The aim of this article is to provide a detailed explanation of normal haemostatic processes in the blood and to outline the ways in which anticoagulant and fibrinolytic drugs interfere with these. The pathophysiology of thrombus formation and the common defects of haemostasis are also described.

After reading the article you should be able to:

1. Describe the three phases of haemostasis.
2. Identify the ways in which commonly used anticoagulant drugs interfere with haemostasis.
3. Use your understanding of the action of anticoagulant drugs to outline the causes of adverse reactions to these drugs and factors that may interfere with drug activity.
4. Outline the theory and clinical outcomes of thrombus formation, and identify the medications that can inhibit or reverse this process.
5. Describe the common coagulation defects and their treatments.
6. Discuss the relevance of common laboratory tests used to assess haemostatic function.

The use of anticoagulants and fibrinolytic drugs is becoming more common in acute care settings and the community, as our understanding of the therapeutic role of these therapies increases. Many surgical patients are routinely given heparin-type drugs post-operatively and most patients with cardiovascular disease are on some form of long-term therapy designed to prevent the formation of thrombi in the blood (Table 1). It is therefore necessary for nurses to maintain an up-to-date understanding of the actions and roles of these drugs, to provide adequate patient education and to be able to anticipate unwanted or adverse responses following administration.

Haemostasis is a physiological process initiated when damage occurs to a blood vessel wall and culminates in the formation of a stable clot that prevents the escape of further blood from the vessel. This occurs in three stages: vasoconstriction, platelet response and blood coagulation. A fourth stage occurs when the clot is dissolved following repair of the blood vessel (Tortora and Grabowski 2000). Figure 1 illustrates these three steps and the way in which they interact to bring about stable clot formation. Each of the phases affects the activity of the others.

The layers in the wall of any blood vessel that is larger than a capillary generally consist of an inner, single layer of endothelial cells and a basement membrane, surrounded by circular layers of smooth muscle and an external layer of elastic and collagen fibres (Tortora and Grabowski 2000).

**Vasoconstriction**

In stage one of haemostasis, the injury to the blood vessel wall triggers a reflex contraction of the circular layers of smooth muscle surrounding the endothelium leading to vasoconstriction. This action compresses the blood vessel to minimise blood loss and may continue for several minutes up to some hours, and is enhanced by the release of platelet factors (Bray et al 1999, Tortora and Grabowski 2000). This is not a permanent solution so the other phases of haemostasis are required to complete the process and to initiate blood effective vessel repair.

**Platelet response**

In stage two there is a complex series of responses by platelets that generate a platelet...
clot at the site of injury. Platelets, sometimes referred to as thrombocytes, are derived from stem cells in the bone marrow and consist of fragments of cell cytoplasm, which do not have a nucleus, but are full of vesicles that contain a variety of chemicals essential to haemostasis (Seeley et al 2003, Tortora and Grabowski 2000). Normally present in the blood, these chemicals are activated by contact with collagen in the wall of the damaged vessel. The pathway triggered by this activation is shown in Figure 2.

Platelets adhere to exposed collagen and become activated. This activation is signalled by changes in the shape of the platelets from smooth discs to spiny spheres, and by the release of the contents of the platelet vesicles. The chemicals contained in these vesicles then act on surrounding tissues to enhance haemostasis (Bray et al 1999, Seeley et al 2003, Tortora and Grabowski 2000).

Thromboxane A2 and serotonin augment vasoconstriction of the smooth muscle. Thromboxane A2 and adenosine diphosphate (ADP) activate neighbouring platelets, making them sticky and allowing the formation of a loose platelet plug. This platelet plug blocks the injured blood vessel and, providing the damaged region is not too extensive, prevents further blood loss. This forms a loose collection of platelets and the presence of fibrin from the clotting cascade stabilises the plug. The presence of platelet phospholipid on the membranes of activated platelets triggers the intrinsic pathway of the clotting cascade (Bray et al 1999).

Blood coagulation
Stage three of haemostasis, the clotting or coagulation process, is referred to as a cascade because each factor in the process acts on many molecules in the next stage of the process. So even though the initial stimulus may have been small, there is a large quantity of the final factor, fibrin, produced (Bray et al 1999, Tortora and Grabowski 2000). Clotting factors are manufactured in the liver and are found in the plasma in fairly low concentrations (Bray et al 1999). These factors are enzymes that as they are activated then activate the next enzyme in the chain. A number of co-factors such as calcium and platelet phospholipid are also required as part of the cascade. The clotting cascade is summarised in Figure 3.

