B12 - Anti-hypertensive Drugs

(a) To classify the mechanisms of action of the anti-hypertensives agents.

Diuretics (Na+ & H2O balance)

- thiazide (BZF)
- loop (frusemide)
- K+ sparring (spirinolactone)

Sympathetic modulators

- beta 1 blockers (esmolol)
- alpha 1 blockers (prazocine)
- central acting inhibitors (clonidine)
- ganglion blockers (trimethaphan)
- vesicular uptake blockers (reserpine)
- norad release blockers (guanethidine)

Vasodilators

- Ca2+ antagonists (verapamil, nifedipine, diltiazem)
- arteriolar direct dilators (hydralazine)
- NO stimulators (Na+ nitroprusside)
- antagonism of 5-HT2 receptors (ketanserin)

Renin-angiotensin system modulators

- ACE I's (accupril)
- angiotensin II receptor antagonists (candesartan)

(b) To describe the pharmacology of centrally acting agents such as clonidine & alpha-methyl dopa.

- bind to the alpha 2 receptor (3 subtypes) -> decreases sympathetic output from the central nerve system.

(1) sedation
(2) slow HR
(3) anti-shivering
(4) vasodilation of vessels
(5) vasoconstriction of smooth muscle
(6) diuresis
(7) analgesia

See diagram - Physiology of alpha 2 - adrenoreceptor

Clonidine

Chemical - aniline derivative

Uses

(1) hypertension
(2) migraine
(3) menopausal flushing
(4) chronic pain
(5) opiate & alcohol withdrawal
(6) regional analgesia

Presentation

- tablets: 0.1 to 0.3mg
- injection: clear, colourless 0.15mg/mL

Route - PO, IV, Epidural

Doses

- PO: 50-600mcg Q8hrs
- IV: 0.15-0.3mg Q8hrs
- epidural: 0.15mg

Onset: 10min
Duration: 3-7hrs

PK

Absorption - 100% bioavailability

Distribution

- very lipid solublw -> penetrates CNS
- 20% protein bound
- Vd = 2L/kg

Metabolism

- less than half hepatically

Elimination

- 60% unchanged in urine
- 20% in faeces
- Cl = 3mL/min/kg
- t1/2 = 20hrs

PD

Main action - antihypertensive, analgesic, sedative & anxiolytic

Mechanism

- alpha 2 agonist -> decrease noradrenaline release -> decrease in sympathetic tone

CVS

- transient rise in BP -> sustained decreased
- HR decreased
- VR decreased
- coronary vascular resistance decreased
- SVR decreased
- rebound hypertension when stopped abruptly

RESP

- minimal depressant effects on ventilation

CNS

- decreased cerebral blood flow
- decreased IOP
- sedaion

GI

- decreases gastric & small bowel motility
- antisialogogue

GU

- reduces renovascular resistance
- little alteration in GFR

Metabolic

- decrease in plasma catecholarmine concentration & renin activity
- BSL increases

Toxicity

- drowiness
- druy mouth
- fluid retension
- impotence
- constipation
- skin rashes

Interactions

- decreases MAC
- decreased post-op shivering & N & V
- decreases amount of propofol for LMA insertion
- decreases postop agitation
- prolongs duration of LA

Alpha-methyl Dopa

Chemical - a phenylalanine derivative

Uses

(1) HT
(2) Pre-eclampsia

Presentation

- tablets: 125 -> 500mg
- suspension: 50mg/mL
- solution: 50mg/mL

Route - IV, PO

Doses

- PO: 0.5 to 3g/day in divided doses

PK

Absorption - bioavailablity = 50%

Distribution

- protein binding 50%
- Vd 0.21 - 0.37

Metabolism

- conjugated to sulphate as transported through intestine
- hepatic

Elimination

- 30% excreted in urine
- 60% unchanged
- Cl = 3mL/min/kg
- t1/2 = 2hr

PD

Main action - anti-hypertensive

Mechanism

- metabolised to alpha-methyl noradrenaline = potent alpha 2 agonist -> decrease CNS sympathetic discharge -> lowers blood pressure

CVS

- decreases SVR
- no change in Q or HR

CNS

GI

GU

- little effect on renal or uteroplacental blood flow or GFR.

