B22 - Endocrine Pharmacology

(a) To describe the pharmacology of insulin preparations and their use.

Chemical

- polypeptide hormone
- human insulin: produced by recombinant DNA techniques
- bovine insulin: differs by 3 aa
- porcine insulin: differs by 1 aa

Uses

(1) DM I
(2) DM II
(3) diabetic emergencies
(4) perioperative control of BSL's
(5) with TPN
(6) provacation tests for GH

Presentations

- wide variety
- standard = 100u/mL
- may have zinc or protamine added to retard absorption

Route - IV, SC, IM

Dose

- titrated according to response
- dose increases by 20% with pig or cow insulin
- rapid acting: onset = 1hr, duration 6 = hrs
- slow acting: onset = 4hrs, duration = up to 36hrs

PK

Absorption - inactive when administered orally

Distribution

- little protein binding
- Vd = 0.08L/kg

Metabolism

- hepatic, muscle & kidney
- by glutathione insulin transhydrogenase

Elimination

- urinary
- Cl = 33.3m/min/kg
- t1\2 = 2min

PD

Main action - stimulation of carbohydrate metabolism, protein synthesis & lipogenesis.

Mechanism

- activates specific membrane bound receptors ->

-> increase in lipoprotein lipase
-> increases rate of transcriptional & translational events during protein synthesis
-> controls ion transport by activating Na+/K+ ATPase

Metabolic

Glucose metabolism

- increase rate of glucose diffusion into cells
- increase glucokinase activity -> phosphorylates glucose & traps it intracellularly
- increases rate of glycogen synthesis via glycogen synthase
- inhibits glycogenolysis by action on phosphorylase
- inhibits gluconeogenesis

Fat metabolism

- causes fat deposition in adipose tissue
- activates lipoprotein lipase -> splits TG's into FFA's so they can be stored in adipose tissue.
- glycerol is used in the storage of TG's

Protein metabolism

- causes active transport of aa's into cells
- increases mRNA translation & DNA transcriptrion
- inhibits the catabolism of proteins

Other effects

- increases K+ & Mg2+ transport into cells.

Toxicity

- hypoglycaemia
- localised allergic reaction
- insulin resistance from antibody formation

Drug interactions

- steroids, thyroxine, thiazides & sympathetomimetics -> antagonises action

(b) To outline the pharmacology of the oral hypoglycaemic agents.

Biguanides - decrease gluconeogenesis and increase peripheral glucose uptake (ie. metformin)

Sulphonylureas - increase production of insulin from the pancreas and possibly increase peripheral glucose uptake (ie. glicazide, glibenclamide)

Metformin

Chemical - a biguanide

Uses - DM II

Presentation - tablets: 500 to 800mg

Route - PO

Dose

- 1 to 3g in divided doses
- duration = 12hrs

PK

Absorption - bioavailability = 50%
Distribution - no protein bound
Metabolism - no metabolites
Elimination - unchanged in urine, t1/2 = 4hrs

PD

Main action - hypoglycaemic

Mechanism

- inhibit intestinal absorption of glucose
- enhance peripheral uptake of glucose
- decrease the rate of gluconeogenesis

GI

- reduces absorption of glucose, folate & B12

Metabolic

- increases the sensitivity to the peripheral action of insulin by increase the number of binding sites for insulin in RBCs
- it doesn't cause hypoglycaemia
- inhibits the metabolism of lactate (lactic acidosis rarely)

Glibenclamide

Chemical - a sulphonylurea

Uses - DM II

Presentation - tablets: 2.5 & 5mg

Route - PO

Dose - 2.5 to 15mg daily

Onset: 2hrs
Duration: 12hrs

PK

Absorption - bioavailability = 100%
Distribution - 97% protein bound, Vd = 0.15L/kg
Metabolism - liver by hydroylation
Elimination - urine:faeces (50:50), Cl = 80mL/min/kg, t1/2 = 2 hrs

PD

Main action - hypoglycaemic

Mechanism

- liberates insulin from pancreatic beta-cells

- binds to membrane and produces prolonged depolarisation -> decreased permeability to K+ -> opens Ca2+ channels -> influx of Ca2+ -> insulin release.

GI

- N & V
- cholestatic jaundice
- LFTs derangement
- rashes

Metabolic

- decrease blood sugar concentration
- decrease the plasma TG, cholesterol & FFA concentration.

Other adverse effects

-> hypoglycaemia
- leucopenia
- thrombocytopenia

Drug interactions

- NSAIDs, salicylates, sulphonamides, oral anticoagulants, MAOIs & beta adrenergic antagonists -> potentiate action of sulphonylureas

- steroids, thiazides, phenothiazines, phenytoin, sympathetomimetics & Ca2+ antagonists -> antagonise the action sulphonylureas

(c) To outline the mode of action & side effects of thyroid hormones & anti-thyroid drugs.

