Anticlotting mechanisms can be pathologically up-regulated leading to excessive bleeding or down-regulated resulting in thrombotic events. Clinicians may then need to intervene with pharmacological agents that either enhance or attenuate a particular response.

Anaesthetists will increasingly encounter patients already on such drugs or may have to give drugs intraoperatively to either prevent excessive bleeding or clotting.

This review focuses on how drugs can exert their effect by acting on anticlotting mechanisms. These drugs can be broadly classified into those that act on the anticoagulant system and those acting on the fibrinolytic system.

### The anticoagulant system

#### Drugs that act on the antithrombin–glycosaminoglycan pathway

Antithrombin (AT) is the main physiological anticoagulant enzyme. It predominantly inhibits thrombin (FIIa) but also limits the activity of FXa and to a lesser extent FIXa. The role of AT as an effective anticoagulant depends on its interaction with glycosaminoglycan substances that act as cofactors and augment its activity. This knowledge has been usefully applied in the manufacture of a group of anticoagulants that act by augmenting AT activity.

Drugs that augment AT activity can be divided into:

- **heparin anticoagulants.** This includes unfractionated heparin (UFH) and low-molecular-weight heparins (LMWHs).
- **Non-heparin anticoagulants.** This group is continuously evolving but presently it comprises the pentasaccharide anticoagulants and danaparoid.

**Heparin**

UFH is a naturally occurring anticoagulant that is produced and stored in the granules of mast cells and basophils. UFH is a heterogeneous mixture of sulphated glycosaminoglycan (mucopolysaccharide) molecules with molecular weights ranging from 3 to 50 kDa. It has the highest negative charge density of any known biological molecule.

The molecules in UFH contain between 10 and 100 saccharide units. The AT binding site is a unique pentasaccharide sequence. Only about 30% of the molecules in UFH have this AT binding site, and this fraction is responsible for most of its anticoagulant activity.

**Actions**

The level of circulating endogenous heparin is low, so heparin does not play a significant role in anticlotting mechanisms *in vivo*.

The main anticoagulant value of heparin is derived when it is administered as an exogenous therapeutic agent.

- Exogenous heparin will augment the activity of AT by a factor of at least 1000-fold. The coagulation enzymes most effectively inhibited by the heparin–AT complex are thrombin (FIIa) and FXa.

For thrombin inactivation, both heparin and AT must bind directly to each other as well as to thrombin, thereby forming a complex in which all three components are linked.

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**Key points**

Drugs that exert their effect via anticlotting mechanisms either act on the anticoagulant system or act on the fibrinolytic system. Agents that augment antithrombin activity are a major group of anticoagulants. They comprise heparins and non-heparin anticoagulants (pentasaccharide anticoagulants and danaparoid).

The reduced protein and cell binding of low-molecular-weight heparin (LMWH) compared with unfractionated heparin accounts for most of its clinical advantages.

Coagulation monitoring is not routinely required in patients on LMWH and non-heparin anticoagulants.

Drugs acting on the fibrinolytic system comprise antifibrinolytics given to treat or prevent excessive haemorrhage and thrombolytics (streptokinase and recombinant tissue plasminogen activators).
Anticlotting mechanisms

- Heparin can also catalyse thrombin inhibition by augmenting the activity of heparin cofactor II. This however requires much higher heparin doses than those needed to augment AT activity. This mechanism may play a significant role in patients with AT deficiency that can manifest clinically as heparin resistance.
- Heparin stimulates the release of tissue factor pathway inhibitor (TFPI). TFPI is the main inhibitor of the tissue factor pathway of coagulation (formerly the extrinsic pathway).
- A recent report suggests that heparin may also augment the activity of protein Z-dependent protease inhibitor (ZPI). ZPI is a circulating plasma enzyme that inhibits FXa. The cofactor for ZPI in vivo is a glycoprotein called protein Z.
- Heparin binds to von Willebrand factor (vWF), thereby inhibiting vWF-mediated platelet adhesiveness.
- It inhibits thrombin-mediated platelet aggregation and activation.

When administered by the i.v. route the onset of action of UFH is immediate with a plasma half-life of about 1 h (0.5–2 h). There is a delayed onset of about 1 h when UFH is given by the subcutaneous route. The bioavailability of UFH by the subcutaneous route is poor especially when low doses are used. This poor bioavailability is further compounded by the tendency of UFH to bind to varied plasma proteins, macrophages, and endothelial cells. This non-specific binding also affects the clearance of UFH. As a result of its unpredictable pharmacokinetics, there is wide variation in patient response to a given dose of UFH that necessitates therapeutic monitoring.

