B15 - Neuropharmacology

(a) To describe the physiology & pharmacology of neurotransmitters & their receptors with particular reference to GABA, excitatory amino acids, Ach, noradrenaline, dopamine & serotonin.

GABA

Neurotransmitter

- gamma aminobutyric acid
- major inhibitory mediator in brain
- transmitter @ 20% of synapses in the brain
- formed by decarboxylation of glutamate under action of glutamate decarboxylase
- metabolised by transamination to succinic semialdehyde under action of GABA transaminase -> succinate in the citric acid cycle

Receptor

- 3 types (1) GABA A, (2) GABA B, (3) GABA C.
- GABA A - CNS
- GABA B - metabotropic (hyperpolarise membranes)
- GABA C - retina

- GABA A & C = pentamers & ion channels
- GABA B = coupled to G proteins -> increase K+ conductance, inhibit adenyl cyclase, inhibit Ca2+ influx- > hyperpolarisation

GABA A

- increases Cl- conductance
- potentiated by benzodiazepines, alcohol, progesterone, deoxycorticosterone & barbiturates

Excitatory amino acids

Glutamate

Physiology

- act directly on cell membranes by iontophoresis (introduction of ions into cell by means of an electric current).
- main excitatory neurotransmitter in the brain.
- formed by reductive amination of the Krebs cycle intermdiate oxaloacetate.

Receptors

- two types: metabotropic & ionotropic

Metabotrophic

- serpentine G protein coupled -> increased in intracellular IP3 & DAG levels or decrease in cAMP ->
- involved in production of synaptic plasticity

Ionotropic

- ligand-gated ion channels that resemble the nicotinic AchR
- 3 types (1) kainate, (2) AMPA, (3) NMDA receptors.
- AMPA = 4 subunits, ion channel permitting Na+ influx, & K+ efflux.
- kainate = 5 subunits, ion channel permitting Na+ influx & K+ efflux
- NMDA = 6 subunits, permitts passage of large amounts of Ca2+

Aspartate

- transmitter in pyramidal cells & spiny stellate cells in the visual cortex.

Ach

- primary transmitter at:

(1) NMJ
(2) pregangionic nerve endings
(3) postganglionic parasympathetic endings
(4) postganglionic sympathetic sweat gland & muscle vasodilator endings
(5) many parts of the CNS

- has either muscarinic or nicotinic actions depending on the AchR involved.
- acetyl ester of the base choline.
- synthetised from the acetyl co enzyme A and choline in nerve ending cytoplasm under influence of choline acetyltransferase.
- metabolised by AchE on the postsynaptic membrane.

Ach Receptors

- pentagonal array of 5 subunits
- two alpha, one beta, gamma & e
- ten times as much as needed of Ach released
- Ach binds to the two alpha receptor sites on a closed channel -> rapid conformational change that opens channel -> influx of Na+ & K+
- opening of 10 4 or 10 5 -> depolarisation of endplate (-90 to -50mV = threshold)

- Ach rapidly hydrolysed to choline and acetate by Achesterase from the basal lamina of the postjunctional membrane.
- choline is either taken up for reproduction as Ach or degraded by pseudocholinesterase.

Dopamine

(1) sympathetic ganglia
(2) CNS - hypothalamus, limbic system & cortex
(3) adrenal medulla

- catecholamine & neurotransmitter
- can be used as an ionotrope & pressor in cardiogenic & septic shock.
- a precursor to adrenaline & noradrenaline
- there is active reuptake of dopamine via an Na+ & Cl- dependent transporter
- metabolised to inactive compounds by MAO (monoamine oxidase) & COMT (catechol-O-methyl-transferase)

Receptors

- 5 different receptors have been cloned.
- all are G protein coupled with 7 transmembrane domains.
- D1 & D5 -> increase cAMP
- D2, D3 & D4 -> all decrease cAMP

Norad

(1) postganglionic sympathetic endings
(2) cerebral cortex
(3) hypothalamus
(4) brainstem
(5) cerebellum
(6) spinal cord

- catecholamine
- immediate precursor of adrenaline
- forms 20% of catecholamines released from the adrenal medulla
- predominately stimulates alpha adrenergic receptors, although does have some beta-effects.
- used as an iontrope & pressor
- formed by hydroxylation & decarboxylation of tyrosine.

