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 targets the vascular system's native thrombo-resistant properties by accelerating and amplifying the conversion of an inactive precursor, plasminogen, to the active enzyme, plasmin. This is via two distinct activators: tissue-type (t-PA) (found in vascular endothelial cells) and urokinase-type (u-PA) plasminogen activator. Plasmin is the main enzyme responsible for fibrinolysis: hydrolyzing the fibrin clot matrix, leading to dissolution (lysis) and restoration of blood flow to the organs.

First-generation agents

Streptokinase is a non-enzymatic protein produced by β-haemolytic streptococci. It activates the fibrinolytic system indirectly, binding to human plasminogen and forming a 1:1 stoichiometric complex, which converts plasminogen into plasmin. It is associated with allergic reactions and can stimulate the production of anti-streptococcal antibodies. For this reason, repeat doses should be avoided.

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

The second generation thrombolytics include recombinant tissue plasminogen activator (rtPA), also known as alteplase, and pro-urokinase. Alteplase was the first recombinant plasminogen activator, mimicking its tissue type predecessor and enhancing the conversion of plasminogen into plasmin. It has limited systemic effects in the absence of fibrin – thus initiating local fibrinolysis and limited systemic proteolysis. An additional interaction between t-PA and its substrate in the presence of fibrin is believed to be responsible.

Both agents are more fibrin-selective than their first generation counterpart and have been studied extensively in the treatment of ischaemic stroke. Pooled analysis' of the ATLANTIS, ECASS and NINDS trials, for example, have shown beneficial effects of alteplase up to 4.5 hours after symptom onset in stroke. Haemorrhagic complications occurred frequently and their use is advised with caution.

Third- and fourth-generation agents

Reteplase (r-PA) is a deletion mutant of t-PA that lacks the terminal domains of alteplase, including the terminal finger, epidermal growth factor and kringle-1 domains. The result of these deletions is prolonged plasma half-life (18 minutes) and reduced fibrin specificity. Given as two IV bolus injections 30

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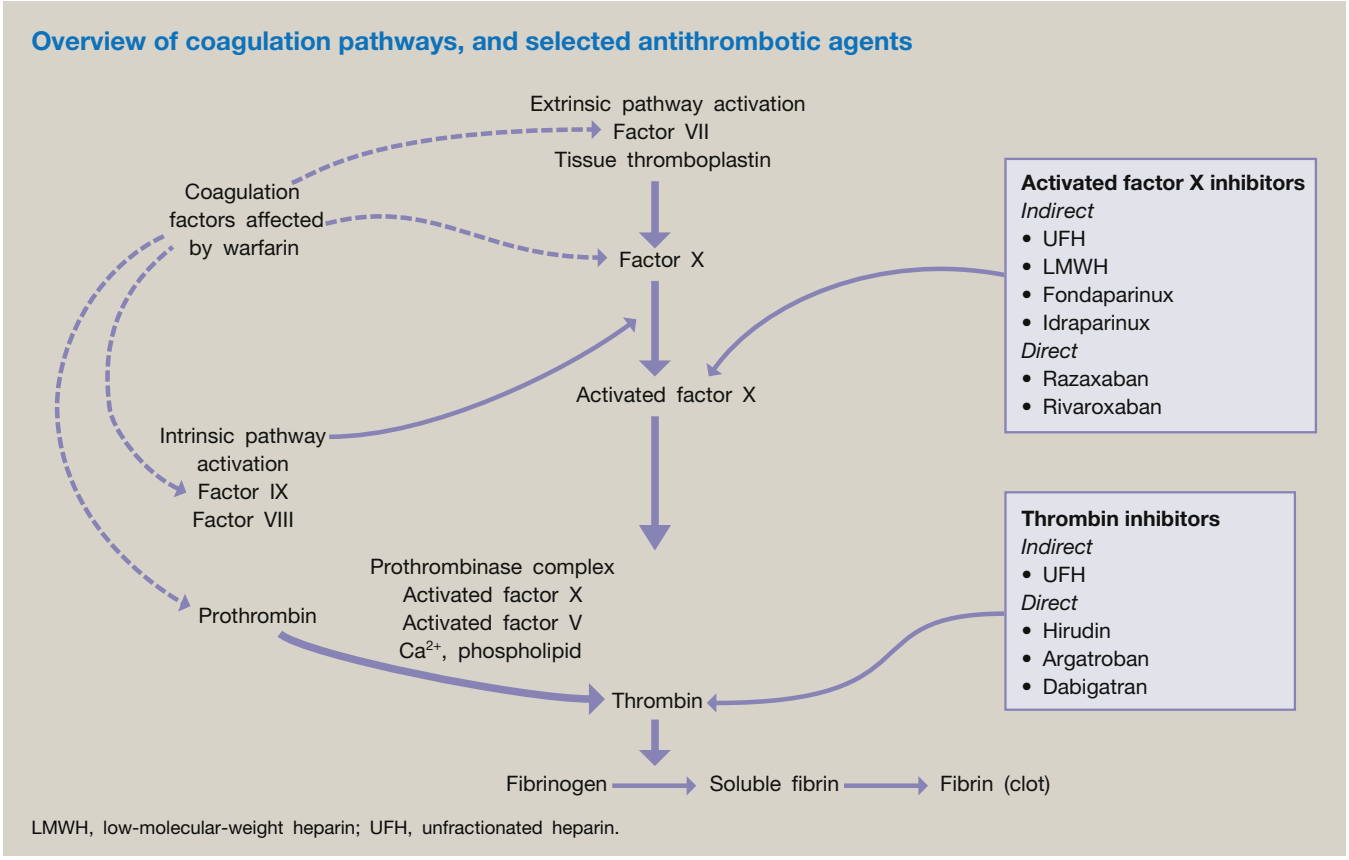

