

Drugs used to prevent surgical VTE

In the sixth article of a series on peri-operative care, **Mohamed H. Rahman** and **Jane Beattie** give an overview of pharmacological prevention of VTE

In addition to mechanical methods (*PJ*, 6 November pp687–9), drugs are also used to prevent venous thromboembolism (VTE) in patients undergoing surgery. To appreciate the different drugs used, it is important to understand the basic principles of haemostasis and these are outlined in Panel 1 (p718).

Unfractionated heparin

Unfractionated heparin (UH) is the traditional agent used to prevent VTE in surgical patients. It is a mixture of linear mucopolysaccharide molecules of differing lengths and molecular weights (MW, ranging between 3,000 and 30,000 Daltons and averaging 15,000Da), commonly prepared from porcine intestinal mucosa.

Mechanisms of action UH acts by binding to antithrombin III and promoting its inhibitory actions on factor Xa and thrombin. In the presence of UH, antithrombin III also more rapidly neutralises other activated coagulation factors in the intrinsic pathway, including factors IXa, XIa and XIIa.

The effect of UH on antithrombin III depends on a specific pentasaccharide sequence, which is present in about one third of the UH molecules in a preparation. The anticoagulant effect of UH also depends on molecular chain length. UH molecules of higher MW (about 5,000Da, ie, those with chains of over 16 monosaccharide units) have a thrombin as well as an antithrombin III binding site. These large heparin molecules form ternary complexes (by simultaneously binding antithrombin and thrombin) and increase the rate at which thrombin is inactivated. Determining activated partial thromboplastin time (APTT), gives a measure of the ability of heparin to inhibit the enzymatic activity of thrombin. Heparin administration prolongs the APTT.

Inhibition of factor Xa does not rely on the formation of a ternary complex — it is achieved solely by UH binding to antithrombin III. This is why, as the MW of UH decreases, its influence on APTT declines but its anti-Xa activity is retained. Monitoring coagulation is not essential at the low (subcutaneous) doses of heparin used to prevent VTEs — overdose is unlikely. However, if monitoring is desirable, anti-Xa assays should be used rather than APTT, because APTT will not be significantly prolonged.

Other mechanisms of heparin action that are independent of pentasaccharide binding

include stimulating the release of other endogenous antithrombotic substances, such as tissue factor pathway inhibitor (TFPI) from the endothelium.

Dosage and administration UH must be administered subcutaneously or intravenously. Intramuscular doses are associated with a risk of haematoma at the injection site. Heparin is metabolised in the liver and inactive metabolites are excreted in the urine. The duration of clinical effect is dose-dependent, with biological half-life increasing and clearance decreasing with increasing dose. With low-dose therapy (5,000 units every eight to 12 hours), anticoagulation appears to result mainly from neutralisation of factor Xa. In contrast, full anticoagulation (continuous iv infusion) with UH, is predominantly due to the neutralisation of thrombin.

The licensed dose of UH for prophylaxis in surgical patients is 5,000u sc, two hours before surgery, then every eight to 12 hours, until the patient is fully ambulant. If a patient is at particularly high risk of VTE (including patients who take long-term oral anticoagulant therapy), a continuous iv infusion of heparin may be required (*PJ*, 20 March, p353).

Intravenous dosing requires close monitoring. And, in this case, APTT measurement is essential and drug infusion rates are adjusted to maintain an APTT of 1.5 to 2.5 times the normal value. Other monitoring parameters for patients receiving higher sc doses or continuous iv infusions are listed in Panel 2 (p719). The anticoagulant effect of UH can be neutralised by an equimolar dose of protamine sulphate.

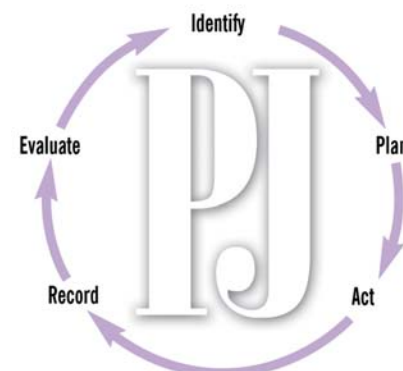
Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Review clinical trial data relating to use of the different pharmacological agents used in preventing VTE in surgical patients.
2. Find out the rationale of why your hospital uses UH or a LMWH in preventing VTE in surgical patients, and the policies for timing of prescriptions.
3. Read about the coagulation cascade in more detail (eg. *The Oxford Textbook of Medicine*).

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?



Identify knowledge gaps

1. What are the general principles of the coagulation cascade?
2. What pharmacological agents are available for preventing VTE in surgical patients, and what are their modes of action?
3. How can heparin effects be neutralised?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: www.rpsgb.org/education). This article relates to "clinical pharmacy" (see appendix 4 of "Plan and record").

