Anticoagulants

Anticoagulants: are drugs that prevent or reduce coagulability of blood. These drugs are also called "blood thinners". They don't actually thin your blood, but they can help prevent clots from forming.

Classification

1. Used in vitro:

a. Heparin.
b. Sodium citrate: Used in blood banks to store blood.
c. Sodium oxalate Used as an anticoagulant in laboratory.
d. Sodium edetate.

2. Used in vivo:

A. Parenteral anticoagulants:
i. Heparin [unfractionated heparin (UFH)].
ii. Low-molecular-weight heparins (LMWHs): Enoxaparin, dalteparin, tinzaparin, ardeparin, reviparin.
iii. Fondaparinux.
iv. Direct thrombin inhibitors: Lepirudin, bivalirudin, desirudin and argatroban.

B. Oral anticoagulants:
i. Vitamin K antagonists: Warfarin, dicumarol.
ii. Direct factor Xa inhibitors: Apixaban, rivaroxaban
iii. Oral direct thrombin inhibitor: Dabigatran etexilate.

A. Parenteral anticoagulants:

Heparin: Heparin is an acidic mucopolysaccharide mixture that is an indirect thrombin inhibitor.

1. High endogenous concentrations occur in the mast cells in the lungs. It is extracted for commercial use from porcine intestinal mucosa.
2. It is a very large, polar, and water-soluble molecule.
   a. It must be given intravenously or subcutaneously.
   b. Distribution is limited to the vascular space, making it useful for anticoagulation during pregnancy.
   c. Inactivation is due to metabolism, which follows zero–order kinetics. Increasing the dose increases the time to eliminate 50% of the drug.
3. Heparin biologic activity is dependent upon the endogenous anticoagulant antithrombin III. Antithrombin III inhibits clotting factor proteases, especially thrombin (IIa), IXa, and Xa, by forming stable complexes with them. In the absence of heparin, these reactions are slow; in the presence of heparin, they are accelerated 1000-fold. The active heparin molecules bind tightly to antithrombin III and cause a conformational change in this inhibitor. The conformational change of

antithrombin III exposes its active site for more rapid interaction with the proteases (the activated clotting factors). Heparin functions as a cofactor for the antithrombin III-protease reaction without being consumed. Once the antithrombin III-protease complex is formed, heparin is released intact for renewed binding to more antithrombin III.

Heparin has two major effects and several minor effects.

a. One major effect is the formation of an inactive thrombin complex by catalyzing the reaction between antithrombin III and thrombin (factor IIa).

b. The other major effect is complexing and inactivation of factor Xa.

c. Minor effects of heparin include the complexing of factors XIIa, XIa, and IXa of the intrinsic pathway.

d. The onset of action is immediate.

e. The goal of treatment is to increase the activated partial thromboplastin time (aPTT) by approximately 2 times the normal value. The aPTT should be measured after 4–5 half lives (approximately 6 hours).

Side effects include:

a. Hemorrhage.

b. Heparin-induced thrombocytopenia (HIT), which can be immunologically or nonimmunologically mediated

i. Type I HIT occurs early after initiation of therapy and involves a mild decrease in platelet count that is not immunologically mediated.

ii. Type II HIT typically occurs within 5–14 days after initiation of treatment, although it can occur earlier in a previously sensitized patient.

(a) The platelets are activated by IgG antibodies against heparin, causing thrombosis and a severe thrombocytopenia.

(b) Type II HIT can be fatal if not recognized. Heparin treatment should be discontinued immediately.

c. Allergic reactions or anaphylaxis.

d. Osteoporosis and mineralocorticoid deficiency after long-term use.

e. Reversible alopecia has been reported.

A mild heparin overdose can be treated by discontinuing administration of heparin.

Protamine sulphate , a strongly basic protein that complexes heparin, is the antidote for heparin and can be administered to treat a more serious heparin overdose. One milligram of protamine sulphate approximately neutralizes 100 units of heparin (chemical antagonism).

