B11 - Adrenoceptor Blocking Agents

(a) To explain mechanisms & physiological consequences of alpha 1, alpha 2, beta 1 & beta 2 receptor blockade.

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. yohimbine
-> 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 -> ....?

(b) To classify alpha & beta receptor blocking agents according to their PK & PD properties.

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 (t1\2 = 10min)
- tolazoline
- phenoxybenzamine (t1\2 = long)

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

(c) To describe the pharmacology of alpha blocking agents & apply this to their clinical use.

Alpha 1 antagonists

Prazocin

Chemical - quinazoline derivative

Uses

(1) HT
(2) Raynaud's
(3) CHF
(4) AR & MR
(5) Phaeochromocytoma
(6) Bladder neck obstruction

Presentation

- tablets of prazocin HCl

Route - PO

Dose

- 1mg Q8-12hrs -> 20mg daily

PK

Absorption - bioavailability = 50%
Distribution - binding 90%, Vd = 0.7L/kg
Metabolism - dealkylation in liver
Elimination - bile & faeces, Cl = 4mL/min/kg, t1/2 = 3hrs

PD

Main action -> vasodilation of smooth muscle

Mechanism

- competitive inhibtion of alpha 1 adrenoreceptor which anatonises 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+

CVS

- dilates coronary arteries, arteries & veins -> decrease BP
- negative chronotropic effects on SA node

RESP

- bronchodilation

GU

- relaxation of bladder & sphincter

Toxicity

- postural hypotension
- drowiness
- fatigue

- nausea
- urinary urgency

Alpha 2 antagonist

Yohibine

Uses

(1) impotence
(2) idiopathetic orthostatic hypotension

PK

Distribution

- crosses BBB

PD

Main action -> dilation of both arterioles & veins

Mechanism

- selective with reversible binding at alpha 2 receptors -> ? enhanced release of norad from nerve endings

- 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

CVS

- tachycardia
- hypertension

CNS

- paraesthesia
- dissociative states

Other adverse effects

- increased sk muscle activity
- tremor

- rhinorrhoea

(d) To describe the pharmacology of beta blockers with particular reference to:

- propanolol
- atenolol
- metoprolol
- esmolol
- carvedilol
- sotatol
- labetalol

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

Atenolol

Chemical - phenoxyproanolamine

Uses

(1) HT
(2) Angina
(3) Tachydysrhythmias
(4) Acute MI
(5) Prevention of MI

Presentation

- tablets: 25, 50, 100mg
- syrup: 0.5%
- injection: clear, colourless solution, 0.5mg/mL

Route - PO, IV

Dose

- PO: 50-100mg
- IV: 2.5 - 10mg or 1mg/min until desired effect

PK

Absorption - bioavailability = 50%

Distribution - 3% protein-bound in plasma, Vd = 0.7 L/kg

Metabolism - <10% metabolised in liver

Elimination

- unchanged in the urine
- Cl = 77mL/min/kg
- t1/2 = 9hrs

PD

Main actions

- -ve iontropic
- -ve chronotropic
- anti-HT
- anti-arrhythmic

Mechanism of action - reversible competitive blockade of cardiac beta 1 & beta 2 receptors

CVS

- SA node automaticity & AV conduction decreased
- increased in refractory period in atrial & AV node
- decreased myocardial O2 consumption
- regression of LVH

RESP

- little c/o cardioselectivity

CNS

- sleep distrubance
- vivid dreams

Metabolic

- increased triglyceride levels
- decreased HDL

Toxicity

- excacerbation of PVD
- bronchospasm
- hypoglycaemia
- depression
- impotence
- altered bowel habit

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

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

Carvedilol

Chemical

Uses

(1) Heart failure
(2) Pre-cardiac transplantation

Presentation - tablets

Route - PO

Dose

- PO: 3.125 to 50mg BD

PK

Absorption - 25% bioavailability

Distribution

- Vd 1.5 L/kg
- 95% protein bound

Metabolism

- hepatic

Elimination

- Cl = 9mL/min/kg
- t1/2 = 2hrs
- urinary excretion < 2% unchanged

PD

Main action - anti-heart failure medication

Mechanism

- non-selective beta-adrenergic blockade & alpha 1 blockade

CVS

- vasodilator & anti-oxidant properties
- decreased myocardial O2 consumption & demand
- less stress on ischaemic myocardium
- attenuation of effects of endogenous catecholamines
- redistribution of coronary blood flow to ischaemic areas
- increased coronary blood flow owing to decrease shear forces
- plaque stabilisation

RESP
CNS
GI
GU
Metabolic
Other adverse effects

Toxicity

Drug interactions

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

Labetalol

Chemical - synthetic salicylamide derivative

Uses

(1) HT
(2) controlled hypotension during anaesthesia
(3) control reflex cardiovascular response to intubation
(4) AMI

Presentation

- tablets: 50 to 400mg
- injection: 5mg/mL

Route - PO, IV

Dose

- PO: 100 to 800mg Q12hrly
- IV: injected over 2min until effect achieved (max 200mg)

Onset: 5-30min
Duration: 60min

PK

Absorption - bioavailability = 70% (but variable)

Distribution

- 50% protein-bound
- Vd = 10 L/kg

Metabolism

- hepatic
- inactive metabolites

Elimination

- urinary
- 5% unchanged
- Cl = 20mL/min/kg
- t1/2 = 6hrs

PD

Main action - anti-hypertensive

Mechanism of action

- selective alpha 1, non-selective beta 1 & beta 2 antagonism
- ratio of alpha:beta effects = 1:3 (PO), 1:7 (IV)

CVS

- 20% decrease in systolic & diastolic BP
- HR & Q decrease by 10%
- decrease SVR 15%
- limb blood flow increased
- coronary vascular resistance decreased

RESP - no effects

CNS - no effects of CBF

GU

- decrease renal vascular resistance -> increase in renal blood flow by 20%

Metabolic

- increase in adrenalin, noradrenaline & prolactin release acutely
- decrease in plasma renin & AGII

Other adverse effects

- inhibition of platelet aggregation

Toxicity

- asthma
- Raynauds
- heart failure
- cramps
- nightmares

Drug interactions

- volatiles -> cardiodepressant activity

(e) To describe the clinical uses of beta receptor blocking agents and their potential adverse effects

Uses

- HT
- controlled hypotension in anaesthesia
- AMI (acute & prevention)
- heart failure treatment
- blunt cardiovascular response to intubation
- controle of supraventricular dysrrhythmias
- mirgraine
- thyrotoxicosis

Side effects

CVS

- -ve inotropy
- -ve chronotropy
- AV conduction slowed
- rate of spontaneous phase 4 depolarisation slowed
- slowing of heart rate -> decreased exercise capacity
- prevent baroreceptor mediated HR increase
- aggrevation of PVD (beta 2 effect)

RESP

- bronchospasm
- depression of ventilation

CNS

- fatigue
- tiredness
- depression

GI

- nausea
- vomiting
- diarrhoea

Metabolic

- hypoglycaemia

Other adverse effects

- fever

- rash
- myopathy
- alopecia
- thrombocytopenia