Continuing Medical Education Article

Anticoagulants in anaesthesia

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Since 1929, when it was first suggested that treatment with heparin may prevent postoperative thrombosis, the use of anticoagulants in clinical practice has increased dramatically. Every anaesthetist now needs a detailed working knowledge of these drugs. The anticoagulants in common clinical use are heparin and the vitamin K-antagonists, of which the most frequently prescribed is warfarin. Heparin and warfarin will be discussed in detail in this review.

History

Heparin

In 1916 Jay McLean, a medical student, discovered a phospholipid anticoagulant by chance while investigating the nature of ether-soluble procoagulants. After further work by Howell and Holt,[1] a water-soluble mucopolysaccharide was isolated in 1918 and given the name heparin, due to its high concentration in the liver. Its use was initially restricted to *in vitro* anticoagulation of stored blood; only in the 1930s when purification techniques were perfected in Sweden and Canada did clinical trials become possible.

Warfarin

The synthesis of warfarin stemmed from observations by Schofield[2] in 1924 that cattle on the plains of Alberta were dying from a haemorrhagic disease that he attributed to the ingestion of spoiled sweet clover hay. Later Roderick[3] established that improper curing of this hay led to a gradual diminution in plasma prothrombin in the cattle. In 1939, Campbell and Link succeeded in isolating and crystallizing the active agent, which was identified as a dicoumarin.[4] Many congeners were synthesized, the most useful of these, warfarin, was prepared by Ikawa *et al.* in 1944.[5] The acronym warfarin was given based on the name of the patent holders, Wisconsin Alumin Research Foundation, plus the suffix "arin" from the coumarin group. It was originally thought to be too toxic for use in man but became a useful rodenticide. After a

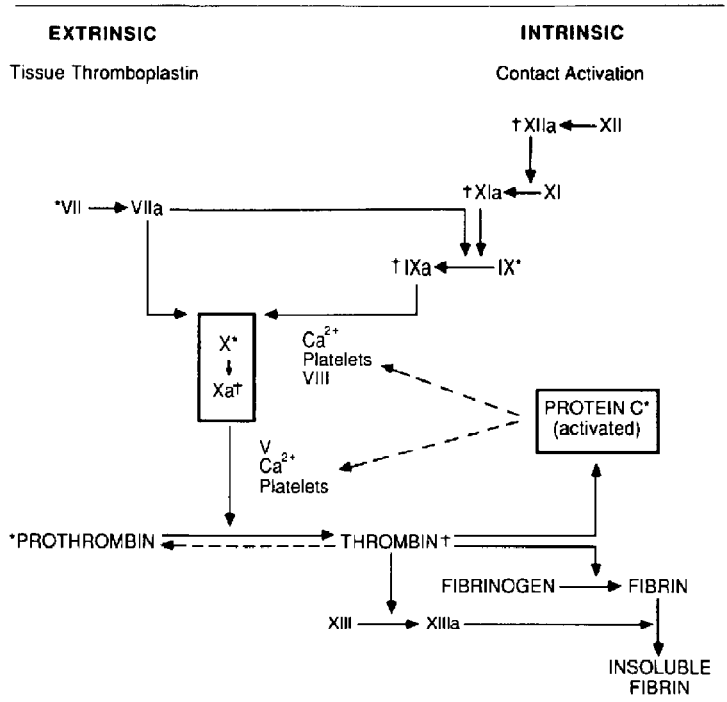

FIGURE 1 The coagulation pathway. Key: → Factor-dependent activation; - - → factor-dependent inhibition; * site of action of oral anticoagulants; † site of action of antithrombin III/heparin complex.

patient survived an attempted suicide with the drug, clinical trials began in 1951.[6]

Pharmacology

Heparin

Heparin is commercially prepared from porcine intestinal mucosa or partially purified bovine lung, and can also be prepared from sheep and whales. Semisynthetic polymers have been developed but not yet tested in man. Preparations are marketed as either sodium heparin or calcium heparin and it is claimed that the calcium salt may produce less bruising.[7]

Heparin binds to and catalyzes antithrombin III (AT III). Antithrombin III, an alpha-$_2$ globulin, is found in human plasma and is an important thrombin inhibitor. Congenital deficiency of AT III produces a hypercoagulatic state, with recurrent thromboembolism.[8] Antithrombin III forms a complex with and neutralizes the activity of protease factors XII, XI, X, IX and II (thrombin) (Figure 1) in reactions that are greatly accelerated in the presence of heparin. The protease-inhibitor complex has a low affinity for heparin, and heparin is released and made available for the catalysis of other reactions. In this way, one molecule of heparin can promote the binding of several molecules of thrombin and AT III.[9]

More recently another heparin-dependent thrombin inhibitor, heparin co-factor II (HC-II), has been identified.[10] This forms a stable enzyme-inhibitor complex that inhibits thrombin in a reaction greatly enhanced by heparin. However, the precise physiological role of HC-II is not yet clear.

Long-term therapy with heparin may reduce levels of AT III and paradoxically increase the tendency to thrombus formation. AT III levels are also reduced in congenital AT III deficiency;[8,11] during use of oral contraceptives;[12] in the postoperative period;[13] after cardiopulmonary bypass;[14] or with liver disease,[15] disseminated intravascular coagulation[16] or venous thrombo-embolism.[17]

Activated factor X (Xa) is at the beginning of the final pathway through which activation of coagulation must pass. There is evidence that the primary target of antithrombin III is Xa rather than thrombin,[18] and the rationale for the use of low-dose heparin is that thrombin

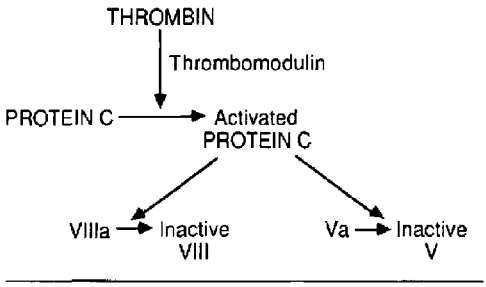

FIGURE 2 Protein C activation and action on factors V and VIII. Thrombomodulin is a thrombin-binding factor found on endothelial surfaces and is required for the activation of protein C.

generation will be limited by a small dose of heparin, if it is given before activation of the coagulation cascade. This effect is mainly mediated through inhibition of factor Xa. However, when recent thrombosis has occurred, particularly if there is continuing generation of thrombin, a much larger dose is required to prevent clot extension; in this situation anticoagulation is mainly due to inactivation of thrombin by AT III, and to a lesser extent, by inhibition of factor Xa.[19]

Heparin has a complex molecular structure and a strong negative charge. It is one of the strongest acids occurring naturally in the body.

