Drugs / Medication List

### Endocrinology (Autumn Term)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Use</th>
<th>Action</th>
<th>Notes (Pharmacokinetics, Unwanted Effects)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>Treats lack of ACTH</td>
<td>Hormone Replacement Therapy</td>
<td>• Check serum cortisol levels</td>
<td>Endocrinology Lecture 1 — See page 3 for more detailed drug info</td>
</tr>
<tr>
<td>Thyrroxine</td>
<td>Treats lack of TSH</td>
<td>Hormone Replacement Therapy</td>
<td>• Check T3/T4 and TSH levels</td>
<td></td>
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<tr>
<td>Ethinyloestradiol / Medroxyprogesterone</td>
<td>Treats lack of LH/FSH – Females</td>
<td>Hormone Replacement Therapy</td>
<td>• Check oestrogen and libido</td>
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<tr>
<td>Testosterone Undecanoate</td>
<td>Treats lack of LH/FSH – Males</td>
<td>Hormone Replacement Therapy</td>
<td>• Check libido</td>
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<tr>
<td>GH</td>
<td>Treats lack of GH</td>
<td>Hormone Replacement Therapy</td>
<td>• Check IGF and growth charts</td>
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<tr>
<td>Octreotide</td>
<td>Acromegaly</td>
<td>Somatostatin Analogue</td>
<td>• Reduces the size of the tumour.</td>
<td>Endocrinology Lecture 2</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Acromegaly / Hyperprolactinaemia</td>
<td>Dopamine (DA₂) Agonist</td>
<td>• Dopamine agonist so decreases prolactin and GH secretion (negative feedback) so reduces tumour size.</td>
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<td>Other Uses:</td>
<td></td>
<td>• Administered by mouth 1/day</td>
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<tr>
<td></td>
<td>• Suppression of Lactation</td>
<td></td>
<td>• Highly plasma bound (93%)</td>
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<tr>
<td></td>
<td>• Cyclical Benign Breast Tumours (Cyclic Breast Pain)</td>
<td></td>
<td>• Hepatic Metabolism – T₁/₂=7 hours (approx)</td>
<td></td>
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<tr>
<td></td>
<td>• Parkinson’s Disease</td>
<td></td>
<td>• Unwanted Effects:</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>o Nausea / Vomiting / Abdominal Cramps</td>
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<td>o Psychomotor Excitation</td>
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<td></td>
<td></td>
<td></td>
<td>o Dyskinesias (diminished voluntary movements)</td>
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<td></td>
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<td></td>
<td>o Postural Hypotension</td>
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</tbody>
</table>
### Cabergoline
- Hyperprolactinaemia
- Dopamine (DA₂ and Moderate DA₁) Agonist
- **Oral administration, 1-2 Times a week**
- **T₁/₂= 40 Hours**
- **Unwanted Effects:**
  - As bromocriptine but less pronounced:
    - Nausea / Vomiting / Abdominal Cramps
    - Psychomotor Excitation
    - Dyskinesias (diminished voluntary movements)
    - Postural Hypotension
    - Vasospasm in fingers and toes (Caution: Reynaud’s Disease)

### Desmopressin (DDAVP)
- Cranial Diabetes Insipidus
- Night-time Enuresis
- Haemophilia
- Vasopressin V₂ Agonist
- **It produces a prompt sustained decrease in urine volume and an increase in urine osmolarity.**
- **Administration can be either oral or nasal.**
- **Distribution: Desmopressin is retained in the extracellular fluids.**
- **Hepatic / Renal metabolism.**
- **T₁/₂ = 5 hours (approx).**
- **Unwanted Effects:**
  - Fluid retention and hyponatraemia
  - Abdominal pain
  - Headaches
  - Nausea

### Terlipressin
- Oesophageal Varices
- V₁ Receptor Agonist
- **Potent Vasoconstrictor**

### Felypressin
- Used to prolong the actions of local anaesthetics
- V₁ Receptor Agonist
- **Potent Vasoconstrictor**

### Thiazides (e.g. Bendroflumethiazide)
- Nephrogenic Diabetes Insipidus
- Increased water reabsorption (see notes)
- **Mechanism unclear, but believed to work by:**
  - Inhibition of the Na⁺/Cl⁻ transport system in the distal convoluted tubule (diuretic effect)
  - Results in volume depletion
  - Compensatory increase in Na⁺ reabsorption from the proximal tubule
convoluted tubule (and small decrease in GFR) as conc. gradient increases.
• Increased proximal convoluted tubule water reabsorption
• Decreased fluid reaches the collecting duct.
• Reduced urine volume.

