ENDOCRINE PHARMACOLOGY

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

Overview of insulin:

- Insulin is synthesised by Islets cells of Langerhans (Beta cells) in the pancreas
- Synthesised as "proinsulin" (single polypeptide chain) that is converted to "insulin" and "C-peptide" (34 a.a. peptide), which are both stored in secretory granules
- Insulin consists of an "A-chain" and "B-chain" joined by two disulphide bridges (Nb. a third disulphide bridge connects two regions of the A-chain)

Mechanism of action of insulin:

- Insulin receptor is a transmembrane "tyrosine kinase" receptor (consisting of two α- and two β-subunits)
- Insulin binds to the α-subunit, which leads to internalisation of the receptor. This causes autophosphorylation of Tyr within the receptor complex, resulting in "tyrosine kinase activity". Various IC receptor substrates are then Tyr phosphorylated, which leads to activation (or inactivation) of numerous IC enzymes
- Effect of insulin:
    - (i) Increased glucose transport into cells (hepatic and extrahepatic) – Due to increased translocation of GLUT 4 transporters to the membrane
    - (ii) Increased glycogen synthesis (stimulates glycogen synthetase)
    - (iii) Inhibits gluconeogenolysis
    - (iv) Increased fat deposition (promotes FFA synthesis and TG storage; inhibits lipolysis)
    - (v) Stimulates protein synthesis, inhibits proteolysis, and increases a.a. uptake
    - (vi) Stimulates uptake of K^+, Mg^{2+} and PO_4^{3-}

Exogenous insulin preparations:

- Uses:
    - Treat insulin-dependent DM patients (Eg. T1DM or insulin-dependent T2DM)
    - Provide a slow, long-acting and continuous supply of insulin that mimicked endogenous basal and post-prandial release of insulin from the pancreas
- Human insulin is made using recombinant DNA technology involving E. coli (Nb. previously insulin was extracted from beef/pork pancreas). There are several types:
    - Rapid acting – Regular crystalline zinc
    - Very rapid acting – Lispro, Insulin aspart
    - Intermediate acting – NPH (lente), which contains protamine (delays absorption of insulin)
    - Long acting – Ultralente, Glargine

Pharmacokinetics of insulin:

- Insulin can be given either:
    - (i) S/C (any insulin preparation) – Regularly dosed insulin is released slowly into circulation, thus causing a sustained effect
    - (ii) IV (only regular crystalline zinc and lispro insulin) – External pump provides basal infusion of insulin, and boluses of insulin pre-prandially (immediate and titratable action)
    - Nb. It cannot be given orally as it is destroyed by GI proteases!
- Insulin is metabolised in the kidney and liver by proteolytic enzymes
- Renal metabolism plays a more significant role (thus, renal dysfunction leads to prolonged effects of insulin)
- Elimination t ½ is 5-10 minutes (rapid metabolism), but pharmacodynamic effect is 30-60 minutes (due to tight binding to insulin receptors)

Issues and side-effects of exogenous insulin:

- (i) Hypoglycaemia
    - Most serious adverse effect as it can lead to coma and death if not treated

    - Occurs when carbohydrates are not taken concurrently with exogenous insulin (Eg. perioperative fasting)
- (ii) Allergic reactions
    - Systemic allergic reactions stem from animal-derived insulin only (and NOT human insulin preparations)
    - Local allergic reactions occur due to non-insulin materials
- (iii) Lipodystrophy
    - Due to anabolic effects of insulin locally at injection site
- (iv) Insulin resistance
    - Occurs when there is impaired IC insulin signal transduction resulting in decreased recruitment of glucose transport proteins and subsequent decreased glucose uptake
    - This leads to compensatory hyperinsulinaemia (Ie. higher exogenous doses) to overcome this resistance
- (v) Drug interactions
    - Drugs that counter the effects of insulin (Adr, glucagon, cortisol)
    - Antibiotics (tetracycline, chloramphenicol) and salicylates increase the duration of insulin
    - MAOi can potentiate the effects of insulin

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

Overview of oral hypoglycaemic agents:

- Oral hypoglycaemic agents are used to control T2DM (or NIDDM)
- Only sulfonylureas and meglitinides can decrease BGL to a point where hypoglycaemia can occur – This is because they stimulate endogenous insulin release from pancreatic islet (beta) cells