Receptors

- alpha (mainly) & beta receptors
- these are typical G protein receptors

Serotonin

(1) hypothalams

(2) limbic system
(3) cerebellum
(4) spinal cord
(5) retina

- 5-Hydroxtryptamine (5-HT)
- formed in the body by hydroxylation & decarboxylation of the essenstial amino acid tryptphan.
- inactivated by MAO to form 5-hydroxyindoleacetic acid.

- also found in GI tract, smooth muscle, platelets, mast cells & peripheral & central nervous systems.
- acts on 7 different classes of receptor -> all via G protein mechanisms except the 5-HT3 receptor which is a fast ion Na+/K+ channel.

Inflammatory mechanisms

- increases vascular permeability
- increased platelet aggregation
- bronchoconstriction
- vasodilation & constriction at different vascular beds

GI function

- increases motility
- H2O & electrolyte secretion

CNS

- inhibitor neurotransmitter in the brainstem, descending spinal pathways, hypothalamus, cortical, limbic & extrapyramdial system
- modulation of pain sensation

Receptors

- many types
- most are G protein coupled

(b) To describe the pharmacology of anxiolytic/hypnotic agents with particular reference to benzodiazepines & barbiturates.

Benzodiazepines

- potentiate action of GABA on CNS GABAa receptors once binding to specific point on receptor.
- GABAa is a Cl- ion channel

- activation -> increase in Cl- conduction into the post-synaptic neuron -> hyperpolarisation -> decreased in action potential conduction & excitation.

Barbiturates

- ?
- mimics the action of the inhibitory neurotranmitter GABA
- decreases the rate of dissociation of GABA from GABAa receptor -> potentiates its effect -> prolonged opening of the Cl- channel -> decreased post-synaptic activity & presynaptic neurotransmitter release.

(c) To describe the comparative pharmacology of benzodiazepines with particular reference to

- midazolam
- diazepam
- lorazepam
- flumazenil

Midazolam

Chemical - imidazobenzodiazepine

Uses:

(1) induction of anaesthesia
(2) sedation
(3) premedication
(4) treatment of chronic pain

Structure - see diagram

Presentation

- clear, colourless solution
- 1, 2, 5mg/mL
- glass vial

Physiochemical

Routes - IV, PR, Intrathecal, Epidural, PO

Dose

IM -0.08mg/kg (premed)
IV - 0.1mg/kg (sedation) - titrated to response, end point = slurred speech

Intrathecal - 0.5 to 2mg
Epidural - 0.1 to 0.2mg/kg

PK

Absorption

- PO bioavailability = 44%
- IM bioavailability = 80 to 100%

Distribution

- 96% protein bound
- Vd = 1 L/kg (may increase to 3 in critically ill)

Metabolism

- hepatic
- to hydroxylated derivatives -> conjugated to glucuronide.
- metabolites are pharmacologically active

Excretion

- occurs in urine
- renal impairment has little effect
- clearance 8mL/min/kg
- elmination t1/2 = 2.5 hours (may be increased to 5.4 hrs in critically unwell).

PD

Main actions

Onset = 2-4min

(1) hypnosis
(2) sedation
(3) anterograde amnesia
(4) anxiolysis
(5) anticonvulsant
(6) muscle relaxation

- short duration due to high lipophilicity, high metabolic clearance & rapid elimination.
- decreases MAC by 15%
- can be reversed with physostigmine, glycopyrronium & flumazenil.

Mode of action

- act via benodiazepine receptor in CNS
- linked and facilitate action of the GABA receptor.
- chloride channel activation -> hyperpolarises membrane.
- also a kappa-opioid agoinst -> benzodiazepine induced spinal analgesia.

CVS

- decreases systolic BP by 5%
- decreased diastolic BP by 10%
- decreases SVR by 25%
- HR increases by 20%
- with fentanyl obtund pressor response to intubation.

RESP

- decreases TV
- increases RR
- apnoea occurs in 10 - 80% when used for induction.
- impairs response to increased CO2

CNS

- cerebral O2 consumption & CBF decreased.

