Hence, the search for the 'ideal' anticoagulant is still on, even though we have 'newer' and more promising anticoagulants. Parenteral direct factor II inhibitors (flovagatran sodium), orally active direct factor X inhibitors apixaban, betrixaban, YM150, edoxaban, and new parenteral factor Xa inhibitors (idraparinux, idrabiotaparinux, biotinylated idraparinux; SSR 126517), ultra-low molecular-weight heparins (ULMWH: AVE5026, RO-14) are the other new anticoagulants undergoing clinical testing[16] in the search for the ideal anticoagulant, which will help simplify treatment paradigms and improve overall clinical outcomes.[48]

The main advantages of the newer anticoagulants are the oral route of administration, rapid onset of action, limited drug interactions, better efficacy with regard to thromboprophylaxis and a lower risk of bleeding with some of these agents. Our concern is that we do not have years of experience or data on pregnant women and children with these drugs, as we have for heparin and warfarin. There may still be a lot to learn about these newer anticoagulants as we introduce them in clinical practice.

At present, the newer oral anticoagulants are not available in India. It will be interesting to note their cost when available here, which would merit a cost-effectiveness analysis in the Indian set-up.

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