Thyroid Hormones

Chemical

- thyroxine & triiodothyroinine
- iodine containing amino acide derivatives of thyronine.

Uses - treatment of hypothyroidism

Presentation

Preparation

Routes

- PO
- IV

Dose

- thyroxine = PO - 12.5 - 50mcg/day in divided doses (acts in 24hrs, peak effect @ 7 days)

- triiodothyronine = IV - 5-20mcg Q 4-10hrly (acts in 6hrs, peak effect @ 24hrs)

PK

Absorption

- both 100% bioavailability with oral administration

Distribution

- thyroxine: 99.9% protein bound, Vd 0.2L/kg
- triiodothyronine: 99.5% protein bound, Vd 0.5L/kg

Metabolism

- both hepatic & renal -> inactive T3
- conjugation to glucuronide & sulphate -> bile
- 30% unchanged in faeces

Excretion

- thyroxine: Cl 2mL/kg/min, t1/2 7 days
- triiodothyronine: Cl 20mL/kg/min, t1/2 2 days

PD

Main action - activate DNA transcription -> protein production

Mechanism of action - combind with receptor in cell nucleus -> activate DNA transcription -> increase rate of RNA synthesis -> increase protein synthesis

CVS

- positive ionotropy & chronotropy c/o increased number of myocardial beta receptors
- increase systolic BP by 20mmHg
- decrease diastolic
- MAP unchanged
- vasodilation from increase peripheral O2 consumption

- increased circulating volume

RESP

- increase RR & TV

CNS

- tremour & hyperflexia
- increased appetitie

GI

- increased gut motility

Other adverse effects

- contraindication in the thyrotoxic

Anti-thyroid Drugs

Carbimzole 30-60mg/day
Thiouracil 50-150mg/day
Potassium percholate 300mg/day
I [131] @ 1-8mg/day

PK

PD

Carbimazole - converted to methimazole
Thiouracil - blocks iodination of precursors
Potassium percholate - compitivie inhibitor of iodine uptake
I [131] - interstitial thyroid irradiation

Adverse effects

Carbimazole - N+V, rash, agranulocytosis, jaundice
Thiouracil - same as carbmizole
Potassium perholate - hypersensitivity, agranulocytosis, nephrotic syndrome.
I [131] - hypothyroidism

(d) To describe the pharmacology of steroid drugs & their adverse effects.

Corticosteroids

- classifed according to the potency of these compounds to:

(a) evoke distal renal tubular reabsorption of Na+ in exchange for K+ (mineralocorticoid effect)
(b) produce an anti-inflammatory response (glucocorticoid effect)

- ie. hydrocortisone, cortisone, corticosterone, desoxycorticosterone, ALD.
- glucocorticoids attach to cytoplasmic receptors to stimulate changes in the transcription of defined on 456 DNA and thus synthesis of proteins.
- at high plasma concentrations -> extert antiinflammatory & immunosuppressive effects.
- prevents host-defense mechanisms that are activated during stress from overshooting & damaging the organism.

- inhibit phospholipase enzyme that is necessary for the inflammation chain reaction along both the cyclooxygenase & lipoxygenase pathways.

Dexamethasone

Chemical - fluorinated derivative of prednisolone

Uses

(1) deficiency states
(2) allergic therapy
(3) asthma
(4) anti-emetic
(5) post-op analgesia
(6) cerebral oedema
(7) aspiration pneumonitis
(8) lumbar disc disease
(9) immunosuppression
(10) antiinflammatory
(11) prem babies to prevent respiratory distess syndrome.

Presentation - clear, colourless soultion for injection

Routes - PO, IM, IV

Dose

- 0.1mg/kg
- duration of action = 2days

PK

Elimination - t1/2 = 4 hours

PD

Main action - see above

Mode of action

- inhibition of prostaglandin synthesis
- increase release of endorphins -> mood elevation & appetite stimulation
- attach to cytoplasmic receptors to stimulate transcription -> protein synthesis

CVS - no effects

RESP - decreased secretions

CNS

- increased neuroses & psychoses (mania & depression)
- cataracts

GI

- peptic ulcer disease

Metabolic

- suppression of the hypothalamic-pituitary-adrenal axis.
- electrolyte disturbances (hypokalaemic metabolic alkalosis -> absorption of Na+ & loss of K+
- oedema
- weight gain
- hyperglycaemia
- osteoporosis
- peripheral blood changes -> increase haematocrit & WCC
- inhibition of normal growth

Other adverse effects

- skeletal muscle myopathy
- increased susceptibility to bacterial infections.