Low molecular weight heparins(LMWHs): e.g., ***enoxaparin*** (Lovenox) & ***dalteparin*** (Fragmin). The LMWHs are heterogeneous compounds about one-third the size of unfractionated heparin. LMWHs complex with antithrombin III and inactivate factor Xa (including that located on platelet surfaces) but do not bind as avidly to thrombin. They are eliminated by the kidney, by first-order kinetics. They should not be used in patients with renal failure.

The following are the advantages of LMWHs:

1. They have a higher s.c. bioavailability as compared to UFH.

2. They have a longer duration of action.
3. They do not routinely require aPTT monitoring, but patients with chronic renal failure may need monitoring by measuring factor Xa activity. LMWHs do not require the same intense monitoring as heparin, thereby saving laboratory costs and nursing time. These advantages make LMWHs useful for both inpatient and outpatient therapy.
4. There is a lower incidence of thrombocytopaenia and osteoporosis.

Therapeutic uses of heparin and LMWHs:

Heparin and the LMWHs limit the expansion of thrombi by preventing fibrin formation. These agents are used for the treatment of acute venous thromboembolism (DVT or PE). Heparin and LMWHs are also used for prophylaxis of postoperative venous thrombosis in patients undergoing surgery (for example, hip replacement) and those with
acute MI. These drugs are the anticoagulants of choice for treating pregnant women, because they do not cross the placenta, due to their large size and negative charge.

Heparin and LMWHs are contraindicated in patients who have hypersensitivity to heparin, bleeding disorders, alcoholism, or who have had recent surgery of the brain, eye, or spinal cord.

Fondaparinux: It is a synthetic parenteral anticoagulant. It binds to antithrombin III and selectively inhibits factor Xa (indirect thrombin inhibitor) and cannot inactivate factor IIa. It does not require routine laboratory monitoring. Fondaparinux is administered subcutaneously. It is useful in pulmonary embolism and deep vein thrombosis (DVT). Incidence of thrombocytopaenia is lower with fondaparinux.

Fondaparinux is eliminated in the urine mainly as unchanged drug with an elimination half-life of 17 to 21 hours allowing for once-daily dosing. It is contraindicated in patients with severe renal impairment. Bleeding is the major side effect of fondaparinux. There is no available agent for the reversal of bleeding associated with fondaparinux.

Parenteral Direct Thrombin Inhibitors:

Bivalirudin and ***desirudin*** combine directly and inactivate thrombin without binding to antithrombin III. They are used in patients who are at risk of heparin induced thrombocytopaenia.
Argatroban is a synthetic anticoagulant given by i.v. route. Argatroban is used for the prophylaxis or treatment of venous thromboembolism in patients with HIT, and it is also approved for use during PCI in patients who have or are at risk for developing HIT. Anticoagulant effects are immediate. Argatroban is metabolized in the liver and has a half-life of about 39 to 51 minutes. Its clearance is not affected by renal disease but is dependent on liver function. Dose reduction is recommended for patients with hepatic impairment. Patients on argatroban will demonstrate elevated INRs. Monitoring includes aPTT, hemoglobin, and hematocrit. As with other anticoagulants, the major side effect is bleeding.

B. Oral anticoagulants:

Oral anticoagulants act only in vivo.

Warfarin:

Clotting factors II, VII, IX and X are synthesized in liver as inactive proteins. These factors are rich in glutamic acid residues and are carboxylated in liver where active form of vitamin K acts as a cofactor. Vitamin K is converted to inactive epoxide form by oxidation and is regenerated to its active form by epoxide reductase enzyme.

Warfarin is a coumarin derivative and has a structure similar to that of vitamin K. Hence, warfarin competitively inhibits epoxide reductase enzyme, thus inhibiting the synthesis of vitamin K-dependent biologically active factors—II, VII, IX and X and produces anticoagulant effect.

Unlike heparin, the anticoagulant effects of warfarin are not observed immediately after drug administration. Instead, peak effects may be delayed for 72 to 96 hours, which is the time required to deplete the pool of circulating clotting factors.

The anticoagulant effects of warfarin can be overcome by the administration of vitamin K. However, reversal following administration of vitamin K takes approximately 24 hours (the time necessary for degradation of already synthesized clotting factors).