Metabolic

- renin activity and norad levels drop

Toxicity

- orthostatic hypotension
- bradycardia
- peripheral oedema
- sedation
- depression
- weakness
- paraesthesia
- dizziness
- thrombocytopenia
- haemolytic anaemia

Interactions

- volatile -> hypotension, decreases MAC

Dexmedetomidine

Chemical - an imidazole derivative

Uses - sedative for post-surgical patients

Presentation

- dextroisomer of medetomidine
- solution: clear, colourless solution (100mcg/m)

Route - IV

Dose

- loading dose: 1mcg/kg (over 10min)
- infusion: 0.2 to 0.7mcg/kg/hr

-> should not be administered for longer than 24hr

PK

Distribution

- 94% protein bound
- Vd = 1L/kg
- distribution t1/2 = 6min

Metabolism

- hepatic
- to methyl & glucuronide conjugates

Elimination

- 95% metabolites excreted in urine
- t1/2 = 2hrs
- Cl = 40L/hr

PD

Main actions

(1) sedation
(2) anxiolysis
(3) analgesia

Mechanism of action

- full agonists at the alpha 1 receptor -> increase K+ conductance

CVS

- decrease in MAP
- decrease in HR

RESP

- slight increase in $PaCO_2$
- decrease in MV
- minimal change in RR

CNS

- sedation
- anxiloysis
- reversible memory impairment

GI

GU

Metabolic

- decrease in plasma epinephrine & norepinephrine

Toxicity

- hypotension
- bradycardia
- nausea
- dry mouth

Interactions

- volatiles -> decreases MAC

(c) To outline the actions of ganglion blocking agents.

Trimetaphan

Chemical - monoquaternary sulphonium derivative

Uses

(1) controlling hypotension
(2) increase perfusion post-cardiac surgery
(3) treatment of hypertensive crisis
(4) attenuate response to tracheal intubation

Dose

- dose = 4mg/min

- onset: 3min
- offset: 10min

PK

Distribution

- doesn't cross the BBB
- largely confined to the plasma

Metabolism

- metabolised by plasma cholinesterase

Elimination

PD

Main action - short acting peripheral vasodilator & ganglion blocker

Mechanism

- blocks both parasympathetic & sympathetic ganglia competitively -> prevents stimulation of postsynaptic membranes by Ach
-> decreased venolar & arteriolar tone
- doesn't stimulate or depolarise ganglion

CVS

- tachycardia

RESP

- depression of hypoxic pulmonary vasoconstriction -> increase V/Q scatter
- orthostatic hypotension

CNS

- mydriasis
- blood flow decreases
- precipitation of glaucoma

GI

- ileus
- constipation
- dry mouth

GU

- urinary retention
- RBF decreases
- sexual dysfunction

Interactions

- may prolong action of mivacurium, sux, procaine

(d) To describe the pharmacology of agents which act at the adrenergic nerve endings.

Blockers of Vesicular uptake

Reserpine

- alkaloid extracted from the roots of an Indian plant, *Rauwolfia serpentina.*
- one of the first effective drugs produced on a large scale in the control of HT

PD

- blockade of aminergic transmitter vesciles to take up & store biogenic amines
- ? interfers with an uptake mechanism that depends on Mg2+ & ATP
-> depletion of norepinephrine, dopamine & 5-HT in both central & peripheral neurons.
- effect is irreversible
- readily enters the brain -> sedation, mental depression & parkinsonianism.

PK

- t1/2 = 2days
- dose: 0.25mg/day

Blockers of Noradrenaline release

Guanethidine

PD

Mechanism

- inhibits release of norepinephrine from sympathetic nerve endings.

- transported across sympathetic nerve endings -> concentrated in transmitter vesicles, replacing norepinephrine -> gradual depletion of norepinephrine in nerve ending
- also inhibition of norepinephrine release caused by guanethidine's LA properties.

