B14 - Therapy of Cardiac Arrest, Ischaemia & Failure

(a) To describe the international cardiopulmonary resuscitation guidelines.

Adult

See diagram - Adult CPR algorhythm

Adjunct priorties

1. Defibrillation
2. Advanced airway/ventilation adjuncts
3. O2
4. IV access

Advanced adjuncts

- ETT
- LMA
- Adr 1mg
- VF/VT: defibrillation, amiodarone 300mg after 3 loops
- asystole: atropine 1mg (x3)
- consider pacing & buffers

Check

- defib: source, settings & electrodes
- ETT & IV placement

Consider & correct

- Hypoxia
- Hypovolaemia
- Hyper/hypokalaemia
- Hyper/hypoglycaemia
- Hyper/hypothermia
- TP
- Tamponade
- Toxicity
- Thrombosis - MI/embolism

Child

See diagram - Child CPR algorhythm

Adjunct priorites

1 Advance airway/ventilation adjuncts
2 O2
3 IV access
4 Defibrillation

Advanced adjuncts

- ETT
- LMA
- Interosseous cannula
- Adr 10mcg/kg every 3 min
- VF/VT: defbrillation, lig 1mg/kg or amiodarone 5mg/kg
- paceing, buffers

Check

- defib: source, source, electrodes
- ETT & IV placement

Consider & Correct

- Hypoxia
- Hypovolaemia
- Hyper/hypokalamia
- Hyper/hypoglycaemia
- Hyper/hypothermia
- TP
- Tamponade
- Toxicity
- Thombosis - PE/MI

(b) To describe the role of defibrillation and its potential benefits & risks during cardiac arrest.

= application of an electrical current across the heart to convert VF/VT -> sinus rhythm

Role

- single most important modality for cardiac arrest management.
- likelihood of these rhythms reverting with defibrillation is inversely proportional to time
- the chance of successful revertions declines at a rate of 7-10% per min from onset of VF.

- current pulse causes synchronous contraction of the heart muscle, hopefully allowing SR to occur following refractor period.

Modern defibrillators:

- capacitor (potential difference between plates of up to 8000V, energy released during discharge is proportional to the potential difference)
- 360J external defib
- 50J internal defib

- after first shock thoracic impedance is reduced -> second shock will deliver greater energy to the heart.

- energy at discharge is released in a waveform (mono & biphasic)

Monophasic

- voltage rises rapidly and then returns to baseline (0 -> +ve -> 0)

Biphasic

- voltage rises, then reverses its direction below baseline before returning to baseline (0 -> +ve -> 0 -> -ve -> 0)
- biphasics have been shown to defibrillate as effectively as monophasic but a lower energy.
- smaller (more portable)
- cheaper

Benefits

- see above: single most important modality for cardiac arrest management.

Risks

- DC more effective & less damaging than AC
- repeated shocks -> myocardial damage
- electrocution of members of resuscitation team
- biphasic less myocardial damage
- burns
- arcing to other metal (backs of GTN patches, inplanted defibrillators)

(c) To describe the pharmacology of:

- adrenaline
- vasopressin
- amiodarone
- lignocaine

with reference to cardiopulmonary resuscitation.

Adrenaline/Epinephrine

Chemical - a catecholamine

Uses

1. Analphylactic/oid shock
2. Asystole
3. Low cardiac output states
4. Glaucoma
5. Local vasoconstictor
6. Added to LA to increase duration of action

Preparation

- injection: clear, colourless, 0.1 & 1mgmL
- eye: topical opthalmic solution (1%)
- aerosol: 280mcg metered doses

Route

- IV, SC, INH
- if given peripherally -> follow with a flush of 20mL of saline

Dose

- IV: 0.1 - 1mg boluses, or 0.01-1mcg/kg/min infusion.
- SC: 0.1-0.5mg
- INH: max 10-20 metered doses/day

PK

Absorption

- inactivated when administered orally
- slower absorption SC & I'M
- well absorbed from tracheal muscoa (need to double dose)

Distribution

Metabolism

- catecho-O-methyl transferase in liver -> metadrenaline & normetadrenaline

- some metabolised by MAO within adrenergic neurons

Elimination

- inactive products appear in urine

PD

Main action - sympathomimetic

Mechanism of action

- direct acting sympatheomimetic -> alpha & beta agonist
- low doses -> beta-effects
- higher doses -> alpha-effects
- maintains coronary & cerebral blood flow

