Anticoagulants

1998b(14)/1995b(14): Outline the chemistry of heparin. Describe its mechanism of action and list its toxic effects
General: Heparin is an endogenous anionic mucopolysaccharide organic acid with many sulphate residues.
PHYSICOCHEMICAL
- Not a single substance, but a mixture of variable weight mucopolysaccharides
  o MW 5000 – 25000 Da
- Located in many tissues including liver, mast cells
- Exogenous heparin is extracted from bovine lung or porcine intestine
- Heparins do not cross BBB / placenta
Presentation
- Prepared as unfractionated (5000 – 25000 Da) or low molecular weight heparin (2000 – 8000 Da)
  o LMWH is derived from depolymerised heparin (chemical or enzymatic degradation)
- Unfractionated: Presented as a Na or Ca salt 1000 – 25000 IU/ml
  o IU used 2° heterogeneity of compound → variable potency
- LMWH: Presented in mg/ml
  o More consistent in terms of potency
PHARMACODYNAMICS
Uses:
- Unfractionated heparin:
  o IV infusion – treatment DVT, PE, unstable angina, peripheral artery occlusion, ACS
  o S/C – DVT prophylaxis
- LMWH: DVT prophylaxis, treatment of PE, ACS
Dose
- Unfractionated heparin:
  o IV infusion: Titrated up from 1000IU/hr to maintain APTT 1.5-2 x control value
  o S/C: 5000IU bd / tds
- LMWH:
  o S/C: 1 – 1.5mg/kg once daily dosing
Mechanism of Action:
- ATIII inhibits effect of thrombin by binding it and forming an inactive complex (ATIII-thrombin complex)
- Heparin binds to ATIII and ↑affinity for thrombin by 1000-fold
- Thrombin is more sensitive to binding → unfractionated heparin binds to both ATIII and thrombin
  o Xa is inhibited to a lesser extent (requires heparin to bind only to ATIII)
  o Higher doses of unfractionated heparin will also bind other plasma proteins including IXa, XIa, XIIa
- LMWH ↑action of ATIII on Xa but have no effect on rate of binding with thrombin

By Amanda Diaz
Anticoagulants

- No binding to other plasma proteins

**Effect:**
- ↓platelet aggregation
- Prevention of propagation of thrombus
- Inhibition of fibrin formation

**Toxic Effects:**
- **Haemorrhage:** Especially in patients with ↑risk (recent surgery, ICH, PUD)
  - Dose-dependent effect
  - Unfractionated heparin
    - monitored with APTT
    - Reversed with protamine (basic protein prepared from fish sperm)
  - LMWH → nil monitoring available, limited reversal with protamine
- **Thrombocytopaenia**
  - Type I (30 – 40%): Non-immune mediated, within 4 days of therapy; minimal clinical significance
  - Type 2 (HITT syndrome) (5%): Immune-mediated; within 4 – 14 days of therapy; **IgG mediated** against PF4-heparin complexes
    - Platelet aggregation / thrombosis
    - ↓Platelets <50 000
    - High mortality once thrombosis begins
    - ↑Risk with unfractionated heparin 2° affinity for PF4

- **Adrenals**
  - Hypoaldosteronism
- **CVS**
  - ↓MAP following rapid IV administration
- **Miscellaneous**
  - Osteoporosis 2° complexing with mineral substances
  - Alopecia

**PHARMACOKINETICS**

**Absorption:**
- Nil oral bioavailability (large molecule)
- Unfractionated heparin → IV, S/C
- LMWH → S/C
- IM avoided 2° haematoma formation

**Distribution:**
- Highly bound to plasma proteins (lesser for LMWH) and ATIII
- Vd low (40-100ml/kg)

**Metabolism:**
- Heparinases in liver, kidney, RES
- Renal clearance for LMWH

**Elimination:**
- t½β 90min
- Kidney:
  - Small amount unfractionated heparin unchanged in urine
  - 1° route of elimination LMWH (not suitable for renal failure)

