B13 - Anti-arrhytmic Drugs

(a) To classify antiarrhythmic agents by their electro-physiological activity and mechanisms of action.

See Notes

Class 1 - inhibit fast Na+ channels

- inhibit fast voltage sensitive sodium channels during depolarisation (phase 0) of cardiac action potential -> decreased depolarization & conduction velocity.

-> membrane stabilisers

1a - Prolongs AP duration

- decrease rate of phase 0 depolarisation -> reducing the excitability of the non-nodal regions in the heart which are important for **propagation** of the action potential.
- lengthen duration of action potential
- ie. quinidine, procainamdie

1b - Shortens AP duration

- decrease rate of spontaneous phase 4 outside the atria -> **decreases automaticity**
- ie. lignocaine, phenytoin

1c - No change in AP duration

- potent Na+ channel blockers -> **decrease in rate** of phase 0 depolarisation and **speed of conduction** of cardiac impulses.
- little effect on the duration of cardiac action potential & effective refractory period in ventricular myocardial cells
- shortens the duration of the action potential in Purkinje fibres.
- ie. flecanide, encainide

Class II - decrease rate of depolarisation (beta blockers)

- beta-adrenoceptor antagonists
- increase effective refractory period of AV node & decreased automaticity, decreased QT duration

-> decrease HR & O2 consumption

- ie. metoprolol, esmolol, propanolol

Class III - inhibit K+ ion channels

- **prolong the refractory period**
- block K+ channel -> prolong cardiac depolarisation, action potential duration & effective refractory period.

-> decrease the time in which the cardiac muscle cells are excitable.

- ie. amiodarone, sotalol, bretylium
- amiodarone has some class I (Na channel), II (beta-blocker), III (K+ channel) & IV effects (Ca2+ channel)

Class IV - inhibit slow Ca2+ channels

- inhibit inward slow calicum ion currents that may contribute to development of VT
- block L type Ca2+ channels -> impair SA node pacemaker activity.
- decrease duration of action potential but no effect on automaticity
- ie. verapamil, diltiazem, nifedipine

(b) To describe the pharmacology of sodium channel blocking agents with particular reference to lignocaine & flecanide.

Sodium channel blockers

- inhibit fast sodium channels during depolarisation (phase 0) of the cardiac action potential with resultant decreases in depolarisation rate & conduction velocity.
- drug combine with Na channel in the open or inactivated state -> block rapidly reversed in diastole because drug affinity is so low when channel recovers to RMP of -90mV
- when cardiac tissue damaged -> more cells are in the open or inactivated state -> relative increase in the binding of Na+ -> decreases Na conductance -> decreased action potential rate and velocity.

Lignocaine

Uses

1. LA
2. Ventricular dsyrhythmias

Chemical - tertiary amine with is an amide derivative of diethylaminoacetic acid

Structure - see diagram

Presentation

- clear, colourless solution
- 0.5, 1, 1.5, 2% solution for injection of lignocaine hydrocholride (with or without adrenaline)

Physiochemical

- pKa 7.7
- heptane:buffer partition coefficient 3

Route - IV

Dose

Bolus: 1mg/kg over 2 min
Infusion: 4mg/min for 1 hours -> 2mg/min for 1 hour -> 1mg/min

PK

Absorption - IV

Distribution

- 70% protein bound
- Vd 1L/kg

Metabolism

- high hepatic extraction ration
- oxidative dealkylation to monoehyl-glycinxylidide -> hydrolysis to xylidide

Elimination

- 10% excreted in urine unchanged
- half life = 2hrs
- clearance 10mL/kg/min
- clearance reduced in the prescence of liver and cardiac failure

PD

Mode of action - reversible neural blockade & class Ib antiarrhytmic action

Mechanism of action

- binds selectively to refractory Na+ channels -> perferentially when cells are depolarised (ie in ischaemia)

CVS

- direct myocardial depression
- hypotension
- bradycardia
- prolonged PR interval
- widen QRS

RESP

- bronchodialtion @ subtoxic levels
- respiratory depression @ toxic dose ranges

CNS

- excitation -> lightheadness, dizziness, visual & auditory disturbances
- inhibition -> toxic plasma concentrations (10mcg/mL) -> drowsiness, disorientation & convulsions

GI - depression of contraction in intact bowel

Metabolic effects - may have some anticholinergic & antihistaminergic activity

Flecanide

Uses

1. supression of ventricular irritable foci - VT, PVC
2. treatment of re-entry dysrhythmia (wPW)
3. chronic pain syndromes

Chemical - amide type LA

Presentation

- PO - 50 & 100mg tablets
- IV 10mg/mL

Dose

- PO - 100-200mg Q12hrly
- IV - bolus - 2mg/kg over 10min -> infusion of 1.5mg/kg for 60min -> 0.25mg/kg/hr