CVS

- +ve inotrope
- +ve chronotrope
- increased Q
- increased O2 consumption
- increased coronary blood flow (increased diastolic blood pressure)
- increased in systolic BP from increased SVR
- increased HR
- plasma volume decreases (loss of protein free fluid into ECF)

RESP

- mild respirator sitmulant
- increased TV & RR
- potent bronchodilator
- increased viscosity of bronchial secretions

CNS

- penetrates CNS but doesn't have excitatory effects.
- increases cutaneous pain threshold
- enhances neurmuscular transmission
- increases CBF
- weak mydriatic effects when applied topically to eye

GI

- decreases intestinal tone & secretions

- splanchnic blood flow increases

GU

- decreases RBF by 40%
- although GFR is unaltered
- bladder tone decreased
- sphincteric tone increased -> difficulty micturating
- inhibits contractions in pregnant woman

Haemotalogical

- increased platelet adhesiveness & blood coagulability from increased factor V

Metabolic

- decreased insulin secretion
- increased glucagon secretion -> glyconeolysis -> increased BSL
- increased renin activity
- increased free fatty acids from activation of triglyceride lipase
- K+ rises -> then decreases (release from liver)
- increases basal metabolic rate by 30%
- pyrexia may result

Vasopressin

Chemical

- ADH
- neuropeptide synthesised in the supraoptic & paraventricular nuclei -> transported down axons to the posterior lobe of the pituitary

Uses

1. Diabetes insipidus (central)
2. Control of bleeding in oesophageal varicies
3. Haemophillia
4. von Willebrands disease
5. Cardiac arrest
6. Haemodynamic stabilization in prescence of haemorrhage & septic shock.

Presentation

- other names:

(1) arginine vasopressin
(2) AVP
(3) ADH

Route - IV, PN, IM

Dose

- cardiac arrest: 40IU once
- oesophageal varicies: 20IU over 5min

PK

Elimination

- t1/2 = 10-20min (longer than adrenaline)

PD

Main actions - potent endogenous vasoconstrictor

Mechanism of action

- intense vasoconstriction in skin & muscle beds
- vasodilation of cerebral beds

CVS

- reverse systemic hypotension associated with sepsis, anaphylaxis & multiple organ dysfunction

- increased systemic BP
- facial pallor
- coronary vasoconstiction -> ischaemia -> infarction

RESP

- increased pulmonary artery pressure

GI

- reduces hepatic blood flow & portal hypertension (marked splanchnic vasoconstriction)
- increased peristalsis -> abdo pain, nausea & vomiting

GU

- stimulation of uterine smooth muscle

Metabolic

- decreased in platelet count

Other adverse effects

- urticaria & anaphylaxis described

Amiodarone

Chemical

- amiodarone hydrochloride
- an iodenated benzofuran derivative

Uses - stabilisation of supraventricular & ventricular dysrhythmias.

Preparation

PO - 100 & 200mg tablets
IV - 30 & 50mg/mL ampoules

Route - PO or IV

Dose

IV - bolus 5mg/kg in 250mL of 5% dextrose (60min) -> infusion 15mg/kg/day

PO - load -> 200mg tds reducing to od

PK

Absorption - bioavailability 20-80%

Distribution

- 97% protein bound
- Vd very vairable according to dose (1-60L/kg)

Metabolism

- not clearly elucidated
- appears hepatic to desethyl-amiodarone which is active

Excretion

- 5% appears in urine
- extensively excreted in faeces and bile
- Cl = 0.5 L/min
- t1/2 = 4 hours to 50 days depending on dose and route (over 4wks)

PD

Main actions - class III anti-arrhythmics

Mechanism of action

(1) Delays K+ efflux
(2) Depresses Na+ influx
(3) Depresses Ca2+ influx
(4) Partial antagonism of alpha & beta receptors buy reducing number of receptors or uncompling adenyl cyclase system

CVS

- slow diastolic depolarisation -> sinus rhythm slowed by 15%
- AV nodal conduction slowed by 30%
- SVR decreases
- coronary vessels dilate -> increase in blood flow
- prolongs QT interval
- HR slow
- peripheral vasodialator -> hypotension

RESP

- pulmonary fibrosis (5-15% - ?unknown cause)

CNS

- corneal microdeposists
- photosensitivity
- peripheral neuropathy
- headache
- proximal muscle weakness

GI

- fatty liver infiltration
- hepatitis

Metabolic

- hyper/hypothyroidism (contains iodine)