The activated partial thromboplastin time (APTT) is used to monitor UFH activity and monitors the inhibitory effects of heparin on thrombin, FXa and FIXa.

Adverse effects

- Rapid administration of large doses can cause temporary chelation of free calcium ions that is reflected by a short-lived dip in blood pressure.
- An immediate mild thrombocytopenia that is non-immune and thought to result from enhanced platelet aggregation.
- IgG-mediated heparin-induced thrombocytopenia (HIT) which usually occurs 5–15 days after initiating therapy. Heparin molecules with more than 11 saccharide units can bind to the positively charged platelet factor 4 (PF-4), which is released from platelet α-granules. This causes a conformational change and creates antigen sites on PF-4 to which IgG binds. The bound IgG then activates platelets via their FcγIIa receptors causing venous, arterial thrombosis or both.
- Hyperkalaemia as a result of heparin-induced aldosterone suppression.
- Osteoporosis as a result of heparin-induced suppression of osteoblast formation and activation of osteoclasts. The risk of osteoporosis appears to be directly proportional to the duration and dose of UFH. There is a greater risk with high doses and if treatment exceeds 3 months.
- Heparin interacts with the glyocalyx coating of the endothelium. It can have a protective effect in ischaemia–reperfusion but possibly a detrimental effect on normal endothelium.

Owing to its short half-life, the anticoagulant effect of UFH can usually be reversed by stopping the drug. When given by infusion, the convention still remains to stop the infusion 4–6 h before surgery. If more rapid reversal is required, then protamine can be given at a dose of 1 mg (100 IU of heparin)–1.

The elimination of UFH is through macrophages and endothelial cell receptors with very little renal clearance. It is therefore considered safer than LMWH in patients with severe renal impairment.

Low-molecular-weight heparin

LMWH is produced by subjecting UFH to cleavage procedures yielding smaller molecules that contain between 10 and 20 saccharide units and have an average molecular weight of 4–5 kDa (range 1–10 kDa).

Heparin molecules with fewer than 18 saccharide units cannot bind simultaneously to AT and thrombin. For this reason, most variants of LMWH have a much reduced ability to catalyse the inactivation of thrombin.

UFH is considered to have an anti-FXa:anti-FIIa ratio of 1:1. In contrast, LMWHs have anti-FXa:anti-FIIa ratios ranging from 2:1 to 4:1 depending on their molecular size distribution.

Actions

- LMWHs exert their main effect by augmenting AT-mediated inactivation of FXa and so act as indirect FXa inhibitors.
- LMWHs also stimulate the release of TFPI from the vasculature. This is thought to contribute to the extended antithrombotic action of LMWH. So, despite a half-life of 4–6 h a once daily dose of LMWH is adequate for thromboprophylaxis.

The smaller molecules in LMWH lack the tendency of UFH to bind to various proteins and cells. The resulting improved bioavailability accounts for most of the clinical advantages of LMWH when compared with UFH (Table 1).

The bioavailability of LMWH after subcutaneous injection approaches 100% even with low doses.

Coagulation monitoring is not usually required. However, in special patient groups such as severe obesity >120 kg (BMI > 50), pregnancy, or severe renal impairment, it is considered prudent to monitor the effect of LMWH therapy.

The most widely available test for monitoring LMWH is an anti-FXa assay that measures the level of anti-FXa activity in the patient’s plasma.

LMWH is excreted mainly by the kidneys and is therefore contraindicated in severe renal insufficiency (eGFR < 30 ml min–1 and acute kidney injury). It is also contraindicated in patients with a recent
Pentasaccharide anticoagulants

Pentasaccharide anticoagulants are synthetic compounds in which the sequence of saccharide units is identical to that of the AT binding site of UFH.

Fondaparinux was the first of this group to be used in clinical practice. In contrast to the heterogeneous nature of the heparins (both UFH and LMWH), each pentasaccharide compound is a single homogenous chemical entity.

Actions

- Pentasaccharide anticoagulants bind strongly and selectively to AT catalysing AT inactivation of FXa. This inhibits thrombin generation.
- Synthetic pentasaccharides have no direct effect on thrombin activity. As a result they are associated with a reduced risk of over anticoagulation and bleeding. This obviates the need for coagulation monitoring.

