Ho Medical
ANAESTHESIA

**Dr Matthew Ho**
BSc(Med) MBBS(Hons) FANZCA

# Endocrine Pharmacology

*Pharm-10A6/07B7 List the main drug groups used in the treatment of diabetes mellitus. For each group explain the mechanism of action, potential adverse effects and give examples.*

1. Diabetes is an endocrine disorder characterised by a relative resistance to, or deficiency of the actions of insulin.

| Group | Mechanism | Adverse Effects | Pharmacokinetics |
|---|---|---|---|
| Insulin | Recombinant produced from E.Coli. Previously from porcine / bovine pancreatic cells.<br>Acts on TK linked receptor:<br>glucose - ↑glycogenesis, ↓GNG, glycogenolysis<br>fat - ↓lipolysis<br>protein - ↑protein storage | Hypoglycaemia<br>Uncontrolled hyperglycaemia.<br>Lipodystrophy at injection site<br>Allergy / anaphylactoid reactions (more common with bovine / porcine) | Short acting (actrapid)<br>Medium Acting<br>Long acting (lantus)<br>Onset: 15min-3 hours<br>Duration: 4-24 hours<br><br>Generally used as a basal-bolus regime.<br>Metabolised in many peripheral tissues. |
| Biguanides: Metformin | Acts via AMP-kinase<br>Peripheral – enhance insulin action, ↓glucagon<br>GI - ↓carbohydrate absorption<br>Liver - ↓GNG, ↑glycogenesis<br>No weight gain or hypoglycaemia<br>Lowers chol, LDL | Lactic acidosis: binds to mitochondrial membrane → ↓aerobic ↑ anaerobic glycolysis → pyruvate converted to lactate. ↑ risk with renal, liver failure.<br>GI: diarrhoea, cramping | A: F = 60%<br>D: non-protein bound<br>M: nil<br>E: urine (renal impairment), $T_{1/2}$ = 3 hours |
| Sulfonylureas: chlorpropamide tolbutamide | Pancreas - binds to β cells → closes K channels → depolarisation → ↑ Ca → vesicle release of insulin<br>Peripheral - ↓insulin resistance, ↓glucagon (↑insulin) | Hypoglycaemia - ↑ risk with long acting (chlorpropamide)<br>Weight gain<br>Sulfur allergy<br>ETOH intolerance<br>GI: upset, N+V, deranged LFTs (tolbutamide)<br>Endo: SiADH<br>Obs: crosses placental → fetal hypoglycaemia | A: F = 100%<br>D: 97% protein bound, competition for binding with warfarin<br>M: hepatic → inactive compounds (influence by induction/inhibition)<br>E: renal (prolonged renal failure), esp. chlorpropamide |
| Thiozolidinediones: Rosiglitazone | Agonist at nuclear PPAR (peroxisome proliferator-activated receptors) → ↑ peripheral insulin sensitivity, anti-inflammatory (gene regulation) | GI: hepatitis<br>CVS: peripheral oedema, CCF<br>Weight gain | A: well absorbed<br>D: 99% protein bound<br>M: hepatic CYP450 |
| α-gluconidase inhibitors: Acarbose | Competitive inhibitor intestinal α-glucosidase → ↓ digestion carbohydrates into absorbable monosaccharides.<br>↓post-prandial BSL, no effect on baseline BSL | GI: N+V, diarrhoea | A: 2% absorption, minimal systemic effects |

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*Pharm-05B6 Discuss the therapeutic and unwanted effects of dexamethasone*

1. Dexamethasone is a synthetic potent glucocorticoid.

2. Mechanism of action: lipid soluble hormone which binds to intra-cellular nuclear receptors and modifies gene transcription within cell nuclei in the body. Effects are generally classified:
    a. Catabolic
    b. Anti-inflammatory
    c. Stress
    d. Haematological
    e. Endocrine regulatory and permissive
    f. Cardiovascular

3. Therapeutic uses:

| **Use** | **Mechanism** | **Clinical** |
|---|---|---|
| Anti-emetic | unknown | 4-8mg IV dexamethasone 1-2 hour prior to end anaesthesia → ↓PONV, rescue agent use |
| Anti-inflammatory | ↓vascular permeability → ↓oedema<br>↓inflammatory cell migration<br>↓inflammatory systems: PG synthesis (↓COX-2 production), complement, cytokines<br>mast cell stabaliser | Croup, COPD<br>Anaphylaxis / allergy<br>Autoimmune diseases<br>Cerebral oedema |
| Regulatory | Replaces endogenous cortisone produced by adrenal gland.<br>Negative feedback on ACTH and CRH release form the HPA | Addison's disease<br>Pituitary adenomas (↓ACTH release)<br>Diagnosis – dexamethasone suppression test |