The beneficial effects of thiazides in nephrogenic DI are enhanced by a reduction in dietary Na+ intake.

| Lithium | Syndrome of Inappropriate ADH (SIADH) | Affects post-receptor events in the collecting ducts (nephrons) thus preventing effective water reabsorption | Can cause diabetes insipidus.  
It is ideal in treating SIADH (where there is an unnecessary release of ADH and increased reabsorption of water), in which the post-receptor events ADH | Endocrinology Lecture 3 |
| --- | --- | --- | --- | --- |
| Dimethyl-Chlor-Tetracycline (DMCT) (Demeclocycline) | Syndrome of Inappropriate ADH (SIADH) | Affects post-receptor events in the collecting ducts (nephrons) thus preventing effective water reabsorption | Can cause diabetes insipidus.  
It is ideal in treating SIADH (where there is an unnecessary release of ADH and increased reabsorption of water), in which the post-receptor events ADH | Endocrinology Lecture 3 |
| CONIVAPTAN VAPTANS (Non-peptide vasopressin analogues) | Congestive Heart Disease and other conditions | V₁ / V₂ Receptor Antagonist | These drugs are currently undergoing clinical trials. | Endocrinology Lecture 3 |
| Levothyroxine Sodium T₄ (Thyroxine Sodium) | Hormone Replacement Therapy (Primary Hypothyroidism) | Replaces deficient Tetraiodothyronine (T₄) – Usually the drug of choice | T₄ can be considered a prohormone (since it needs to be converted to T₃ for metabolism)  
Both drugs are active orally, although Liothyronine Sodium can be given intravenously in myxoedema coma.  
T₄ plasma half-life is 6 days, with a peak effect of 9 days. Half-life for decline of response is 11-15 days.  
T₃ plasma half-life is 2-5 days, with a peak effect in 1-2 days. Half-life for decline of response is 8 days  
Hence both accumulate if given daily.  
They are almost 100% bound to plasma proteins – mainly thyroxine binding globulin (TBG).  
Some T₄ is converted to T₃ in tissues. | Endocrinology Lecture 4/5 |
| Liothyronine Sodium T₃ | | Replaces deficient Triiodothyronine (T₃) – Used for more rapid action, such as during myxoedema coma (rare) - intravenous | | |
### Further metabolism occurs in the liver (de-iodination, deamination and conjugation).

- Free and conjugated hormone is secreted in the bile and urine:
  - $T_3$ is cleared in a few hours
  - $T_4$ is cleared in about 6 days

### Unwanted Effects:
- Signs and symptoms of hyperthyroidism
  - High BMR, Increased temperature, Sweating, Sensitivity to heat, Nervousness, Increased appetite
- Consequences of enhanced activity in the sympathetic NS
  - Tremor, Risk of precipitating angina pectoris, cardiac dysrhythmias or cardiac failure

### Specific Clinical Uses:
- Daily treatment of hyperthyroid conditions:
  - Mainly diffuse toxic goitre / Graves' Disease / Exophthalmic Goitre
  - IgG against component of follicle cell membrane (possibly TSH receptor) – stimulates $T_3/T_4$ secretion
    - [cf benign neoplasm, toxic nodular goitre, Plummer's disease is usually treated surgically if necessary]
  - Treatment prior to surgery
  - Reduction of symptoms while waiting for radioiodine to act.

  _Treatment regime may involve propranolol → rapidly reduces tremor and tachycardia_

### Pharmacokinetics:
- The drug is orally active.
- Carbimazole is a prodrug, it has to first be converted to methimazole.
- Plasma $T_{1/2} = 6$-15 hours
- The drug can cross placenta, and is secreted in the milk.
- The drug can be metabolised in the liver and is secreted in the urine.