Sulfonylureas:

- *Types*:
  - 1st generation (no longer used) – Chlorpropamide, Tolbutamide, Acetohexamide
  - 2nd generation (currently used) – Glibenclamide, Gliclazide, Glipizide
- *Mechanism of action*:
  - (i) Stimulates insulin secretion from pancreatic islet (beta) cells (Nb. not used for T1DM due to absence of beta cells) – Inhibits ATP-sensitive K^+ channels, which results in depolarisation of beta-cells. This causes an influx of Ca^{2+} and stimulation of exocytosis of insulin storage granules
  - (ii) Decreases insulin resistance (minor)
  - (iii) Decreases TG and VLDL levels
- *Pharmacokinetics*:
  - Good oral bioavailability (> 80-100%)
  - Extensive protein binding in plasma (esp albumin; 90-98%) due to it being weakly acidic – This results in a small $V_{DISTRIBUTION}$
  - Extensive hepatic metabolism to active and inactive metabolites, which are then eliminated in urine via tubular secretion by kidneys (Nb. chlorpropamide is not extensively metabolised by the liver, and instead mainly eliminated in the urine unchanged)
- *Side-effects*:
  - (i) Hypoglycaemia (MAIN adverse effect)
    - Only oral agent that can cause hypoglycaemia as it stimulates endogenous insulin release
    - Hypoglycaemia tends to be more prolonged (cf. insulin) as sulfonylurea drugs have longer t ½ (esp chlopropamide – longest acting drug (36-72 hr duration) and delayed effect (1-2 weeks))
    - Risk factors:
      - (a) Perioperative period (due to fasting)
      - (b) Elderly (due to reduced renal function)
      - (c) Impaired renal function (especially chlopropamide, as it is mainly excreted unchanged in the urine)
      - (d) Drug interactions – 1st generation drugs bind proteins by ionic forces (cf. 2nd generation), and thus easily displaced by warfarin, salicylate, phenylbutazone
  - (ii) GI disturbances (N/V, deranged LFTs)
  - (iii) Inhibits ischaemic preconditioning due to inhibiting of K_{ATP} channels (esp tolbutamide)
  - (iv) Foetal hypoglycaemia (as sulfonylureas can cross placenta)

Biguanides:

- *Types*: Metformin
- *Mechanism of action*:
  - (i) Increases peripheral insulin sensitivity (Ie. this requires the presence of insulin), which increases peripheral glucose utilisation (Eg. increased GLUT-4 upregulation)
  - (ii) Inhibition of hepatic and renal gluconeogenesis
  - (iii) Delayed uptake of glucose from GI tract

    - (iv) Lowers plasma cholesterol, TG, LDL
- *Pharmacokinetics*:
    - Slow GI absorption (oral bioavailability of 60%), but rapid onset (peak levels in 2 hours)
    - Not bound to plasma proteins
    - Not metabolised
    - Heavily dependent on renal clearance as it is excreted unchanged in urine (Nb. thus renal impairment prolongs its action)
- *Side-effects*:
    - (i) Severe lactic acidosis
        - Metformin binds to mitochondrial membranes and causes decreased IC ATP and increased IC AMP – This causes glucose to be metabolised anaerobically (rather than aerobically), leading to increased pyruvate production, which is then reduced to lactate
        - Lactic acidosis occurs with:
            - Low C.O. states (Eg. AMI, CCF, sepsis)
            - Renal dysfunction (due to reduced drug elimination)
            - Liver dysfunction (as lactate is metabolised in the liver)
            - Dehydration (due to pre-renal dysfunction)
            - Use of IV contrast
            - Hypoxaemia (due to increased anaerobic glucose metabolism to lactate)
    - (ii) GI disturbance (esp diarrhoea, nausea, anorexia)
    - Note: Hypoglycaemia is NOT a side-effect as biguanides do NOT stimulate the release of insulin