The molecular weight of heparin varies with the source and method of isolation. In general, forms with high molecular weight have antithrombin and anticoagulant properties and prolong the values obtained from the tests of the intrinsic coagulation pathway, whereas forms with low molecular weight have enhanced anti-factor Xa but little anticoagulant effect. In animal experiments these low molecular weight compounds prevent the development of experimentally induced thrombus and, used prophylactically in man, they may be as effective as conventional heparin but with the advantage of reduced bleeding.[20,21]

Heparin is not absorbed from the gastrointestinal tract and must be administered parenterally, following which it acts immediately. It is metabolized in the liver by heparinase, and inactive metabolites are excreted renally. After large intravenous doses small amounts of unchanged heparin are excreted in urine.[22] The plasma half-life in normal individuals is about 90 minutes, with values ranging from 30–360 minutes.[23]

Vitamin K antagonists

There are two types of vitamin K antagonists: (1) The coumarins (e.g., warfarin); (2) The inanediones (e.g., phenindione).

Vitamin K antagonists are organic compounds of low molecular weight that are rapidly absorbed from the gastrointestinal tract, and reach peak concentration within one hour of ingestion. All are strongly bound to albumin, so that less than ten per cent of the circulating drug is pharmacologically active, and undergo almost complete metabolic transformation before excretion in altered form in urine and stool. The half-life of warfarin is 42 hours.[24] Their mode of action is by competitive inhibition of vitamin K, which is required for the formation of gamma carboxyglutamic acid in the liver. This amino acid is necessary for the synthesis of prothrombin, factors VII, IX and X, and protein C (a plasma inhibitor that inactivates factors V and VIII) (Figures 1 and 2). Therefore, inhibition or deficiency of vitamin K results in the production of proteins deficient in gamma-carboxyglutamic acid. These proteins have been referred to as Proteins Induced by Vitamin K absence or Antagonist or "PIVKA." The carboxyl groups of carboxyglutamic acid are essential for the binding of calcium, which normally forms the link between clotting factors and phospholipid. As this link cannot be formed there is impaired activation of the coagulation factors.[25] Furthermore, proteins deficient in carboxyl groups (PIVKAs) may *directly* decrease prothrombin activation and hence inhibit thrombin formation. This is the "PIVKA effect."[26]

The anticoagulant effect of these drugs is delayed until the concentration of normal coagulation factors falls. The half-lives for factors VII, IX, X and II are 5, 20–30, 45–72 and 60 hours respectively. Thus, although peak levels of warfarin occur within one hour of oral administration the peak hypothrombinaemic effect does not occur until after 36–72 hours.[27]

In contrast to heparin, warfarin increases AT III levels, but the significance of this is uncertain.[11] It is possible that this is more important than depression of factors II, VII, IX and X.

Because vitamin K is necessary for the synthesis of protein C, treatment with oral anticoagulants decreases protein C levels.[28] This decrease may paradoxically result in increased activity of factors V and VIII at the site of thrombin formation.

Indications

An overall view of the indications for anticoagulant therapy is given in Table I. Some of these will be discussed in this section.

The main indications for the use of anticoagulants are in the treatment of thrombo-embolism, and in the prophylaxis of deep venous thrombosis.

Venous thrombosis

Untreated peripheral venous thrombosis carries a high

TABLE I Indications for anticoagulation*

	Duration	
Condition	*Permanent*	*Temporary*
Thrombo-embolism	Deep venous thrombosis/ pulmonary embolism	Deep venous thrombosis/ pulmonary embolism
Foreign body	Cardiac valve prosthesis	Cardiopulmonary bypass Haemodialysis Vascular surgery Arterial catheters
Prophylaxis	Atrial fibrillation Congestive heart failure Recurrent pulmonary embolism Recurrent venous thrombosis Malignancy	Peroperative immobilization Sepsis Respiratory failure
Others	Cerebrovascular disease (Progressive strokes/transient ischaemic attacks) Mitral valve disease	Myocardial infarct Disseminated intravascular coagulation Cardioversion

*Modified from Ellison N, Ominsky AJ.[29]

risk of pulmonary embolus.[30] Few trials have specifically examined the use of heparin in deep venous thrombosis. It will not dissolve formed thrombi, but may stimulate fibrinolysis, and its prophylactic value and role in the treatment of pulmonary embolism justify its use in the treatment of venous thrombosis.[31]

The treatment of existing venous thrombosis has three goals:
- to minimize thrombus extension,
- to minimize damage to the deep venous system of the leg,
- to prevent pulmonary embolism.

Pulmonary embolism

After general surgical procedures the incidence of fatal pulmonary emboli is about 0.1–0.8 per cent. After total hip replacement the incidence is three per cent and after hip fractures four to seven per cent.[32,33] Most patients with potentially fatal acute massive pulmonary embolism do not survive long enough for treatment to be instituted. Embolectomy is rarely indicated but is probably the treatment of choice in patients with grossly impaired cardiac output.[34] It is associated with operative mortality of 23–57 per cent.[35] Outcomes after embolectomy in chronic recurrent emboli are more encouraging.[36]

The remaining alternatives for patients at risk for pulmonary embolism are full anticoagulation, thrombolytic therapy or vena caval interruption. Large doses of heparin may suppress platelet-mediated respiratory distress due to platelet adhesion to emboli,[37] and may be life saving when given as an initial bolus intravenous injection of 15,000 units.[38] Barritt and Jordan[27] in 1960 showed that of the patients who had pulmonary embolus and underwent anticoagulation with heparin, only 3.7 per cent died, compared with 32 per cent of untreated patients. Thrombolytic therapy with streptokinase or urokinase activates plasminogen with resultant clot lysis. The Urokinase Pulmonary Embolism Trial (UPET)[35] compared anticoagulation with thrombolytic therapy in pulmonary embolism. Pulmonary perfusion improved sooner with urokinase, although after one year there were no differences in perfusion, recurrence or mortality rates. However, there were significant improvements in haemodynamics in the urokinase group.

If anticoagulation or fibrinolysis is contraindicated or there is recurrent embolism despite adequate anticoagulation, vena caval filters or vena caval plication have been used with success.[39]

For smaller pulmonary emboli, treatment is aimed at preventing further emboli from detaching. After heparinisation during the acute phase, patients should be maintained on oral anticoagulants for three months.

Prophylaxis

In 1944 Olovson[40] hinted at the possible use of low-dose heparin as a prophylactic measure, but this approach was not followed up until the work of Sharnoff[41] and Kakkar *et al.*[42] in the 1960s and 1970s.