Warfarin is almost completely absorbed after oral administration. Food interferes with the absorption of warfarin. It can also be given intravenously or rectally.

It is highly bound to plasma albumin. It freely crosses placental barrier. It is metabolized in the liver by the CYP450 system (mainly CYP2C9)and the inactive metabolites are excreted in urine and stool. It has a long half-life of about 40 hours, and the duration of action is 2–5 days.

Warfarin has a narrow therapeutic index. Therefore, it is important that the INR is maintained within the optimal range as much as possible, and frequent monitoring may be required.

Adverse effects:

1. Bleeding can occur anywhere—skin, pulmonary, gastrointestinal and urinary tract, cerebral, hepatic, uterine, etc.

Bleeding can be controlled by oral or parenteral vitamin K1 (depending on severity). Fresh frozen plasma should be given in severe bleeding. Oral anticoagulant therapy is monitored by measuring international normalized ratio (INR).

In patients on oral anticoagulants, with a stable INR <4, the risk of significant bleeding is low following a dental procedure. Oral anticoagulants should not be discontinued in a majority of such patients requiring outpatient dental treatment as it increases the risk of thrombosis. Adequate hemostasis can be obtained in such patients by gelatin, oxidised cellulose, fibrin, collagen sponges or tranexamic acid mouthwash without discontinuation of anticoagulants.

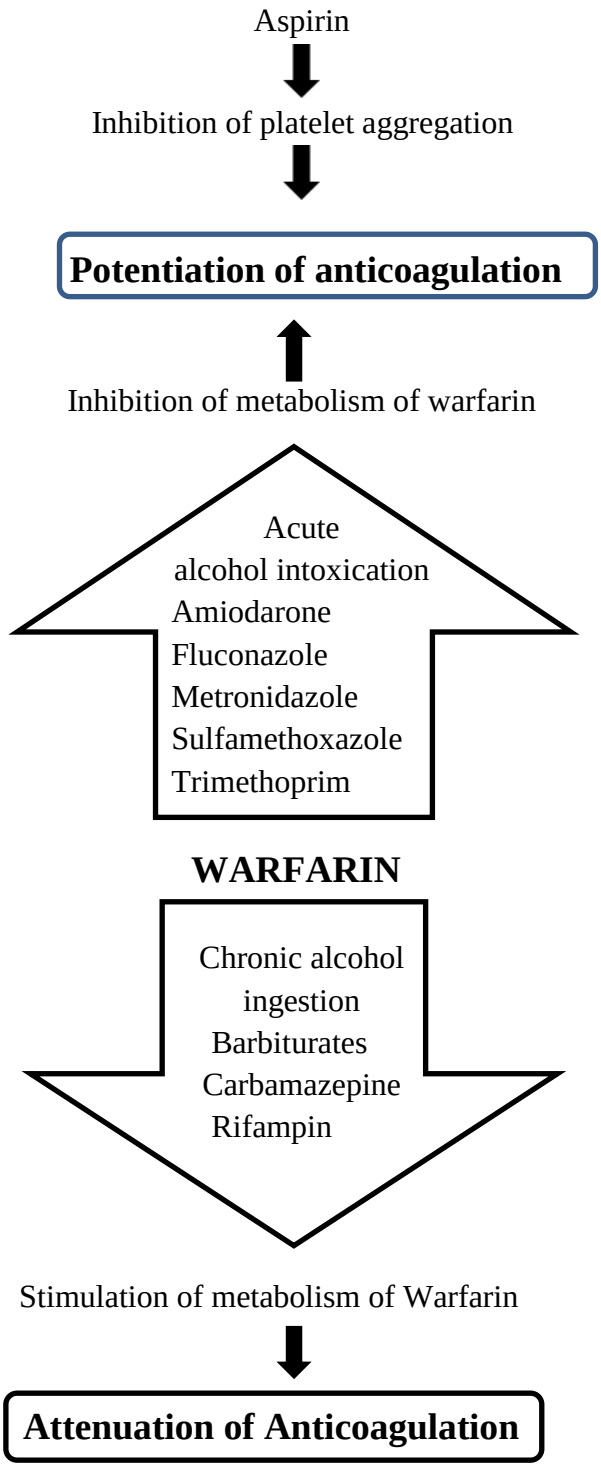
2. Purple toe syndrome, a rare, painful, blue-tinged discoloration of the toe caused by cholesterol emboli from plaques, has also been observed with warfarin therapy.