Other adverse effects

- inflammation of peripheral veins

Lignocaine (fast in, fast out)

Chemical - amide derivative of diethylaminioacetic acid

Uses

(1) reversible neural blockade
(2) treatment of ventricular dysrrhytmias (class Ib antiarrhythmic)

Structure - see diagram

Physiochemical

- pKa 7.7 (fast onset)
- 65% protein bound (moderate duration)
- preservative free
- 35% nonionized at pH of 7.4

Presentation:

- injection - clear, colourless solution
- gel
- ointment (5%)
- spray (10%)
- aqueous solution (4%)
- cream suppositories +/- hydrocortisone

Infiltration - 5mg/mL (0.5%), 10mg/mL (1%)
Peripheral nerve blocks - 10 (1%), 15 (1.5%), 20mg/mL (2%) with or without adrenaline.
Epidural - 10, 15 & 20mg/mL solutions
Spinal - 50mg/mL solution
Topical - 2% jelly, 2.5% & 5% ointment.

Route

- infiltration
- topical

- IV
- spinal
- epidural

Dose

- max IV dose = 300mg
- max dose 3mg/kg
- max dose with adrenaline 7mg/kg

- dose for ventricular arrhythmias = 1 mg/kg bolus over 2min -> infusion @ 4mg/kg for first 60min, then 2mg/kg for next hour, then 1mg/kg after that.

PK

Absorption

- related to site, dose and presence of vasoconstrictors.
- bioavailability PO = 30% - high first pass metabolism.

Distribution

- Vd = 1L/kg
- 64% protein bound (to alpha-1 acid glycoprotein)

Metabolism

- hepatic (70%)
- N-dealkylation to monoethylglycinexylidide -> hydrolysis to xylidide

Elimination

- <10% excreted in urine unchanged.
- Cl = 10mL/min/kg
- Elimination t1/5 = 100 min
- reduced in cardiac & hepatic failure.

PD

Main action - antiarrhythmic

- acts within 10min
- lasts within 200-400min

Mode of action

- delays the rate of spontaneous phase 4 depolarisation by preventing or diminishing the gradual descrease in K+ permeability
- prolongs cardiac action potential & delaying refractory period

CVS

(1) increases shock energy required for defibrillation
(2) reduces likelihood that patient will develop VF

- reduces BP
- decreases HR

- CC/CNS 7:1 = 7 times as much drug dose required to produce CVS collapse compared to convulsions.
- depression of rate of cardiac AP
- hypotension from smooth muscle relaxation & myocardial depression.
- prolongation of P-R & QRS.

RESP

- bronchodilation
- respiratory depression @ toxic doses.

CNS

- reversible neural blockade -> biphasic effect
(1) excitation - lightheadness, dizziness, visual & auditory disturbances, fitting.
(2) blockade of inhibitory pathways in cortex - drowsiness, disorientation & coma

GI - depress contraction of the intact bowel.

Metabolic - anticholinergic & antihistaminergic activity.

(d) To describe the pharmacology of drugs used to manage myocardial ischaemia/infarction with particular reference to:

- nitrates
- beta-blockers
- calcium antagonists
- anti-platelet agents
- anti-coagulants
- fibrinolytics agents

Management

1. telemetry
2. IV access
3. high flow O2
4. aspirin 300mg
5. morpine (decrease preload)
6. GTN SL/IV (decrease afterload)
7. beta-blockers
8. Ca2+ antagonists
9. Reperfusion treatment

Nitrates

- ie. nitroglycerin, ISMN

Nitroglycerin

Chemical - organic nitrate

Structure - see diagram

Uses

(1) angina pectoris
(2) decreases hypertension associated with laryngoscopy & intubation
(3) cardiac failure (relieves pulmonary oedema)
(4) acute hypertension
(5) controlled hypotension

Preparation

Route - SL, PO, transdermal or IV

Dose

- SL: 0.5mg Q5min
- transdermal: 5-10mg/24hrs

Onset - SL within 4min

PK

Absorption

- SL limits the amount of first-pass metabolism

Distribution

- large Vd (only 1% in plasma)

Metabolism

Elimination

- t1/2 = 1.5min

PD

Main action - vasodialation

Mechanism of action

- that acts principally on:

(1) venous capacitance vessels (preload)
(2) large coronary arteries
(3) decreases cardiac wall tension
(4) arterial vessels (afterload)