<u>Thiazolidinediones</u>:
- *Types*: Rosiglitazone, Pioglitazone
- *Pharmacokinetics*:
    - High oral bioavailability
    - Extensive metabolism by hepatic CYP450 into inactive metabolites, which are excreted in urine
- *Mechanism of action*:
    - Activates nuclear peroxisome proliferators-activated receptor γ (PPARγ), which regulate genes involved in glucose and lipid metabolism:
        - (i) Increase insulin sensitivity in skeletal muscle and adipose tissue (Nb. this requires the presence of insulin)
        - (ii) Decreased TG
        - (iii) Increased HDL/LDL
- *Side-effects*:
    - (i) Weight gain due to fluid retention (thus, avoid in CCF)
    - (ii) Deranged LFTs and hepatitis (esp troglitazone)
    - Nb. Hypoglycaemia is NOT a side-effect

<u>Alpha-glucosidase inhibitors</u>:
- *Types*: Acarbose
- *Mechanism of action*:
    - Delays intestinal glucose absorption by competitive inhibition of intestinal α-glucosidase. This prevents metabolism of polysaccharides into absorbable monosaccharides
- *Side-effects*:
    - (i) Mainly GI adverse effects (esp borborygmi, flatulence and diarrhoea) due to large carbohydrate load reaching bacteria in large bowel
    - (ii) May cause hypoglycaemia when used concurrently with insulin, sulfonylurea or meglitinides

Meglitinides:

- *Types*: Repaglinide, Metiglinide
- *Mechanism of action*: Similar to sulfonylurea
- *Pharmacokinetics*:
    - Oral bioavailability of 50%
    - Highly protein-bound (98%)
    - Hepatic metabolism (CYP3A4)
    - Rapid-acting (1 hr) and short-acting (4 hr), and is taken post-prandially
- *Side-effects*: Risk of hypoglycaemia (due to release of endogenous insulin), but risk is low as it is taken post-prandially and has a short duration of action

Incretins:

- *Types*: DPP-4 inhibitors (sitagliptin, vildagliptin) and GLP-1 agonists (exenatide)
- *Mechanism of action*:
    - GLP-1 agonists – Mimics the effects of Glucagon-like peptide (GLP), which is released post-prandially and acts on β-cells to increase insulin secretion (and reduce glucagon secretion).
    - DPP-4 inhibitors – GLP is broken down by dipeptidyl-peptidase (DPP-4). This class of drugs work by inhibiting this enzyme, thus prolonging the secretion of insulin caused by GLP
- *Side-effects*: Mainly hypoglycaemia

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

Thyroid hormone replacement:

- Two types:
  - (i) Levothyroxine
    - Synthetic T4 given orally for long-term thyroid replacement therapy for hypothyroidism
  - (ii) L-triiodothyronine (or Liotyronine)
    - L-isomer of T3 given IV in emergent situations (Eg. myxoedema coma) or PO for thyroid replacement therapy for hypothyroidism
    - Faster onset and 2-3X more potent than levothyroxine (thus used for emergency situations), but short duration of action (thus limiting its use as long-term thyroid replacement therapy)
- Mechanism of action:
  - Synthetic T4 and T3 enter the cell via a carrier mechanism
  - T4 requires conversion to "active" T3, which acts on receptors within the cell nucleus and mitochondria
- Pharmacokinetics:
  - Good oral bioavailability
  - 99% protein-bound (esp to albumin and thyroxine-binding globulin)
  - Some T4 converted within liver and kidney to "active" T3 or "inactive" reverse T3
  - 60% of T3/T4 are metabolised by the liver and excreted in bile; 40% excreted unchanged in urine
- Adverse effects:
  - (i) Hyperthyroidism
  - (ii) Precipitate myocardial ischaemia, arrhythmia and heart failure (this is because T3/T4 have +ve ino- and chronotropic effects)

Drugs used to treat hyperthyroidism:

(1) Thioureylenes:

- (a) Carbimazole
  - Used to treat (i) thyroid storm, and/or (ii) hyperthyroidism prior to elective thyroidectomy
  - Mechanism of action:
    - A pro-drug that requires conversion to Methimazole in vivo
    - Methimazole then prevents synthesis of new T3 and T4 by inhibiting thyroid peroxidase (TPO) – Nb. TPO is an enzyme that oxidises iodide to iodine, thereby facilitating incorporation of iodine onto Tyr residues of thyroglobulin (Ie. iodotyrosine synthesis and coupling of iodotyrosine moieties)
    - Antithyroid effects only seen after days-to-weeks because preformed or stored T3/T4 need to be depleted first
  - Pharmacokinetics:
    - Good oral bioavailability. However, cannot be given parentally (Ie. NGT is needed for administration during a thyroid storm)
    - Requires hepatic conversion from a pro-drug (Carbimazole) to the active form (Methimazole)
    - Minimal protein-binding
    - Excreted in the urine
  - Adverse effects:
    - Skin rash and pruritis
    - Arthralgia