PK

Absorption - bioavailabilty of 90%

Distribution

- 60% protein bound
- Vd 10Lkg

Metabolism

- hepatic via meta-O-dealkylation

Elimination

- 30% unchanged in urine
- clearance 10mL/min/kg
- T1\2 10hrs (IV)
- use reduced dose in renal or hepatic failure

PD

Main action - class Ic antiarrhythmic

Mode of action

- reduces maximum rate of depolarisation in heart muscle -> slows conduction esp in Purkinje system
- suppresses accessory pathways
- suppresses ventricular ectopics
- depresses responsiveness and conduction velocity with no effect on the duration of action potential

CVS

- not effect on BP or HR
- has negative iontropic potential

CNS

- visual disturbances
- dizziness
- headaches
- paraesthesiae

GI

- liver damage can occur
- nausea

(c) To describe the pharmacology of betablockers with reference to their antiarrhythmic properties.

Betablockers

- 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

Esmolol

Chemical - an aryloxypropanolamine

Uses

(1) acute supraventricular dysrhythmia (AF)
(2) peri-operative hypertension
(3) MI

Presentation

- clear solution for injection
- 10, 250mg/mL of esmolol hydrochloride

Route - IV

Dose

Infusion - 50-150micrograms/kg/min according to response.

Peak effect: 5-10min
Duration of effect: 20min

PK

Distribution

- 50% protein bound
- Vd 3.5L/kg

Metabolism

- hydrolysis by esterases located in RBC's -> methanol & primary acid metabolite

Elimination

- 80% primary acid metabolite
- 1% unchanged
- Cl 280mL/min/kg
- t1/2 9 min
- use with caution in patients with renal disease

PD

Main action - negative inotropism & chronotropism

Mechanism of action

- competitive blockade of beta-adrenoreceptors
- selectively permeable for B1 receptors

CVS

- fall in BP
- fall in HR
- Q falls by 20%
- slow AV conduction

RESP

- little effect of AWR
- toxic doses -> bronchospasm

GI

- toxicity -> N & V, alteration in taste

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

Propranolol

Chemical - propranolol hydrocholoride (aromatic amine)

Uses

(1) HT
(2) angina
(3) a variety of cardiac tachydysrhythmias
(4) essential tremor
(5) adjunctive treatment of anxiety
(6) thyrotoxicosis
(7) hypertrophic obstructive cardiomyopathy
(8) phaeochromocytoma (prophylaxis)
(9) post MI
(10) migraine

Preparation

- tablets: 10 to 160mg

- solution: 1mg/mL

Route - PO or IV

Doses

- PO: 30 to 320mg/day in divided doses
- IV: 1 to 10mg/day

PK

Absorption

- 30% bioavailability -> extensive first-pass metabolism

Distribution

- 95% protein bound
- Vd 3.5L/kg

Metabolism

- extensive hepatic metabolism -> oxidative deamination & dealkylation -> glucuronidation
- reduce dose in hepatic failure

Elimination

- <1% unchanged
- Cl 1L/min
- t1/2 3

PD

Main action - negative inotropism & chronotropism

Mechanism of action

- competitive antagonism of beta 1 & 2 adrenoceptors
- membrane stabiliser in high doses through inhibition of Na+ channel.

CVS

- decrease HR
- increase in MAP
- decrease Q
- decrease in myocardial O2 consumption

RESP

- increase in AWR -> decrease in FEV1
- decreases response to hypercapnia
- bronchospasm

CNS

- crosses BBB
- decreases tremor
- decreased intraocular pressure
- sleep disturbances & nightmares

GU

- decreases uterine tone

Metabolic

- decreases plasma renin activity -> supresses ALD release
- decrease in plasma free fatty acids
- hypoglycaemia from blocking of gluconeogenesis
- increases total body Na+ concentration -> ECF

Other adverse effects

- precipate heart failure
- precipitate heart block
- exacerbate PVD
- impair exercise tolerance

(d) To describe the pharmacology of potassium channel blockers with particular reference to amiodarone, sotalol & ibutilide.

Calcium channel blockers

-> competitive blockade of slow Ca2+ channel
-> decreased influx of Ca2+ ions into vascular smooth muscle & myocardial cells
-> electrochemical uncoupling of contraction & relaxation
-> coronary & peripheral vasodilation

- prolong the refactory period - suppress reentrant rhythms
- greatly increase the action potential duration

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

- prolongs cardiac action potential & delaying refractory period

(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

Sotalol

Uses

1. SVT
2. VF
3. AF

Presentation

Route - PO

Dose

- PO: 240-320mg bd

PK

Distribution

- doesn't bind to plasma proteins
- dosen't cross BBB

Metabolism

- not metabolised

Elimination

- renal

PD

Main action

- low doses = non-selective beta receptor antagonist
- high doses = prolongs action potential

CVS

- prolongs QT interval
- torsades de pointes
- decreased myocardial contractility
- bradycardia
- delayed conductin of cardiac impulses through AV node

RESP

- dysnpoea
- not recommended in asthma

CNS

- fatigue
- vertigo

GI

- nausea

Ibutilide

- effective for conversion of recent onset AF
- hepatic metabolism
- VT with or without prolongation of QT

(e) To describe the pharmacology of Ca2+ antagonists with reference to their antiarrhythmic properties.