Side effects

- hypotension
- bradycardia
- decreased SVR
- marked hypotension (postural)
- diarrhoea
- impaired ejaculation
- increased GI motility

PK

- too polar to enter CNS
- t12 = 5 days
- onset: gradual over 2 weeks

(e) To describe the pharmacology of alpha & beta blockers with reference to management of hypertension.

Alpha 1 antagonists

- ie. prazosin
-> vasodilation of smooth muscle

- inhibtion of the following pathway:

- Gs protein activation -> increase in phospholipase C -> hydrolysis of phospholipid PIP2 -> inositol 1, 4, 5 triphosphate (IP3) & diacylglycerol (DAG) -> increases Ca2+ & phosphatidyl serine -> activation of protein kinase -> phosphorylation of intracellular proteins -> opening of L-type Ca2+ channels -> increase in cytosolic Ca2+

Alpha 2 antagonist

- ie. yohibine
-> dilation of both arterioles & veins

- inhibition of the following pathway:

- activation of Gi protein which inhibits adenyl cyclase -> decreased cAMP -> decreased Ca2+ entry into nerve channels -> decrease phophatidyl inositol metabolism

Beta 1 antagonist

- ie. betaxolol, esmolol, atenolol, metoprolol, acebutolol (BEAMA)
- located in heart & smooth muscle of intestine
-> decrease in chronotropic, inotropic & dromotropic effects.

- inhibition of the following pathway

- Gs protein stimulation -> increase in adenyl cyclase -> increase in cAMP -> increase in Ca2+ availability -> increase in excitation-contraction coupling

Beta 2 antagonism

- ie. propanolol, oxprenolol, labetolol (non-selective beta blockers)
-> -ve ionotropy, chronotrophy, vascular & bronchial constriction, decrease in glyconeolysis & lipolysis

- inhibition of the following path:

- Gs protein stimulation -> increase in adenyl cyclase -> increase in cAMP -> ....?

PK

Distribution

Highly lipid soluble beta blockers - metoprolol & propanolol

Less lipid soluble beta blockers - atenolol

Protein binding - propanolol 90%, sotalol 0%.

Metabolism

Esmolol - plasma esterases
Propanolol - liver
Atenolol - kidneys

Elimination

Renal - atenolol, esmolol, sotalol, labetolol

Liver - metoprolol, prazocin, nadolol

PD

Alpha 1 blockers

- prazocin

Alpha 2 blockers

- yohimbine

Non-selective alpha blockers

- phentolamine
- tolazoline
- phenoxybenzamine

Beta 1 blockers

- betaxolol
- esmolol
- atenolol
- metoprolol
- acebutolol

(BEAMA)

Beta 2 blockers

- NONE!

Non-selective beta blockers

- propanolol
- oxprenolol
- alprenolol
- sotalol

Alpha & Beta blockers

- labetolol
- carvedilol

See - B12 - Adrenoreceptor blockers (c) for individual medications.

(f) To describe the pharmacology & physiology of the vascular endothelium & smooth muscle with particular reference to nitric oxide.

Nitric Oxide

Chemical - inorganic gas

Uses as a selective pulmonary vasodiator in:

(1) ALI
(2) pulmonary HT
(3) bronchospasm
(4) COPD

Presentation

- aluminium or stainless steel cylinders
- 100 tp 2000ppm nitric oxide in nitrogen
- typically 40L

Route - INH

Dose

- 5-80ppm
- monitor dose via a chemiluminescent monitor or electrochemical detector.

PK

Absorption

- highly lipid soluble -> diffuses freely across cell membranes

Metabolism

- rapidly converted to nitrates & nitrites in the prescence of O2
- readily oxidises with Hb -> metHb

Elimination

- t1/2 = <5sec

PD

Main action - vasodiator

Mechanism of action

- is produced in vivo by NO synthase which uses the L-arginine substrate.
- diffuses across vascular smooth muscle
- stimulates guanylate cyclase -> increase in cGMP -> activtes phosphorylation cascade -> smooth muscle relaxation & vasodilation

CVS

- vasodilation -> hypotension
- inhaled -> pulmonary vasodilation
- inhibits platelet aggregation & adhesion
- inhbits WCC adhesion

RESP

- preferentially increases blood flow through well-ventilated ares of lung -> inproves the V/Q relationship.