4. Adverse effects:

| **System** | **Effect** | **Clinical** |
|---|---|---|
| Immunosuppression | Delayed wound healing<br>↑ mortality in sepsis<br>↑ anastamosis wound breakdown | Aggressive early antibiotic treatment |
| HPA suppression | Rapid suppression of ACTH and CRH with courses > 10 days. May last up to 2 years.<br>Abrupt withdrawal → Addisonian crisis | Prolonged doses of dexamethasone require gradual weaning over months. |
| Cardiovascular | Fluid retention<br>↑ response to catecholamines | HTN |
| Endocrine | Permissive to glucagon, cortisol, catecholamines, Anti-insulin<br>Fat redistribution<br>Protein catabolism<br>↑ osteoclastic activity → bone resorption → osteoporosis | ↑BSL → diabetogenic<br>Cushingoid appearance<br>Muscle wasting<br><br>Osteoporosis risk |
| Gastrointestinal | ↓PG synthesis → ↑gastritis, PUD | Use prophylactic PPI |
| Other | Cataracts<br>Skin striae<br>Osteoporosis<br>Psychosis, agitation<br>Glaucoma | |

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*Pharm-02B8 Outline the pharmacological effects of vasopressin*

1. Vasopressin is the synthetic form of the hormone ADH. This is a nonapeptide, produced in the hypothalamus neuroendocrine cells, and released from the posterior pituitary. Its actions are:

| **Receptor** | **Location** | **Effects** |
|---|---|---|
| $V_1$ ($G_qCR$) | Vascular smooth muscle<br>Platelets | Constriction → ↑SVR<br>↑vWF |
| $V_2$ | CD principle cells:<br>Aquaporin insertion<br>ADH-urea channel insertion | ↑water reabsorption → ↓urine output, ↑ urine concentration → fluid retention<br>Urea reabsorption → ↑medullary tonicity → ↑concentration urine |
| $V_3$ | Anterior pituitary | ↑ACTH release |

2. Vasopressin pharmacology:

| **Property** | **Vasopressin** |
|---|---|
| Physiochemical | |
| Group | Synthetic nonapeptide, ADH analogue |
| Presentation | IV – evaluation<br>Intranasal – DDAVP with selective $V_2$ effects |
| Uses | Diagnosis – nephrogenic (no-response) vs. central (↓urine output) diabetes insipidus<br>Central diabetes insipidus (↓ADH production posterior pituitary)<br>vWF – premedication to ↑vWF<br>Bleeding of oesophageal varicies |
| Dose | 1-4U/hour<br>Arrest: 40IU bolus |
| **Pharmacodynamic** | |
| Mechanism | $V_1$ R: vascular smooth muscle constriction → most selective sphlancnic circulation (↓portal circulation). Not antagonized by denervation / adrenoreceptor blockers ($\alpha_1$ independent mechanism). DDAVP does not act at these receptors<br>$V_2$R: CD and DCT → ↑aquaporin and urea channel insertion → ↑reabsorption of water and urea into medullary interstitium. |
| System effects:<br>CVS<br><br>Renal<br>GI<br>Uterus<br>Haeme | <br>↑SVR, ↑intravascular volume → ↑MAP, cutaneous constriction → pallor<br>Coronary vasoconstriction → angina, ischaemia<br>↑ water, urea reabsorption<br>↑peristalsis → abdominal cramping<br>↑ uterine tone (large doses)<br>↑vWF → useful in hemophilia preoperatively |
| Toxicity | Cardiac ischaemia, HTN, CCF, fluid overload<br>Allergy – can induce antibody formation |
| Interactions | Synergistic cardiovascular effects with sympathomimetics |
| **Pharmacokinetics** | |
| Absorption | Poor PO due to peptide nature (broken down by proteases) |
| Distribution | Unknown |
| Metabolism | Plasma proteases → amino acids<br>Prolonged use → antibodies → ↑breakdown → ↓duration action |
| Excretion | Recycled in amino acid pool |