- 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

(f) To decribe the pharmacology of digoxin with reference to its anti-arrhythmic properties.

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

(g) To describe the pharmacology of adenosine with reference to its antiarrhythmic properties.

Chemical - a naturally occurring purine nucleoside

Uses - diagnosis & treatment of paroxysmal supraventricular tachycardia.

Presentation

- clear, colourless
- 3mg/mL
- in saline

Route - IV

Dose

- rapid IV bolus followed by saline flush
- 3mg -> 6mg -> 12mg (adult)

- 0.04 to 0.25mg/kg (children)

Onset - 10 seconds
Duration - 10 seconds

PK

Absorption - inactive when administered orally

Metabolism

- absorped into RBCs & vascular endothelium -> phosphorylated to AMP or deaminated to inosine & hypoxanthine

Elimination

- t1/2 = 10sec

PD

Main action

- depression of SA & AV nodal activity
- antagonises cAMP-mediated catecholamine stimulation of ventricular muscle

-> negative chronotropy & dromotropy

Mechanism of action

- direct agonist at specific cell membrane receptors (A1 & A2)
- A1 = coupled to K+ channels by a guanine nucleotide-binding protein in supraventricular tissue.

CVS

- depression of SA & AV nodal activity -> termination of paroxysmal supraventricular tachycardia.
- atrial dysrhythmias are revealed by AV nodal block leading to transient slowing of ventricular response.
- continuous high dose infusion -> dose-dependent reflex tachycardia & increased Q
- coronary vasodilation via A2 receptors
- pulmonary vessel vasodilator

RESP

- increased depth of respiration
- fall in PaCO2
- bronchospasm

CNS

- increase CBF
- can induce neuropathic pain, hyperalgesia & ischaemic pain

GU

- renal & hepatic arterial vasoconstriction @ hypotensive doses

Metabolic

- inhibits lipolysis & stimulation of glycolysis

Other adverse effects

- flushing
- SOB
- chest discomfort

Drug interactions

- isoflurane -> decreased MAC & post-op analgesic requirements.

(h) To describe the pharmacology of magnesium with reference to its anti-arrhythmic properties.

Chemical - Magnesium Sulphate (an inorganic sulphate)

Uses

(1) pre-eclampsia & eclampsia
(2) hypomagnesaemia (in malabsorption & critical illness)
(3) premature labour
(4) AMI
(5) torsades de pointes & VF
(6) barium poisoning
(7) asthma
(8) cerebral oedema
(9) spasms in tetanus
(10) autonomic hyperreflexia secondary to chronic spinal cord injury
(11) in cardioplegic solutions

Presentation

- clear, colourless
- 10 mmol in 10mL

Route - IV or IM

Doses

- see hospital protocol

PK

Absorption - 50% absorbed
Distribution - 30% protein bound

Metabolism -

Elimination - 50% in urine

PD

Main action - essential cofactor in >300 enzyme systems & essential for the production of ATP, DNA, RNA & protein function.

Mechanism of action

- ?
- pre-synaptic inhibition of Ach at NMJ

CVS

- vasodilation & hypotension
- slows SA node impulse & prolongs conduction time, PR interval & AV nodal refractory period.

RESP

- bronchodilation
- decreases hypoxic pulmonary vasoconstriction

CNS

- CNS depressant
- anti-convulsant
- high concentrations can inhibit catecholamine release from nerve terminals & adrenal medulla

GI

- osmotic laxative when adminstered orally

GU

- diuretic
- renal vasodilator effect
- decreases uterine tone & contractility
- crosses the placenta -> fetal hypotonia & neonatal depression.

Metabolic

- prolongs the clotting time of whole blood
- inhibits platelet aggregation via decreasing thromboxane synthesis

Toxicity

- monitor for loss of deep tendon reflexes
- somnolence, areflexia, AV and intraventricular conduction delays
- muscular weakness
- cardiac arrest

-> treatment is IV calcium

Drug interactions

- other CNS depressant -> enhances activity
- neuromuscular blockers -> increased effect
- sux -> premed with Mg2+ -> decrease muscle pain & hyperkalaemia

(i) To describe the adverse effects of the anti-arrhythmic agents with particular reference to the potential pro-arrhythmic properties.

See above for details.