Drugs affecting coagulation

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Abstract

For more than half a century, heparin and vitamin K antagonists have defined anticoagulant therapy in both the short-term and long-term management of thrombotic diseases. However, the limitations of these traditional anticoagulants have prompted the development of new drugs. In the past 15 years new agents with improved safety profile and greater ease of use that target almost every step of the coagulation cascade have been developed. These include factor Xa inhibitors and direct thrombin inhibitors. The mechanism of action of these new anticoagulants and also the 'older' agents are reviewed in this article.

Keywords ADP receptor antagonists; dabigatran; fondaparinux; glycoprotein IIb/IIIa antagonists; heparin; rivaroxaban; warfarin

Royal College of Anaesthetists CPD Matrix: A102

Learning objectives

After reading this article, you should be able to:

- outline the process of coagulation
- compare and contrast the different drugs used for anticoagulation
- evaluate anticoagulant drugs and their uses in patients undergoing surgery

Coagulation is a major defence mechanism against bleeding. Following injury to the vessel wall, tissue factor is exposed on the surface of the damaged endothelium. The interaction between tissue factor and factor VII activates the coagulation cascade, which produces thrombin and culminates in the formation of an insoluble clot (Figure 1). Thrombin is central to the clotting process because it converts soluble fibrinogen to fibrin, activates factors V, VIII and XI (which generates more thrombin) and stimulates platelets. The coagulation cascade is regulated by natural anticoagulants, such as tissue factor pathway inhibitor (TFPI), the protein C and protein S systems, and antithrombin, all of which help to restrict the formation of a haemostatic plug at the site of injury.

Thrombolytic agents

Thrombolytic therapy uses the vascular system's native thromboresistant properties by accelerating and amplifying the conversion of an inactive precursor, plasminogen, to the active enzyme, plasmin. In turn, plasmin hydrolyses the fibrin clot matrix, leading to dissolution (lysis), thus restoring vital blood flow to the organs.

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First-generation agents

Streptokinase is a non-enzymatic protein produced by β-haemolytic streptococci. It activates the fibrinolytic system indirectly by forming a 1:1 stoichiometric complex with plasminogen, thus activating plasminogen into plasmin.

Urokinase is a trypsin-like serine protease composed of two polypeptide chains connected by a disulphide bridge. It activates plasminogen directly, converting it to active plasmin.

Anistreplase (anisoylated plasminogen streptokinase activator complex, Eminase) is a purified human plasminogen. It is a bacterial acylated streptokinase complex, which leads to deacylation when administered, thus activating the streptokinase—proactivator complex. It is given by rapid intravenous injection and has enhanced clot selectivity. It has more activity at clot-associated plasminogen than at free blood plasminogen, thus its thrombolytic activity is greater.

Second-generation agents

Tissue plasminogen activator (t-PA) — native t-PA is a serine protease which consists of one polypeptide chain of 527 amino acids. In the plasma, this molecule is converted to a two-chain activator linked by one disulphide bridge though cleavage of the bond. It is a poor enzyme in the absence of fibrin, as fibrin strikingly enhances the activation rate of plasminogen. This unique property is explained by an increased affinity of fibrin-bound t-PA for plasminogen without significant influence on the catalytic efficiency of the enzyme. Fibrin essentially increases the local plasminogen concentration by creating an additional interaction between t-PA and its substrate. Therefore, the high affinity of t-PA for plasminogen in the presence of fibrin allows efficient activation of the fibrin clot, whereas no efficient plasminogen activation by t-PA occurs in the plasma.

Third-generation agents

Reteplase (r-PA) or recombinant plasminogen activator is a deletion mutant that contains the kringle-2 and protease domains of the parent t-PA molecule. It has a prolonged half-life (18 minutes) and is given in two abbreviated intravenous infusions (lasting 2 minutes), 30 minutes apart. It is approved in the UK for the treatment of acute myocardial infarction.

Lanoplase (n-PA) or lanoplase is a deletion and point mutant of wild-type t-PA. The deletion of the finger and epidermal growth factor domains and a point mutation within the kringle-1 domain contribute to the molecule's long circulating half-life (30—45 minutes). In clinical trials n-PA was found to have a thrombolytic activity equivalent to r-PA, albeit with a higher incidence of bleeding.