GI

- decreased hepatic blood flow
- decreased PONV as compared to thiopentone + fentanyl.

GU - decreases RBF

Metabolic

- decreases adrenergic response to stress
- doesn't effect cortisol or renin reponse
- inhibits phagocytosis and WCC activity.

Other adverse effects

- occasional discomfort on injection
- in children withdrawal phenonmenon can occur after prolonged infusion

Diazepam

Uses

(1) sedation during minor procedures
(2) co-induction/premed
(3) anxiolysis - short term treatment
(4) anticonvulsant - status epilepticus
(5) muscle spasm

Presentation

- tablets: 2, 5, 10mg
- syrup: 0.4mg/mL
- suppositories: 2, 4mg/mL
- injection: clear yellow solution & as a white oil-in-water emulsion (5mg/mL)

Route - PO, PR, IV, IM, PR

Dose

- PO: 2-60mg/day (adult)
- IV: 10-20mg -> titrated to clinical effect

PK

Absorption - bioavailability PO = 100%

Distribution - 99% protein bound, Vd 1 L/kg

Metabolism

- hepatic
- major metabolites =

(1) desmethyldiazepam
(2) oxazepam
(3) tempazepam

- they are all active

Elimination

- excreted in the urine as oxidised & glucuronide derivatives
- < 1% excreted unchanged
- Cl = 0.4mL/min/kg
- t1/2 = 30hrs

PD

Main actions

(1) hypnosis
(2) sedation
(3) anxiolysis
(4) anteriorgrade amnesia
(5) anticonvulsant
(6) muscular relaxation

Mode of action

- ?
- specific benzodiazepine receptor found at synapses throughout the CNS
- mainly cortex & mid brain
- receptors closely linked to the GABA receptor -> increase conductance of Cl- -> hyperpolarise the membrane

- also has kappa-opioid agonist activity in vitro (may explain benzodiazepine-induced spinal analgesia)

CVS

- transient decrease in BP & Q
- coronary arterial vasodilation -> coronary blood flow increased
- decrease in myocardial O2 consumption

RESP

- respiratory depression
- hypoxic & hypercapnic drive depressed

CNS

- anxiolysis
- decreased aggression
- sedation
- hypnosis
- anterograde amnesia
- anticonvulsant
- analgesia
- depresses spinal reflexes

GU

- upset

GU

- urinary retention

Other adverse effects

- irritant to veins
- rashes

Toxicity

- drowiness
- ataxia
- headache

Tolerance & dependence

Acute withdrawal

- insomnia
- anxiety
- confusion
- psychosis
- hallucinations

Lorazepam

Chemical - a hydroxybenzodiazepine

Uses

(1) short-term treatment for anxiety
(2) hypnotic
(3) premed
(4) treatment of status epilepticus

Preparation

- tablet: 1, 2.5mg
- injection: clear, colourless solution (4mg/mL)

Route - PO, IM, IV, SL

Dose

- PO, SL: 1-4mgday in divided doses
- IV, IM: 0.05mgkg

PK

Absorption - bioavailability of 90%

Distribution

- 90% protein bound
- Vd 1 L/kg
- extensively distributed -> long duration of action despite short t1/2

Metabolism

- conjugated in liver to glucuronide -> inactive water-soluble metabolite

Elimination

- urine
- Cl = 1mL/min/kg
- t1/2 = 20hrs
- uneffected by renal disease

PD

Main actions

(1) hypnosis
(2) sedation
(3) anxiolysis
(4) anterograde amnesia
(5) anticonvulsant
(6) muscular relaxation

Mechanism of action

- ?
- act via benzodiazepine receptors found at synapses
- closely associated with GABAa receptor
- facilitates the activation of GABAa -> increase in Cl- conductance -> hyperpolarisation of membrane

CVS - no direct cardiac effects

RESP - mild respiratory depression

CNS

- sedation
- anterograde amnesia
- anticonvulsant

GI - decreases pentagastrin-stimulated gastric acid secretion by 25%

Metabolic - fall in circulating cortisol & glucose levels

Other adverse effects

- IM injection is painful

Toxicty

- drowiness
- sedation
- confusion
- impaired coordination
- tolerance & dependence may occur with prolonged use of benzo's