By Amanda Diaz
1999a(15): List the drugs used clinically as anticoagulants and antithrombotics. Write short notes on their mechanisms of action

Anticoagulants: Drugs which inhibit / prevent the activation / propagation of the coagulation cascade
Antithrombotics: Drugs which impair platelet adhesion / activation / aggregation

ANTICOAGULANTS

Unfractionated Heparin
- MW 5000 – 25000 Da
- MOA: Endogenous substance which ↑rate of formation of ATIII-thrombin complex (x 1000)
  - Complex is inactive → prevents further fibrin formation
- Also inhibits Xa at therapeutic doses
- Higher doses inhibits IXa, XIa, XIIa
- Ix: APTT measures activation of intrinsic pathway → reflection of heparin activity
- Reversing agent: Protamine

LMWH
- MW 2000 – 8000 Da
- MOA: 1° inactivates Xa, minimal effect on rate of formation of ATIII-thrombin complex (Affinity Xa:IIa → 4:1)
- Ix: Is not able to be clinically measured as has no effect on intrinsic pathway activity
- Reversing agent: Nil

Warfarin
- Coumarin derivative
- MOA: Prevents the hepatic synthesis of vitamin K-dependent factors II, VII, IX, X
  - By preventing the reduction of oxidised Vitamin K (Vitamin K is oxidised during γ carboxylation of glutamic acid residues of the factors)
    ▪ Therefore, prevents γ carboxylation → ↓factor synthesis
  - Also inhibits synthesis of protein C & S → inhibited faster than coag factors → initial procoagulant effect
- Nil effect on circulating factors (time to effect ~72hrs)
- Ix: INR / PT → PT measures extrinsic pathway activation (VII)
- Reversing agent: dependent on time needed to reversal
  - Immediate: FFP
  - Days: Vitamin K (PO / IV)
    ▪ 1mg sufficient
    ▪ 10mg will impair anticoagulation for >>days

ANTITHROMBOTICS

Aspirin
- Salicylic acid
- MOA: Irreversible blockade of platelet COX-1 → arachidonic acid conversion to ↓TXA2 → ↓platelet aggregation / ↓vasoconstriction
  - Reversible blocks other tissue COX-1 / COX-2 (reason for S/E)
Anticoagulants

Clopidogrel
- MOA: Blockade of ADP receptor on platelet surface → prevents conformational change in GP IIb/IIIa receptor (required for cross-linking with fibronectin to vessel walls and platelet aggregation)

Dipyramidole
- MOA:
  o Blocks platelet adenosine uptake
    ▪ ↓platelet adhesion to vessel walls
  o Reversible blocks phosphodiesterase → ↑cAMP → ↓Ca^{2+} → ↓phospholipase A_{2} → ↓arachidonic acid → ↓TXA_{2}
    ▪ ↓platelet aggregation
    ▪ Smooth mm relaxation
  o Potentiates endothelial prostacyclin
    ▪ Relaxes smooth mm
    ▪ ↓adhesion

GP IIb/IIIa Receptor Antagonists
- MOA: Blockade of GP IIb/IIIa R which is the final common pathway for platelet aggregation (prevents platelet cross-linking with vWF / fibronectin)
  o Abciximab: monoclonal Ab with high affinity for GP IIb/IIIa R
  o Tirofiban: Intermediate affinity for GP IIb/IIIa R

Dextran 40 / 70
- Fermented long chain polysaccharide solution
- MOA: ↓platelet adhesion, ↓vWF function, provides an endothelial ‘barrier’

Prostacyclin (PGI_{2})
- Endogenous PG
- MOA: Smooth mm relaxation, Antagonises platelet TXA_{2}
2002a(15): Describe the mechanism of the anticoagulant effect of the coumarin derivatives and what determines the onset and offset of the effect