Initially, there are two separate pathways in the clotting cascade. The intrinsic pathway is activated when the clotting factors circulating in the blood come into contact with collagen or foreign matter. The extrinsic pathway is initiated when tissue factor III, thromboplastin, released by damaged cells, enters the blood (Bray et al 1999, Tortora and Grabowski 2000). The two pathways meet at the activation of factor X, which then converts prothrombin to thrombin. Thrombin is the final activator in the pathway and it converts fibrinogen into fibrin fibres that in conjunction with factor XIII and calcium stabilise the platelet clot.
The removal of any of the co-factors of the clotting cascade, such as calcium, will inhibit the process and prevent coagulation of the blood. When collecting blood samples for testing coagulation it is normal to use citrate tubes as calcium can be readily added to the sample in the laboratory to replace that removed in the collection tube. As the repair of the damaged blood vessel proceeds, fibrin is broken down by the protein plasmin and the clot dissolves (fibrinolysis). Plasminogen is present in the blood normally but is only converted to plasmin when it encounters tissue plasminogen activator – a substance that is released from endothelial cells.

Drugs used to decrease haemostatic activity in the blood can be divided into three categories (Rang et al. 1999):

I Those that interfere with coagulation.
I Those that alter platelet function.
I Those that increase the rate of breakdown of stabilised fibrin.

Anticoagulants

The most common oral anticoagulant drug is warfarin, a drug that interferes with the action of vitamin K. Vitamin K is a fat-soluble vitamin found in green vegetables and manufactured by bacteria in the gut. Absorption from the gut requires the presence of bile salts. Vitamin K is used in the liver as a co-enzyme in the manufacture of a number of clotting factors (Figure 3). Because warfarin inhibits the manufacture of clotting factors, the effect of treatment will not be evident until clotting factors already in circulation have been used or destroyed. For this reason, the peak therapeutic effect of warfarin is about 48 hours after the initial dose (Rang et al. 1999). Warfarin is metabolised in the liver before being excreted by the kidneys. The liver plays an important role in determining the potency of warfarin. Liver disease may lead to increased effect of warfarin through either a decrease in clotting factor synthesis or a decrease in the ability of the liver to metabolise the drug. In addition, the metabolic pathway for warfarin used in the liver is shared by a variety of other drugs; the presence of these may decrease the metabolism of warfarin and thereby increase its potency. Examples of drugs that act in this manner are: cimetidine, imipramine, co-trimoxazole, ciprofloxacin, metronidazole and amiodarone (Rang et al. 1999). Excess alcohol may also decrease warfarin metabolism in the liver (Navuluri 2001a). The effect of warfarin on clotting may also be altered by the concentration of vitamin K. Decreased production of bile salts, the destruction of intestinal flora by, for example, broad spectrum antibiotics, or malabsorption syndromes such as coeliac disease decreases the amount of vitamin K available for clotting factor synthesis, so the effect of warfarin administration may be increased (Rang et al. 1999).

A diet that contains excessive amounts of green vegetables can lead to increased vitamin K production and thereby decrease the effect of warfarin. Conversely, a diet that is low in vitamin K can lead to an increased effect of warfarin.

**Figure 1. The three stages of haemostasis**

1. Vasoconstriction
2. Platelet response
3. Blood coagulation

**Figure 2. Platelet response in haemostasis**

- Exposure of subendothelial collagen
- Increased vasoconstriction
- Platelet adhesion
- Release reaction
- Further clumping of platelets
- Thromboxane A2
- Adenosine diphosphate (ADP)
- Serotonin

**TIME OUT 1**

Ethylene-diamine tetra-acetic acid (EDTA) and trisodium citrate are examples of chemicals used in vitro in blood collection tubes and donor bags. These chemicals remove calcium from blood. What effect will this have on clotting?
Vegetables such as cabbage or spinach may increase the concentration of vitamin K and therefore reduce the effect of warfarin. The therapeutic impact of warfarin is monitored by measuring the prothrombin time or INR (international normalised ratio). In the event of overdose or haemorrhage, vitamin K may be given. Guidelines for the use of warfarin can be found at a number of websites, for example, the Scottish Heart and Arterial Risk Prevention (SHARP 2002) and the National Guideline Clearinghouse (2001).