The institution of any prophylactic regimen depends on establishing criteria by which results can be assessed and groups of patients at risk can be identified. It is in this area that the prophylaxis of venous thrombosis has caused the most controversy, because results have been judged according to various criteria: mortality; incidence of fatal or non-fatal pulmonary emboli; and reduction in thrombi seen at contrast venography or I^{125}-labelled fibrinogen leg scanning, techniques that themselves have been criticized. Many studies have shown that low-dose heparin significantly reduces the development of positive I^{125}-labelled fibrinogen leg scans in postoperative patients. However, dangerous proximal venous thrombosis can occur without being preceded by smaller clots in calf veins, and without being detected by positive I^{125}-labelled fibrinogen scanning. While low-dose heparin can suppress the formation of thrombi in small calf veins, it may have no effect on thrombi in large ileofemoral veins, in particular after hip fracture.[43]

The overall incidence of deep venous thrombosis in the untreated surgical population is 20–30 per cent.[44] The incidence in various patient groups has been identified, using I^{125}-labelled fibrinogen leg scanning or venography, as follows: neurosurgery 20–25 per cent,[45] abdominal or thoracic surgery 3–60 per cent,[46] prostatic surgery 25–50 per cent,[46] gynaecological surgery 18 per cent,[47] hip fractures and elective hip surgery 40–70 per cent[45] and knee surgery 60–70 per cent.[45]

The risk of thrombo-embolic complications is increased by other factors such as age, malignancy and obesity.

The international multicentre trial of Kakkar *et al.*[48] in 1975 compared 2,045 patients aged 40 years or older undergoing major elective surgery who were given 5,000 units of heparin subcutaneously two hours preoperatively and then every eight hours for seven days, with a group of 2,076 untreated controls. There were two fatal pulmonary emboli in the treated group compared with 16 in the untreated patients. Deep venous thrombosis was detected by I^{125}-labelled fibrinogen scanning in 7.7 per cent and 24.6 per cent, respectively. There was no significant difference in blood transfusion requirements but the incidence of wound haematoma was higher in the treated group. The trial has been criticized for the absence of simultaneous treatment of the two groups, the lack of randomization and the use of different methods of identification of thrombosis.[49] However, a similar but smaller double-blind trial with proper randomization confirmed these results using 12-hourly heparin and concluded that low-dose heparin prophylaxis is effective and should be used in patients over 40 years old undergoing major operations.[51]

Bergqvist[51] reviewed methods of prophylaxis of venous thrombo-embolism; in 22 of 24 studies using 5000 units of heparin every 12 hours, significantly fewer thrombotic events were seen in the treated group (eight per cent) than the placebo group (26 per cent).

The very high incidence of potentially fatal proximal thrombi in hip surgery has prompted many studies of prophylaxis in these patients. One study indicated that low-dose heparin was ineffective, with a radiofibrinogen uptake test showing an incidence of venous thrombosis of 24.4 per cent in the placebo group and 16.8 per cent in the treatment group.[52] The poor results obtained with low-dose heparin alone can be improved by combining it with dihydroergotamine.[52,53] Dihydroergotamine mesylate is a potent vasoconstrictor that acts predominantly on the capacitance vessels of the limbs. Since it has little effect on the resistance vessels, it encourages venous drainage, reducing venous stasis and the potential for thrombus formation.

Low-dose heparin failed to prevent deep venous thrombosis in patients undergoing surgery following fractured neck of femur,[54] whereas warfarin prevented deep vein thrombosis and fatal pulmonary embolus in a similar group of patients.[55,56] After trauma, thrombin generation has probably already occurred in these patients and large amounts of heparin are required to neutralize the thrombin through the action of AT III.[54]

The available evidence suggests that, for routine prophylaxis of patients over the age of 40 years at risk due to immobility or reversible medical conditions or following major elective surgery, low-dose heparin is the most satisfactory regimen. However, it is of less value after major orthopaedic surgery of the hip, femur or knee. In a high-risk patient, oral anticoagulation is more effective, although it carries the risk of unwanted haemorrhage.[57,58]

Intensive care

Patients in the Intensive Care Unit are particularly vulnerable to venous thrombo-embolism. Many have been ill for a significant period before their hospital admission, have activity restrictions secondary to their disease or have significant problems with venous stasis (e.g., congestive heart failure).[59]

Pitt *et al.*[60] showed that the incidence of deep venous thrombosis after acute myocardial infarction could be halved by treatment with low-dose heparin, while de Vries *et al.*[61] noted a significant decrease in the incidence of repeated infarction or mortality in similar patients. More recently, low-dose heparin has been shown to reduce significantly the frequency of deep venous thrombosis in critically ill patients in the Intensive Care Unit.[62] In a retrospective study of low-dose heparin on a respiratory Intensive Care Unit, Pingleton *et al.*[63] showed that the use of this prophylaxis decreased the incidence of

TABLE II Dosage regimen for heparin*

	Loading dose	*Maintenance dose*	*Control*
Continuous			
– Normal	5,000 units	24,000 units/24 hr	APTT 1.5–2 × normal
– Postoperative	2–4,000 units	15–20,000 units/24 hr	APTT 1.5–2 × normal
Intermittent	Nil	5–7,000 units /4 hr	APTT 1.5 × normal Daily values
Subcutaneous	Nil	10,000 units/8 hr 15,000 units 12 hr	Daily values
Prophylaxis	5,000 units (2 hr preoperatively)	5,000 units/8 or 12 hr (Starting 12 hr postoperatively and continuing until the patient is mobile)	Unnecessary[18]

*Modified from Hirsh J, Gallus AS.[24]

pulmonary embolus (diagnosed by ventilation-perfusion lung scan, by pulmonary angiography or at postmortem) from 13 of 98 patients not given heparin to 1 of 99 receiving heparin, with no increase in haemorrhagic complications. They concluded that prophylactic low-dose heparin should be used in patients with respiratory failure unless specific contraindications exist, and that patients in whom low-dose heparin is contraindicated may benefit from other methods of prophylaxis for deep venous thrombosis.

Administration

Heparin

Heparin may be administered by continuous or intermittent intravenous infusion, or by intermittent subcutaneous injection (Table II). One hundred international units (iu) of heparin is approximately equivalent to 1 mg, but since the specific activity of various preparations may differ, heparin should always be prescribed in international units.

