Anticoagulants

Antithrombinactivators

Heparin

- Heterogeneous mixture of branched glycosaminoglycans
- Potentiates the inhibition of IIa, IXa, Xa, XIa, XIIa by AT (2, 9, 10, 11, 12)
- Binds to AT through a unique pentasaccharide sequence leading to a conformational change
- Given s.c. or i.v.
- Binds to plasma proteins, endothelial cells & macrophages
- Elimination
  - Depolymerisation in endothelial cells & macrophages (rapid, saturable)
  - Renal (slow, non-saturable) and RES
- Variable protein binding
- Clearance varies with chain length
- Therefore, anticoagulant response monitored by activated partial thromboplastin time (APTT)
- Target 1.5 – 2.5 times control

clinical uses

- Venous thrombosis ± embolism
- Acute coronary syndromes
- Arterial thrombosis
- Extracorporeal devices (e.g. haemodialysis)

adverse effects

- Bleeding
- Heparin-induced thrombocytopenia (HIT) – Immune-mediated
- Osteoporosis

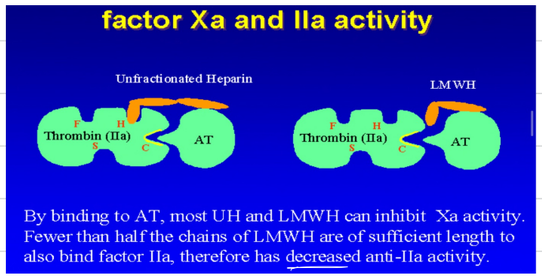
Low-molecular-weight heparins (LMWHs)

- Dalteparin
- Enoxaparin
- Tinzaparin

- Derived from UFH (unfractionated heparin) by chemical or enzymatic depolymerization
- Molecular weight 2000 – 9000
- About 15 monosaccharide units per molecule

Differences in Mechanism of action

- Any size of heparin chain can inhibit the action of factor Xa by binding to antithrombin (AT)
- In contrast, in order to inactivate thrombin (IIa), the heparin molecule must be long enough to bind both antithrombin and thrombin
- Less than half of the chains of LMWH are long enough



Advantages ⇒ Low inhibition of platelet- function. (HIT syndrome)
Lower incidence of thrombocytopenia & thrombosis
No need for laboratory monitoring (May be useful in specific instances)
Higher bioavailability ⇒ 90 % vs 30%
Longer t 1/2 ⇒ 4-6 hrs vs 0.5-1 hr renal (slower)

- Renal insufficiency creating >2 mg/dl
- obese patients with altered drug pK
- major bleeding risk factors

Synthetic pentasaccharide analogues

	Bioavailability(s.c.)	elimination	half life (h)
LMWH	80-90%	renal	4
Fondaparinux	100%	renal	17
Idraparinux	100%	renal	80

Direct thrombin inhibitors

Recombinanthirudins

- Given i.v. , s.c.
- Elimination renal • Half life 1-2 h

Bivalirudin

- Given i.v.
- Elimination renal & hepatic • Half life 25 min

Ximelagatran / Melagatran

- Promising oral direct thrombin inhibitor
- Converted to the active form melagatran in vivo
- No dosing problems
- No monitoring needed.
- Recent atrial fibrillation study showed it to possibly be superior to warfarin.

Dabigatran

- Given orally
- Elimination renal
- Half life 12 h
- Substrate for P-glycoprotein in kidney, GIT

Direct Factor Xa inhibitors

Apixaban

- Direct Factor Xa inhibitor
- Oral bioavailability 60%
- Half life 12 h
- Elimination hepatic > renal

Rivaroxaban

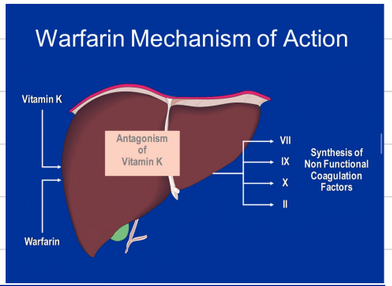
- Direct Factor Xa inhibitor
- Oral bioavailability 80%
- Half life 7-11 h
- Elimination renal > hepatic

Drugs that oppose action of Vitamin K

Warfarin

Reduces the post-translational carboxylation of glutamate residues of factors II, VII, IX, X

- Anticoagulant effect seen after 2-3 days (Bridging!)
- Monitored by international normalized ratio (INR)
- Well absorbed form GIT
- Highly protein bound
- Metabolised by CYP-450
- Clearance is slow - 36 hrs
- Can cross placenta - do not use during pregnancies



adverse effects

- Bleeding
- Rashes
- Alopecia
- Teratogenicity

Reversing action of warfarin

- Plasma
  - Rapid but short-lasting
- VitaminK
  - Not rapid, but lasts 1-2 weeks. Do not use if wishing to restart warfarin within next week.

Drug interaction with Warfarin cont:

Drugs that promote bleeding ↑	Inhibition of platelets	NSAID, Aspirin
	Inhibition of clotting Factors	heparin
Drugs that decrease Warfarin activity ↓	Induction of metabolizing Enzymes	Barbiturates Griseofulvin
	Promote clotting factor Synthesis	Vitamin K
	Reduced absorption	cholestyramine colestipol