Figure 1

minutes apart, it is licensed in the UK for the treatment of acute myocardial infarction.

Desmoteplase; a new thrombolytic agent, is a serine protease that occurs naturally in the saliva of the bat *Desmodus rotundus*. It has pharmacologic and toxicologic properties superior to human t-PA, including higher fibrin selectivity, lower incidence of haemorrhagic side-effects, longer half-life (4 hours) and lack of NMDA-mediated neurotoxicity. It is currently undergoing phase III trials (DIAS-3, DIAS-4) in the treatment of acute ischaemic stroke.

Direct thrombin inhibitors (DTI)

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, exosite 2 serves as the heparin-binding domain. Bivalent inhibitors (such as hirudin and bivalirudin) block thrombin at the active site and exosite 1. Univalent inhibitors (such as argatroban and melagatran) (and its oral precursor, ximelagatran) bind only to the active site. The first oral thrombin inhibitor melagatran, and its prodrug ximelagatran, were voluntarily withdrawn from the market in 2006 because of reported severe liver injuries post administration.

Argatroban is an L-arginine derivative that binds to free and clot-associated thrombin, preventing fibrin formation, factors V, VIII and XIII activation and platelet aggregation. In 2002 the FDA approved argatroban for the treatment of thrombus in patients with heparin-induced thrombocytopenia (HIT), and in 2002 during PCI in patients with, or at risk of, HIT. Argatroban is predominantly cleared by hepatic metabolism and requires dose adjustment in patients with hepatic dysfunction.

Lepirudin is a desulfated recombinant hirudin that inhibits both free and clot-bound thrombin. It is not activated by platelet factor 4 and is thus more effective in the presence of platelet rich thrombi.

Dabigatran etexilate (Pradaxa™) is a potent thrombin inhibitor with a concentration dependent effect. It is the only oral direct thrombin inhibitor that is available for clinical use. Administered as a prodrug, it is rapidly absorbed and converted to active dabigatran by esterase-catalyzed 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 predictable. It is renally excreted (the majority as unchanged dabigatran), with a terminal elimination half-life of 12–17 hours. No dosing adjustments are required for extremes of body weight (<50 kg or >110 kg).

The pharmacokinetic profile of various direct thrombin inhibitors is shown in Table 1. DTIs with a predominant renal clearance, such as hirudin and dabigatran, are likely to accumulate in patients with impaired renal function.

The monitoring of treatment with these agents has not been clearly established. Indeed, the majority of assays that measure DTIs in clinical laboratories are activity based and provide indirect measurements of levels making them vulnerable to