Prophylactic low-dose heparin is usually given subcutaneously every 12 hours. Administration every eight hours produces a slightly lower frequency of thrombosis, although not of fatal emboli; however, it has a higher incidence of haemorrhagic complications and is not recommended.[64]

Recently, the use of microdose heparin has been advocated, with continuous per- and postoperative infusions at a rate of 1 iu·kg^{-1} body weight/hour resulting in a lower incidence of deep venous thrombosis and pulmonary embolism.[65] At this low dose, heparin is not detectable in the blood and may localize at the boundaries between endothelial cells, where it prevents platelets and coagulation factors from making contact with subendothelial collagen.[66]

In conventional full anticoagulation, Salzmann *et al.*[67] demonstrated that intermittent intravenous heparin given every four hours produced a seven-fold increase in major haemorrhagic problems compared with continuous intravenous heparin (both regimens being controlled according to an activated partial thromboplastin time (APTT) of 50–80 seconds) but was no less effective in preventing thrombo-embolism.

Vitamin K antagonists

Warfarin has a half-life of 42 hours and is given as a once-daily oral dose. A baseline prothrombin time should be measured before therapy is initiated. In elective anticoagulation three initial daily doses of warfarin 10 mg are recommended and subsequent doses are adjusted according to daily prothrombin times.[68] Smooth control of anticoagulation may take up to one week to establish.

When immediate anticoagulation is required, intravenous heparin should be commenced, followed by oral warfarin. Heparin will not affect the prothrombin time as long as the APTT is in the range of 1.5–2.5 and heparin must be continued until the prothrombin time is 1.5–2.5 times control. Phenindione has a half-life of five hours, and a twice-daily dosage regimen is necessary. Therefore, smooth control may be difficult to achieve.

Of absorbed warfarin, 97 per cent is bound to plasma protein; the pharmacological effect of the drug is due to the small unbound fraction. Therefore, other drugs competing for protein-binding sites result in a higher proportion of unbound drug and, consequently, increased anticoagulant action (Table III). Metabolism is through hydroxylation by hepatic microsomal enzymes, and pharmacological induction of these enzymes results in

TABLE III Drugs that affect oral anticoagulation

Drugs that potentiate oral anticoagulants		
Alcohol (dose dependent)	Disulfiram	Phenylbutazone
Anabolic steroids	Glucagon	Quinidine
Aspirin	Metronidazole	Sulfinpyrazone
Cimetidine	Oxymethalone	Thyroxine
Clofibrate	Oxyphenbutazone	Trimethoprim
Drugs that may potentiate oral anticoagulants		
Allopurinol	Diazoxide	Monoamine oxidase inhibitors
Aminoglycosides	Disopyramide	Nalidixic acid
Aminosalicylic acid	Erythromycin	Naproxen
Ampicillin	Ethacrynic acid	Penicillin
Antacids	Hydrocodone	Propylthiouracil
Cephalosporins	Isoniazid	Quinine salts
Chloral hydrate	Liquid paraffin	Sulindac
Chloramphenicol	Mercaptopurine	Sulfonamides
Chlorpromazine	Mefenamic acid	Tetracyclines
Chlorpropamide	Methaqualone	Tolbutamide
Corticosteroids	Methotrexate	Trenilic acid
Cycloserine	Methylphenidate	Tricyclic antidepressants
Cyclophosphamide	Miconazole	Triclofos sodium
Drugs that may antagonize oral anticoagulants		
Antihistamines	Dichloralphenazone	Oral contraceptives
Barbiturates	Glutethimide	Phenytoin
Carbamazepine	Griseofulvin	Rifampin
Cholestyramine	Haloperidol	Spironolactone
Corticosteroids	Mercaptopurine	Vitamin K

more rapid degradation of free warfarin and decreased anticoagulant activity. The anticoagulant effect is also influenced by variations in vitamin K uptake by the gastrointestinal tract. The uptake may be affected by factors other than diet, such as the administration of broad-spectrum antibiotics or laxatives. Requirements may be reduced in patients with liver disease or congestive cardiac failure, or those on total parenteral nutrition.

Monitoring

Tests to monitor anticoagulant effect can be performed on whole blood, platelet-rich plasma (PRP) or platelet-poor plasma.[35]

Heparin

Platelets contain a cationic protein with anti-heparin activity. Therefore, there are theoretical advantages to measuring the anticoagulant effect of heparin in whole blood or PRP.

The whole-blood clotting time (WBCT, or Lee-White time) is a useful and convenient method to monitor heparin therapy but its laboratory use has diminished because of the length of time required to achieve its end-point in the presence of therapeutic amounts of anticoagulant. The clotting time, which is normally five to ten minutes, should be kept at two to three times normal for adequate therapeutic effect. A WBCT of 30 minutes is roughly equivalent to an activated clotting time (ACT) of 190 seconds,[69] and for this reason in the operating room it has largely been replaced by the ACT. (Activated clotting time is discussed below.)

The most commonly used laboratory method of controlling heparin therapy is the Activated Partial Thromboplastin Time (APTT). This test is performed by adding partial thromboplastin solution and kaolin solution to oxalated plasma, to initiate coagulation. After the addition of calcium chloride the coagulation time is recorded. It is a relatively sensitive test of the intrinsic pathway, and is prolonged by deficiencies of factors XII, XI, X, IX, VIII and V, prothrombin and fibrinogen. It is prolonged when factor VIII or IX concentrations fall below 30–50 per cent of normal. Values for adequate control are shown in Table II.

Although it is generally felt that the monitoring of low-dose heparin therapy is unnecessary,[18] some have argued that, due to the wide variation in response to heparin, laboratory monitoring is recommended, at least initially.[69]

For more acute control, during cardiac surgery in particular, the ACT is a satisfactory monitor of heparinisation (see Cardiopulmonary Bypass section).[70] The

ACT is a relatively insensitive test, and is prolonged when levels of coagulation factors within the intrinsic pathway are markedly depressed.

Vitamin K antagonists

The effect of oral anticoagulant drugs must be regularly and frequently assessed to ensure adequate treatment without excessive anticoagulation.

The most widely used test is the Prothrombin Time (PT) of Quick,[71] so called because Quick thought that he was measuring prothrombin content and was unaware of the importance of other factors. The test is sensitive to alterations in levels of prothrombin and factors V, VII and X, but because of variations in technique and reagents, the results obtained are relevant only for a particular laboratory and a particular day. Prothrombin time is also prolonged when fibrinogen concentration is less than 100 $mg \cdot dl^{-1}$, and when heparin or fibrinogen degradation products are present. The normal value is 11–13 seconds, and maintenance at values of 1.5–2.5 times control is associated with a low risk for thrombosis recurrence.

