"Drugs in Thromboembolic Disorders"

Thrombosis is a pathological condition results in formation of clots despite absence of bleeding.

A-[Anticoagulants]

Prevent the development and propagation of thrombi by disrupting the coagulation cascade and suppress production of fibrin. They are more effective *in venous thrombi because these are mainly composed of fibrin*.

-Injectable anticoagulants

A-Heparin (unfractionated heparin) (UFH)

b- Low molecular weight heparins (LMWHs) ex. enoxaparin

c- Direct inhibitors of thrombin ex. Lepirudin

d- LMW heparinoids ex. danaparoid

	UFH	LMWHs
structure	Large molecule -sulphated mucopolysaccharides containing fractions varying in molecular weights between 6000-25,000	Smaller molecule -contain only the low molecular weight fractions of heparin
Mechanism of action	Heparin has fast anticoagulant effect. It binds to antithrombin III and increasing the rate of its inactivating effect on thrombin and of activated factor X(Xa). This inhibition prevents the formation of blood clots.	Fast effect bind to antithrombin and increasing the rate of its inactivating effect on factor Xa
PKS:		
Routes of administration	it is not absorbed from GIT as it is polar due to its strong negative charges and I given (i.v.) or (s.c.)	Injected i.v. or s.c.
Elimination kinetics	It binds to several plasma proteins and to sites on	are less protein bound and have a Predictable dose-

	endothelial cells and some is excreted by kidney. Due to these, elimination of heparin involve a combination of zero-order and first-order kinetics, the effect of which is the plasma biological effect t1/2 (biological t1/2) alters disproportionally with dose. Heparin administration Requires hospital admission and dose needs to be adjusted by monitoring patient's activated partial thromboplastin time (APTT), to avoid bleeding due to overdose. The optimum therapeutic range of APTT is 1.5 – 2.5 times the pretreatment level	response profile and fixed t1/2. Dose can be administered according to body weight at home or in out-patient without monitoring of APTT
Duration of action	short (6)hours ; necessitates frequent injections	Longer, require once-daily administration
Safety during pregnancy	Safe as it cannot pass the placental membrane due to its polarity.	safe
Main side effects	1)bleedinng 2)Heparin-induced thrombocytopenia (HIT) charectrized by arterial thrombosis and bleeding 3) dose-related Osteoporosis on several months use; mostly seen during pregnancy	Less incidence of HIT and osteoporosis

Antidote(if bleeding occur due to overdose)	Protamine sulphate: a positively charged basic protein, given IV,can bind heparin forming an inactive complex that is excreted.	Effectivness of protamine sulphate is unknown
Uses	1- acute deep venous thrombosis (DVT) and pulmonary embolism 2- prevention of Postoperative DVT and pulmonary embolism in high risk patients i.e after major abdominal surgery 3- DVT and pulmonary embolism during pregnancy 4 – Prevention of thrombi in Unstable angina and acute myocardial infarction. 5-prevention of clotting in blood samples for laboratory tests as it can prevent clotting in vitro.	Same uses

Direct inhibitors of thrombin:- ex.

Lepirudin:

Inhibits thrombin, by forming irreversible complex with it, that is excreted by kidney.

Use: prevents thrombosis in patient gets HIT.

LMW haparinoid ex.

danaparoid :similar mechanism of action and kinetics to LMWHs but contain haparin molecule from animal source .

Oral anticoagulants

a-Coumarins ex. Warfarin
b-Indandiones ex.phenindione are obsolete because of their allergic toxic effects.

WARFARIN:

Mechanism of action:.

In liver, gamma-carboxylation of factors II, VII, IX and X is important for activation of these factors. During this process, active (reduced) vitamin K act a a co-factor and is oxidized to an inactive epoxide and must be reduced by the enzyme vitamin K epoxide reductase to become active again. Warfarin is structurally similar to vitamin K and competitively inhibit epoxide reductase, so limiting availability of the active form of the vitamin to form coagulant factors. The overall result is a shift in haemostatic balance in favor of anticoagulation because of the accumulation of clotting factors with absent or decreased gamma-carboxylation sites. Due to this indirect mode of action, anticoagulation is delayed until the functioning clotting factors already present in the circulation have been eliminated; the net result is that anticoagulant protection is not effective until about 72h after the first dose.

If a rapid anticoagulation is required i.e. acute DVT an initial dose of heparin or LMWH should be used with warfarin for the first 3 days.

The anticoagulant effect also continues for 72 hours after drug discontinuation till the non-functioning clotting factors are eliminated.

PKS:

- Plasma protein binding = 99% …… Clinical significance: Drugs as Sulphonamides that displace warfarin from plasma protein binding sites can increase the anticoagulant effect. Because the anticoagulant effect of warfarin is directly related to the plasma concentration,bleeding may occur unless warfarin dose is reduced.
- Metabolism: warfarin is readily absorbed from the GI tract. It is metabolized by hepatic CP450 …… Clinical significance: Enzyme inhibitors as cimetidine, metronidazole, chloramphenicol can increase warfarin plasma concentration so the anticoagulant effect. Bleeding can occur unless warfarin dose is reduced.
- Enzyme inducers as carbamazepine, rifampicin can reduce the anticoagulant effect, thrombosis may occur unless the dose of warfarin is increased.