-> decrease in myocardial O2 requirements

- nitroglycerin -> glutathione & glutathione-S-transferase -> generates NO -> stimulates cGMP -> peripheral vasodialation

CVS

- vasodialation of arterioles (hypotension)
- venodilation -> decreased VR -> decreased L & R ventricular end-diastolic pressure
- decrease in Q

RESP

- pulmonary as well as systemic vasodilation -> decrease in PVR
- inhibition of hypoxic-pulmonary vasoconstriction
- bronchial dialation

CNS

- headache
- facial flushing

GI

- relaxation of sphincter of Oddi
- oesophageal tone decreased

GU

- decreased ureteric & uterine tone

Metabolic

- methhaemoglobinaemia: metabolite capable of oxidising the ferrous ion in Hb -> ferric state

Other adverse effects

- tolerance: can develop with constant exposure over 24hr
- inhibition of platelet aggregation

Drug interactions

- decrease sensitivity to heparin

Beta-blockers

- competitive blockade of beta-adrenoreceptors
- competes with catecholamines
-> decreased rate of spontaneous firing of SA node
-> decrease ability to mount tachycardia

- beta-adrenergic receptor are G protein coupled -> activate adenylate cyclase -> cAMP -> protein kinase activation -> phosphorylation of proteins (L-type voltage dependent Ca2+ channels & troponin C) -> positive chronotropic, ionotropic & dromotropic effects

- beta-receptor antagonist block this cascade

Classification

Non-selective (for beta 1 and beta 2 receptors)

- propanolol
- nadalol
- timolol
- pindolol

Cardioselective (for beta 1 receptors)

- metoprolol

- atenolol
- acebutolol
- betaxolol
- esmolol
- bisoprolol

Contraindications

- bradycardia
- hypotension
- heart block
- IDDM
- asthma
- heart failure

Metoprolol

Chemical - metoprolol

Uses

(1) hypertension
(2) migraine
(3) IHD
(4) arrhythmias
(5) thyrotoxicosis
(6) acute MI

Route - IV, PO

Dose

- PO: 100-200mg bd
- IV: titrate to response

PK

Absorption

- readily absorped from the GI tract
- substantial first pass metabolism
- bioavailability = 40%

Distribution

- protein binding 10%

Metabolism

- hepatic
- no active metabolites

Elimination

- urinary
- t1/2 = 4hrs

PD

Main action - selective beta 2 antagonist

Mechanism of action

- prevents iontropic & chronotropic responses to beta-adrenegic stimulation.

CVS

- in high doses can exacerbate PVD

RESP

- in high doses can produce bronchoconstriction

Calcium Antagonists

- diverse group of structurally unrelated compounds that selectively interfere with inward Ca2+ ion movement across myocardial and vascular smooth muscle cells.
- Ca2+ plays a key role in electrical excitation of cardiac & vascular smooth muscle.

Types:

(1) Phenyalkylamines (verapmil)
(2) Dihydropyridines (nifedipine)
(3) Benzothiazepines (diltiazem)

See diagram - types of Ca2+ channel blockers

Mechanism:

- bind to receptors on voltage gated Ca2+ channels (L, N or T subtypes) -> maintenance of channels in closed state -> decrease in Ca2+ influx -> reduction in intracellular Ca2+

- L type = a pentamer (2 alpha, beta, gamma & delta)
- responsible for phase 2 of cardiac action potential -> important in (1) excitation/contraction coupling, (2) depolarisation in SA & AV node

-> slowing of HR
-> reduced myocardial contractility
-> decreased speed of conduction of cardiac impulses through AV node
-> decrease in SA node activity
-> vascular smooth muscle relaxation

Verapamil

Chemical

- phenylalkyamine
- a synthetic papaerine derivative

Uses

(1) antianginal
(2) antihypertensive
(3) treatment of SVT, AF

Presentation

- PO: 40 to 240mg tablets
- IV: clear solution 2.5mg/mL

Routes - IV, PO

Doses

- PO: 240 to 480mg/day in divided doses
- IV: 5 - 10mg over 30sec

Peak effect = 5min
Duration of action = 20min

PK

Absorption

- bioavailability = 20%

Distribution

- 90% protein bound
- Vd 4 L/kg

Metabolism

- hepatic
- demethylation and dealkylation

Elimination

- 70% urine, 20% faeces
- Cl = 10mL/min/kg
- t1/2 = 6hrs

PD

Main actions - antihypertensive & antianginal

Mechanism of action

- competitive blockade of cell membrane slow Ca2+ channel -> decreased influx of Ca2+ into vascular smooth muscle & myocardial cells -> electomechanical decoupling, inhibition of contraction & relaxation -> coronary & systemic arterial vasodilation.