The thrombotest remains a satisfactory method of assessment of overall clotting activity, and is widely used in anticoagulant clinics. The result depends on the levels of factors II, VII, IX and X, as well as the PIVKA effect, and is expressed as percentage activity by reference to dilution curves. The ideal therapeutic range is between 8–12 per cent.[72]

When assessing anticoagulation, particularly at times of change in therapy, it should be remembered that false results may be produced by other concurrent anticoagulant treatment. Large doses of coumarin may affect APTT through factor IX depression within the intrinsic system or through factor X or prothrombin. Large doses of heparin may reduce conversion of prothrombin to thrombin and of fibrinogen to fibrin, and so lengthen the PT.[29]

Side effects

The main complication of anticoagulant therapy is haemorrhage. With full anticoagulation this may include haematuria, haemarthroses, wound haematomata and, more commonly, gastrointestinal bleeding.

Heparin

The incidence of haemorrhagic complications with low-dose heparin is variously reported as 10–27 per cent,[73] and there have been claims that the low-dose regimen may produce a fully anticoagulated state.[74] Bleeding is more common during prophylaxis with conventional doses after surgery than during the treatment of a pre-existing condition. Spontaneous haemorrhage is unlikely when the APTT is in the therapeutic range, but in postoperative patients, the elderly, patients with an underlying haemostatic defect and those on salicylate therapy, there is likely to be an increased risk of bleeding.[24] The risk of haemorrhagic complications in patients with carcinoma may be as high as 50 per cent, and conventional anticoagulation does not appear to be a safe or effective therapy for venous thrombo-embolism in these patients.[75]

The incidence of other complications associated with heparin therapy is low. Thrombocytopenia is well recognized, with an incidence of up to 33 per cent in patients treated.[76] Two types have been described: the first, more common type is acute and secondary to reversible clumping, agglutination and peripheral sequestration of platelets after a direct interaction with heparin. The second, more important, type usually occurs 7–14 days after treatment and is thought to result from heparin-induced platelet antibodies.[77] It may be associated with subsequent heparin resistance.[78]

Hypersensitivity reactions and anaphylactoid reactions are rare, but asthma, urticaria, rhinitis, lacrimation and fever have all been reported following the administration of heparin.[22] It has been suggested that all patients with a history of allergy should be given a test dose of 1000 units of heparin before full anticoagulation to minimize the risk of hypersensitivity reactions.[22] Neuropathy, transient alopecia and priapism may also occur.[79,80] Osteoporosis and spontaneous fractures have been reported in patients receiving doses of 15,000 to 30,000 units of heparin per day for more than six months.[24] Heparin has also been implicated in delayed wound healing.[81]

Vitamin K antagonists

Twenty-five per cent of all deaths associated with coumarin therapy are due to massive gastrointestinal bleeding, usually in association with unsuspected peptic ulceration or neoplasm. Some form of haemorrhagic complication is said to occur in two to four per cent of patients treated,[22] the most common being bleeding from mucous membranes, skin and the gastrointestinal tract. Therefore, the anaesthetist should be alert for ecchymoses, epistaxis, haemoptysis and bleeding gums. Purpura, urticaria and alopecia have been reported in patients on long-term therapy. Necrosis of skin and breast tissue may also occur.[22] Warfarin crosses the placenta and there is a high risk of fetal haemorrhage and maceration. Warfarin-induced embryopathies may occur during the first 6–12 weeks of pregnancy, while central nervous system and ocular anomalies may occur at any time during pregnancy. For example, there is evidence linking warfarin given during the first trimester to chondroplasia punctata, a cartilaginous disorder.[82] Furthermore, when given during the second and third trimesters, warfarin may induce hypoprothrombin.

TABLE IV Regimen for reversal of vitamin K antagonists*

Prothombin time (seconds)	*Condition*	*Action*
50–90	No haemorrhage	Withhold therapy for 1 or more days, according to PT.
>90	No haemorrhage	Consider giving vitamin K 1–2 mg PO or IV.
±50	Haemorrhage present or temporary reversal for surgery	Give plasma.
Any	Life-threatening haemorrhage	Give vitamin K 2.5–50 mg IV slowly. Consider giving Factor IX concentrate.

*Reproduced, with permission, from Duxbury BM.[68]

Anaesthesia

General anaesthesia

Anticoagulation is not a contraindication to general anaesthesia. Full anticoagulation to the point of total inhibition of the coagulation mechanism during cardiac surgery has shown that surgery can be safely performed on patients without inherent haemostasis. Consequently, surgery in patients on anticoagulants is becoming less controversial and is probably acceptable, except when the eye or the central nervous system is involved, or when there are large denuded surfaces of the liver. However, because of the high incidence of haemorrhagic complications and fears of delayed wound healing, it is prudent to operate on a patient on full (i.e., rather than prophylactic) anticoagulation only in an emergency or when the risk of cessation of anticoagulation outweighs the risk of its continuance.

For patients receiving long-term oral therapy, anticoagulants should be discontinued two to three days before surgery and a heparin infusion substituted to maintain APTT in the therapeutic range. If necessary, heparin can then be reversed preoperatively with protamine sulfate to ensure normal anticoagulation preoperatively.[83] (A suggested protocol to restore normal haemostasis in patients receiving warfarin is given in Table IV.)

When it is essential to administer general anaesthesia to a patient already on anticoagulants, a few simple precautions should be followed. Ideally, intramuscular and subcutaneous administration of drugs should be avoided. Premedication should be oral or intravenous. When intramuscular administration is necessary the arm should be used, since local haemorrhage is easier to detect and treat. All venipuncture and arterial puncture should be carried out meticulously. It has been suggested that the insertion of central venous lines by the subclavian or internal jugular route is contraindicated,[84] and if central venous access is necessary the antecubital fossa should be used. The external jugular vein is an acceptable alternative, as haematoma formation at this site is easier to treat with external pressure.[85] Because of the risk of bleeding from mucous membranes, laryngoscopy and tracheal intubation should be atraumatic. The relatively high incidence of epistaxis may preclude the use of nasogastric tubes, nasopharyngeal temperature probes or nasotracheal tubes.

No precautions are necessary in the patient receiving prophylactic low-dose heparin, although some authors advocate a preoperative screening including haematocrit, PT, partial thromboplastin time and platelet count.[69] Patients should not take salicylates or other inhibitors of platelet aggregation for five days before surgery.[18]

Regional analgesia

The role of regional analgesia in patients receiving anticoagulants is more controversial. Many anaesthetists believe that it is contraindicated. However, others argue that the benefits of regional anaesthesia outweigh the speculative assessments of the risks in an environment of altered haemostasis. Moore,[86] for example, feels that the fears of uncontrollable haemorrhage after lumbar sympathetic block in such patients are unfounded, provided that both situations are proficiently managed. Nevertheless, most anaesthetists rule out any regional anaesthetic technique for the head, neck or trunk (e.g., brachial plexus block, stellate ganglion block), although more peripheral techniques, such as intravenous regional anaesthesia and single nerve blocks in the upper and lower limbs, are probably acceptable.