Broad spectrum antibiotics eliminate the intestinal flora that
Synthesize vitamin K and can potentiate the anticoagulant effect of warfarin.

Dose monitoring:
is by assessing INR (international normalized ratio), which is estimated from patient's prothrombin time.

Uses: because it can be given orally so it is used for

- **Long term** Treatment and prevention of :

1- DVT and pulmonary embolism.
2- thromboembolism associated with prosthetic heart valves
3- thromboembolism associated with atrial fibrillation .
4- thromboembolism following myocardial infarction.

Side Effects:
1-Bleeding
Reversal of anticoagulant effect (antidote for overdose): vitamin K_1
2-skin necrosis and ecchymoses
3- **teratogenic -** contraindicated during pregnancy as it crosses the placenta and can cause congenital malformation an increase in the chance for hemorrhage in both the baby and mother.

Contraindications of anticoagulant drugs: in conditions which there is a tendency to bleed such :
1-Haemophilia 2-Thrombocytopenia 3-Severe hypertension
4- Intracranial hemorrhage 5-active peptic ulcer, esophagial varices and ulcerative colitis 6- Renal or hepatic Impairment 7- Recent surgery to the brain, spinal cord, or eye
8- warfarin during pregnancy and conditions that disrupt hepatic synthesis of clotting factors as liver disease and alcoholism.

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B- [Fibrinolytics, thrombolytics]

Mechanism of action**:** They dissolve thrombi by activating plasminogen leading to formation of plasmin, a proteolytic enzyme that breaks the insoluble fibrin (the framework of thrombi) to soluble fibrin products.

"Examples"

Alteplase:	**Streptokinase**:
a tissue plasminogen activator obtained by rDNAtechnology	Obtained from streptococci
-specifically activates plasminogen that binds to fibrin in the clot so plasmin is	-binds to circulating plasminogen to form an activator complex which then causes

formed and dissolve fibrin locally . -has no effect on circulating plasminogen and less likely to cause systemic coagulation disturbance. It can dissolves aging and resistant thrombi	conversion of other plasminogen molecules to plasmin. -Because of this it can cause systemic circulation disturbance and bleeding.
given IV	also
Uses: 1-acute myocardial infarction 2-DVT 3- pulmonary embolism 4- Ischemic stroke 5- peripheral arterial thrombosis	Same uses
Side effects: 1-Bleeding 2-microemboli due to disintegration of thrombus.	Same side effects in addition to hypotension and allergic reactions due to antistreptococcal antibodies.
Antidote :Tranexamic acid	same

C- Antiplatelets

Prevent platelets aggregation. They are used in prophylaxis of arterial thrombosis because these are mainly composed of platelets.

- **Aspirin low dose**:(80-325 mg/day)inhibits platelets aggregation by Inhibiting the synthesis of TXA_2 due to irreversible acetylation of cyclooxygenase.
- **Clopidogrel:**inhibits platelets'ADP receptors that is involved in binding of platelets to fibrinogen and to each other. It is given once daily orally and antiplatelets effect lasts 7-10 days
- **Abciximab**: monoclonal antibody that blocks platelet GP IIb/III receptors that is involved in the final step binding of platelets binding to fibrinogen .
- **Dipyridamole**: inhibits phosphodiesterase enzyme, so increased platelet c AMP which inhibits platelet aggregation.
- **Epoprostenol (prostacyclin):**stimulats adenylcyclase enzyme, therby increased cAMP formation which inhibits platelet aggregation.

Uses:

1-prevention of M.I in patient with atherosclerosis or unstable angina.

2-prevention of recurrence of MI.

3-cerebral ischemic attacks
4. atrial fibrillation
5.coronary artery grafting

[Drugs used to control bleeding]

Tranexamic acid

Mechanism of action: competitively inhibits binding of plasminogen to tissue plasminogen activator so prevents conversion of plasminogen to plasmin, thus prevents fibrinolysis .

Uses: Bleeding *due to*

1-overdose of fibrinolytics 2- thrombocytopenia 3-haemophilia
4- prevention of hyperplasminaemic bleeding that results from damage to tissues rich in plasminogen activators i.e. after prostatic surgery, tonsillectomy, uterine cervical biopsy , menorrhagia and bleeding due to intrauterine contraceptive device

Vitamin K preparations:

Vitamin K1: is a fat soluble vitamin, requires bile salt for absorption if given orally and can be given I.M, S.C and I.V.
Rapid intravenous injection cause anaphylactic reactions with dyspnea, chest tightness, back pain and even death.
Uses: 1.Dietary vitamin K deficiency 2. haemorrhagic diseases of newborns
3. warfarin overdose .It Stops bleeding in 12 h.

Vitamin K3 (menadiol): is a water soluble synthetic analogue, and takes 24 hours to act, but its effect lasts several days,can be given orally .I.M, and I.V.
Use:hypoprothrombinaemia due to malabsorption
Side effects: haemolytic anaemia in G6PD deficient patients and neonates.