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Post-operative thromboprophylaxis: new oral thrombin and factor X inhibitors and their place in clinical practice

Miodrag Filipovic* and Thomas Schnider

Address: Institute of Anaesthesiology, Kantonsspital St Gallen, CH 9007 St Gallen, Switzerland

* Corresponding author: Miodrag Filipovic (miodrag.filipovic@kssg.ch)

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Abstract

Thromboprophylaxis can reduce the incidence of postoperative thromboembolic events by two-thirds. Traditionally, unfractionated heparin, low-molecular-weight heparins, vitamin K antagonists, and mechanical methods have been used. Recently, thrombin and factor Xa (FXa) antagonists have been introduced in clinical practice. Advantages are oral administration, potentially higher efficacy in reducing thromboembolic events without increasing major bleeding, and no need for monitoring of the anticoagulatory effect. So far these drugs have mainly been tested after total hip and knee arthroplasties. However, data after most other orthopedic and surgical procedures are sparse. In special populations – for example, patients with renal failure – these drugs have not been sufficiently tested yet. Accordingly, the clinical use of these promising new drugs should be restricted to situations where efficacy has been proven with clear evidence from controlled clinical trials.

Introduction and context

Perioperative thromboembolism

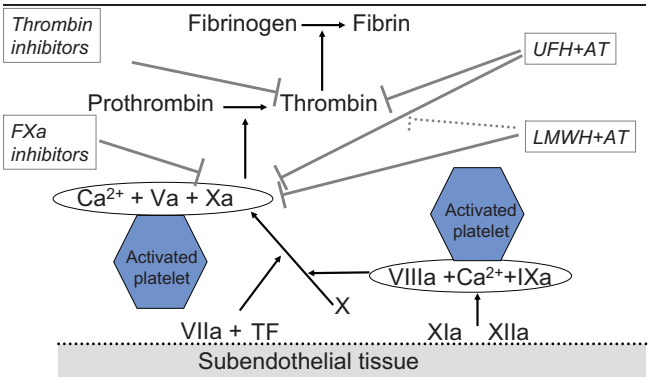
Without adequate prophylaxis against thromboembolism, the incidence of objectively confirmed, hospital-acquired deep vein thrombosis may be as high as 10-40% among general surgical patients and 40-60% following major orthopaedic surgery [1,2]. The incidence of potentially fatal thromboembolic events can be reduced by two-thirds with mechanical and drug based prophylaxis [1]; therefore, routine prophylaxis is established clinical practice nowadays [2,3]. However, recent data suggest that a substantial portion of events occur after hospital discharge and after stopping routine prophylaxis [4,5].

Traditional thromboembolic prophylaxis

Traditional thromboembolic prophylaxis was mainly based on the administration of unfractionated heparin, low-molecular-weight heparins (LMWHs), vitamin K antagonists, and mechanical methods [6]. Vitamin K antagonists block biosynthesis of coagulation factors II (prothrombin), VII, IX, and X. The main disadvantages are the need for close monitoring and the risk of interactions with ingested food and other drugs. Unfractionated heparin and LMWHs modulate coagulation by enhancing the activity of antithrombin. Unfractionated heparin inhibits FXa and thrombin activity (along with coagulation factors); in contrast, LMWHs predominantly inhibit FXa (Figure 1) [7]. Disadvantages of the heparins include the need for monitoring when used in higher doses, the risk of heparin-induced thrombocytopenia, and the need for parenteral application, which can be a challenge in outpatient settings. An advantage of unfractionated heparin is the reversibility of the anticoagulatory effect by protamin administration.

Properties of an ideal anticoagulant are oral administration, rapid onset of action, no increased risk of bleeding, predictable pharmacokinetics and pharmacodynamics, fixed-dose administration, a wide therapeutic window, and no need for monitoring [7]. The development of new antithrombotic drugs aims to meet these requirements and has focussed mainly on FXa and thrombin (Figure 1).

Figure 1. Simplified coagulation cascade and the targets of heparins and thrombin and factor Xa inhibitors



AT, antithrombin; FXa, factor Xa; LMWH, low-molecular-weight heparin; TF, tissue factor; UFH, unfractionated heparin. IXa, Va, VIIa, VIIIa, X, Xa, XIa, XIIa refer to factors.