UH is contraindicated in patients who are bleeding (menstruation is excluded) or who have severe liver disease or thrombocytopenia (including a history of thrombocytopenia). The risk-benefit ratio of using UH should be considered in patients with bleeding tendency or with actual or potential bleeding sites (eg, peptic ulceration or bleeding haemorrhoids etc).

Low molecular weight heparins

Low molecular weight heparins (LMWHs) generally consist of fractionated segments of UH, derived by chemical or enzymatic depolymerisation digestion methods. They are mucopolysaccharide molecules of different chain lengths and physicochemical properties.

LMWHs are increasingly replacing UH. There are currently six LMWHs licensed in the UK for surgical prophylaxis: bemiparin, certoparin, dalteparin, enoxaparin, reviparin and tinzaparin. The main mode of action of LMWHs is considered to be antithrombin III mediated anti-Xa activity, and this is considered to be a general measure of their potency. As already mentioned, below a critical size (<5,000Da) heparin predominantly affects anti-Xa activity, and above this size it affects both anti-Xa and anti-thrombin activity. Since only about a third of LMWH molecules are large enough to form the ternary

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Panel 1: Mechanisms of haemostasis

There is a fine balance between blood coagulation in response to tissue damage (to minimise blood loss) and mechanisms to maintain blood flow. Procoagulation mechanisms need to be regulated to prevent excessive thrombosis.

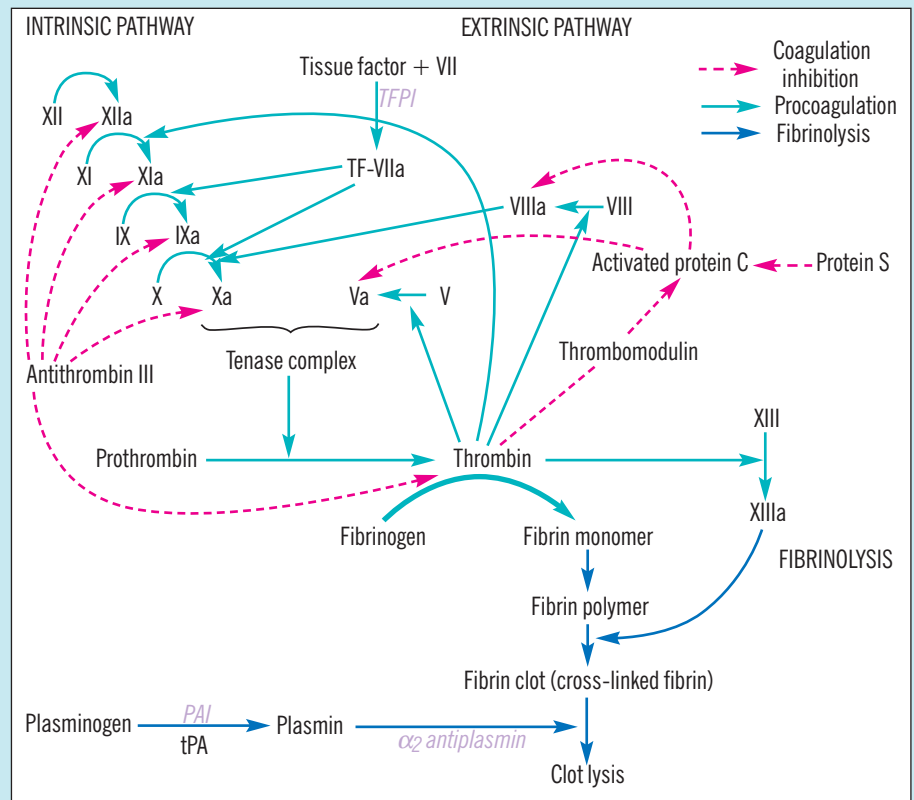
Coagulation is complex, involving a wide variety of essential proteins with different functions. Readers looking for a comprehensive account of coagulation are advised to use a medical or haematology text book. The diagram shows the clotting pathways. Prevention of blood loss has three important tissue components: the endothelium, platelet actions and the coagulation factor cascade.

Endothelium The endothelium acts as a physical barrier separating circulating haemostatic blood components from substances in the subendothelium. Its negative charge is thought to repel platelets (preventing platelet adhesion), and nitric oxide and prostacyclin produced by the endothelium inhibit platelet aggregation. The endothelium's anticoagulant properties are also enhanced by the production of thrombomodulin and heparan sulphate. If there is tissue damage, (eg, during surgery), the subendothelium becomes exposed. Exposed collagen, fibronectin and von Willebrand factor (a protein made by the endothelium and secreted into the subendothelium) promote platelet adhesion.

