B20 - Drugs & Coagulation

Anti-coagulants = drugs that prevent the clotting of blood by direct or indirect actions on the coagulation system.

Antithrombotics = inhibit the formation of thrombus by interfering with platelet adhesion & aggregation.

Thrombolytics (fibrinolytics) = destroy formed clot by lyses of fibrin.

(a) To classify anti-coagulants

(1) Heparin - potentiates antithrombin III -> inhibition of IIa, IXa, Xa, XIa, & XIIa.

(2) LWMH - potentiates antithrombin III -> inhibition of Xa

(3) Coumarin compounds - blocks convertion of vitamin K -> prevents synthesis of vitamin K dependent clottng factors II, VII, IX, & X.

(4) Hirudin - inhibitor of fibrin by binding thrombin (IIa)

(b) Describe the pharmacodynamics & pharmacokinetics of heparin & LMWH including their side effects.

Heparin

Chemical - mixture of acid mucopolysaccharides extracted from bovine lung or porcine intestinal mucosa

Uses

(1) prevention of venous thromboembolism
(2) priming of cardiopulmonary bypass or haemodialysis
(3) maintenance of patency of indwelling lines
(4) DIC
(5) fat embolism

Presentation

- clear colourless solution of Na-heparin (1000 to 25,000IU/mL)
- heparin calcium (25,000IU/mL)

- MW 6,000 to 36,000

Routes - IV, SC

Dose

- IV: titrated to APTT
- SC: 5000 12hrly

PK

Absorption - poorly lipid soluble

Distribution

- 1/3 bound to anti-thrombin III
- 2/3 bound to albumin, fibrinogen & proteases
- Vd = 40-100 mL/kg

Metabolism

- desulphated and depolymerised in liver, kidneys & reticuloendothelial system

Elimination

- small amount unchanged in urine
- Cl = 1mL/kg/min
- t1/2 = 2hrs

PD

Main actions - anticoagulant

Mechanism of action

- binds reversibly to antithrombin III -> enhances ability by 1000x to inhibit proteases in the coagulation cascade:

- 2 (thrombin)
- 9
- 10
- 11
- 12
- 13
- plasmin

- also binds directly to several coagulation proteases and thereby facilitates their reaction with anti-thrombin III.

Haematological

- above
- inhibits platelet aggregation by fibrin
- excessive bleeding (haemorrhagic stroke)
- thrombocytopenia (5%,

Metabolic

- increases hepatic triglyceride actvity -> increase in FFA
- osteoporosis (heparin-collegase bonding -> increase breakdown)
- ALD suppression

Other adverse effects

- full heparisation -> no spinal or regional
- alpopecia

LMWH

Chemical - pig intestine mucopolysaccharide

Use - thrombosis prophylaxis (DVT)

Presentation

- injection: clear, colourless

- MW 2,000-6,000

Route - SC

Dose

- 20mg od (low risk)
- 40mg bd (high risk)

- duration: 9hrs

PK

Absorption - doesn't bind so readily to other coagulation factors (higher bioavailability than heparin)

Elimination

- t1/2 = 2-3hrs

PD

Main action - mainly anti-thrombotic

Mechanism

- potentiates the action of antithrombin III on Xa

Adverse effects

- decreased incidence of HITS
- protamine only partially reverses
- spinal haematoma (1:1000 to 1:10,000) -> no epidural for 12 hours, & don't give for 2 hours post removal.

(c) To describe the mode of action & side-effects of protamine.

Chemical - purified mixture of low-molecular weight cationic proteins prepared from fish sperm (salmon).

Uses

(1) to neutralise the anti-coagulant effects of heparin
(2) to prolong the effects of insulin

Presentation

- clear, colourless solution
- 10mg/mL
- protamine sulphate

Route - IV

Dose

- 1mg protamine : 100u heparin
- adjust based on amount & time since heparin was given.
- max: 50mg in any 10min period

PK

Metabolism - ?
Elimination - t1/2 = 60min

PD

Mode of action - neutralisation of anticoagulation effects of heparin

Mechanism

- strongly basic protamine + strongly acid heparin -> forms stable salt -> removed by reticuloendothelial system.
- inhibits formation and activity of thromboplastin (extrinsic pathway)

CVS

- myocardial depressant
- activation of complement & release of leukotriene -> bradycardia, hypotension.