        - Agranulocytosis (serious but rare complication)
        - Foetal hypothyroidism (carbimazole can cross the placenta)
        - Nb. Not contraindicated while breastfeeding despite small amounts crossing into breast milk
- (b) Propylthiouracil is similar to carbimazole, except for the following:
    - Mechanism of action – Prevents iodination of Tyr by inhibiting TPO (like carbimazole), but it also inhibits peripheral conversion of T4 to T3
    - More effective in treating thyroid storm – This is because PTU has a faster onset as it inhibits peripheral deiodination of T4 to active T3
    - Reserved for patients who are intolerant to carbimazole
    - Safer to use during pregnancy and post-partum – Higher protein-binding in plasma limits placental passage and crossing into breast milk of PTU
    - Higher incidence of agranulocytosis
    - Does not require conversion from a pro-drug in the liver, and is more protein-bound in plasma

(2) Iodide:
- Used to treat (i) thyroid storm, and/or (ii) hyperthyroidism prior to elective thyroidectomy
- Mechanism of action:
    - Oral Lugol's iodine (aka. Potassium iodide) is converted in vivo to iodide
    - Acutely high plasma levels of iodide:
        - (i) Temporarily inhibits release of thyroid hormone by antagonising the effect of TSH on thyroid gland
        - (ii) Inhibits thyroid hormone production by blocking iodide uptake (Ie. saturates iodide transporters during hyperthyroid state), thereby preventing iodination of Tyr on thyroglobulin
        - (iii) Inhibits proteolysis of thyroglobulin
        - (iv) Reduces vascularity of the thyroid gland
    - Takes 1-2 days for anti-thyroid effect
    - Chronically high plasma level of iodide is associated with recurrence of previously suppressed excess thyroid gland activity (thus, iodide is not used for chronic treatment of hyperthyroidism)
- Main adverse effect is allergic reactions, which include life-threatening angio- and laryngeal oedema

(3) Thiocyanate and Perchlorate:
- Act similar to iodide by interfering with iodide uptake into the thyroid gland (Ie. inhibits the iodide transport mechanism)
- Perchlorate is rarely used as it causes aplastic anaemia

(4) Radioactive iodine (I^{131}):
- Used to treat hyperthyroidism in elderly patients and those with heart disease
- Mechanism of action:
    - Rapidly and efficiently taken up by the thyroid gland (using the iodide transporter mechanism), and then incorportated in thyroglobulin
    - I^{131} exerts its cytotoxic effects on the thyroid gland cells by emitting β-rays locally
    - A single oral dose takes 2-3 months to ablate the gland's activity
- Adverse effects:
    - Iatrogenic hypothyroidism
    - Radiation risk (potential carcinogen to surrounding tissues, contraindicated during pregnancy as it can be taken up by the foetal thyroid gland)

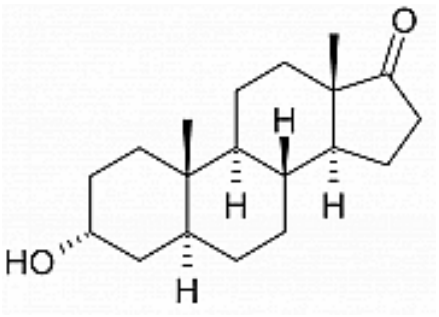
(5) Propranolol:

- Used (i) as initial treatment of hyperthyroid symptoms in patients receiving antithyroid therapy (I^{131} or thioureylene) or awaiting elective thyroidectomy, or (ii) to treat thyroid storm
- Mechanism of action:
    - (i) Beta-blocker effect – Directly blocks the sympathetic effects of the thyrotoxic state on the CVS (Eg. tachycardia, dysrhythmia) and CNS (Eg. tremor, agitation)
    - (ii) Blocks peripheral conversion of T4 to active T3
    - Potential issues with use in patients with COPD or CCF