Heparin and its derivatives can be given by subcutaneous or intravenous injection only. This is due to the large size and insolubility of the heparin molecule, which prevents absorption from the gut. Heparin occurs naturally in the body and increases the activity of antithrombin III, an enzyme inhibitor that blocks the activity of clotting factor Xa and thrombin. More recently smaller forms of heparin, collectively called the low-molecular-weight heparins (LMWHs), have been used, for example, enoxaparin sodium. These act against factor Xa, but not against thrombin. LMWHs take longer to be metabolised than heparin, therefore frequency of administration is reduced (Morris et al 2002). The effect of heparin on coagulation is monitored by testing partial thromboplastin times (Table 2).

Unwanted effects of anticoagulant drugs

The most serious adverse effect of any anticoagulant therapy is haemorrhage, particularly into the brain and bowel (Rang et al 1999). Signs and symptoms

Vascular disorders

Figure 3. Summary of the clotting cascade

Intrinsic pathway

Extrinsic pathway

XII

XI

XIa

IX*

X*

VIIa

VII*

X*

Xa

IXa

Prothrombin*

Thrombin

Fibrinogen

Loose fibrin

Calcium

XIII

Stable fibrin

Plasminogen

Plasmin

Clot dissolved

XIIa

Thromboplastin

Common names of some clotting factors

I

Fibrinogen

II

Prothrombin

III

Thromboplastin

VIII

Anithaemophiliac factor

IX

Christmas factor

XII

Hageman factor

* vitamin K-dependent factors

Table 2.

Partial thromboplastin times (seconds)

Drug

INR

Heparin

2-3

LMWH

2-4

Warfarin

2-4
of mild haemorrhage would depend on the site and may include fresh blood in stools, black stools, haematuria, excessive bruising, or bleeding into the joints. Severe haemorrhage is indicated by hypotension, tachycardia, tachypnoea and cerebral symptoms, and anticoagulant therapy should be halted immediately. The therapeutic half-life of heparin is relatively short (one to two hours) so this may be all that is necessary (Navuluri 2001b). However in serious cases, administration of antagonist drugs may also be required: vitamin K for warfarin and protamine sulphate for heparin. Protamine sulphate binds to, and inactivates, heparin (Rang et al 1999). Intravenous clotting factors may be required in patients with life-threatening haemorrhage.

Heparin may, rarely, cause thrombocytopaenia (reduced numbers of platelets in the circulation) due to an immune reaction triggered by heparin binding to platelet factors in the blood. This immune response leads to increased destruction of platelets. LMWHs are less likely to induce this response (Rang et al 1999).

Warfarin may also initially cause thrombosis because it also interferes with the synthesis of an anticoagulant factor (protein C) and its action on this protein is much more rapid than on clotting factors. For this reason, it is usual to commence treatment with heparin before beginning warfarin therapy (Rang et al 1999). Heparin rarely causes thrombosis, but this can occur through the activation of platelets. Warfarin is teratogenic and must not be used in pregnancy, particularly in the first trimester. In the last trimester it is associated with intracranial haemorrhage in the baby during delivery (Rang et al 1999).

Warfarin should be used with caution in breastfeeding mothers as it crosses into the breast milk and also because babies do not produce vitamin K until their guts have been colonised by bacterial flora after birth. Babies who have been administered vitamin K after birth are not at such risk.

Antiplatelet drugs
Aspirin is the key antiplatelet drug used to prevent thromboembolic disease. It acts on the pathway that synthesises thromboxane A2 (Figure 2). Aspirin prevents the formation of thromboxane by binding irreversibly to an enzyme in this pathway (the COX-1 enzyme), thus preventing platelet clumping or aggregation (Rang et al 1999, Seeley et al 2003). Because platelets are unable to synthesise more COX-1 enzyme, the effect of a single dose of aspirin will last until exposed platelets have been removed from the blood, approximately seven days (Rang et al 1999).

Other antiplatelet drugs include those that inhibit the action of thromboxane A2 and ADP on platelets (known as GPIIb/IIIa inhibitors), for example: ticlopidine, clopidogrel and abciximab, and dipyridamole, a phosphodiesterase inhibitor that enhances...
Vascular disorders

TIME OUT

Within the arterial circulation 'red' thrombi occur, so-called because they contain erythrocytes, and are more jelly-like, with a tail that streams away in the circulation. This can give rise to ischaemia and necrosis of the tissue involved. Within the venous circulation 'red' thrombi occur, so-called because they contain erythrocytes, and are more jelly-like, with a tail that streams away in the circulation. This can give rise to ischaemia and necrosis of the tissue involved.