- decreases automaticity & conduction velocity
- increases refractory period

CVS

- AV conduction slowed
- decrease in SVR
- potent coronary artery vasodialator
- flushing
- 1st or 2nd degree HB

CNS

- cerebral vasodialation
- has LA properties
- dizziness

GI

- nausea

GU

- decreases renovascular resistance

Drug interactions

- volatiles -> increased myocardial depression
- dantrolene -> hyperkalaemia -> VF
- volatile -> decreases MAC
- neuromuscular blockers (depolarising and non-depolarising) -> potentiation

Nifedipine

Chemical - a dihydropyrimidine

Uses

(1) angina
(2) hypertension
(3) raynauds phenonmenon
(4) coronary graft spasm during angiography/plasty

Presentation

- capsules: 5-10mg
- tablets SR: 10 to 60mg
- combination with atenolol

Routes - IV, PO

Dose

- PO: 10 to 20mg Q8hrly
- IV: 100-200mcg over 2min

- onset: 20min

PK

Absorption - bioavailability = 50%

Distribution

- 95% protein bound
- Vd 1L/kg

Metabolism

- hepatic
- inactive metabolites

Elimination

- urinary (90%), faeces (10%)
- Cl = 50L/hr
- t1/2 = 10hrs

PD

Main action - relaxation of smooth muscle

Mechanism of action

- competitive blockade of slow Ca2+ channels -> decrease in intracelluar Ca2+ -> decreased electromechanical coupling for muscle contraction -> relaxation of cardiac & smooth muscle

- also increases RBC deformability
- prevents platelet clumping through thromboxane release.

CVS

- decreases MAP by 25% -> increase in HR
- decrease in SVR & pulmonary vascular resistance
- LV end-diastolic & pulmonary artery pressure
- Q increased
- sustained relaxation of epicardial vessels -> increased coronary blood flow

RESP

- inhibition of hypoxic pulmonary vasoconstrictor mechanism.

CNS

- marginal increase in cerebral blood flow from vasodilation.
- headache
- dizziness
- eye pain

GI

- contractility decreased
- lower oesophageal tone decreased
- hepatic blood flow increased
- gum hyperplasia

GU

- no change in RBF or GFR
- uterine activity decreased (tocolytic)

Metabolic

- increased renin activity
- increased catecholamine activity
- platelet aggregation impaired

Other adverse effects

- oedema

Drug interactions

- volatiles -> increased myocardial depression, increased risk of sinus arrest, reduces MAC
- neuromuscular blockers -> increased efficacy

Diltiazem

Chemical - a benzothiazepine

Uses

(1) angina
(2) hypertension
(3) SVT
(4) raynauds phenonmenon
(5) migraine
(6) oesophageal motility disorders

Presentation

- tablets: 60 to 300mg (onset: 20min)
- IV

Route - PO, IV

Dose - 30 to 120mg Q8hrs

PK

Absorption

- bioavailability = 40%

Distribution

- 80% protein bound
- Vd 5 L/kg

Metabolism

- deacetylation & demethylation in liver -> conjugation to glucuronide & sulphates
- metabolites are active

Elimination

- 4% unchanged in urine
- Cl = 15mL/min/kg
- t1/2 = 6hrs

PD

Main actions

- increased myocardial O2 supply
- decreases myocardial O2 demand

Mechanism of action

- dose dependent blockade of myocardial Ca2+ channels -> coronary vasodilation

CVS

- potent peripheral & coronary arterial vasodilator -> decreased in SVR & pulmonary vascular resistance
- Q increases
- decreases AV conduction
- bradycardia

RESP

- bronchodilation

CNS

- headache
- dizziness

GI

- reduction in lower oesophageal pressure

GU

- renal artery dilation -> increased RBF -> diuresis
- uterine activity decreases

Metabolic

- platelet aggregation decreased (in vivo)

Other adverse effects

- oedema

Drug interactions

- beta-blockers -> bradycardias
- volatile -> myocardial depression, sinus arrest, reduce MAC
- neuromuscular blockade -> increased
- digoxin -> increase plasma concentration
- bupivacaine -> increase toxicity

