CHAPTER 5: DRUGS AFFECTING HEMOSTASIS AND HEMATOPOIESIS

I. DRUGS WHICH AFFECT BLOOD COAGULATION

Injury to blood vessels results in a series of events aimed at preventing blood loss (hemostasis), which include vasoconstriction, platelet aggregation, and the deposition of fibrin. THROMBOSIS can be defined as the inappropriate response of the hemostatic process to alterations in the circulatory system, lesions in vascular walls, or other stimuli. EMBOLISM occurs when thrombi are dislodged and are carried by the circulation to small vessels, where they may cause occlusions and tissue ischemia. Thrombosis is treated by pharmacological intervention designed to inhibit platelet function, inhibit fibrin deposition, or to enhance fibrinolysis.

A. DRUGS WHICH INHIBIT PLATELET FUNCTION (Antithrombic Drugs)

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<th>Drug</th>
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<tr>
<td>Aspirin</td>
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<td>Dipyridamole</td>
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<td>Sulfinpyrazone</td>
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<td>Ticlopidine</td>
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When platelets are stimulated to aggregate, arachidonic acid is liberated from platelet phospholipids, and may be metabolized to thromboxane A$_2$ by the sequential actions of cyclooxygenase and thromboxane synthetase. As this occurs, platelet levels of cyclic AMP decrease, and ADP is released. Both ADP and thromboxane A$_2$ are potent stimuli for platelet aggregation.

1. ASPIRIN acetylates platelet cyclooxygenase and irreversibly inhibits the enzyme. Aspirin is usually given at a dose of 325 mg per day for its antithrombic effects. Major adverse effects include GI distress and bleeding.

2. SULFINPYRAZONE has a less reliable antithrombic effect than aspirin, but does not cause bleeding abnormalities. It may reversibly inhibit cyclooxygenase activity.

3. DIPYRIDAMOLE inhibits platelet ADP release by increasing cyclic AMP levels, through two apparent mechanisms. Dipyridamole increases adenosine concentrations in the blood, which stimulates adenyl cyclase. Dipyridamole is also a phosphodiesterase inhibitor, and slows cyclic AMP catabolism. Dipyridamole also decreases the adhesion of platelets to artificial surfaces.

4. TICLOPIDINE inhibits ADP-induced platelet fibrinogen binding and subsequent platelet-platelet interactions. Ticlopidine is indicated for patients who have experienced thrombotic stroke or stroke precursors, and is recommended for patients who cannot take aspirin.

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B. DRUGS WHICH DECREASE FIBRIN FORMATION (Anticoagulants)

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<th>Heparin</th>
<th>Oral Anticoagulants</th>
<th>Enoxaparin</th>
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1. HEPARIN is an endogenous sulfated mucopolysaccharide found in mast cells bound to histamine. The drug is commercially prepared from pork stomach and beef lung. Heparin combines with, and catalytically activates, a plasma cofactor named antithrombin-III. This complex neutralizes several activated clotting factors, particularly factors IIa (thrombin) and Xa. Heparin is active to a lesser extent against activated forms of factors VIII, IX, XI, and XII. It has no therapeutic effects other than the inhibition of clotting. Heparin causes the release of lipoprotein lipase from tissues, which hydrolyzes plasma triglycerides and has a "clearing" effect on turbid plasma.

   a. Absorption, Fate and Excretion:
      1) Poor oral absorption; given i.v. or s.c. Do not give i.m.
      2) Duration of action; 2-4 hours
      3) Dosage is adjusted according to coagulation time (activated partial thromboplastin time) in therapy of acute thrombotic episodes. For prophylaxis, low doses of heparin are given which cause little change in clotting time.
      4) Dosage expressed in units (1 mg is approximately 100 units)
      5) Main metabolic fate is uptake by macrophages and endothelial cells. Some liver metabolism and urinary excretion also occur.

   b. Adverse Effects:
      1) Hemorrhage. PROTAMINE SULFATE is an antidote for heparin, and forms a 1:1 complex with the anticoagulant.
      2) Thrombocytopenia. May be mild and transient, or severe if anti-platelet antibodies are formed.
      3) Osteoporosis, when long-term heparin therapy is necessary.
      4) Allergy, probably develops to animal proteins in the solution.

2. ENOXAPARIN is a low molecular weight heparin which also binds antithrombin-III, but the complex is less effective than the heparin-activated complex against thrombin. As a result, enoxaparin exerts an antithrombotic effect (primarily attributed to inhibition of clotting factor Xa), but has little effect on bleeding time.

   a. Absorption, Fate and Excretion:
      1) Given by s.c. injection
      2) Enoxaparin is less susceptible to degradation by platelet factor 4 than heparin, and has a longer half-life. The usual dose is 30 mg every 12 hours.