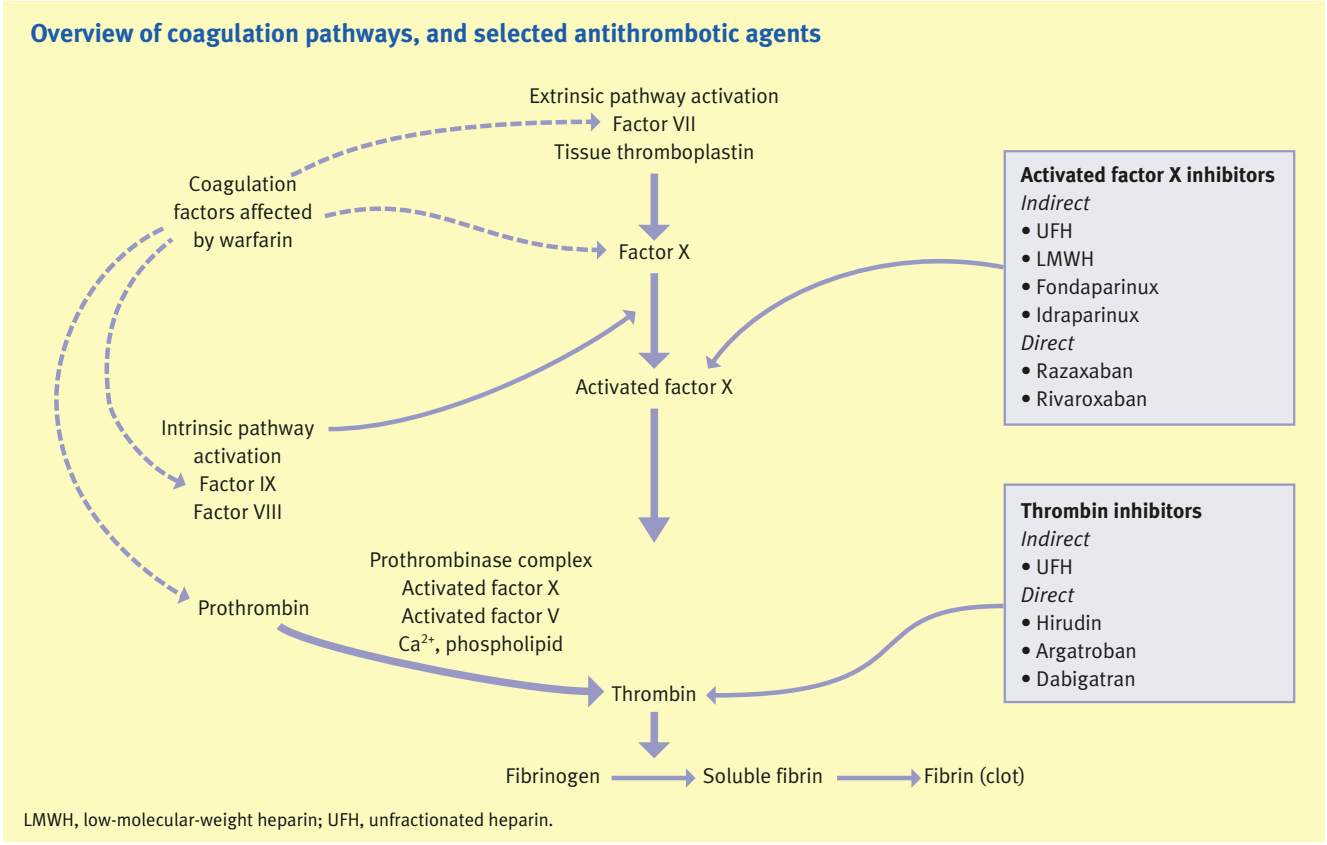

Figure 1

Direct thrombin inhibitors

Thrombin-inhibiting drugs can block the action of thrombin by binding to three domains: the active or catalytic site and exosites 1 and 2, located near the active site. Exosite 1 acts as a dock for fibrin and exosite 2 serves as the heparin-binding domain. Bivalent inhibitors (such as hirudin and bivalirudin) block thrombin at the active site and exosite 1, while univalent inhibitors such as argatroban and melagatran (and its oral precursor, ximelagatran) bind only to the active site. By reducing the thrombin-mediated activation of platelets, these inhibitors also have an antiplatelet effect. Ximelagatran (Exanta™), a prodrug and its active compound — Melagatran, the first oral thrombin inhibitor was voluntarily withdrawn from the market in 2006 because of reported severe liver injury developing several weeks after cessation of the drug.

Direct thrombin inhibitors do not bind to plasma proteins. They produce a more predictable response than heparin, and should be more effective than low-molecular-weight heparin (LMWH) as they inhibit fibrin-bound thrombin.

The pharmacokinetic profile of various direct thrombin inhibitors is shown in Table 1. These agents are predominantly renally cleared, and drugs such as hirudin and melagatran are likely to accumulate in patients with impaired renal function.

Dabigatran etexilate (Pradaxa™) is a potent thrombin inhibitor with a concentration dependent effect. Following oral administration, dabigatran etexilate is rapidly absorbed and is converted to active dabigatran by esterase-catalysed hydrolysis in the plasma and liver. Peak plasma concentrations are reached within 2 hours. Dabigatran binds with high affinity to inactivate thrombin. As this binding is highly selective, rapid and reversible, the anticoagulant effects of dabigatran are more predictable. It is renally excreted (the majority as unchanged dabigatran, with a terminal elimination half-life of 12—17 hours). Dabigatran has been licensed for use in prophylaxis of venous thrombo-embolism in patients having total arthroplasty of the hips or knees. Three randomized trials of dabigatran etexilate (each including two dosing regimens) versus enoxaparin have been published:

RE-NOVATE: a pivotal phase III, double-blind randomized controlled trial (RCT) of elective *total hip replacement patients where* dabigatran etexilate 150 mg or 220 mg once daily (started 1—4 hours after surgery with a half dose of 75 mg or 110 mg, respectively) was compared with 40 mg enoxaparin once daily (started the day before surgery). Both treatments were continued for 28—35 days (n=3494 randomized).

RE-MODEL: a pivotal phase III, double-blind RCT of elective *total knee replacement patients where* dabigatran etexilate 150 mg or 220 mg once daily (started 1—4 hours after surgery with a half dose of 75 mg or 110 mg, respectively) was compared with 40 mg enoxaparin once daily (started the day before surgery). Both treatments were continued for 610 days (n=2101 randomized).

RE-MOBILIZE: described in the manufacturer's submission as a supporting North American, phase III, double-blind RCT of