Flumazenil

Chemical - imidazobenzodiazepine

Uses

(1) weaning & neurologica assessment of ventilated patients who have received benzo's in ICU
(2) wake up test during scoliosis surgery
(3) reverse oversedation
(4) facilitate gastric lavage in patients after benzodiazepine OD
(5) treatment in hepatic encephalopathy
(6) alcohol intoxification

Preparation

- clear, colourless solution
- 100micrograms/mL

Route - IV

Dose - 100micrograms increments

Onset: 45sec
Duration 60min

PK

Distribution

- 50% protein bound
- Vd 1 L/kg

Metabolism

- extensively metabolised in liver -> carboxylic acid & glucuronide.
- both inactive

Elmination

- 95% excreted in urine
- Cl = 1000mL/min
- t1/2 = 53min

PD

Main action - reversal of actions of benzodiazepines

Mechanism of action - competitive antagonism at central benzo receptors

CVS - no intrinisic effects
RESP - no intrinsic effects
CNS - mild anticonvulsant effects
GI - no intrinsic effects
GU - no intrinsic effects

Toxicity

- hypertension
- dysrhythmias
- dizziness
- N & V
- facial flushing
- anxiety
- headache

(d) To outline the pharmacology of the anti-depressant medications & their adverse effects. To describe the potential adverse drug interactions with these agents.

3 types

- Serotonin re-uptake inhibitors (ie. fluoxetine)
- Tricyclic anti-depressants (ie. amitriptyline)
- Monoamine oxidase inhibitors (ie. phenelzine)

SSRI's

- block the reuptake of serotonin
- fluoxetine, paroxitine, sertraline, fluvoxamine, citalpram

- lack anti-cholinergic side effects of TCA's:

- postural hypotension
- delayed cardiac conduction
- doesn't effect seizure threshold

- common side-effects:

- insomnia
- agitation
- headache
- nausea
- diarrhoes
- sexual dysfunction (delayed ejaculation, anorgasmia, decreased libido).

Fluoxetine

Chemical - a propylamine derivative

Uses

(1) depression
(2) bulimia
(3) OCD

Presentation

- tablet: 20 to 60mg
- suspension: 4mg/mL

Route - PO

Dose - once a day 20-60mg

PK

Absorption - bioavailability 70%
Distribution - 95% protein bound, Vd 3 L/kg
Metabolism - hepatic -> desmethyl-metabolite (active)
Elimination - 60% administered in urine, Cl 43L/hr, t1/2 = 3 days

PD

Main action - antidepressant

Mechanism of action - selective inhibition of neuronal uptake of 5-HT by presynaptic serotonin re-uptake pump.

CVS - no effects
RESP - no effects
CNS - see above

GI

- decreased appetite
- dose related nausea, abdo pain, diarrhoea

Metabolic

- decreased serum Na+ (inappropriate ADH secretion)
- elevates corticosterone concentration

Other adverse side effects

- PK is altered by hepatic but not renal dysfunction

Drug interactions

- co-administration of pentazocine -> severe CNS excitatory responses.
- potent inhibitor of certain CYP450 enzymes -> decrease in hepatic metabolism -> increase in concentration of drugs...

- TCA's
- cardiac antidysrhythmics
- beta-adrenergic antagonists

- MAOI's -> serotonin syndrome (anxiety, restlessness, chills, ataxia & insomnia)
- fluoxetine + lithium + carbamazepine -> fatal syndrome

TCA's

- surplanted as the first line anti-depressants because of unfavourable side-effects (anti-cholinergic, anti-adrenergic & anti-histaminergic)
- have a narrow theraputic index -> lethal in OD (inhibition of Na+ channels -> slowing of cardiac impulses -> arrhythmia)
- structure resembles that of a LA (hydrophobic portion linked to an amide via a linear moiety).
- tricyclic = three ringed structure

Mechanism

- block reuptake of 5-HT & norad @ presynaptic terminals -> increasing their availability.