Anti-platelet Drugs

- Aspirin
- Clopidogril
- IIb/IIIa inhibitors

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

- 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)
- used with aspirin to prevent clotting of coronary stents

Side effects:

- neutropenia
- thrombocytopenic purpura
- hepatic dysfunction
- intra-cranial & GI haemorrhage

Platelets glycoprotein IIb/IIIa antagonists

- ie. abciximab

- act at the corresponding fibrinogen receptor that is important for 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

Anti-coagulants

- heparin
- LMW heparin

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)

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 to inhibit proteases in the coagulation cascade:

- XIII
- XII
- XI
- X
- IX
- plasmin
- thrombin

- 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
- thrombocytopenia (5%)

Metabolic

- increases hepatic triglyceride actvity -> increase in FFA
- osteoporosis
- ALD suppression

Other adverse effects

- full heparisation -> no spinal or regional

Thrombolytics

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

Absolute contraindications

- active bleeding
- trauma or surger 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 83min

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

(e) To describe the pharmacology of drugs used to manage acute or chronic cardiac failure with particular reference to:

- sympathomimetics
- phosphodiesterase inhibitors
- digoxin
- diuretics
- ACE inhibitors
- nitrates
- beta-blockers

Sympathomimetics

Dobutamine

Chemical - synthetic isoprenaline derivatvie

Uses - for low Q states from:

(1) MI
(2) cardiac surgery
(3) cardiomyopathy
(4) PEEP
(5) Septic shock
(6) cardiac stress testing

Presentation

- vials which hold solution
- 12.5 or 50mg/mL
- dobutamine HCl

Route - IV

Dose

- 0.5 to 40mcg/kg/min
- acts within 2 min

PK

Distribution

- t1/2 = 2min
- steady state reached in 10min
- Vd = 0.2 L/kg

Metabolism

- methylation by catechol-O-methyl transferase to 3-O-methyldobutamine

Elimination

- urine (80%), faeces (20%)
- Cl = 244 L/hr
- t1/2 = 2min

PD

Main action - +ve iontrope

Mechanism of action

- acts directly on catecholamine receptors -> activates adenyl cyclase -> converts ATP -> cAMP -> increased in Ca2+ permeability -> increase depolarisation & contractility

CVS

- increased contractility from beta 1 receptor agonism
- SA node automaticity increased
- increased HR
- increased AV node conduction velocity
- moderate activity at alpha & beta 2 adrenoceptors -> decrease in SVR

- dysrrhythmias
- excessive tachycardia
- hypertension

CNS

- stimulation at high doses
- fatigue
- nervousness
- headache

GU

- increased u/o c/o increased Q

Metabolic

- enhances natural killer cell activity
- increased BSL
- increase plasma FFA

Phosphodiesterase inhibitors

Chemicals - milirirone & amilrinone (bipyridines)

Uses

(1) after MI

(2) cardiosurgery
(3) cardiac failure

Dose

- amirinone: 2-10mcg/kg/min
- milrinone: 0.5mcg/kg/min

PK

Absorption - oral or IV
Elimination - renal

PD

Main actions

- increase ionotropy
- increase vascular & bronchial muscle relaxation

Mechanism of action

- non receptor mediated inhibitors of peak cAMP phosphodiesterase III isoenzyme -> decrease the hydrolysis of cAMP
- increase cAMP -> is like activating a Gs protein -> increase in adenyl cyclase -> increase protein kinases -> increased phosphorylation of proteins -> net influx of Ca2+ into muscle.

- located in cardiac, vascular muscle & platelets.

CVS

- hypotension
- thrombocytopenia

GI

- hepatic dysfunction

Digoxin

Chemical - glycoside (sterol lactone + a sugar)

Uses

(1) AF

(2) heart failure
(3) prevention of supraventricular dysrrhythmia

Presentation

- tablets: 0.0625mcg to 2.5mg
- elixir: 0.05mg/mL
- solution: 0.25mg/mL

Routes - PO, IV

Dose

- loading dose: 1mg over 24hrs
- maintenance: 10-20mcg/kg/day in divided doses

PK

Absorption - bioavailability = 60 to 90%

Distribution

- 30% protein bound
- Vd = 10 Lkg

Metabolism

- <10% hepatically metabolised by cleavage o sugar moieties

Elimination

- 60% excreted unchanged in urine
- Cl = calculated by formula

PD

Main action - +ve ionotrope + slowing of ventricular response

Mechanism of action

- direct: inhibition of Na+/K+ ATPase within sarcolemma -> increase in intracellular Na+ -> displaces Ca2+ from proteins -> +ve ionotropism also slowing of AV conduction with decreased K+ concentration.

