Anticoagulants and the Management of Coagulopathy

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The prevention of blood loss from a damaged blood vessel is an essential feature of life. Injury to the skin and underlying structures leads to vasoconstriction, adhesion and activation of platelets to form a plug, or thrombus, that stops the bleeding, and fibrin formation, which reinforces the plug. A white thrombus forms initially in high-pressure arteries when platelets adhere to the damaged endothelium. The growing thrombus reduces arterial flow and the local stasis causes fibrin to be deposited, trapping erythrocytes so that a red thrombus is formed around the initial white thrombus. This may cause local ischaemia by blocking the artery. In low-pressure veins, red thrombi can develop without a central white thrombus and they often have a long tail of fibrin and trapped red cells, which can break free and form an embolus remote from the initial area of damage.

The blood coagulation cascade is shown in Figure 1. Modification of this cascade by drugs is clinically useful when there is a disorder of coagulation (coagulopathy).

Role of vitamin K

Vitamin K is a cofactor for the action of carboxylase enzymes that are important in the production of coagulation or clotting factors II, VII, IX and X. In addition, there are several other vitamin K-dependent proteins including osteocalcin in bone. Vitamin K is a fat-soluble vitamin derived from two sources. Vitamin K (phytomenadione) occurs in plants. Bacteria in the gut synthesize vitamin K$_2$ (menaquinone), which is a series of compounds with side chains of different length. Both vitamins require bile salts for absorption, and deficiencies can arise due to obstructive jaundice when bile secretions are inadequate or absent. Such malabsorption syndromes may be treated with menadiol sodium phosphate, a water-soluble preparation. However, this is ineffective for haemorrhagic disease of the newborn or relative overdoses of coumarin-like anticoagulant drugs (see later) in which phytomenadione is the treatment of choice.
Anticoagulants affecting coagulation proteins

Warfarin and the coumarin anticoagulants

A haemorrhagic disease of cattle was found to be caused by a deficiency in plasma prothrombin caused bybishydroxycoumarin, a toxin found in spoiled sweet clover silage. This was synthesized as dicoumarol and subsequently its derivatives, particularly warfarin, have been widely used commercially as rodenticides and clinically as antithrombotic agents in humans. Warfarin is the most commonly used drug in the group and others, such as acenocoumarol and phenindione, are used only in patients who show idiosyncratic adverse reactions to warfarin. Vitamins K₁ and K₂ are activated in the body by reduction of the epoxide, generated by the carboxylation of prothrombin, to the hydroquinone form. This step is sensitive to the coumarins, which act effectively as vitamin K antagonists. The synthesis of all the vitamin K-dependent clotting factors is partially inhibited so the onset of the anticoagulant effect of coumarins is dependent on the degradation rate of the clotting factors in the plasma. The onset of action usually takes about 12 hours and maximum effects occur several days after the commencement of treatment. This long delay poses several problems in achieving a balance between giving enough to prevent excessive coagulation and giving too much, resulting in unwanted haemorrhage. Measuring the prothrombin time monitors treatment. Warfarin crosses the placenta readily. It is teratogenic in early pregnancy and may cause intracranial haemorrhage in the neonate during birth. It is thus avoided during pregnancy. Warfarin is also excreted in breast milk. This could pose a problem for suckling infants because they are inherently deficient in vitamin K owing to their lack of gut flora. However, phytoenadione treatment of the neonate is now routine and treatment of the mother with warfarin is not contraindicated. There are many drug interactions with coumarin anticoagulants of which the most important appears to be the risk of haemorrhage with the concurrent use of antibiotics such as co-trimoxazole and co-amoxiclav.

Heparin

Heparin is present in mast cells and is extracted from animal tissue such as beef lung or porcine intestinal mucosa. It is a family of sulphated glycosaminoglycans with a range of molecular weights and, because its constitution is variable, it is bioassayed against an international standard and is measured in units of activity rather than mass. Heparin is a rapidly acting anticoagulant given intravenously or subcutaneously, with a short duration of action. It may be referred to as standard or unfractionated heparin to distinguish it from the low-molecular-weight heparins (e.g. dalteparin sodium, enoxaparin) which have a longer duration of action and are administered subcutaneously. Heparin is used in the treatment of deep vein thrombosis and pulmonary embolism and low doses may be used in anaesthesia to prevent the development of these two conditions in high-risk patients undergoing general surgery. The low-molecular-weight heparins are being increasingly used for this purpose. Heparin is used to maintain the extracorporeal circuits in cardiopulmonary bypass surgery and haemodialysis.