Amitriptylline

Chemical - a dibenzocycloheptadiene derivative

Uses

(1) depression
(2) nocturnal enuresis
(3) adjunct to treatment of chronic pain syndromes:

- chronic tension headache
- post-herpetic neuralgia
- painful neuropathies
- chronic spinal syndromes

Presentation

- tablets: 10, 25, 50mg
- injection: clear, colourless 10mg/mL
- syrup: 2mg/mL

Route - PO, IV

Dose

- PO: 75-150mg/day -> decrease to 50-100mg maintenance
- IV: 10-20mg Q6hrly

- takes: 2-3wks to become effective

PK

Absorption - bioavailability 40%

Distribution

- 95% protein bound
- Vd 20 L/kg

Metabolism

- N-demethylation & hydroxylation -> conjugation to glucuronide & sulphate

Elimination

- urinary
- Cl = 12mL/min/kg
- t1/2 = 24hrs

PD

Main action

- anti-depressant
- sedative
- analgesic

Mechanism of action

- potentiation the action of biological amines within the CNS by preventing reuptake
- antagonise muscarinic, alpha 1 adrenergic & histamine receptors.

CVS

- postural hypotension
- sinus tachycardia
- dysrhythmias
- increased conduction time through the AV node
- QT & PR interval may be prolonged

RESP

- respiratory depression (in toxic doses)

CNS

- anti-depression
- sedation
- weakness
- fatigue
- blurred vision

- fine tremor in 10%

GI

- constipation
- dry mouth

GU

- urinary retension

Drug interactions

(1) sympathomimetics

- blood pressure response is unpredictable (exaggerated pressor response from increased circulating norad)
- start low, go slow

(2) inhaled anaesthetics

- increased incidence of dysrhythmias

(3) anti-cholinergics

- increased risk of post-op delirium & confusion
- use glycopyrrolate

(4) anti-hypertensives

- rebound hypertension after discontinuation of clonidine

(5) opioids

- in animals this interaction -> increase analgesic & ventilatory depressant effects.

Toxicity

- agitation -> seizures -> coma
- depression of ventilation
- hypotension
- hypothermia
- anticholinergic effects: mydriasis, flushed dry skin, urinary retension, tachycardia
- QRS >100ms

Treatment:

- may need phytostigmine for treatment of anti-cholinergic symptoms
- diazepam for seizures
- alkalization of plasma (pH>7.45) using NaHCO3
- lignocaine & phenytoin for cardiac dysrhythmias.
- ionotropes as needed

MAO inhibitors

- block the enzyme that metabolises biogenic amines -> increase availability in the brain.
- bad side effect profile
- patients must stick to a tyrosine-free diet as tyrosine + MAOI = hypertension (treat with Na-nitroprusside)

- MAO = flavin-containing enzyme found on outer mitochondrial membranes
- acts by oxidative deamination of dopamine, 5-HT, norad, adrenaline

- MAOI act by forming a stable, irreversible comples with MAO enzyme (especially in cerebral neuronal MAO) -> increases the amount of neurotransmitter available & also in the whole body.

Side effects:

CVS

- orthostatic hypotension

CNS

- sedation
- insomina (with some types)
- paraesthesias

GI

- hepatitis (rare)

GU

- impotence
- anorgasmia

Metabolic

- weight gain

Other adverse effects

- dietary restrictions:

- cheese
- liver
- fava beans
- avocados
- chianti wine

Drug interactions

- can produce: hypertension, CNS excitation, delirium, seizures, death.

(1) opioids

- pethidine ->

(1) agitation, headache, sk muscle rigidity, hyperpyrexia
(2) hypotension, respiratory depression, coma

- fentanyl, sufentanil, alfentanil -> same effect but incidence much lower.

(2) sympathomimetics & MAOI's

- exaggerated BP responses
- start low & go slow.