- indirect: modifies automoic activty (increases vagal activity)

CVS

- increase contractility
- HR slowed
- ECG changes: prolongation of PR interval, ST segment depression, T wave flattening, shortened QT

CNS

- headache
- drowiness
- confusion
- visual disturbance
- weakness

GI

- anorexia
- n & v
- diarrhoea
- abdominal pain

GU

- mild intrinsic diuretic effect

Drug interactions

- sux, pancuronium or beta-agonists -> dyrhythmia
- co-administration of: verapmil, nifedipine, amiodarone & diazepam

Diuretics

- spirinolactone
- frusemide

Sprinolactone

Chemical - synthetic steroid

Uses

(1) congestive heart failure
(2) hepatic cirrhosis with ascites & oedema
(3) refractory oedema
(4) hypertension

(5) nephrotic syndrome
(6) combination with loop or thiazide to conserve K+
(7) diagnosis & treatment of Conn's sydrome

Presentation

- tablets: 25 to 100mg

Route - IV

Doses

- 100 - 400mg/day (onset = 4 days)

PK

Absorption

- bioavailability 70%

Distribution

- >90% protein bound

Metabolism

- rapidly & extensively hepatically metabolised

Elimination

- urinary & biliary
- t1/2 = 2hrs

PD

Main action - diuretic

Mechanism of action

- competitive antagonism of ALD at its receptor site in DCT -> Na+ reabsorption inhibited & K+ ion reabsorbed

CVS

- decrease BP

CNS

- sedation
- weakness

GI

- n & v

GU

- diuresis
- mentrual disturbances

Metabolic

- inhibition of ovarian androgen secretion -> antiandrogenic effect
- increase in renal Ca2+ excretion -> hypercholraemic metabolic acidosis
- increase plasma urea concentration
- hyperkalaemia
- gynaecomastia in men

Drug interactions

- decreased response to pressors & anaesthetic agents

Frusemide

Chemical - an anthranilic acid (sulphonamdie) derivative

Uses

(1) oedema of cardiac, renal or hepatic origin
(2) chronic renal failure
(3) hypertension
(4) raised ICP
(5) symptomatic hypercalcaemia
(6) conversion from oliguric -> polyuric renal failure

Presentation

- injection: clear solution, must be protected from light
- tablets

Route - IV, IM or PO

Doses

- PO: 20 -> 2000mg
- IM: 20 -> 50mg
- IV: 10 -> 1000mg

PK

Absorption

- bioavailability 60%

Distribution

- 96% protein bound
- Vd = 0.1 L/kg

Metabolism

- in kidney to glucuronide

Elimination

- 80% kidney, 20% faeces
- Cl = 2mL/min/kg
- t1/2 = 60min

PD

Main action - diuretic

Mechanism of action

- inhibition of Na+ & Cl- reabsorption in PT & ascending LOH -> reduces tonicity in renal medulla -> diuresis

CVS

- vasodilation (pulmonary & systemic)

RESP

- decrease SOB

GU

- diuresis occurs in 2min and lasts 2hrs

- O2 consumptin in the LOH is reduced

Metabolic

- metabolic alkalosis
- increased in serum urate
- hypkalaemia
- hypocalaemia
- hypomagnesaemia

Other adverse effects

- ototoxicity
- pancreatitis
- skin rashes
- bone marrow depression
- interstitial nephritis

ACE inhibitors

- captopril
- enalapril
- lisinopril
- quinapril
- ramipril

Mechanism of action

- ACE I block the conversion of AGI -> AGII
- AGII = a potent vasocontrictor, increased ALD secretion, & sympathetic stimulation.
- binding of AGII to AT1 receptor -> increased Ca2+ release from sarcoplasmic reticulum to produce vasoconstriction
- decreased AGII

(1) decreased vasocontrictive effects
(2) decreased ALD -> decreased Na+ & H2O retention
(3) increase circulating bradykinin (vasodialating substance)

Side effects

CVS

- hypotension with surgery -> ARF

RESP

- cough
- upper respiratory congestion
- rhinorrhoea
- rarely angioedema

GU

- decreased GFR

Metabolic

- hyperkalaemia

Nitrates

See above

Beta-blockers

See above