3. Teratogenic effect: Warfarin is contraindicated during pregnancy as it may cause fetal CNS abnormalities, fetal haemorrhage, abortion or intrauterine death.

4. Skin necrosis: It is a rare complication that occurs within the first week of therapy. The skin lesions are commonly seen on breast, buttocks, abdomen and thighs.

5. Other rare side effects: These include diarrhea, alopecia, urticaria, dermatitis, abdominal cramps and anorexia.

Warfarin Interactions:



Warfarin has numerous drug interactions that may potentiate or attenuate its anticoagulant effect.

Direct factor Xa inhibitors: ***Apixaban***, ***betrixaban***, and ***rivaroxaban*** are oral inhibitors of factor Xa. Inhibition of factor Xa reduces the production of thrombin (IIa) from prothrombin. They represent a new class of oral anticoagulant drugs that require no monitoring.
Rivaroxaban has high oral bioavailability when taken with food. The drug is extensively protein-bound. It is a substrate for the cytochrome P450 system and the P-glycoprotein transporter. Drugs inhibiting both CYP3A4 and P-glycoprotein (eg, ketoconazole) result in increased rivaroxaban effect. One third of the drug is excreted unchanged in the urine and the remainder is metabolized and excreted in the urine and feces. Abrupt discontinuation of the factor Xa inhibitors should be avoided.

Oral direct thrombin inhibitor:

Dabigatran etexilate is the prodrug. Both clot-bound thrombin and free thrombin are inhibited by dabigatran. Dabigatran etexilate is administered orally. It is hydrolyzed to the active drug, dabigatran, by various plasma esterases. Dabigatran is metabolized by esterases. It is a substrate for P-glycoprotein (P-gp) and is eliminated renally.
The major adverse effect, like other anticoagulants, is bleeding. Dabigatran should be used with caution in renal impairment or in patients over the age of 75, as the risk of bleeding is higher in these groups. GI adverse effects are common with dabigatran and may include dyspepsia, abdominal pain, esophagitis, and GI bleeding. Abrupt discontinuation should be avoided, as patients may be at increased risk for thrombotic events. Routine coagulation monitoring unnecessary.
The drug is contraindicated in patients with mechanical prosthetic heart valves and is not recommended in patients with bioprosthetic heart valves.
Idarucizumab is a humanized monoclonal antibody that binds to dabigatran and reverses the anticoagulant effect.

Therapeutic Uses of Anticoagulants:

The main aim of anticoagulant therapy is to prevent formation of intravascular thrombus or further extension of the already formed clot. They do not dissolve the clot or thrombus once it is formed. Treatment is initiated with an LMWH or UFH and continued for at least 4–5 days. An oral anticoagulant, warfarin, is usually started simultaneously as it has a delayed onset of action.

1. Deep vein thrombosis and pulmonary embolism: Venous thrombi are mainly formed of fibrin network with a long tail that can easily detach and result in embolization of pulmonary arteries. Anticoagulants are used for the treatment and prevention of thromboembolism in high-risk cases, e.g. prolonged hospitalization, prolonged immobilization, major surgery, major trauma, etc. Anticoagulants are used along with low-dose aspirin to prevent thromboembolism in patients undergoing haemodialysis and those with prosthetic heart valves.
2. Myocardial infarction: Anticoagulants (heparin, LMWH or fondaparinux) are used in patients with a high risk of embolism as they prevent the extension of the thrombus. Anticoagulants help to prevent recurrent attacks of myocardial infarction and stroke, especially when given in combination with low dose of aspirin. Heparin is used during coronary angioplasty.
3. Other uses: Unstable angina, atrial fibrillation and disseminated intravascular coagulation.