(3) anaesthetic agents

- growing appreciation that anaesthesia can be carried safely and soundly without having to stop medications.
- minimise sympathetic nervous system stimulation & hypotension
- don't add adrenaline to LA for regional techniques

(e) To outline the pharmacology of antipsychotic medication

5 categories

(1) Phenothiazines (chlorpromazine)
(2) Thioanthenes (chlorprothixene)
(3) Dibenzodiazepines (clozapine)
(4) Butyrophenones (haloperidol, droperidol)
(5) Benzisoxazole (resperidone)

PK

Absorption

- erratic absorption post PO administration

Distribution

- highly lipid soluble -> accumulate well in the brain.
- passage across placenta is possible

Metabolism

- oxidation in liver -> conjugation

Elimination

- urinary
- t1/2 = 10-20hrs

PD

Mechanism of action

- dopamine receptor blockade
- especially the D2 receptor in basal ganglia & limbic system

Extrapyramidal

- associated with use over 1 yr
- tardive dyskinesia
- actue dystonic reactions (2%) = muscular rigidity, cramping, respiratory distress
- tremor
- masked facies
- sk muscle rigidity
- restlessness

CVS

- decrease in BP
- miosis (alpha-blockade)
- prolonged QT interval -> VT

- chlorpromazine -> cardiac dysrhythmias
- risperidone -> exaggerated hypotension with spinal

CNS

- sedation
- decrease in seizure threshold

GI

- anti-emesis
- obstructive jaundice

Metabolic

- prolactin level increase -> galactorrhoea & gynaecomastia
- amenorrhoea
- decreased secretion of corticosteroids
- weight gain
- abnormalities in thermoregulation

Other adverse effects

- skeletal muscle relaxation

Neuroleptic malignant syndrome

- 1%
- increased with dehydration & intercurrent illness

Clinically

- hyperthermia
- generalized hypertonicity of sk muscles
- instability of autonomic nervous system
- hypertension
- tachycardia
- cardiac dysrhythmias
- fluctuating LOC

- mortality 20-30%

Treatment

- supportive
- dantrolene
- dopamine agonists (bromocriptine or amantadine)

- looks like MH

- difference = in NLMS NDNMBD work, in MH they don't.

(f) To outline the mechanisms of action & pharmacology of the anticonvulsant drugs.

- 1 to 2% of the population have epilepsy
- epilepsy = sudden onset, recurrent disturbances in sensory, motor, autonomic or psychic origin associated with abnormal discharges of the EEG.

- carbamazepine
- gabapentin
- lamotrigine
- phenobarital
- phenytoin
- Na valproate

Mechanism of Action

- ?
- decreasing neuronal excitability or enhancing inhibition of neuronal transmission.
- achieved through altering intrinsic membrane ion currents (Na+, K+, Ca2+) or by affecting of inhibitory neurotransmitters (GABA)

- action on both Na+ & Ca2+ ion channels = phenytoin, carbamazepine, lamotrigine

- GABA mediating neuronal inhibition = benzo's & phenoparital

PK

Absorption

- absorption from the GI tract occurs slowly

Distribution

- protein binding varies greatly (0% for gabapentin, 90% for phenytoin)
- prinicpally bound to albumin

Metabolism

- all hepatic
- many agents are enzyme inducers -> need increased doses of thio, propofol, midazolam, opioid & NDNMBD.

Elimination

- renal
- Cl = hours to days
- t1/2 = hours to days

PD

Main action - see above

Mechanism - see above

CVS

- carbamazepine: hypertension, cardiac dysrhythmias

CNS

- carbamazepine: sedation, vertigo, diplopia,
- gabapentin: somnolence, fatigue, ataxia, vertigo
- lamotrigine: headache, dizziness, diplopia, ataxia, tremor
- phenobarbital: sedation (adults), irritability & hyperactivity (children), depression, confusion, nystagmus, ataxia
- phenytoin: nystagmus, ataxia, diplopia, vertigo, peripheral neuropathy
- Na+ valproate: fine distal tremor

GI

- carbazepine: nausea & vomiting, diarrhoea, cholestatic jaundice
- lamotrigine: nausea & vomiting
- Na+ valproate: anorexia, nausea & vomiting, hepatotoxicity

GU

- carbamazepine: oliguria

Metabolic

- carbamazepine: increased secretion of ADH -> hyponatraemia, aplastic anaemia, thrombocytopenia
- phenytoin: hyperglycaemia -> glycosuria
- Na+ valproate: weight gain

Other adverse effects

- in pregnancy can cause increased of malformations.