CNS

- increases CBF
- has a neurotransmitter effect in the autonomic & CNS

GI

- a determinant of GI motility
- modulates morphine-induced constipation

GU

- mediator or penile erection

Metabolic

- released with superoxide from macrophages -> free radical peroxynitrite -> toxic to bacteria

Toxicity

- exposure to >500ppm -> metHbaemia + pulmonary oedema

(g) To describe the pharmacology of calcium antagonists with reference to the management of hypertension.

- 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

See B13 - for individual Ca2+ blocking drug pharmacology

(h) To describe in detail the pharmacodynamics & pharmacokinetics of sodium nitroprusside & glyceryl trinitrate including adverse effects.

Sodium nitroprusside

Chemical - an inorganic complex

Uses

(1) hypertensive crises
(2) aortic dissection
(3) LVF
(4) produce hypotension during surgery

Presentation

- solution: 10mg/mL
- must be diluted before administration
- must be protected from light

Route - IV

Dose

- 0.5 - 4mcg/kg/min
- titrated according to response
- need art line

Onset: immediate

PK

Distribution

- confined to the plasma
- Vd = same as ECF volume (15L)

Metabolism

(1) reaction with sulphdryl groups on amino acids in plasma
(2) rapid, non-enzymatic hydrolysis within RBC's

- 5 cyanide ions are produced by the degradation of each molecue of Na nitroprusside.

- 1 reacts with metHb -> cyanometHb
- 3 react with thiosulphate -> thiocyanate (catalyed by hepatic rhodanese)
- 1 reacts with hydoxy-cobalamin -> forms cyanocobalamin (vitamine B12)

Elimination

- thiocyanate & cyanocobalamin -> urine
- t1/2 of thiocyanate = 3 days

PD

Main action - vasodiator & hypotension

Mechanism of action

- dialates both resistance & capacitance vessels by direction on vascular smooth muscle.
- acts by interacting with sulphdryl groups in smooth muscle membrane & preventing Ca2+ influx necessary for initiation of contraction

CVS

- decrease in systemic BP
- compensatory tachycardia (in heart failure will HR will decrease)
- no change in contractility

RESP

- reversible decrease in PaO2 from decrease in hypoxic pulmonary vasoconstriction

CNS

- cerebral vasodilation -> increase in ICP
- autoregulation curve is shifted to the left

GI

- decrease lower oesophageal spinchter tone
- paralytic ileus

GU

- RBF & GFR maintained

Metabolic

- increase in catecholamine
- increase in renin
- metabolic acidosis may occur

Toxicity

MAJOR ISSUE - liability to cyanide toxicity

- risk increased by hypothermia, malnutrition, vitamin B12 deficiency, hepatic or renal impairment

- related to rate of infusion rather than total dose.

- cyanide ion combines with cytochrome C -> impairment of aerobic metabolism -> metabolic lactic acidosis

signs:

- tachycardia
- dysrhythmias
- hyperventilation
- sweating

treatment:

- stop Na+ nitroprusside infusion
- supportive measures
- sodium thiosulphate
- dicobalt edentate
- sodium nitrite

Glyceryl Trinitrate

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 -> No through 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

(i) To describe the pharmcology of the ACE inhibitors & angiotensin receptor antagonists with reference to the management of hypertension.