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

Adrenal cortex releases three classes of steroidal hormones:

- (1) Glucocorticoids (from zona fasciculata) – Cortisol (hydrocortisone), cortisone, corticosterone
- (2) Mineralocorticoids (from zona glomerulosa) - Aldosterone
- (3) Androgens (from zona reticulata) – DHEA (dehydroepiandrosterone) and androstenedione



Overview of glucocorticoids (GC):

- Mechanism of action:
  - GC enters the cell by diffusion where they bind cytoplasmic GR-α and GR-β receptors (which are found in ALL tissues)
  - Steroid-receptor complex becomes "activated" – It undergoes a conformational change that exposes a DNA-binding domain, and then it forms a "dimer" with another steroid-receptor complex
  - The dimer enters the nucleus and binds steroid-response DNA elements:
    - (i) Causes repression of gene transcription – Inhibits transcription factors that mount an inflammatory and immunosuppressive response (Eg. COX2, cytokines, adhesion factors, inducible NOS)
    - (ii) Causes induction of gene transcription – Activate transcription factors that lead to:
      - Synthesis of enzymes involved in metabolism (esp cAMP-dependent kinase)
      - Formation of lipocortin-1, which inhibits PLA-2 (anti-inflammatory effect), and produces –ve feedback on the anterior pituitary and hypothalamus
- Role of GCs – GCs maintain homeostasis in response to stress via two actions:
  - (1) Permissive action
    - Occurs at low [GC]
    - Prepares the individual for responding to stress – Achieved by maintaining a basal level of HPA activity through –ve feedback of GC level and setting a threshold for response to stress
  - (2) Protective action
    - Occurs at high [GC]
    - During times of stress, it acts to:
      - (i) Maintain energy demands during stress by redirecting metabolism
      - (ii) Prevent self-harm from host-defence mechanism via anti-inflammatory and immunosuppressive effects
- Effect of GCs:
  - (1) Metabolic effects:
    - Carbohydrate

                - Increased BGL due to increased hepatic gluconeogenesis and glucose release from the liver, AND decreased peripheral uptake and utilisation of glucose
                - Glycogen deposition in the liver (due to stimulation of insulin secretion by hyperglycaemia)
            - Protein – Increased protein catabolism; decreased anabolism
            - Fat – Redistribution of fat from peripheral tissue to central tissues (due to increased lipolysis in peripheral tissues, and increased lipogenesis in central tissues)
    - (2) Adrenal suppression:
        - GCs exert a –ve feedback on the hypothalamus and anterior pituitary, thereby attenuating the release of CRF and ACTH, respectively
    - (3) Immunosuppressive and anti-inflammatory effects:
        - Inhibits the early and late manifestations of inflammation (Ie. AIR with erythema, heat, pain swelling; CIR with wound healing and tissue proliferation)
        - Mechanism:
            - Prevents migration and inhibits function of PMNL and macrophages in inflamed tissues
            - Attenuates activity and proliferation of T-lymphocytes (due to decreased IL 1 and 2)
            - Decreased fibroblast function (Ie. less collagen and GAGs)
            - Decreased production of immunoglobulins (esp IgG)
            - Suppression of inflammatory mediators – Decreased PGs/LTs (due to increased lipocortin-1 inhibition of PLA2, and decreased COX-2), decreased cytokine and cell-adhesion factors (IL, TNF), decreased histamine and induced NO production
    - (4) Water and electrolyte balance:
        - GCs have weak MC activity – Causes Na^+ and H_2O retention, and K^+ and H^+ excretion at the distal renal tubule
    - (5) Altered Ca^{2+} balance:
        - Increased osteoclastic activity and decreased osteoblastic activity
        - Reduced Ca^{2+} absorption in GIT and increased Ca^{2+} excretion by kidneys
    - (6) "Permissive effects" to catecholamines:
        - Catecholamines increase IC cAMP levels, while GCs increase synthesis of cAMP-dependent kinases
        - The "permissive effects" to catecholamines by GCs include its – Lipolytic effects, bronchodilator effects, vascular SM effects, and calorigenic effects of glucagon
- Therapeutic uses of GCs:
    - (1) Replacement therapy for adrenal failure (Addison's)
    - (2) Anti-inflammatory/immunosuppressive therapy for:
        - Asthma
        - Inflammatory conditions (Eg. eczema, allergic conjunctivitis, uveitis, iritis)
        - Hypersensitivity states (Eg. severe allergic reactions)
        - Autoimmune disease (Eg. RA, IBD, ITP)
        - Preventing GVHD and organ transplantation rejection
    - (3) Adjunct to cytotoxic agents in treating neoplastic disease (Eg. ALL, Hodgkin's lymphoma)
    - (4) Reduce or prevent cerebral oedema due to intracranial lesions
    - (5) Antiemetic therapy (for PONV or chemotherapy-induced emesis)
    - (6) Post-operative analgesia (due to inhibition of COX-2/PLA-2)
    - (7) Management of lumbar disc disease (epidural steroids reduce inflammation and oedema of spinal nerve roots)