RESP - bronchospasm

Toxicity

- acute hypotension
- bradycardia
- dyspnoea
- flushing
- anaphylactoid rxn

BEAWARE - protamine + vasectomised patient -> allergy!

(d) To describe the pharmacology of wafarin.

Chemical - synthetic coumarin derivative

Uses

(1) prophylaxis of systemc embolisation in rhematic heart disease, AF, prosthetic valves & ventricular aneurysms.
(2) prophylaxis & treatment of DVT & PE.

Presentation

- tablets: 0.5, 1, 3 & 5mg
- racemic mixture of warfarin sodium

Route - PO

Dose

- as per INR/PT
- maximum effect at 24-72hrs

PK

Absorption - 100% bioavailability

Distribution

- 99% protein bound
- Vd = 0.15L/kg

Metabolism

- liver
- L form -> oxidised
- D form -> reduced
- then conjugated with glucuronide

Elimination

- excreted in faeces & urine
- Cl = 3.5mL/min/kg
- t1/2 = 40hrs

PD

Main action - anti-coagulation

Mechanism of action

- prevents the synthesis of vitamin K dependent clotting factors
- II, VII, IX & X in liver
- prevents the reduction of vitamin K 2, 3-epoxide -> vitamin K

No adverse effects - other than anti-coagulation

Toxicity

- bleeing from everywhere
- vitamin K takes 12 hrs to work
- FFP immediately corrects

Drug interactions

- teratogenic in pregnancy
- potentiation of warfarin by:

- ET-OH
- amiodarone

- cimetidine
- sulphonmides
- salicylates
- NSAIDs
- co-trimoxazole
- erythromycin
- ginko
- ginseng
- camomile
- fever few

- activity decreased by:

- barbiturates
- OCP
- carbamazpine

(e) To classify and describe the pharmacology of anti-platelet drugs.

- Aspirin
- Clopidogrel
- IIb/IIIa inhibitors - tirofiban, abciximab
- Dipyridamole
- LMWH

Aspirin

Chemical - aromatic ester of acetic acid

Uses

(1) analgesia
(2) anti-inflammatory
(3) anti-pyretic
(4) prevention of MI
(5) prevention of graft occlusion post bypass/stent
(6) pre-eclampsia
(7) prevention of TIAs/CVA
(8) DVT prophylaxis post joint replacement or NOF #

Presentation - 75 to 600mg tablets

Routes - PO, PR

Dose - 300 to 900mg 8hrly

PK

Absorption - bioavailability = 70%

Distribution

- rapidly hydrolysed to salicyclic acid
- 90% protein bound
- Vd = 10 L/kg
- limited ability to cross BBB

Metabolism

- 50% -> salicylurate in liver (saturable)
- 20% -> salicylphenolic glucuronide (saturable)
- 10% -> salicylacyl glucuronide
- 5% -> gentisic acid

Elimination

- t1/2 varies with dose given

PD

Main action - anti-pyretic, analgesic & anti-inflammatory

Mechanism of action

- inhibition of cyclo-oxygenase enzyme -> decreased conversion of arachidonic acid to cyclic endoperoxides -> decreased production of thromboxane & prostaglandins

- prostaglandins are involved in the sensitisation of peripheral nerve endings to pain

- also irreversibly inhibits cyclo-oxygenase in platelets (but not on endothelium)

CVS

- platelet aggregation inhibited
- bleeding time prolonged

RESP

- increase O2 consumption, increase CO2 production -> uncoupling oxidative phosphorylation
- bronchospasm

- OD: hyperventilation -> respiratory failure

CNS

- analgesic effect is centrally & peripherally mediated
- anti-pyretic action is inhibition of hypothalamic prostaglandin synthesis

GI

- increases gastic acid production
- GI haemorrhage
- gastric ulceration
- large doses -> hepatic failure

GU

- proteinuria
- increased number of renal tubular casts
- large doses -> renal failure

Metabolism

- BSL decreases
- increase in serum urea
- elevated LFTs
- lipogenesis decreased
- large doses -> steroid secretion