Fondaparinux does not bind to platelets or platelet factor-4 and so should not cause HIT. It has no effect on platelet function. There is as of yet no clear consensus on whether fondaparinux should be used as anticoagulant therapy in patients who have developed HIT.

Other advantages of the pentasaccharide group over UFH include a reduced risk of osteoporosis.

Fondaparinux is administered subcutaneously and bioavailability after a subcutaneous injection is 100%. It has a half-life of 17 h and is excreted almost completely by the kidney.5

Fondaparinux activity cannot be monitored by APTT. If a laboratory assessment of effect is necessary, then a specific anti-FXa assay chromogenic test is performed. This assay is different from that used for LMWH and has to be calibrated with fondaparinux.

Protamine does not reverse the anticoagulant activity of fondaparinux.

A recent report suggests that recombinant activated FVII (NovoSeven®) may be used as a reversal agent for serious bleeding in patients who are anticoagulated with pentasaccharide anticoagulants.5

Idraparinux is a second-generation long-acting pentasaccharide anticoagulant. It is more negatively charged than fondaparinux and so binds more avidly to AT. As a result of this tight binding, the half-life of idraparinux is similar to that of AT (around 80 h).6 This prolonged anticoagulant activity of idraparinux confers the advantages of convenience and simplicity of management of deep vein thrombosis.

It however raises questions about how to safely manage excessive bleeding because of over anticoagulation if it occurs. The quest to find an antidote led to the development of the biotinylated version—idrabiotaparinux.

Biotinylation is the process of covalently attaching biotin (a water soluble B-complex vitamin) to a compound. The anticoagulant effect of idrabiotaparinux can be rapidly antagonized with an infusion of avidin. Avidin is a protein extract derived from egg white that binds tightly to biotin.

An initial study has shown idrabiotaparinux to have similar efficacy to idraparinux for the treatment of deep venous thrombosis but with the added safety feature of rapid reversal if needed.7 Further studies are required before definite conclusions can be made.

Danaparoid

Danaparoid is a heparinoid (chemically distinct from heparin). It is a mixture of three low-molecular-weight glycosaminoglycans—heparan sulphate (84%), dermatan sulphate (12%), and chondroitin sulphate (4%).

Actions

- Danaparoid augments the anticoagulant activity of AT, thereby inhibiting FXa and to a much lesser extent thrombin (22:1 anti-FXa:anti-FIIa ratio).8
- It potentiates the action of heparin cofactor II and inhibits thrombin via this mechanism.

Danaparoid does not contain heparin or heparin fragments and is recommended when non-heparin anticoagulant therapy is needed in HIT.9 This is presently the main indication for the drug.

Danaparoid does not interfere with platelet function and can be given by either i.v. or s.c. route. The bioavailability by the subcutaneous route is 100% with a half-life of 25 h. It is mainly excreted through the kidneys.

Coagulation monitoring is not needed routinely but if required the anti-FXa assay can be used.

There is no antidote, which is a problem if excessive bleeding occurs because of the long half-life.

Drugs that act on the protein C pathway

Warfarin

Warfarin is thought of as an anticoagulant but it also reduces protein C and S levels. As a result, in the early stages of warfarin therapy,
there is reduced anti-clotting activity. In situations such as HIT, this can lead to microvascular thrombosis causing severe skin necrosis.

**Recombinant thrombomodulin**

Thrombomodulin is a natural anticoagulant cofactor that is found on endothelial cells. The thrombin–thrombomodulin complex is a potent activator of protein C, thereby suppressing further generation of thrombin. Recombinant human soluble thrombomodulin (ART-123) can be administered by either the i.v. or s.c. route. It has been investigated with promising results for the treatment of disseminated intravascular coagulation and deep vein thrombosis.

**Recombinant activated protein C**

Activated protein C is a potent anticoagulant. By degrading FVa and FVIIIa, it inhibits the amplification cascade that greatly increases thrombin generation. The use of its recombinant form in severe sepsis despite early promise remains controversial.

**Antifibrinolytic agents**

**Lysine analogues**

Tranexamic acid is a synthetic compound derived from lysine. It exerts its antifibrinolytic action by reversibly blocking lysine-binding sites on plasminogen. This prevents the conversion of plasminogen to fibrinolysin, the enzyme responsible for fibrin degradation. Tranexamic acid is used in the prevention or treatment of haemorrhage in scenarios ranging from routine cardiac surgery to trauma. The CRASH studies demonstrated reduced bleeding in trauma with tranexamic acid use. A perceived advantage is that it does not interfere with coagulation. In high doses, it can cause seizures although the mechanism and significance of these are unclear.