It is in the field of epidural and spinal anaesthesia that most controversy exists. Bromage[87] advised against the use of epidural anaesthesia in patients receiving anticoagulants. In a review of five patients who had epidural catheters inserted and were subsequently given anticoagulants, De Angelis[88] warned of the hazard that exists with any combination of epidural or spinal puncture in patients receiving anticoagulants. Stanley and Lunn[89] conceded that it may be safer and more rational to avoid continuous

epidural anaesthesia whenever possible if anticoagulants are to be used. However, they noted that the incidence of epidural haematoma formation associated with epidural catheterization in patients who are subsequently given anticoagulants is unknown. Since spontaneous epidural haematoma formation is a well recognized complication of any form of anticoagulant therapy, it is possible that the presence of a catheter in the epidural space at the time of anticoagulation has little to do with the formation of the haematoma.

Cunningham *et al.*[90] reported 100 consecutive patients who had epidural catheters inserted and were subsequently given heparin 3000 units during abdominal vascular surgery, with no evidence of epidural haematoma formation. They concluded by acknowledging the consensus among anaesthetists that heparinisation excludes the safe use of epidural anaesthesia, but suggested that their series justified the use of the technique with low-dose systemic heparinisation. In a study of 12 patients, Fuchs *et al.*[91] gave epidural anaesthesia followed by transient heparinisation during a vascular constructive procedure without any neurologic complications related to epidural cannulation. However, the degree of anticoagulation achieved was not specified. Mathews and Abrams[92] gave intrathecal morphine to 40 cardiac surgical patients 50 minutes before heparinisation and encountered no neurologic complications.

In the largest series to date, Rao and El-Etr[93] studied the incidence of neurologic complications after epidural catheterization in 3,164 patients and after subarachnoid blockade in 847 patients. These patients were subsequently given anticoagulants with a mean dose of 2600 units of heparin every six hours to produce a mean ACT of 174 seconds. Four patients in the epidural group developed short-lived paraesthesiae in the thigh and one patient in the spinal group suffered loss of sensation over the thigh, which persisted for six months. There were no other neurological sequelae.

In another large series Odoom and Sih[94] gave 1,000 epidural blocks to 950 patients who were already receiving oral anticoagulants preoperatively, and who were then given heparin peroperatively in boluses of 200–400 units followed by an infusion of heparin at 25–30 units·min^{-1} (1500–8000 units·hour^{-1}). There were no neurological complications during the first three months after surgery. Ten per cent of patients complained of backache lasting three to five days. In conclusion, they offered some guidelines for the management of epidural anaesthesia in patients on anticoagulants.

1 Epidural anaesthesia is contraindicated in the presence of blood dyscrasia, thrombocytopenia or alcoholism.
2 ACT must be measured at frequent intervals and be less than 200 seconds.
3 The midline approach is recommended to minimize risk of damage to the epidural veins.
4 The epidural catheter must be inserted gently and for not more than 3–5 cm.
5 The catheter must be removed one hour before administration of the next dose of heparin.
6 Motor and sensory function must be tested before each top-up dose of local anaesthetic solution is given. Neurologic follow-up must be maintained.

The conclusion from this series has been criticized,[95] however, on the grounds that the mean thrombotest was 19.3 per cent, which is outside the range of 8–12 per cent considered adequate for anticoagulation.[72] In reply, Odoom[96] stated that he cannot recommend the use of epidural analgesia in patients with thrombotest values of less than ten per cent.

The use of regional anaesthesia in patients receiving prophylactic low-dose heparin is less controversial. Provided that tests of coagulation are normal its use is probably acceptable, and testing of whole-blood clotting time in the operating room is a convenient method of assessment. However, claims that low-dose heparin may induce full anticoagulation[74] may suggest that these patients are still at substantial risk. To date, serious haematoma formation following regional anaesthesia has not been reported in low-dose heparin therapy.

On balance, the use of epidural or spinal analgesia in any combination with systemic anticoagulation is contraindicated by the standards of most anaesthetists.[87,88,97–99] Some reports of the use of continuous epidural analgesia in patients on "full" anticoagulation, either before initiation of the block or subsequently, have in reality been performed in the absence of therapeutic levels of anticoagulation. "Single-shot" epidural or spinal analgesia may be safer, but is still not without considerable risks.

Cardiopulmonary bypass

Heparin is administered during cardiopulmonary bypass (CPB) to ensure total inhibition of the coagulation pathway. Various dosage regimens have been used to achieve this goal.[100] Perhaps the simplest is a fixed time-dosage protocol that involves the initial administration of a dose based on body weight or surface area, with increments at regular intervals during bypass. For example, heparin 300 units/kg body weight as well as 1000–2000 units per 500 ml of clear prime is given intravenously before insertion of the aortic and vena caval cannulae. However, such a regimen fails to produce safe anticoagulation in a significant number of patients during CPB.[100] There are five main reasons why this regimen may be unsatisfactory:[70]

1 Different heparin preparations vary in potency.

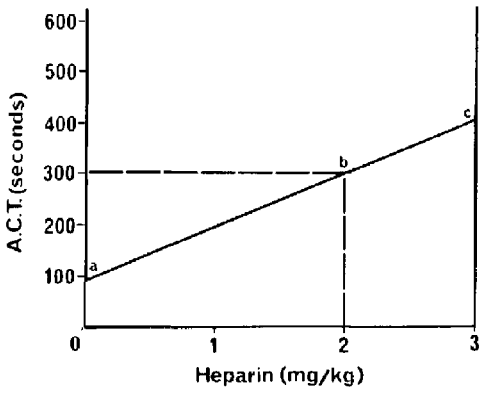

FIGURE 3 Heparin dose–response curve. Baseline ACT (a) and ACT after heparin 2 mg/kg body weight is given (b) are plotted. The amount of heparin necessary to prolong the ACT to a given value (c) is extrapolated.

2 Hypothermia reduces the rate of decay of heparin differently in each patient.
3 The relationship between body mass and volume of distribution of heparin is non-linear.
4 Circulating blood volume changes in association with the use of extracorporeal circulation.
5 Individual genetic variations exist within the coagulation pathway.

Some form of monitoring of heparinisation is therefore essential during CPB.