Other adverse effects

- aplastic anaemia

Drug interactions

- anti-coagulants -> increased effect

Clopidogrel

Chemical - clopidogrel hydrogen sulphate

Used - with aspirin to prevent clotting of coronary stents

Presentation

- clopidogrel hydrogen sulphate (75mg tab)

- lactulose anhydrous
- pregelatinized maize starch
- macrogol 6000
- microcrystalline celluose
- hydrogenated castor oil
- hypromellose
- titanium dioxide
- iron oxide
- carnauba wax

Route - PO

Dose - 75mg/day

PK

Absorption - rapid

Distribution - 90% protein bound to albumin

Metabolism - hepatic to SR26334

PD

Main action - anti-thrombotic

Mechanism of action - irreversible modificatin of ADP receptor.

- prodrug converted to active metabolites in liver
- block ADP receptors on surface of platelets -> inhibits platelet activation, aggregation & degranulation.
- irreversibly modify ADP for the life of the platelet (7-10 days)

CNS

- intra-cranial & GI haemorrhage

GI - hepatic dysfunction

GU - bleeds rarely

Other effects - rash

Haematological

- neutropenia
- thrombocytopenic purpura

Drug interactions

- warfarin, phenytoin, NSAIDs -> metabolism effected.

Platelets glycoprotein IIb/IIIa antagonists

- ie. abciximab

- act at the corresponding fibrinogen receptor that is involved in the final pathway to platelet aggregation.
- block fibrinogen binding to platelet glycoprotein IIb/IIIa receptors in the final common pathway of platelet aggregation

Uses

(1) MI
(2) unstable angina
(3) angioplasty failure
(4) stent thrombosis

Dipyridamole

Uses

(1) anti-anginal
(2) anti-thrombotic for prostatic valves
(3) anti- thrombotic in ischaemic TIA's/CVA
(4) PVD

Presentation

- yellow crystalline powder
- bitter taste

Route - PO

Dose - 100mg QID

PK

Absorption - bioavailability = 50%

Metabolism

- hepatic

- to glucuronides

Eliimination

- bile
- t1/2 alpha = 40min
- t1/2 beta = 10hrs
- Cl = 2mL/min/kg

PD

Main action - anti-platelet

Mechanism

- potentiates the effect of prostacyclin or by inhibiting phosphodiesterase enzyme activity -> increase intracellular cAMP
- inhibits cellular uptake of adenosine -> more available to act on coronary vessels -> vasodilation.

CVS - decreases coronary vascular resistance

(f) To describe the fibrinolytic pathway & outline the pharmacology of the thrombolytic agents.

Fibrinolytic pathway

See diagram in Haematology - the Fibrinolytic Pathway.

Thrombolytic Agents

- streptokinase
- altplase (recombinant tissue plasminogen activator)
- anistreplase (aniosylated plasminogen streptokinase activator complex)

Absolute contraindications

- active bleeding
- trauma or surgery in last 14 days
- recent HI or known intracranial aneurysm
- history of haemorrhagic cerebrovascular accident
- systemic BP > 200/120
- previous allergic rxn
- traumatic CPR
- suspected dissecting aorta
- diabetic haemorrhagic retinopathy
- pregnancy

Relative contraindications

- trauma or surgery > 14 days previously
- chronic or severe hypertension
- active peptic ulcer disease
- anti-coagulation treatment
- known bleeding diathesis
- significant liver dysfunction
- prior exposure to streptokinase or anistreplase

Streptokinase

Chemical - protein obtained from Group C beta-haemolytic streptococci

Uses

(1) AMI
(2) DVT/PE
(3) treatment of acute occulsion of peripheral arteries

Presentation

- freeze-dried powder in vials containing 250,000 or 750,000 or 1.5 million units of streptokinase

Route - IV

Dose

- in 50 to 200mL of saline
- AMI: 1.5 million units over 60min
- thrombi/emboli: 250,000 units over 30min

- then 100,000 units/hr for 72hrs
- monitor thrombin & prothrombin time

PK

Elimination - t1/2 = 80min

PD

Main action - fibrinolysis

Mechanism of action

- indirectly on plasmin
- forms streptokinase-plasminogen complex which then converts plasminogen molecule -> plasmin -> plasmin then digests fibrin to produce fibrinolysis.