Heparin is an effective anticoagulant in vivo and in vitro. It activates a protease inhibitor, antithrombin III, which inhibits many of the active forms of the coagulation factors (Figure 1). Thrombin is particularly sensitive to standard heparin, which provides a catalytic template to which antithrombin III and thrombin bind. The low-molecular-weight heparins are not long enough to bind to both antithrombin and thrombin and have their main anticoagulant action via inhibition of activated factor X (Figure 1). They have minimal effects on clotting in vitro.

Heparin exhibits saturation kinetics with the apparent half-life increasing with dose. In contrast, the low-molecular-weight heparins have longer half-lives than standard heparin.
and because they follow first-order kinetics the half-life is not dependent on dose. This simplifies dose regimens.

The main unwanted effect of heparin is haemorrhage, which can be controlled by stopping drug administration or, if more active treatment is required, by administering the antagonist, protamine sulphate. It is a strongly basic protein that forms an inactive complex with the acidic heparin molecule. It is important that patients are not overdosed with this heparin antagonist because it can prolong bleeding time. Like most strong bases, protamine can release histamine and rapid intravenous injections can result in hypotension. It also activates the immune system and IgG- and IgE-mediated allergic responses have been described, particularly in patients with a history of fish allergy (protamine is derived from fish) or neutral protamine Hagedorn (NPH) insulin-dependent diabetes. Catastrophic pulmonary vasoconstriction is a rare, but often fatal, consequence of the use of protamine to neutralize heparin. A recent paper suggests that inhaled nitric oxide, a potent pulmonary vasodilator, is an effective treatment for this condition. Thrombocytopenia can occur with standard heparin, but is unlikely to be a serious problem in anaesthetic use unless therapy is prolonged.

Danaparoid sodium
Danaparoid sodium contains heparan sulphate (84%), dematan sulphate (12%) and chondroitin sulphate (4%). Its main effect is to inhibit factors Xa and IIa at a ratio greater than heparin with minimal effects on platelet function. In the USA, it is approved for the prophylaxis of deep vein thrombosis in patients undergoing elective hip replacement. It exhibits low cross reactivity with heparin antibodies and may be the treatment of choice for heparin-induced thrombocytopenia. It has recently been approved in the UK. Dematan sulphate is a glycosaminoglycan related to heparin and inhibits thrombin selectively. Its potential use as a sole agent in place of heparin is under investigation.

Antiplatelet drugs
Antiplatelet drugs are particularly effective in reducing thrombus formation in the arterial circulation where the anticoagulants mentioned above have little effect. Aspirin is the most important drug in this group because it alters the balance between thromboxane A₂, which promotes aggregation, and prostacyclin, which inhibits it (see Anaesthesia and Intensive Care Medicine 3:6: 225). Prostacyclin can be used to prevent platelet aggregation but it is too short lived to have widespread application. It must be given by infusion and causes vasodilatation, resulting in flushing and headache.

Thrombin activates platelets (Figure 1) by inducing the expression of glycoprotein IIb and IIIa receptors which bind fibrinogen thus linking adjacent platelets. Inhibitors of this receptor have been recommended by the National Institute for Clinical Excellence (NICE) for high-risk patients with unstable angina or non-Q-wave myocardial infarction and patients undergoing percutaneous coronary intervention. Abciximab is a monoclonal antibody that binds to the receptor, but should be used only once for the last group of patients. Eptifibatide and tirofiban are licensed for high-risk patients with unstable angina or non-Q-wave myocardial infarction. Platelet activation is also induced by adenosine diphosphate (ADP) released from degranulating platelets. Clopidogrel and ticlopidine inhibit the binding of ADP to its platelet receptor. They are licensed for the prevention of ischaemia, stroke or myocardial infarction in at-risk patients.

Fibrinolytic and antifibrinolytic drugs
Fibrin and fibrinogen are broken down by the protease plasmin, which is produced by the conversion of inactive plasminogen. Drugs that activate plasmin break up thrombi and are used in the treatment of life-threatening venous thrombosis and pulmonary embolism. Streptokinase, extracted from β-haemolytic streptococci, binds to the plasminogen exposing its active site and thus inducing plasmin-like activity. Antibodies to streptokinase appear after about 4 days and the drug should not be used again for at least 1 year. Alteplase, reteplase and tenecteplase are recombinant tissue plasminogen activators. Alteplase is unmodified human tissue plasminogen activator while the others have some amino acid sequences deleted to increase the elimination half-life to allow bolus administration. They are more selective for fibrin-bound plasminogen than for free plasminogen and are thus promoted as being clot selective.

Inhibition of plasminogen activation can be achieved with drugs such as tranexamic acid, which are used in conditions where there is a risk of haemorrhage such as prostatectomy and dental extraction for patients with haemophilia. Aprotinin inhibits proteolytic enzymes and is used for patients at risk of significant blood loss during surgery.