General: Coumarin derivative anticoagulant commonly known as warfarin

Uses:
- Prophylaxis of thrombosis / embolus formation in patients with
  - Artificial heart valves
  - Arrhythmias (AF)
  - h/o PE, peripheral arterial thrombosis, DVT

Presentation:
- Tablets 0.5 / 1 / 3 / 5mg
- Racemic mixture

Mechanism of Action:
- Prevents the hepatic synthesis of factors II, VII, IX, X
- Synthesis is vitamin K dependent

Vitamin K is oxidised during the \( \gamma \) carboxylation of the glutamic acid residues of the above factors
- Vitamin K reductase (and Vitamin K epoxide reductase) returns oxidised Vitamin K to reduced form in order to allow reactions to progress
  - Warfarin competitively inhibits these \( \rightarrow \) prevents the reduction of Vitamin K
- Results in depletion of the Vitamin K dependent factors
- Also inhibits Protein C & S production \( \rightarrow \) Effect faster than inhibition of coagulation factors \( \rightarrow \)**initial procoagulant effect

Onset:
- Warfarin detectable in plasma at 1hr post administration
  - Peak 4-8 hrs post administration
- Nil action on circulating clotting factors
- Therefore, biological effect (\( \uparrow \)INR) not seen for ~3-5 days
- Vitamin K Stores
  - Rapid SoO: Loading dose regimen; low vit K stores (seen perioperatively); liver failure
  - Slow SoO: High vit K stores, high vit K diet
- Circulating clotting factors
  - Rapid SoO: perioperatively (dilution of circulating factors); liver failure (\( \downarrow \)synthesis)
- Warfarin
  - Rapid SoO /\( \uparrow \)free fraction: \( \downarrow \)alb (postop / liver failure / sepsis); displacement reactions (amiodarone); \( \downarrow \)cytP450 activity (Cimetidine)
  - Slow SoO: \( \uparrow \)cytP450 activity (phenytoin, barbiturates)
- Other anticogulants (NSAIDs, heparin) \( \rightarrow \) \( \uparrow \)risk haemorrhage

Offset:
- Rapid (min-hrs): FFP, Prothrombinex (cryoprecipitate) II, IX, X concentrate
- Day: 1mg vitamin K (10mg impairs anticoagulation for days)

By Amanda Diaz
Anticoagulants

2004a(8): Briefly describe the side-effects and complications of heparin therapy

General: Heparin is a large MW anionic mucopolysaccharide organic acid
- Endogenously: present in many tissues including liver, mast cells
- Exogenously: derived from bovine lung or porcine intestinal mucosa

Prepared as either
- Unfractionated heparin – MW 5000 – 25000 Da
- LMWH (depolymerised) – MW 4000 – 8000 Da

Mechanism of Action
- ATIII binds thrombin forming an inactive ATIII-thrombin complex → prevents fibrin formation
- Heparin ↑ ATIII–thrombin complex formation by 1000-fold
  o Heparin bound ATIII also complexes with Xa → inactive
  o Higher doses will bind other factors IXa, XIa, XIIa
- Unfractionated heparin: 1° action is ATIII-thrombin complex
- LMWH: 1° action inactivating Xa (min effect on thrombin)