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

Captopril

Chemical - a mercapto alkanoyl derivative

Uses

(1) essential & renovascular HT
(2) CHF
(3) diabetic nephropathy
(4) IHD

Presentation

- tablet: 12.5 to 50mg

Route - PO

Doses

- PO: 12.5 to 50mg Q 6hrly
- introduce cautiously -> profound hypotension

PK

Absorption - bioavailability = 75%
Distribution - 30% protein bound, Vd = 0.8L/kg
Metabolism - disulphide dimer & cysteine disulphide

Elimination

- 95% excreted in urine (50% unchanged)
- Cl = 12mL/kg/min
- t1/2 = 2hrs

PD

Main action - anti-hypertensive

Mechanism

- inhibition of ACE
- 30,000 higher affinity than AGI

- prevents the formation of AGII
- also modulates sympathetic tone of the kallikren-prostaglandin system

CVS

- SVR decreases 30%
- Q increases by 20%
- HR may increase or decrease

RESP

- persistent dry cough
- occassional bronchospasm

GU

- decrease in renal vascular resistance
- natriuresis

Metabolic

- renin activity increases
- decrease in ALD -> hyperkalaemia
- Cr & urea may increase in patients

Other adverse effects

- loss of taste
- cough
- rashes
- agranulocytosis
- aphthous ulceration
- cholestatic jaundice

Interactions

- anaesthetic agents -> additive hypotension
- dehydration + NSAIDS -> ARF

Angiotensin receptor antagonists

Candesartan

Chemical - candesartan cilexetil

Uses - HT

Presentation - tablets: 4, 8, 16mg

Route - PO

Doses - 8 -> 16mg od

Onset: 2hrs

PK

Absorption - 40% bioavailability
Distribution - 99% protein bound, 0.1L/kg
Metabolism - minor hepatic
Elimination - unchanged in urine & bile, t1/2 = 9hrs, Cl = 0.4mL/min/kg

PD

Main action - anti-hypertensive

Mechanism of action

- prodrug -> ester hydrolysis to candesartan
- AG II receptor antagonist (binds tightly & has slow dissociation) -> decreased in plasma ALD levels + decrease in SVR -> decreases BP

CVS

- decrease in BP
- no change in HR or Q

RESP

- no cough
- URTI

CNS

- headache
- backpain
- dizziness

GI - nausea

Metabolic - hyperdkalaemia

(j) To outline the pharmacology of hydrallazine & potassium channel activators (nicorandil & minoxidil)

Hyrdrallazine

Chemical - a pthalazine derivative

Uses

(1) HT (acute or chronic)
(2) PET
(3) CHF

Presentation

- tablets: 25-50mg of hydrallazine HCl
- injection: 20mg powder -> reconstitiuted in H2O

Route - IV, PO

Dose

- PO: 50-200mg/day in divided doses
- IV: 20mg slowly

Onset: 20min
Duration: 2-6hrs

PK

Absorption - bioavailability = 20%

Distribution

-90% protein bound
- Vd 4L/kg
- crosses placenta

Metabolism

- acetylation & oxidation -> conjugation

Elimination

- 80% urine
- 20% faeces
- Cl = 1.4L/kg/hr
- t1/2 = 2hrs

PD

Main action - peripheral vasodilator

Mechanism

- appears to act directly on vascular smooth muscle
- inhibits uptake or release of Ca2+ -> dissociation of electro-mechanical contraction.

CVS

- arteriolar vasodilation -> decreased SVR
- increase in Q

CNS

- increases CBF

GU

- RBF increases
- Na+ retention
- decreased u/o

Metabolic

- plasma renin increases

Other adverse effects

- headache
- flushing
- nausea
- vomiting
- exacerbate IHD
- peripheral neuropathies (rare)
- blood dyscrasias (rare)

Interactions

- volatiles -> hypotension additive

K+ channel activators

Nicorandil

- used to treat & prevent angina
- causes arterial & venous vasodilation

- onset: 30-60min
- dosage: 10-30mg bd
- side-effects: headache, vomiting, dizziness, hypotension

Minoxidil

- opens K+ channels in smooth muscle membranes -> stabilises the membrane at its RMP

- dilates arterioles not veins

- side-effects: reflex sympathetic stimulation, Na+ & fluid retension, angina, oedema, headache, sweating, tachycardia, hirsutism, pericardial tamponade

- 90% absorbed from GI tract
- hepatically metabolised -> glucuronide
- t1/2 = 4hr