HAEMATOLOGY PHARMACOLOGY 2

Anticoagulants There are both parenteral and oral anticoagulants. Currently available parenteral anticoagulants include heparin, low-molecular-weight heparin (LMWH), and fondaparinux, a synthetic pentasaccharide. The available oral anticoagulants are the vitamin K antagonists and the newer factor Xa inhibitors such as rivaroxiban. Heparin is an anionic, mucoploysaccaride, organic acid containing many sulphide residues. It occurs naturally in the liver and mast cell granules and has a variable molecular weight of 5000 - 25000 Daltons. It is used for the treatment and prevention of VTE, ACS, and in haemodylasis and ECMO. It is derived from porcine mucosal cells rich in mast cells. It is available only in injectable form (SC or IV) and is described in terms of international units not weight. Heparin acts as an anticoagulant by activating antithrombin and accelerating the rate at which antithrombin inhibits clotting enzymes, particularly thrombin and factor Xa. Once bound to antithrombin, heparin induces a conformational change in the reactive center loop of antithrombin that renders it more readily accessible to its target proteases. Heparin binds avidly to endothelial cells which has several pharmocokinetic consequences. Firstly it reduces the bioavailability if delivered via the SC route. Secondly it causes a rapid clearance from plasma at low doses which becomes saturable at higher doses, leading to a prolonged half life at higher doses. In addition to endothelial binding its anionic nature means that it also binds plasma protiens avidly. It is not lipid soluble and does not cross the BBB. Side effects relate primarily to bleeding which may be reduced with the administration of protamine (1mg per 100U) which binds heparin avidly. Other side effects include heparin induced thrombocytopaenia and osteopaenia in the setting of prolonged administration. LMWH - Low Molecular Weight Heparin Consisting of smaller fragments of heparin, LMWH is prepared from unfractionated heparin by controlled enzymatic or chemical depolymerization. The mean molecular weight of LMWH is 5000, one-third the mean molecular weight of unfractionated heparin. It has similar indications to unfractionated heparin. Usually given SC, but can be given IV for a more rapid response. Like heparin, LMWH exerts its anticoagulant activity by activating antithrombin. With a mean molecular weight of 5000, which corresponds to about 17 saccharide units, at least half of the pentasaccharide-containing chains of LMWH are too short to bridge thrombin to antithrombin. Consequently, LMWH catalyzes factor Xa inhibition by antithrombin more than thrombin inhibition. Pharmacokinetically, LMWH have one major drawback, they are renally excreted and may accumulate in the setting of renal impairment. They do however have several distinct advantages. They have higher bioavailablilty when compared to heparin when given SC, the bind significantly less to plasma protients and endothelial cells and have more predictable responses (reducing the need for monitoring and dose adjustment) and the clearance is dose dependent. Fondarinux is a synthetic analogue of the pentasaccharide sequence located on heparin, with a molecular weight of 1728 Da. It therefore acts exclusively on Xa catalysing. It is renally cleared and contraindicated in patients with significant renal impairment. Warfarin is a water soluble coumarin derivative and is used for the prophylaxis of systemic thromboembolism in patients with AF, valvular heart disease and in the prevention of VTE and PE. Warfarin is a racemic mixture of two enantiomers R and S with the biological effects more prominent in the S isomer. It is presented as oral tablets in a range of dosages and requires careful titration according to INR in all patients. Warfarin inhibits vitamin K epoxide reductase (VKOR), thereby blocking the γ-carboxylation process of clotting factors II, VII, IX and X and the anticlotting Protien C and S. This results in the synthesis of vitamin K–dependent clotting proteins that are only partially γ-carboxylated. Warfarin acts as an anticoagulant because these partially γ- carboxylated proteins have reduced or absent biologic activity. The onset of action of warfarin is delayed until the newly synthesized clotting factors with reduced activity gradually replace their fully active counterparts. Warfarin is rapidly and completely absorbed when given orally. It has a small volume of distribution, and is highly protien bound, other medications which displace warfarin from protiens may result in an exagerated effect (only the unbound protien is active). It is metabolised hepatically and via the CYP2C9 system, there are two common variants of this enzyme which lead to decreased metabolism and therefore reduced maintenence doses. The main side effect of warfarin is bleeding. In the setting of uncontrolled haemorrhage vitamin K may be given along with FFP in accordance with the INR. Other side effects include idiosyncratic skin necrosis. There are extensive interactions with other meds, diet and protien binding. May cause a prothrombotic state during initiation due to Protien C ad S being blocked first. Rivaroxiban is one of the newer agents which act via direct, selective and reversible inhibition of factor Xa (FXa) in both the intrinsic and extrinsic coagulation pathways. EDTA and Citrate are anticoagulant most commonly used in pathology collection and sometimes used in haemodialysis which act by binding calcium ions and forming a soluble complex.