Side-effects / complications
- Haemorrhage (slightly ↑ risk LMWH)
  o Prevention of platelet aggregation / haemostatic plug formation
  o ↑ risk perioperative period, h/o ICH, PUD
  o Dose-dependent effect
  o Unfractionated heparin → APTT monitoring (aim 2-2.5 control value) → narrow therapeutic window
    ▪ Reversible with protamine (basic protein prepared from fish sperm)
  o LMWH → nil monitoring available; nil reliable reversal
- Hypotension with rapid IV administration
  o 2° vasodilation effect of heparin
- Thrombocytopaenia (slightly ↑ risk with LMWH)
  o Type I: Incidence 30-40%
    ▪ Within 4 days of therapy
    ▪ Non-immune mediated
    ▪ Subclinical
  o Type 2: Incidence 5% (heparin induced thrombosis thrombocytopaenia HITT)
    IgG mediated
    ▪ Within 4-14 days of therapy
    ▪ PF4-heparin complexes formed. IgG against these → platelet aggregation / thrombus formation
    ▪ Platelets < 50 000
    ▪ High mortality
    ▪ ↑ Risk unfractionated heparin → ↑ affinity for PF4
- Adrenal insufficiency (hypoaldosteronism)
- Alopecia
- Osteoporosis 2° heparin complexing with mineral substances (↑ risk LMWH)
- Allergy / Anaphylaxis (↑ risk bovine)
- Drug displacement (competes for protein binding)
2005a(5): List the antiplatelet agents and outline their mechanisms of action, adverse effects, mode of elimination and duration of action

ASPIRIN (salicylic acid):

**MOA**
- **Irreversible blockade** of platelet COX-1 → prevents conversion of arachidonic acid to TXA₂
  - ↓platelet adhesion / activation / aggregation
  - ↓vasoconstriction
- Reversibly inhibits COX-1 / COX-2 throughout body
  - Endothelium (↓prostacyclin)
  - Renal arteries → ↓PG production
  - GIT → ↓PG production

**Adverse Effects**
Related to non-specific blockade of COX-1 and COX-2 → ↓PG synthesis
- GIT: ↑gastric acid production, ↓mucosal barrier → peptic ulceration / GIT upset
- Renal: ↓PG-dependent renal artery dilatation → renal impairment / failure in those susceptible; papillary necrosis is chronic users
- Resp: ↑O₂ consumption / CO₂ production at therapeutic doses → uncouples oxidative phosphorylation
- OD: ↑RR → resp alkalosis 2° direct stimulation of respiratory centre, metabolic acidosis 2° nature of drug

**Mode of Elimination**
- Hepatic:
  - 50% metabolised via saturable enzyme pathway to salicyurate
  - 20% glucuronidated (also saturable)
- Urinary Excretion
  - Obeys non-linear kinetics 2° presence of 2 saturable pathways
  - Dose dependent elimination

**Duration of Action**
- Platelet activity is irreversible → therefore action is present for the lifespan of the platelet (7-10 days)

CLOPIDOGREL

**Mechanism of Action**
- **Irreversible blockade** of the ADP receptor on the surface of platelets
- ADP released from dense granules during platelet release reactions (activation phase)
  - Role of ADP → platelet aggregation
  - Prevents GP IIb/IIIa receptor transformation into active form

**Adverse Effects**
- Bone marrow suppression 2° ADP receptor blockade
  - Neutropaenia
- Thrombotic thrombocytopenic purpura
- Haemorrhage → cerebral / GIT (↑risk with coadministration with aspirin)

**Mode of Elimination**
- Extensive hepatic metabolism → carboxylic acid derivative / glucuronide (not active)
- Elimination of metabolites in urine

**Duration of Action**
- Due to irreversible blockade of ADP receptor → action lasts for lifespan of platelet (7-10 days)

DIPYRIDAMOLE (Asasantin)

**Mechanism of Action**
- Inhibition of platelet adenosine uptake
  - ↓platelet adhesion to damaged vessels
- Potentiates effects of endothelial prostacyclin
  - ↓vasoconstriction

By Amanda Diaz
- Reversible inhibition of **phosphodiesterase** activity in platelet (Phosphodiesterase metabolises cAMP → AMP)
  - ↑cAMP → ↓Ca^{2+} → ↓phospholipase A$_2$ activity → ↓arachidonic acid → ↓TXA$_2$ formation
    - ↓platelet aggregation
    - Smooth muscle relaxation
- ↓Platelet adhesion > ↓platelet aggregation