Prednisone

Chemical - synthetic glucocorticosteriod

Uses

(1) adrenocortical deficiency
(2) allergy & anaphylaxis
(3) hypercalaemia
(4) asthma
(5) autoimmune disorders
(6) leukaemia chemotherapy
(7) immunosuppression after organ transplantation

Presentation

- tablets: 1 to 20mg
- solution: 25mg/mL
- eye/ear drops

Route - PO, IV, TOP

Dose

- PO: 1 -> 60mg/day
- IM/IV: 25-100mg once or twice a week

PK

Absorption - 90% bioavailability
Distribution - 90% protein bound, Vd = 0.5L/kg
Metabolism - hepatic hydroxylation -> conjugation
Elimination - 10% unchaned in urine, Cl = 200ml/min, t1/2 = 4hrs

PD

Main action - anti-inflammatory

Mechanism

- reacts with cytoplasmic receptors to form complexes that directly influence rate of RNA transcription
- controls rate of protein synthesis (lipocortins)
- prednisone converted to predinisolone in liver

- X4 more potent than hydrocortisone
- X6 less potent than dexamethasone

1mg Prednisone =

4mg Hydrocortisone =
0.15mg Dexamethasone

CVS

- positive effect on myocardial contractility
- increases the number of alpha adrenoreceptors & beta adrenoreceptors -> vasoconstriction.

RESP

- decrease in bronchial secretions & oedema

CNS

- euphoria
- increase in appetite

GI

- increased risk of peptic ulcer disease
- decreased absorption of Ca2+

GU

- weak mineralocorticoid effects
- Na+ retension & K+ excretion
- increased urinary excretion
- increases GFR
- increases tubular secretory activity

Metabolic

- stimulate gluconeogenesis & inhibit peripheral utilisation of glucose
- redistribution of body fat
- enhance lipolysis
- reduced the coversion of aa -> proteins

Haemotology

- blocks lymphokine action & inhibits plasminogen activator -> inhibits neutrophil & macrophage recruitment
- increase RBC, neutrophil & Hb concentration
- depresses other WCCs & activity of lymphoid tissue

Toxicity

Cushing syndrome ->

- growth arrest
- central obesity
- moon face
- buffalo hump
- striae
- acne
- hirsutism
- fragile, thin skin
- altered glucose tolerance
- fluid retension
- hypokalaemic alkalosis
- OP
- proximal muscle myopathy
- cataracts
- mania
- peptic ulcer disease

Drug interactions

- anti-cholinesterase drugs -> antagonism

Hydrocortisone

See Prednisone above

Also used in ICU -> relative adrenal insufficiency in the critically ill (decreases time to shock reversal) & may decrease mortality.

Dose

- IV: 100 to 500mg Q6hrly
- PO: 10-20mg/day

Onset: 3 hrs
Duration: 8hrs

PK

Absorption - 50% bioavailability
Distribution - 90% protein bound
Metabolism - liver -> tetrahydrocortisone
Eliimination - Cl = 200mL/min, t1/2 = 2 hrs

(d) To outline the pharmacology of glucagon.

Glucagon

- produced by the alpha cells in islets of Langerhans.
- MW 3500
- acts on the liver via cAMP to stimulate glycogenolysis.

- secreted in response to:

(1) low blood glucose levels
(2) amino acids
(3) catecholamines - adrenaline via beta receptors
(4) growth hormone
(5) glucocorticoids

- inhibited by:

(1) glucose
(2) insulin
(3) FFAs

Chemical - a polypeptide hormone extracted from the alpha-cells of the pancreas of Langerhans.

Uses

(1) treat hypo's
(2) facilitate radiological investigation of the GI tract
(3) cardiogenic shock
(4) renal colic
(5) acute diverticulitis
(6) propanolol OD

Presentation

- vials containing 1 to 10mg of lyophilised glucagon HCl
- lactose
- reconstitiuted in H2O & glycerol

Route - IV, SC, IM

Dose

- bolus: 1-5mg
- infusion: 1-20mg/hr

Onset: 1min (IV), 10min (IM or SC)
Duration: 20min

PK

Absorption - inactive when given PO
Distribution -
Metabolism - proteolysis in splanchnic & hepatic & renal circulation
Elimination - Cl = 10min, t1/2 = 5min

PD

Main actions

- elevation of plasma glucose
- positive inotropism
- positive chronotropism
- relaxation of smooth muscle

Mechanism

- acts via cell membrane receptors -> increase adenylate cyclase -> increase in cAMP -> increase protein kinase activity

CVS

- +ve inotrope
- +ve chronotrope
- synergistic action with beta-adrenergic agonist

GI

- decreased GI tone
- gastric & pancreatic secretion inhibited

GU

- decreased ureteric tone
- renal failure -> decreased clearance

Metabolic

- increases gluconeogenesis, glycogenolysis, lipolysis, proteolysis & ketogenesis -> increase BSL
- increase catecholamine release -> hypokalaemia

Toxicity

- nausea
- hypoglycaemia/hyperglycaemia
- diarrhoea
- allergy

Drug interaction

- increases action of warfarin

(e) To describe the pharmacology of vasopressin and its analogues.

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