Aminocaproic acid is also a synthetic lysine analogue. It binds reversibly to plasminogen and prevents its activation to fibrinolysin.

**Aprotinin**

Aprotinin is a non-specific SERPIN that was used to reduce blood loss particularly in cardiopulmonary by-pass (CPB) surgery. It was withdrawn in 2007 because of concerns that it caused serious cardiovascular and renal toxicity and increased the risk of death following the results of the BART study. However, the BART study has since been questioned and recently aprotinin has been re-licensed in Europe for specific indications.

Aprotinin acts on multiple sites and inhibits both coagulation and fibrinolytic enzymes. It exerts its antifibrinolytic effect by the following mechanisms:

- It inhibits t-PA, thereby preventing the conversion of plasminogen to fibrinolysin
- It directly inhibits fibrinolysin, thereby slowing down fibrinolysis
- It inhibits kallikrein. Plasma kallikrein is a serine protease that is synthesized as the inactive precursor prekallikrein. Kallikrein directly catalyses the conversion of plasminogen to fibrinolysin. It also indirectly leads to enhanced levels of t-PA by cleaving high-molecular-weight kininogen to release bradykinin. Bradykinin then causes increased t-PA formation. Kallikrein also converts FXII to FXIIa. This initiating step in the contact activation pathway (formerly intrinsic pathway) of coagulation is an important procoagulant mechanism during CPB surgery.

**Thrombolytic agents**

**Streptokinase**

Streptokinase is a protein secreted by streptococci. It activates plasminogen indirectly. It binds to human plasminogen and the streptokinase–plasminogen complex converts plasminogen to plasmin which then breaks down fibrin. It is an emergency drug used to dissolve arterial thrombi in myocardial infarction or pulmonary embolism. As streptokinase is of bacterial origin, it can cause allergic reactions in humans. It is also highly antigenic stimulating the production of anti-streptococcal antibodies. For this reason, repeat doses are avoided. It has an elimination half-life of ~23 min.

**Recombinant tissue plasminogen activators**

Alteplase was the first recombinant tissue plasminogen activator. It mimics tissue-type plasminogen activator. It has a plasma half-life of 4–6 min and is not antigenic, so repeat doses can be given.

Reteplase is a second-generation, recombinant, tissue-type plasminogen activator. Compared with alteplase, it has a faster onset of action and a longer plasma half-life of 13–16 min.

Tenecteplase has an even longer half-life and because of their longer half-lives reteplase and tenecteplase have the advantage of being given by a bolus injection that simplifies administration. Tenecteplase also has enhanced fibrin specificity and demonstrates resistance to inhibition by plasminogen activator inhibitor.
Desmoteplase is a new thrombolytic agent. It is derived from the saliva of vampire bats. Its advantages include a longer half-life of 4 h. Its activity is also highly fibrin-specific. As a result of this high fibrin specificity, it does not cause activation of systemic plasminogen and fibrinogen depletion. It is undergoing clinical trials for acute ischaemic stroke (DIAS-3 and DIAS-4).

The common indication for this group of drugs is a massive arterial thrombotic event such as ST-elevation myocardial infarction (STEMI), massive pulmonary embolism, or acute ischaemic stroke.

The administration of a thrombolytic agent during a cardiac arrest has implications on the duration of cardiopulmonary resuscitation (CPR). Current practice is to continue CPR for 60–90 min if a thrombolytic agent has been given to treat a known or suspected pulmonary embolus.

**Conclusion**

It is increasingly realized that a lack of consideration of anticlotting mechanisms can have serious adverse clinical consequences, especially in the field of massive haemorrhage. The unbalanced use of pro-coagulants to correct coagulopathy without addressing the needs of the anticlotting systems can lead to unwanted arterial and venous thrombosis, such as massive systemic thrombosis after recombinant activated FVII administration.

The quest for better drugs that will reduce perioperative blood loss, especially during CPB and liver surgery, continues and new drugs such as CU-2010 and CU-2020 are currently undergoing trials.12

**Declaration of interest**

None declared.

**References**

2. VanTeeffelen JW. How to prevent leaky vessels during reperfusion? Just keep that glycoalyx sealant in place! Crit Care 2008; 12: 167

Please see multiple choice questions 17–20.