Recent advances

Factor X inhibitors

The pentasaccharide fondaparinux indirectly inhibits FXa by activating antithrombin. Fondaparinux has been widely investigated and is recommended for thromboembolic prophylaxis in patients undergoing major orthopedic surgery [2,3]. The evidence for a beneficial effect of fondaparinux is even higher than that for LMWHs (i.e., enoxaparin 40 mg once daily) for patients who have had surgery for hip fracture [2]. Fondaparinux is administered by one subcutaneous injection per day. The slow elimination (half life of 13-21 hours), and the irreversibility of FXa inhibition are shortcomings in situations when surgical revision is required. The drug is eliminated unmetabolised by the kidneys. It should be used cautiously in patients with renal failure. Monitoring of the effect of fondaparinux in clinical practice is challenging because the anti-FXa tests developed for LMWHs are inappropriate and a drug-specific anti-FXa test has to be used.

Rivaroxaban is a selective direct FXa inhibitor that is administered orally. Several studies have demonstrated the efficacy of the drug for prevention of thromboembolism after hip and knee arthroplasties. Compared with the LMWH enoxaparin, rivaroxaban significantly reduced the incidence of venous thromboembolism by around a half without evidence for an increased risk of major bleeding [8-13]. In hip and knee arthroplasty patients, rivaroxaban is started after surgery and continued for up to 4 weeks. Following oral administration, the drug is absorbed rapidly and maximal inhibition of FXa is observed after 2-3 hours [14]. Several dose-finding studies have been performed. However, the recently published large trials in patients after hip and knee arthroplasties all used a fixed dose of 10 mg rivoroxaban given once daily [9,11-13]. It is important to notice that patients with renal failure (creatinine clearance <30 mL/minute) have been excluded from the studies and that the use of the drug in these patients should be considered as contraindicated.

Rivaroxaban prolongs classical coagulation tests, such as prothrombin time and activated partial thromboplastin time [14]. The latter has been suggested for monitoring of the antithrombotic effect of rivaroxaban. However, its clinical usefulness in this setting is unproven, and so far no other tests are available.

Apixaban, otamixaban, betrixaban, idraparinux, and edoxaban are examples of other FXa inhibitors currently under clinical investigation [15-18]. Oral apixaban (2.5 mg twice daily) was equally efficient or even superior to enoxaparin after knee and hip arthroplasties but caused less bleeding [15,19]. In contrast, studies with idraparinux produced evidence for increased incidences of bleeding [18,20].

Thrombin inhibitors

The direct thrombin inhibitors are small molecules that bind directly to the active catalytic site of thrombin. Hirudin was the first direct thrombin inhibitor introduced in clinical practice. It is administered parenterally. Along with other thrombin inhibitors (lepirudin, argatroban, and bivalirudin), hirudin is mainly used in patients with heparin-induced thrombocytopenia [21].

Ximelagatran is an orally acting thrombin inhibitor with promising results in the prevention of thromboembolic events. However, it was withdrawn from the market because of hepatotoxic effects.

Dabigatran is a newer orally administered thrombin inhibitor. The prodrug dabigatran etexilate is rapidly absorbed and converted to the active form, dabigatran. The terminal half-life is 14-17 hours [7]. Dabigatran was as effective as LMWHs (enoxaparin 40 mg once daily) in the prevention of thromboembolic events after total hip arthroplasty with a similar safety profile [22,23]. In patients after knee arthroplasty, dabigatran showed inferior efficacy compared with enoxaparine 30 mg twice a day [24]. Moreover, patients with severe renal failure have been excluded from the study populations. Bivalirudin is another direct thrombin inhibitor. The drug is administered intravenously. Promising results have been obtained in patients with acute coronary syndromes [25]. However, the drug has not been investigated for prophylaxis of thromboembolic events after surgery.

Implications for clinical practice

The new anticoagulants seem to have many advantages over the traditionally used LMWHs. Oral administration and potentially higher efficacy in reducing thromboembolic events without increase in major bleeding are two of them. As the duration of antithrombotic treatment after major surgery is under debate and might be prolonged based on recent data, oral administration is an important advantage.

If efficacy and freedom from serious adverse events, including major bleeding, are confirmed in clinical practice, these drugs will replace traditionally used medication in many situations. So far, however, their use should be restricted to situations where their efficacy has been proven with clear evidence from controlled clinical trials. It is important to note that data on the use of the newer drugs in patients with renal failure are lacking. Another unresolved problem is the monitoring of the effect of the drugs. Monitoring is considered unnecessary in most clinical settings but could be important if major bleeding occurs, in patients who have taken higher than recommended doses, or in cases of severe renal or hepatic failure. In addition, reversal of these drugs is difficult as there are no antidotes available.

It is crucial that surgeons, anesthetists, and all other physicians involved in the perioperative care of surgical patients are aware of the properties of the new drugs and make sure that their use is correctly incorporated in clinical routines.

Abbreviations

FXa, factor Xa; LMWH, low-molecular-weight heparin.

Competing interest

The authors declare that they have no competing interests.

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