CVS

- transient hypotension
- dysrrhythmia
- excessive haemorrhage

CNS

- polyneuropathy

Metabolic

- pyrexia

Other adverse effects

- repeated exposure -> allergy

Alteplase

Chemical - recombinant DNA-derivative version of a naturally occuring glycoprotein

Uses - AMI

Preparation

- dry powder in vials
- 10mg or 50mg
- reconstituted with H2O prior to injection

Route - IV

Dose

- within 6 hrs of pain
- 1.5mg/kg over 3 hrs
- coronary reperfusion should take place within 30min

PK

Distribution - Vd 1 L/kg

Metabolism - hepatic

Elimination

- Cl = 10mL/min/kg
- t1/2 = 30hrs

PD

Main action - thrombolysis

Mode of action

- binds to clots & selectively converts fibrin-bound plasminogen -> plasmin -> lyses fibrin clot.

CVS

- EF increases
- LV end-diastolic pressure decreases
- dysrrhythmia decreases
- bleeding

CNS

- intracerebral haemorrhage

GI

- nausea & vomiting

(g) To outline the pharmacology of anti-fibrinolytic agents such as epsilon aminocaproic acid, tranexamic acid & aprotinin.

Aminocaproic acid

Chemical - similar to lysine (synthetic inhibitor of fibrinolysis)

Uses

(1) haemphillia
(2) bleeding from thrombolytic therapy
(3) prophylaxis for re-bleeding from intracranial aneurysms

Presentation

- tablets: 500mg

- syrup: 250mg/mL
- injection: 250mg/mL

Route - PO, IV

Dose

- PO: 1g Q6hr
- IV: load with 5g over 30min (avoids hypotension)

PK - rapidly absorbed -> extreted by kidneys

PD

Main action - inhibition of fibirinolysis

Mechanism

- competitively inhibits plasminogen activation

Side effects

- intravascular thrombosis
- hypotension
- myopathy
- abdominal discomfort
- diarrhoea
- nasal stuffiness

Transexamic acid

Chemical - derivative of lysine

Presentation

- injection: lear, colourless solution, 100mg/mL
- tablets: 500mg
- syrup: 100mg/mL

Uses

(1) short term adjunct to management of haemorrhage due to increases fibrinolysis or fibringenolysis (ie. post-prostatectomy, epistaxis, cerebral aneurysms)
(2) priory to dental extractions in haemophiliacs
(3) prior to repeat cardiac surgery

(4) reverse thrombolytic therapy
(5) menorrhagia
(6) hereditary angioneurotic oedema

Route - PO, IV

Dose

- PO: 1g Q6hrly
- IV: 20mg/kg over 5min

PK

Absorption - bioavailability = 34%
Metabolism - little
Elimination - 95% unchanged in urine. t1/2 = 2hrs

PD

Main action - inhibition of fibrinolysis

Mode of action - competitive inhibits activation of plasminogen -> plasmin.

Side effects

- thrombin time increases
- GI tract disturbance

Aprotinin

Chemical - single chain polypeptide which occurs naturally in bovine lung & other tissues

Uses

(1) life-threatening haemorrhage from hyperplasminaemia
(2) acute pancreatitis
(3) reduction of blood loss during bypass surgery, prostatectomy & liver transplantation
(4) prevention of DVT

Presentation

- clear, colourless solution
- 1.4mg/mL in 0.9% saline = 10,000 kallidrein inactivator units

Route - IV

Doses

- adult: 500,000 - 1,000,000 KIU -> 200,000 KIU/hr until bleeding stops

PK

Absorption - destroyed when taken orally
Distribution - highly protein bound
Metabolism - in lysosomes of kidney
Elimination - t1/2 = 1hr

PD

Main action - inhibition of fibrinolysis

Mechanism of action

- inhibition of human typsin, plasmin & tissue kallikrens by forming reversible enzyme-inhibitor complexes.
- inactivation of free plasmin -> haemostasis

Side effects

- decreased GFR
- inhibition of platelet aggregation -> prevents microaggregate formation
- in high doses -> limitatin of complement activation
- thrombophlebitis
- hypersensitivity