Acute myocardial infarction requires immediate treatment to re-establish blood flow to the tissue supplied by the artery involved. Depending on the location of the DVT the patient may experience pain or tenderness, swelling in the leg, and heat. The leg may change colour and may experience pain or tenderness, swelling in the leg, and heat. The leg may change colour.

Thrombus formation

The first factor of the triad is injury to the blood vessel wall, for example, the rupture of an unstable atherosclerotic plaques or large pulmonary emboli. They act by causing antibody formation. These drugs act mainly on plasminogen which is already bound to fibrin, rather than plasminogen which is free in the circulation, the patient may suffer angina or myocardial infarction.

Fibrinolytic drugs

Fibrinolytic drugs are given intravenously. Following administration the patient will develop increasing platelet manufacture due to bone marrow disorders, or increased destruction, for example, the dissolution of coronary thrombus. Fibrinolytic drugs mainly to dissolve clots that have already occurred, rather than plasminogen which is free in the circulation. These drugs act mainly on plasminogen which is already bound to fibrin, rather than plasminogen which is free in the circulation. These drugs act mainly on plasminogen which is already bound to fibrin, rather than plasminogen which is free in the circulation.

Streptokinase is derived from streptococci bacteria and is considered a first-line agent for acute myocardial infarction. It is effective in dissolving clots in coronary arteries and is rapidly initiated. Streptokinase can cause mild side effects, but the development of antibodies to the drug and these reduce its effectiveness. For this reason, streptokinase cannot be re-administered within one year.

Other fibrinolytic drugs are derived from human plasma and are contraindicated where there is active bleeding or the patient has a history of cerebral haemorrhage. This is also used in an oral form in the treatment of menorrhagia. Aspirin is the most effective drug available for the prevention of thrombus formation. Aspirin works by inhibiting platelet aggregation. It is available as a non-prescription drug and is used to prevent myocardial infarction and stroke. Aspirin is available as a non-prescription drug and is used to prevent myocardial infarction and stroke.

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Assessment of patient risk should include a history of immobility or with atrial fibrillation, conditions that affect blood coagulability and physiological factors, alone or in combination may lead to formation of a thrombus. There are three predisposing factors for thrombus formation, collectively known as Virchow's triad.

TIME OUT

Within Virchow's triad? How do the preventive measures you take address the three factors of the triad?
Sensible, eliminating the causative factors, and transfusion membranes (Porth 1998, Tortora and Grabowski bleeding from wounds, puncture sites and mucous failure and distressing necrotic ulcers on the skin. widespread activation of clotting factors through-absorption of fats. platelet adhesion factors. Treatment of these dis-
defect in factor VIII and a defect in one of the IX. Von Willebrand's disease is characterised by a number of clinical studies (Rang inhibit platelet aggregation, since these clots are of 'white' thrombi is best achieved with drugs that clot but it is associated with too many risks to be in the body. Fibrinolysis would cause dissolution of clot is resolved by normal physiological mechanisms bus once it has formed, but they prevent its exten-
sance of regular monitoring and strict dosage patients more frequently. Those undergoing anti-

TIME OUT 4

Disorders of coagulation

Heparin and warfarin will not dissolve the throm-

TIME OUT 5

Laboratory tests in anticoagulant therapy

Before beginning intravenous heparin therapy, it

Table 2 provides an explanation of these tests and

Conclusion

There are numerous tests associated with anti-

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routines and also be aware of potential bleeding

problems. Nurses who understand the underlying

impact on health outcomes increases more specific

understanding of the process and its potential

Normal haemostasis is a complex process. As scientific

LMWHs are fairly predictable in comparison to

one. Close monitoring is essential until a steady

culated on the basis of the INR results. It is difficult

and again after the dosage of heparin has been

rechecked according to local protocols but usually

is usual for baseline values to be tested. These are

mal values listed on the results form.

results should always be compared with the nor-

on the laboratory where the test is performed. Test

values for some of the tests might vary depending

the normal values. It should be noted that normal

boplastin time (PTT), activated partial thrombo-

is vital, particularly in the initial stages until a stable

undergoing treatment with heparin and warfarin

coagulation therapy. Close monitoring of patients

bleeding can recur.

transfused factors may be used up rapidly and