- carbamazepine: skin rash

- phenobarbital: rash, megaloblastic anaemia, osteomalacia
- phenytoin: gingival hyperplasia, acne, hirsutism

(g) To outline the pharmacology of the antiparkinsonian drugs.

- PD = neurodegenerative disease -> deficiency of dopaminergic innervation of the basal ganglia from the substantia nigra.
- depletion of dopamine
- dopamine = major inhibitory neurotransmitter in extrapyramdial system.
- Ach = major excitatory one.
- goal of treatment is to enhance the inhibitory effects of dopamine & decrease the excitatory effects of Ach.
- decreased dopamine & increased Ach action -> progressive tremor, sk muscle rigidity, bradykinesia & disturbance in posture, depression.

Treatment options

(1) Levodopa
(2) Peripheral decarboxylase inhibitors
(3) Synthetic dopamine agonists
(4) Anticholinergic drugs
(5) Amantadine
(6) Selegiline

Levodopa

PK

Metabolism

- 95% converted into dopamine by liver (can't cross BBB)
- 30 metabolites

Elimination

- t1/2 = 2hrs
- metabolites excreted in kidneys

PD

Main action - increase in dopamine concentration in CNS

Mechanism of action

- crosses the BBB and is converted to dopamine by aromatic-L-amino-acid decarboxylase

CVS

- alpha & beta effects
- transient flushing of skin
- orthostatic hypotension
- cardiac dysrhythmias (sinus tach, atrial & ventricular ectopics, AF, VT)

RESP

- exaggerated respiratory movements -> irregurlar gasping

CNS

- facial tics
- grimacing
- rocking movements of arms, legs & trunk

- confusion
- visual hallucinations
- paranoia

Metabolic

- inhibit secretion of prolactin
- hypokalaemia

Other adverse effects

- urinary measurement of ketones -> false positive

Drug interactions

- antipsychotics can antagonise the effects of dopamine

- don't use droperidol -> severe muscular rigidity

- metaclopramide interfers with dopamine activity

- MAOI's may exaggerate the effects of levodopa (hypertension, hyperthermia)

- pyridoxine -> abolish the effect of levodopa by enhancing activity of pridoxine-dependent dopa decarboxylase -> increasing metabolism of levodopa.

Peripheral decarboxylase inhibitors

- levodopa is usually administered with one of these (carbidopa or beserzide)
- allows more levodopa to escape metabolism peripherally and enter the CNS

- combined preparations (levodopa & a peripheral decarboxylase inhibitor) = sinemet & mardopar

Synthetic dopamine agonists

- act directly on post-synaptic dopamine receptors
- ie. bromocriptine, pergolide
- side effects: hallucinations, hypotension, dykinesia.

Anticholinergic drugs

- ie. trihexyphenidyl, benztropine
- they blunt the effects of the excitatory neurotransmitter Ach
- help control tremor, decrease salivation
- bad side effect profile: memory disturbance, hallucinations, confusion, sedation, mydriasis, adynamic ileus, urinary retension.

Amantadine

- antiviral for prophylaxis against influenza A
- mechanism not known
- helps with muscular rigidity & bradykinesia

Selegiline

- highly selective & irreversible inhibitor of MAOI type B
- has an antiparkinsonian effect when used
- MAOI B = a cataboic pathway for dopamine in the CNS
- blocking enzyme action -> increases available dopamine

(h) To outline the pharmacology of drugs used to treat migraine.

Pathogenesis

- reduction in cerebral blood flow (aura) -> increase cerebral & extracranial blood flow -> headache
- attack associated with changes in 5-hydroxtryptamine (5-HT)

Hypotheses about how drugs work

(1) activation of of 5-HT1 receptors on presynaptic trigeminal nerve endings -> inhibit the release of vasodilating substances

(2) vasocontrictor actions of direct 5-HT agonists may prevent vasodialation and stretching of the pain endings

Prophylaxis

(1) Pizotifen - 5-HT antagonist

(2) Na valproate, verapamil, clonidine, propanolol, amitryptilline

Acute attacks

- aspirin
- paracetamol
- sumatriptan (5-HT1 agonist)
- ergotamine (5-HT agonist - constricts cranial arteries)
- breathing into a paper bag
- warm or cold packs to head may ease pain