Tissue factor is secreted, which initiates the coagulation cascade. Plasminogen activator inhibitor (PAI) is also secreted and this impairs fibrinolysis (digestion of fibrin which forms the matrix of clots, by the enzyme plasmin), allowing generation of the fibrin matrix — clot formation. Endothelial surface expression of thrombomodulin is also reduced.

Platelets Platelets have three principle roles: adhesion (to the site of damage), activation (to generate thrombin) and aggregation (formation of a "platelet plug"). Platelet adhesion occurs when a complex bond forms between the platelet and subendothelial von Willebrand factor. Further processes result in irreversible platelet adhesion. Platelets also bind to fibrinogen which promotes further aggregation.

Coagulation cascade The coagulation cascade involves a series of proteolytic enzymes. Each enzyme of the pathway is present in the plasma in an



inactive form and needs to undergo cleavage to make it into an active protease (activated factor). Each activated factor then activates another clotting factor and so on. The ultimate goal of the cascade is to produce thrombin (also known as factor IIa).

Thrombin is needed to convert soluble fibrinogen (factor I) into fibrin (factor Ia), and eventually into a cross-linked fibrin molecule (the basis of the clot), with the assistance of factor XIII. Thrombin also induces platelet aggregation and activates factors V, VIII, XI and XIII.

Factor Xa (active form), derived from factor X (inactive form), is one of the key factors needed to produce thrombin, the other being factor Va. Production of Xa is facilitated by a complex of activated factor VII and exposed tissue factor. This complex is, however, rapidly inactivated by tissue factor pathway inhibitor (TFPI), and therefore, further production of Xa is promoted by factors IXa and VIIIa. It is also thought that factor Xa activates further factor VII, but it is unclear exactly how this happens. Factor Xa eventually combines with factor Va to form

a tenase complex (factor Xa-factor Va) that rapidly converts prothrombin to thrombin.

Coagulation is limited by the action of the anticoagulant system. This is vital to avoid widespread thrombosis. Among other mechanisms, antithrombins (mainly antithrombin III) inhibit various clotting factors and the protein C system inhibits factors Va and VIIIa. In some circumstances thrombin can lose its procoagulant property; it becomes an anticoagulant by binding to surface bound thrombomodulin. This action activates protein C. Protein S also enhances protein C activity.

Fibrinolysis is another important element. Tissue plasminogen activator (tPA) released from endothelial cells, helps convert plasminogen to plasmin. Plasmin facilitates proteolysis (breakdown) of fibrinogen, fibrin and factors V, VIII and XIII. Excessive fibrinolysis is prevented by PAI and alpha-2-antiplasmin inhibiting the actions of tPA and plasmin.

structure, they have less effect on factor IIa (thrombin) than UH, but retain their anti-factor Xa activity. Thus APTT is not used to assess the activity of LMWHs — they require the specific anti-Xa assay. This may be particularly important in patients with renal impairment because the LMWHs are predominantly eliminated via the kidneys. Panel 3 lists ratios of anti-Xa to anti-IIa (thrombin) activity for various heparins.

LMWHs also possess antithrombin III-independent effects (eg, release of TFPI and tissue plasminogen activator [tPA] or decreasing circulating von Willebrand factor) but most of these are not routinely measured.

Although the mean molecular weights of LMWHs fall within a narrow range (2,000 to 8,000Da), there are significant differences in functional properties. Differences in manufacturing methods result in structural variations, which influence pharmacokinetic and pharmacodynamic properties. Products differ in their relative content of low and high MW molecules, degree of sulphation, charge density and modification of the end-groups and internal structure. These result in distinct effects on factor Xa and thrombin. LMWHs are, therefore, not always therapeutically interchangeable, although their pharmacological and clinical characteristics are similar.

However, there is insufficient evidence determining the therapeutic equivalence of LMWHs in direct comparison studies.

LMWHs have been shown to be at least as efficacious as UH and have many advantages. For example, because of their reduced plasma protein and cellular binding, LMWHs have a higher bioavailability and exhibit less inter- and intra-patient variability in response to a given dose than UH. For example, the bioavailability of the six LMWHs is close to 90 per cent, compared with less than 50 per cent for sc UH. In addition, because of their longer plasma half-life, LMWHs can be given once daily instead of two or three times daily.