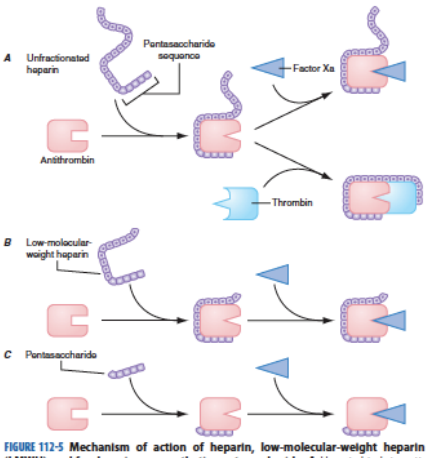

FIGURE 112-5 Mechanism of action of heparin, low-molecular-weight heparin (LMWH), and fondaparinux, a synthetic pentasaccharide. ***A.*** Heparin binds to antithrombin via its pentasaccharide sequence. This induces a conformational change in the reactive center loop of antithrombin that accelerates its interaction with factor Xa. To potentiate thrombin inhibition, heparin must simultaneously bind to antithrombin and thrombin. Only heparin chains composed of at least 18 saccharide units, which corresponds to a molecular weight of 5400, are of sufficient length to perform this bridging function. With a mean molecular weight of 15,000, all of the heparin chains are long enough to do this. ***B.*** LMWH has greater capacity to potentiate factor Xa inhibition by antithrombin than thrombin because, with a mean molecular weight of 4500–5000, at least half of the LMWH chains are too short to bridge antithrombin to thrombin. ***C.*** The pentasaccharide only accelerates factor Xa inhibition by antithrombin because the pentasaccharide is too short to bridge antithrombin to thrombin.

Fibrinolytics act by converting plasminogen to plasmin, which catalyses the breakdown of fibrin. The main drugs in this class are streptokinase, alteplase (also known as r-TPA) and tenecteplase. Streptokinase is derived from beta haemolytic strep, the other two are formed from recombinant DNA. The indications for these drugs are acute STEMI, acute massive VTE in patients who are haemodynamically unstable, peripheral artery thromboembolism, Acute ischaemic stoke within 3 hours of onset of symptoms and thrombolised IV catheters. Plasminogen activators that preferentially activate fibrin-bound plasminogen are considered fibrin-specific. In contrast, nonspecific plasminogen activators do not discriminate between fibrin-bound and circulating plasminogen. Activation of circulating plasminogen results in the generation of unopposed plasmin that can trigger the systemic lytic state. Alteplase and its derivatives such as tenecteplase are fibrin-specific plasminogen activators, whereas streptokinase, anistreplase, and urokinase are nonspecific agents. The action of streptokinase is to bind to plasminogen to form a complex which then activates other plasminogen molecules to plasmin, hence the non specific action. Alteplase and tenecteplase in comparison are only activated when bound to fibrin, hence their greater specificity. All fibrinolytics are delivered IV. The fibrinolytics have small volumes of distribution. Streptokinase has a half life of between 20-80 minutes, with the half life of alteplase <10 minutes. Tenecteplase was developed to extend the half life of alteplase. Most are metabolised in the plasma. The major side effect of these drugs is haemorrhage. This is theoretically increased in streptokinase due to a higher likelyhood of a systemic lytic state. Studies however have not definitively confirmed this difference clinically. There are strict contraindications to fibronlysis which include; 1. Surgery within 10 days, including organ biopsy, puncture of noncompressible vessels, serious trauma, cardiopulmonary resuscitation 2. Serious gastrointestinal bleeding within 3 months 3. History of hypertension (diastolic pressure >110 mm Hg) 4. Active bleeding or hemorrhagic disorder 5. Previous stroke or active intracranial process 6. Aortic dissection 7. Acute pericarditis.

Antifibrinolytics Aprotinin is a natural polypeptide with 58 amino acids and has a molecular weight of 6512 Daltons. It is a naturally occuring proteolytic enzyme acting on trypsin, plasmin and tissue kallikrein. It inhibits the fibrinolytic activity of streptokinase-plasminogen complex. In addition it has been suggested that it preserves platelet function and decreases activation of the clotting cascade. It has been used for the treatment of haemorrhage due to hyperplasminaemia and in patients at high risk of bleeding following cardiothoracic surgery. Plasma aprotinin concentrations decrease rapidly after intravenous administration because of redistribution to peripheral tissues. It is metabolised and eliminated via the kidney. Tranaxemic acid is a synthetic antifibrinolytic used in the prevention of haemorrhage in patients with coagulopathies undergoing minor procedures. It is also used in the treatment of menorrhagia. It is available in both IV and oral formulations and may be used as a mouthwash for dental procedures. The mechanism of action is by inhibiting binding of plasmin and plasminogen to fibrin. It has an oral bioavailability of 45%, and is minimally protien bound. It not significantly metabolised and most is excreted in urine (95%) unchanged, therefore it is important to dose adjust in the setting of renal failure. It increases the risk of clotting events, and commonly causes nausea, vomitting and diarrhoea. Aminocaproic acid is a synthetic antifibrinolytic used for treatment of uncontrolled bleeding. It is available as both oral and IV formulations. Binds competitively to plasminogen; blocking the binding of plasminogen to fibrin and the subsequent conversion to plasmin, resulting in inhibition of fibrin degradation (fibrinolysis). It is minimally metabolised by the liver and is excreted via the kidney up to 65% unchanged, hence caution should be used when given in the setting of renal impairment. It has a half life of around 2 hours.

Christopher Andersen 2012