Heparinisation may be assessed in two main ways.[101]

1 Measurement of its effect, by determining the clotting time.
2 Measurement of the level of heparin per ml of whole blood or plasma, usually by titration with protamine.

One test that measures effect is the Activated Clotting Time (ACT), first described in 1966.[102] It is now determined using a comparatively simple piece of apparatus such as the Hemochron 400 (International Technidyne Corporation, Edison, New Jersey). Three ml of whole blood is placed in an evacuated test tube containing a contact activant (commonly diatomaceous earth, although a saline version is available) and a small magnet. After the tube is inverted several times to ensure adequate mixing, a timer is started and the tube is rotated mechanically. When a clot forms it enmeshes the magnet, causing it to rotate along with the tube, which activates a detector that stops the timer. The normal ACT is 90–105 seconds.[102] For CPB it should be greater than 300 seconds. Since ACT can be affected by other factors, contamination with heparin, heparinised saline, tissue juices and other drugs should be avoided when blood samples are withdrawn. Bull *et al.*[101] compared ACT with a quantitative protamine titration (QPT) test and found that variations in patient sensitivities to heparin and in plasma volume caused inaccuracies when using QPT or other protamine titration tests. These variables, however, did not affect ACT when used in conjunction with a simple dose–response curve. They concluded that the rapidity, simplicity and minimal expense involved in using the ACT in the operating room render it desirable.

Kamath and Fozard[103] showed that patients with a history of subacute bacterial endocarditis required significantly more heparin, as did patients on an intra-aortic balloon pump before or during bypass. Because of the marked individual variation in sensitivity to heparin they also cautioned against the use of fixed protocol regimens, and suggested that in the absence of monitoring facilities a heparin dose of 4 mg/kg body weight may be safer.

Bull *et al.*[104] described the use of a dose–response curve relating heparin dosage to its effect on the ACT (Figure 3). The correct dose of protamine to be administered at the end of the procedure can be determined using the same curve and a fixed heparin-protamine ratio. (Reversal of heparin is discussed more fully below.)

Cohen[70] confirmed the reliability of the ACT during CPB in conjunction with a dose-response curve as recommended by Bull and coworkers, and made four observations relevant to its successful use:

1 The curve must be generated before bypass begins and not during the first hour of bypass.
2 During the first hour of bypass the ACT is a valid indicator of anticoagulation but not a reliable predictor of heparin level.
3 An ACT greater than 500 seconds is not linearly related to dose and must not be used in performing dose-response calculations.
4 Errors in defining ACT endpoint must be avoided.

The most accurate assessment of heparinisation is by measurement of heparin levels, but the inability to measure these rapidly and accurately has limited clinical use of such assays. Recently, the combination of a rapid plasma separator ("STATSEP") and the "Protopath" system, which measures heparin activity by its ability to inhibit the action of thrombin on a synthetic substrate, has enabled estimation of heparin levels within four to seven minutes.[105] This system is sensitive to only one variable (heparin activity) and may therefore have advantages over the ACT method.

Heparin resistance during CPB is rare. Possible causes include failure to inject the total heparin dose, use of heparin with reduced activity and errors in ACT measurement. Inherited or acquired AT III deficiency may result in a hypercoagulable state, and possible heparin resistance.[106] Reduced activity of AT III (by as much as 50

per cent) is seen during CPB, and normal preoperative levels may not be restored until the second postoperative day.[14] If AT III deficiency is the cause of heparin resistance, administration of fresh frozen plasma is indicated to rapidly restore AT III levels to normal.[107]

In conclusion, the most commonly used regimen consists of an initial intravenous bolus of heparin 3 mg/kg body weight with measurement of the ACT before heparinisation, after heparinisation but before insertion of arterial and venous cannulae, and at 30-minute intervals during CPB. If ACT falls below 300 seconds, heparin 1 mg/kg body weight increments should be given and the ACT checked after five minutes.

Developments

Surface-bound heparin, currently in use for arterial shunts, chest tubes and peritoneo-venous shunts, may have a future role in extracorporeal circulation, reducing or even abolishing the need for systemic heparinisation. Toomasian *et al.*[108] obtained moderate success using tridodecylmethyl ammonium chloride (TDMAC)-bound heparin to coat polyvinyl chloride tubing used for extracorporeal circulation in rabbits with or without prostacyclin and systemic heparinisation. Such work, however, is still very experimental.

Other developments aim at avoiding systemic heparinisation by allowing full heparinisation of blood entering the extracorporeal circulation, enzymatically removing the heparin before returning the blood to the patient. Experimental work has been performed using filters containing immobilized heparinase, which degrades heparin into small polysaccharides.[109] Such filters could also be used to remove heparin at the termination of CPB.

Anticoagulation by hypofibrinogenaemia alone may avoid the use of any form of heparinisation. Observation that victims of bites from the Malayan pit viper had severe hypofibrinogenaemia without excessive haemorrhage led to speculation that hypofibrinogenaemia may be useful in the treatment of venous thrombosis. Two purified forms of venom are available for human use – ancrod and batroxobin. They have a thrombin-like action, but produce an unstable fibrin that is more susceptible than normal fibrin to lysis by plasmin (Figure 1).[110] They have no effect on other coagulation factors. Ancrod has been used successfully during CPB in the dog,[111] and early clinical trials are currently in progress.

Reversal

Heparin and protamine

The half-life of heparin is about 90 minutes, and often all that is necessary to reverse its anticoagulant effect is to discontinue administration. However, if haemorrhage is life threatening, or if anticoagulation must be reversed for other reasons (e.g., termination of CPB), a specific heparin-antidote, protamine sulfate, must be given. Protamine was first described in 1901,[112] and introduced as a heparin antagonist in 1937.[113] It is a highly charged cationic protein that is isolated from the sperm or testis of salmon. The appropriate dose depends on the source of the protamine, the total dose of heparin, its route of administration and the time since administration. When used within minutes of heparin administration, 1 mg of protamine per 100 iu heparin should be given for reversal. A longer time interval between heparin and protamine allows the protamine dose to be reduced.