Panel 2: Monitoring

- Activated partial thromboplastin time (APTT)
- Baseline haematological tests (preferably a full blood count). Platelet counts should be measured in patients who receive heparin for more than five days. Treatment should be stopped immediately in patients who develop thrombocytopenia or in whom platelet count is reduced by 50 per cent.
- Liver and renal function. Liver function helps to assess bleeding risk. Patients with impaired liver or renal function can require dose reduction.
- Electrolytes. According to the Committee on Safety of Medicines, heparins inhibit aldosterone secretion so can cause hyperkalaemia. Patients with diabetes mellitus, chronic renal failure or acidosis and those taking potassium sparing drugs are particularly susceptible.
- Health care professionals should look out for adverse local effects (eg, bruising at injection site) as well as signs of deep vein thrombosis or pulmonary embolism (*PJ*, 6 November, p687)

Because of their preferential inhibitory effect on factor Xa, and fewer inhibitory effects on thrombin and platelet activity LMWHs are purported to have lesser risk of haemorrhagic complications than UH, while retaining anticoagulant effect. However, this decreased effect has not been convincingly shown in trials. LMWHs have also been associated with lower propensity to induce heparin-induced thrombocytopenia but they should be avoided in patients with this condition because of cross-reactivity

With long-term use, there is also less bone loss and heparin-induced osteoporosis because of reduced binding to, and activation of, osteoclasts.

One disadvantage of LMWHs is that their effect cannot be stopped as fully and quickly as that of UH. With protamine, only the anti-IIa activity of LMWHs is reversed, and the anti-Xa effect is only partially reduced. For example, the maximum reduction of enoxaparin activity with high dose protamine is 60 per cent. There are many opinions about which is the best LMWH, for prophylaxis of VTE in surgical patients. As the market expands, drug use reviews are being constantly scrutinised. It is beyond the scope of this article to appraise each LMWH critically.

Fondaparinux

Fondaparinux (Arixtra) is the first of a new class of antithrombotic compounds, the oligosaccharides. It is a synthetic product that selectively inhibits factor Xa (the rate limiting factor of the coagulation cascade), thereby inhibiting thrombin generation without deactivating thrombin itself. It consists of five saccharide units with sulphate groups strategically positioned to bind strongly and exclusively to antithrombin III. By selectively

binding to antithrombin III, fondaparinux modifies its conformation, and this potentiates (by 300 times) the natural inhibition of factor Xa. Fondaparinux does not interact with platelets.

Fondaparinux is licensed for thromboprophylaxis in patients undergoing major orthopaedic surgery of the lower limbs. Its linear pharmacokinetic profile allows once-daily sc administration. It has demonstrated greater efficacy compared with enoxaparin for the prevention of VTE in major orthopaedic surgery.¹

There is no specific antidote for fondaparinux. In the event of an overdose associated with bleeding complications, the manufacturer recommends its discontinuation, and consideration be given to surgical haemostasis, blood replacements, fresh plasma transfusion and plasmapheresis.

Other drugs

Danaparoid (Orgaran) and lepirudin (Refludan) are indicated for patients who develop heparin-induced thrombocytopenia. Danaparoid (MW 5,500Da) is a mixture of LMW sulphated glycosaminoglycuronans derived from animal mucosa comprising heparan, dermatan and chondroitin sulphates. It is administered sc at a dose of 750 anti-factor Xa units, twice daily, with bioavailability approaching 100 per cent. The manufacturers report a low incidence (<10 per cent) of platelet cross-reactivity with plasma from patients sensitised by heparin. However, a cross-reactivity test is recommended before use and platelet count must be monitored regularly. The anti-Xa activity of danaparoid is mediated by antithrombin III and not inactivated by endogenous heparin neutralising factors.

Lepirudin (MW about 7,000Da) is a recombinant DNA product derived from yeast cells. It is a highly specific direct inhibitor of thrombin. Its mode of action is independent of antithrombin III. Lepirudin is administered intravenously, and dose is adjusted according to APTT.

Panel 3: Anti-Xa:anti-IIa activity

| | |
|-------------------------|-------|
| Bemiparin (Zibor) | 8:1 |
| Certoparin (Alphaparin) | 2:1 |
| Dalteparin (Fragmin) | 2.2:1 |
| Enoxaparin (Clexane) | 3.9:1 |
| Tinazaparin (Innohep) | 1.9:1 |
| Unfractionated heparin | 1:1 |

When platelets meet a damaged vessel, they become activated

There is no specific antidote to danaparoid or lepirudin.

Note about epidurals

Whether receiving LMWHs or UH for prevention of VTE, patients will be at greater risk of developing an epidural or spinal haematoma if central nerve blocks are used to provide peri-operative pain relief. This can result in permanent neurological problems (eg, paralysis). Spinal or epidural blocks should only be undertaken if there is a sufficient interval from the administration of heparin. This is usually at least six hours from UH administration, or 12 hours for prophylactic doses of LMWHs. The concomitant use of antiplatelet drugs or recent warfarin administration increases the risk of spinal haematoma.

Conclusion

There is a wide variation between hospitals in heparins used for VTE prophylaxis and it is not only during an inpatient stay that VTE prophylaxis should be considered. The need for continuing VTE prophylaxis should be assessed immediately before discharge. The optimal duration of anticoagulant therapy remains open to debate.

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Resources

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