    - (8) Treatment of aspiration pneumonitis
    - (9) Prevention of neonatal respiratory distress syndrome
- Adverse effects of GCs – Generally occur with high dose or prolonged systemic administration of steroids as an anti-inflammatory or immunosuppressive agent (Ie. does NOT occur with replacement therapy)
    - (1) Risk of acute adrenal insufficiency
        - High doses or prolonged systemic steroid therapy results in adrenal cortical suppression due to –ve feedback on CRH and ACTH release from the hypothalamus and anterior pituitary, respectively. Note that adrenal gland atrophy and suppression can last for many months after ceasing steroid treatment
        - Thus, with abrupt withdrawal of steroids or during periods of stress (Eg. infection, surgery) the adrenal cortex cannot produce enough GC, thereby resulting in an Addisonian crisis (Eg. hypotension and CVS collapse)
    - (2) Suppression of protective response to infection or injury
        - Immunosuppressive effects of GCs result in a risk of serious intercurrent infection and reactivation of latent infection (Eg. TB)
        - Anti-inflammatory effects of GCs result in impaired wound healing (due to impaired CIR) and risk of peptic ulceration (due to decreased protective gastric mucosal barrier)
    - (3) Metabolic side-effects
        - Hyperglycaemia and risk of DM
        - Redistribution of fat from peripheral tissues (from arms) to central tissues (to face, neck, supraclavicular areas and trunk) – Causes Buffalo hump, central adiposity (and obesity), supraclavicular fat pads, moon face and thin arms
        - Net protein catabolism causing –ve nitrogen balance, thinned skin (and striae), easy bruising, and muscle wasting (esp proximal myopathy)
        - Altered Ca^{2+} metabolism resulting in osteoporosis and fractures
    - (4) MC side-effects
        - Oedema, CCF and HTN due to Na^+ and H_2O retention
        - Hypokalaemia and metabolic alkalosis due to H^+ and K^+ loss
    - (5) Central effects
        - Psychiatric effects – Euphoria, depression, psychosis
        - Increased appetite
        - Raised ICP (benign intracranial HTN)
    - (6) Ocular effects – Glaucoma and cataracts
    - (7) Avascular necrosis of femoral head (due to decreased blood supply)
    - (8) Growth inhibition (in children)

<u>Overview of mineralocorticoids (MC)</u>:

- Mechanism of action:
    - Diffuse across cell membrane and bind to specific IC receptors that are found in high [ ] in specialised tissues (esp distal tubules of kidney, epithelium of colon and bladder)
    - These cells also contain "11-beta-hydroxysteroid dehydrogenase", which coverts GCs only (NOT MCs) to metabolites with low affinity for MC-receptors – This ensures these cells are influenced only by bona fide MCs
    - Steroid-receptor complex undergoes conformation changes similar to the GC-receptor, and then enters the cell nucleus to initiate DNA transcription and production of specific proteins – Increased synthesis of Na^+ and K^+ channels in the apical membrane, and Na^+/K^+ ATPase in the basolateral membrane
- Effect of MCs:
    - Increases Na^+ and H_2O retention – Due to increased Na^+ reabsorption in the distal tubules

- Increased K^+ and H^+ efflux – Due to increased K^+ and H^+ secretion in the distal tubules

Types of therapeutic steroids:

Steroid	GC effect (anti-inflammatory)	MC effect (Na^+/H_2O retention)	Equivalent dose (mg)	Elimination half-time (hrs)	Duration of action (hrs)	Important features
Cortisol (hydrocortisone)	1	1	20	1.5-3.0	8-12	- Endogenous GC - Used to treat adrenal insufficiency (as it has both GC and MC effects)
Cortisone	0.8	0.8	25	0.5	8-36	Same as cortisol
Prednisolone and Prednisone	4	0.8	5	2-4	12-36	- Synthetic analogue of cortisol - Used to treat adrenal insufficiency (as it has both GC and MC effects) - Used as an anti-inflammatory and immuno-suppressive agent (as MC effect is not excessive) - Prednisone is rapidly converted to prednisolone in vivo
Methylprednisone	5	0.5	4	2-4	12-36	- Synthetic methyl derivative of prednisolone - Used IV for intense anti-inflammatory/immuno-suppressive effects - Used in epidural to manage lumbar disc disease and intra-articularly for arthritis
Betamethasone	25	0	0.75	5	36-50	- Fluorinated derivative of prednisolone - Lacks MC effect (used when water/salt retention is not desired; cannot be used alone for adrenal insufficiency)
Dexamethasone	25	0	0.75	5	36-50	- Fluorinated derivative of prednisolone. Isomer of betamethasone - Used to treat cerebral oedema, PONV, chemo-induced N/V, increase appetite and mood, and RDS
Triamcinolone	5	0	4	5	12-36	- Fluorinated derivative of prednisolone - Used to treat lumbar disc disease
Aldosterone	0	3000				
Fludrocortisone	10	250	2		24	- Synthetic analogue of

						aldosterone - Used to treat adrenal insufficiency

Pharmacokinetics of therapeutic steroids:

- Administration – Most agents are active when given orally. All agents can be given parentally (IM for prolonged effects; IV for quick rise in plasma [ ]). Topical routes (nebulised, skin, nasal, intra-articular, ocular) are associated with less systemic toxic effects
- Distribution – Corticosteroid-binding globulin (CBG) binds 90% of cortisol but does NOT bind any synthetic steroids. Albumin has lower affinity for cortisol, but can bind synthetic steroids
- Metabolism and elimination – Cortisone and prednisone are inactive until they are converted in vivo to hydrocortisone and prednisolone, respectively. Steroids are generally inactivated by the liver by reduction of a double-bond.

(e) ***To outline the pharmacology of glucagon.***

Overview of glucagon:

- Polypeptide hormone produced by alpha cells within the Islets of Langerhans of the pancreas
- Acts by GPRC (Gs – Increases formation of IC cAMP via adenylyl cylase)
- Effects of glucagon:
    - (i) CVS effects
        - Acute +ve inotropic and chronotropic effects (Nb. inotropy >> chronotropy; nil sustained effects with chronic usage)
            - Increase in SV and HR independent of adrenergic receptor stimulation
            - Causes an increase in MAP (without change or fall in SVR)
            - Enhances automaticity of SA and AV nodes without increasing automaticity of ventricles
        - Partly caused by stimulation of endogenous catecholamines release
        - Acts synergistically with beta-agonists
    - (ii) Endocrine effects
        - Elevates BGL due to increased gluconeogenesis/glycogenolysis
        - Increased lipolysis
        - Increased proteolysis
        - Increased ketogenesis
    - (iii) GU and GI effects
        - Increased RBF and U/O (similar to low-dose dopamine, but less potent)
        - Decreased pancreatic and biliary secretions
        - Decreased uterine SM tone
        - Reduced GI and GU SM tone

Clinical uses of glucagon:

- (1) Management of hypoglycaemia (Nb. BGL increases ONLY after 10-30 mins!)
- (2) Treatment of beta-blocker overdose
- (3) Management of cardiogenic shock (increasing myocardial contractility and HR), especially in the presence of beta-adrenergic blockade
- (4) Treatment of renal colic

Pharmacokinetics of glucagon:

- Poor oral bioavailability (due to degradation by intestinal peptidases), thus given IV or IM or S/C (1-5 mg)
- Degraded by proteolysis in liver, kidneys or splanchnic circulation, with a clearance of 8-12 mL/kg/min and elimination t ½ of 3-6 minutes (Nb. prolonged effect with hepatic or renal impairment)

Side-effects of glucagon:

- (1) BGL disturbance
    - Mainly hyperglycaemia initially
    - Paradoxical hypoglycaemia occurs if there is insufficient hepatic glycogen stores to offset reflex insulinaemia
- (2) K^+ disturbance
    - Mainly hyperkalaemia initially
    - Paradoxical hypokalaemia occurs due to reflex insulinaemia
- (3) N/V
- (4) Systemic HTN and tachycardia (esp with undiagnosed phaeochromocytoma) due to excessive catecholamine release
- (5) Can potentiate anticoagulant effects of warfarin

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

Overview of vasopressin:

- Vasopressin (aka. Arginine vaspressin or Antidiuretic hormone) is a peptide hormone produced by the hypothalamus (SON/PVN)
- It is then secreted by the posterior pituitary in response to:
    - (i) Rise in plasma osmotic pressure (main factor)
    - (ii) Fall in plasma volume
    - (iii) Angiotensin II

Functions of vasopressin:

- (1) Via V2 receptor (act via GPRC – Gs):
    - Conserves body H_2O by increasing permeability of renal distal tubule and collecting duct membrane to H_2O and urea (Ie. concentrates urine) – This occurs by upregulation of AQ2 transporter on the apical membrane
- (2) Via V1 receptor (act via GPRC – Gq):
    - Stimulates vasoconstriction (and increase in SVR), thereby leading to raised BP – This is used as a compensatory mechanism against hypotension due to hypovolaemic shock (Eg. haemorrhage)
    - Increases haemostasis – Causes platelet aggregation, and induces release of vWF and CF VII from vascular endothelium

Types of exogenous vasopressin:

- (i) Vasopressin – Can be given IV or S/C
- (ii) DDAVP (Desmopressin)
    - Synthetic analogue of AVP given intranasally
    - Has an intensive antidiuretic effect (via V2R), and thus useful in managing diabetes insipidus
    - Less pronounced pressor effect (via V1R), but can be used to control bleeding with vWD and mild haemophilia A due to haemostatic effect (via V1R)
- (iii) Lypressin – Synthetic analogue of AVP similar to DDAVP

Pharmacokinetics of exogenous vasopressin:

- Poor oral bioavailability (AVP is a peptide that is rapidly cleaved by intestinal protease, esp trypsin)
- Given parentally:
    - Either IV or S/C vasopressin – Rapid enzyme metabolism in tissues by peptidases (esp kidney peptidases), thus plasma t ½ of 10 minutes only
    - Intranasal (DDAVP or lypressin) – Longer lasting effect (t ½ of 3-4 hours as AVP is not subjected to tissue peptidases) and less pronounced pressor effects (Ie. rise in BP)

Uses of exogenous vasopressin:

- (1) Investigation and treatment of AVP-sensitive diabetes insipidus
    - Central DI is due to inadequate secretion of AVP from the posterior pituitary – This can be managed with exogenous AVP
    - Renal DI cannot be managed with exogenous AVP
- (2) Adjunct for control of bleeding oesophageal varices
    - AVP causes marked decrease in portal circulation blood flow (and total HBF) due to splanchnic vasoconstriction
- (3) Management of refractory cardiac arrest
    - Used as an alternative to Adr during ALS of refractory cardiac arrest
    - Acts (i) as a vasoconstrictor at high doses (redistributes blood volume from peripheral to central compartments), and (ii) synergistically with catecholamines
- (4) Management of haemorrhagic and/or septic shock

    - AVP can be used to treat catecholamine-resistant shock due to excessive vasodilation caused by PGs and NO
    - AVP also has synergistic effects with catecholamines to treat hypotension associated with shock

Side-effects of exogenous vasopressin:

- At high doses (Ie. doses higher than used to treat diabetes insipidus):
    - (i) Hypertension due to vasoconstriction – Degree of rise in systolic BP depends on whether BRR is intact (Ie. intact BRR minimises the rise in BP)
    - (ii) Stimulation of GI smooth muscle (Ie. peristalsis), leading to N/V and abdominal pain
    - (iii) Stimulation of uterine smooth muscle
- At smaller doses:
    - (i) Coronary artery vasoconstriction, leading to myocardial ischaemia
    - (ii) Decreased platelet count (due to platelet aggregation)
    - (iii) Allergic reactions (including anaphylaxis)