Intravenous protamine may be associated with adverse haemodynamic effects. Hypotension has been attributed to peripheral vasodilation and decreased systemic vascular resistance,[114] direct myocardial depression,[114,115] histamine release,[116] hypocalcaemia[117] and anaphylaxis.[118] It may cause a marked increase in pulmonary vascular resistance, particularly in patients with pre-existing pulmonary hypertension.[119] Some of these haemodynamic effects may result from a direct, non-cytotoxic, non-immune effect on mast cells, although there is increasing evidence that activation of the complement system may play a role.[120,121]

After CPB, protamine must be given with great caution to patients with poor left ventricular function who are unable to compensate for falls in systemic vascular resistance with a significant increase in cardiac index.[112]

To minimize these cardiovascular effects, protamine is usually given slowly by the intravenous route, often combined with positive inotropes and prophylactic fluid loading. However, some workers claim to have demonstrated that protamine has minimal cardiovascular effects when given into the aorta or left atrium over a period of 0.2–2.0 minutes.[116,123] It is postulated that the release of one or more vasoactive substances from the lungs is avoided by bypassing the pulmonary circulation,[116,123] although this is controversial.[124]

Other adverse reactions to protamine are uncommon, but thrombocytopenia,[125] rash,[117] urticaria[116] and anaphylaxis[121,126,127] and cardiac arrest[128] have all been reported. IgE-mediated, type I, hypersensitivity reactions may occur following previous exposure to the drug, or to protamine-containing insulin preparations (e.g., isophane insulin or protamine zinc insulin suspensions).[118] In a study of diabetic patients who had received isophane insulin suspension, 53 per cent were shown to have significantly raised antiprotamine IgE levels.[121] It is possible that similar findings may be obtained in patients with a history of fish allergy,[129] and antiprotamine antibodies have been found in 33 per cent of vasectomized

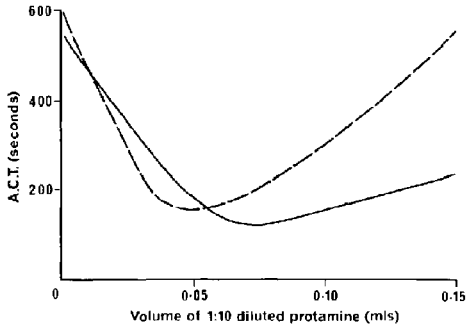

FIGURE 4 Protamine dilution curve: examples from two patients (modified from Dutton *et al.*[131]).

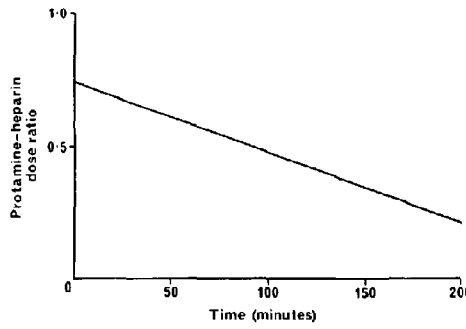

FIGURE 5 Protamine requirements decrease with time after the administration of heparin (modified from Dutton *et al.*[131]).

males.[130] These groups of patients may be at increased risk of having severe reactions to protamine.

Because of these potentially harmful effects, attempts have been made to minimize the dose of protamine given after the termination of CPB, at a time when patients are particularly susceptible to sudden changes in systemic and pulmonary vascular resistance, and to myocardial depression. Various protocols have been used to reverse heparin after CPB, some of which are based on arbitrary amounts of protamine to neutralize a given amount of heparin, while others are calculated from known heparin-protamine interactions. Because it is difficult to measure heparin levels rapidly and accurately, excessive and potentially harmful amounts of protamine are often given. The heparin-ACT dose-response curve is one of the simplest ways of avoiding this, but, as has been mentioned, it may be inaccurate.

A more specific method of protamine titration minimizes dosage requirements.[131] One ml of standard protamine sulfate is diluted to 10 ml with normal saline. A series of Hemochron tubes is primed with differing volumes (0.05–0.20 ml) of the diluted solution, a control ACT is recorded and, after 3 ml of venous blood is added to each tube, the ACT for each blood sample is determined. The ACT is graphed against volume of diluted protamine to determine the optimal dose of protamine (i.e., the dose resulting in the shortest ACT) (Figure 4). Calculation of the actual protamine dose assumes normovolaemia.

This method allows a specific protamine dose for each patient and avoids the problems of overdosage. Using such a method, Dutton and co-workers[131] showed a linear relationship between heparin/protamine dose ratio and the time interval since heparin administration (Figure 5). During CPB, however, such a relationship is still susceptible to the restraints mentioned above. *It is recommended that it be used only as a guide to protamine dosage.*[126] In children, the relationship may be altered because of increased heparin requirements. This method may be the most accurate, but can be laborious and time-consuming, and the use of a fixed protamine–heparin ratio may remain more practical, despite its disadvantages.

In conclusion, at the termination of CPB an intravenous protamine dose (in mg) equivalent to the total dose (in mg) of heparin administered during CPB should be given slowly, and ACT should be checked. If ACT remains above pre-heparinisation levels, further increments of protamine (0.1–0.2 mg/kg body weight) may be given.

Ideally, protamine dosage should be calculated from a heparin dose–response curve.

Vitamin K antagonists

When it is necessary to reverse the action of oral anticoagulants (e.g., for emergency surgery) there are three alternatives: vitamin K, blood or plasma and factor IX concentrate.

1 *Vitamin K.* Vitamin K is the specific antidote to the oral anticoagulants, and can be given orally or intravenously. Whichever route is used, PT will not be shortened for three to six hours. The dose prescribed depends on the indication: if there is no bleeding and anticoagulation must be reversed for elective surgery, the PT time will shorten over the next 24 hours after one dose is withheld; where the risks of stopping treatment completely are considered too great, small doses of vitamin K (0.5–1.0 mg) will reduce the PT without the risk of the patient becoming refractory to oral anticoagulant therapy; for complete reversal, larger doses of vitamin K (50 mg) should be given for up to three days. There is considerable patient variability and the PT should be monitored daily.
2 *Whole blood and plasma.* Whole blood and plasma

immediately reverse the effects of oral anticoagulants. The four factors (II, VII, IX and X) in the prothrombin complex are all present in stored bank blood; therefore, it is not necessary to use fresh blood. The amount of coagulation factors present in each unit of blood or plasma is variable, which, associated with differing degrees of factor depression in individual patients, means that there is no specific formula for the administration of these blood products. However, 15 ml of blood or plasma/kg body weight is recommended for an initial effect, with the simultaneous administration of vitamin K.[23]

3 *Factor IX concentrate*. The concentrate is prepared from a very large donor-pool and carries a substantial risk of serum hepatitis. Therefore, its use should be restricted to the treatment of congenital deficiencies.

A suggested regimen for the management of excessive anticoagulation by vitamin K antagonists is given in Table IV.

Conclusion

This article has reviewed some of the more important aspects of anticoagulant therapy relevant to the anaesthetist. We hope that it will enable a rational approach to the management of the patient receiving anticoagulant therapy, and to the management of acute anticoagulation.

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