**Adverse Reactions**
- Vasodilation / Hypotension

**Mode of Elimination**
- 1° hepatic metabolism (glucuronidation)
- Excretion via bile
- Negligible renal excretion

**Duration of Action**
- Short

**GP IIb/IIIa RECEPTOR ANTAGONISTS (Abciximab, Tirofiban)**

**Mechanism of Action**
Block final common pathway of platelet aggregation → Prevents cross-linking of vWF/fibronectin
- Abciximab → monoclonal antibody → high affinity for GP IIb/IIIa R
- Tirofiban → intermediate receptor affinity
Don’t block platelet adhesion / activation / release reactions

**Adverse Effects**
- Allergy
- Thrombocytopenia
- ↑risk bleeding with abciximab

**Mode of Elimination**
- Abciximab → unknown
- Tirofiban → renal (65%) / bile (25%)

**Duration of Action**
- Abciximab → up to 15 days
- Tirofiban → short (hours)

**DEXTRAN (40 and 70)** → plasma volume expanders → polysaccharides (bacterial fermentation)

**Mechanism of Action**
- Specific inhibition of vWF
- ↓platelet adhesion

**Adverse Effects**
- Fluid overload
- Allergy / anaphylaxis

**Mode of Elimination**
- Metabolised

**Duration of Action**
- 

**PROSTACYCLIN (PGI$_2$)**

**Mechanism of Action**
- Inhibits platelet adhesion / aggregation 2° ↑adenyl cyclase activity
  - ↑cAMP → ↓Ca$^{2+}$ intracellular → ↓release reactions / ↓TXA$_2$ from arachidonic acid

**Adverse Effects**
- 2° vasodilation
  - ↓MAP, reflex ↑HR, flushing, headache

**Mode of Elimination**
- 

**Duration of Action**
- 

By Amanda Diaz
2007b(2): Outline the important pharmacological considerations when stopping warfaring and commencing LMWH in the perioperative period

**Stopping warfarin**
- Coumarin derivative
- MOA: Prevent synthesis of Vitamin K dependent factors by inhibiting oxidation of reduced vit K (important step in factor synthesis)
  - Coags 2, 7, 9, 10; protein C/S
- Long-acting drug
- t½ 40hrs; metabolised in liver (low CL)
  - Need to stop warfarin with enough time for coag factor synthesis to resume (3-5 days)
- Monitoring: INR
  - ↑warfarin duration of action:
    - ↓metabolism → liver impairment, enzyme inhibition (phenytoin, fluconazole)
    - ↓synthesis → liver impairment, vit K deficiency, cephalosporins
- Reversal:
  - vit K (IV) → 1mg at a time → difficult to rewarfarinise afterward
  - FFP → rapid reversal → risk with blood products
- Post-op
  - Restart when minimal risk surgical bleeding
  - Initially hypercoaguable → protein C/S inhibited 1st → need keep LMWH

**Starting LMWH**
- Mucopolysaccharide
  - MW 5000 – 8000 Da
- MOA: enhance (1000-fold) the action of ATIII in inactivating Xa → prevent activation of common pathway coagulation
- Commence 2-3 days after ceasing warfarin
  - s/c administration → high bioavailability
  - Home use feasible
- Daily dosing 1-1.5mg/kg
- Nil monitoring required
- Reversal:
  - Nil available (try protamine)
- Renal impairment → ↓dose (renally eliminated)
- Last dose 12hrs pre-op / neuraxial blockade

By Amanda Diaz
Fondaparinux
- Synthetic pentasaccharide
- Resembles part of heparin molecule
- Inhibits only thrombin through its effect on ATII-thrombin complex formation (1000 fold)
- s/c daily
- ↓incidence of HITTS cf LMWH
  - No affinity for PF4
- Renally excreted → use with caution in Pts with renal failure
Ximelagatran
- Anticoagulant touted as replacement for warfarin
- Direct thrombin inhibitor
- Orally administered as prodrug
- Caused unacceptable hepatotoxicity at trial
- Withdrawn from development