### Unwanted Effects:
- Agranulocytosis, granulocytopenia (reduction in / absence of granular leukocytes) – rare and reversible on withdrawal of drug.
- Rashes (relatively common)
| Potassium Iodide (KI) | Hyperthyroid Conditions | Inhibition of thyroid hormone secretion by:  
Inhibits iodination of thyroglobulin  
Inhibits $H_2O_2$ generation (thyroperoxidase) | • Doses of at least 30 times the average daily requirement of iodide are required.  
• Uses:  
  o Preparation of hyperthyroid patients for surgery  
  o Severe thyrotoxic crisis (thyroid storm)  
• Main Actions include:  
  o Inhibition of thyroid hormone secretion  
  o Hyperthyroid symptoms reduce within 1-2 days  
  o Vascularity and size of gland reduces in 10-14 days  
• Unwanted Effects:  
  o Allergic reactions (e.g. rashes, fever, angio-oedema)  
• Pharmacokinetics:  
  o Given orally  
  o Maximum effects after 10 days continuous administration | Endocrinology Lecture 4/5 |
|----------------------|-------------------------|---------------------------------|------------------------------------------------|---------------------------------|
| Radio-Iodine ($^{131}$I) | Hyperthyroid Conditions  
Papillary and follicular thyroid carcinoma | Cytotoxicity of thyroid tissue | • Treats hyperthyroidism and thyroid tumours.  
• Mode of action:  
  o Isotope is processed in the same way as stable iodide, and becomes incorporated into thyroglobulin and therefore concentrates in the colloid region.  
  o Isotope emits $\beta$-particles (very short range) with cytotoxic effects limited to follicular cells.  
• Administer as a single oral dose (370-555 MBq)  
• Radioactive half life is around 8 days.  
• Radioactivity is negligible after 2 months, maximum effects of about 2-3 months.  
• Avoid in children and pregnant patients.  
• Low doses of $^{131}$I (or Technecium 99 pertechnetate) tests thyroid function (when administered intravenously), with negligible cytotoxicity. | Endocrinology Lecture 4/5 |
NB: Oxytocics (e.g. oxytocin, ergometrine and prostaglandins) increase motility.

Abortifacients (e.g. prostaglandins and progesterone antagonists) are used in abortion.

Tocolytics (e.g. β-adrenoceptor agonists) are used

| Oxytocin (Oxytocics – increase motility) | Clinical Uses:  
1. Induction of labour at term (controlled i.v. infusion)  
2. Prevention treatment of post-partum haemorrhage (slow i.v. injection/infusion, Local pressor action in uterus suppresses bleeding)  
3. Facilitation of milk let-down (intranasal spray) | Increase Motility  
In Uterus:  
• Rhythmic contraction (Fundus → Cervix)  
  Requires local PG production  
• Dilation of cervix  
• Suppressed by progesterone, enhanced by oestrogen  
• Most marked in late stages of pregnancy  
In mammary glands:  
• Contraction of myoepithelial cells  
• Milk Ejection  
CVD (Pharmacological)  
• Transient vasodilation and tachycardia  
• Constriction of umbilical arteries and veins  
Renal (Pharmacological)  
• Anti-Diuresis and secondary hyponatraemia (i.e. VP like) | Targets for Oxytocin:  
• Therapeutic advantage (Major) in uterus and mammary gland (myoepithelial cells)  
• Unwanted Effects (Minor) in cardiovascular system and kidneys  
• Additional physiological effects in CNS.  
Clinical Uses:  
• Induction of Labour at term  
  ○ Controlled i.v. infusion  
• Prevention treatment of post-partum haemorrhage  
  ○ Slow i.v. injection/infusion  
  ○ Local pressor action in uterus suppresses bleeding  
• Facilitation of milk let-down  
  ○ Intranasal Spray  
Pharmacokinetics  
• Administration  
  ○ i.v. infusion/slow injection  
  ○ Intranasal Spray  
• Distribution  
  ○ Extracellular Fluid  
• Metabolism  
  ○ Liver, Kidney, Plasma (Placenta-derived enzyme)  
  ○ T\(_1/2\) is short (about 5 minutes)  
Unwanted Effects (Oxytocin overdose)  
• Compromised placental exchange of O\(_2\) / nutrients leading to foetal distress  
• Foetus forced against an undilated cervix leading to lacerations / trauma  
• Uterine rupture | Endocrinology Lecture 6 |
| **CNS (Physiological)** | **Ergometrine** (Oxytocics – increase motility)  
(Physiological)  
• Maternal/paternal behaviour  
• Social Recognition  
• Bonding  
• Trust  
• Transient (but serious) hypotension with reflex tachycardia  
• Water intoxication of mother and foetus  
CNS effects – trust, paternal/maternal bonding etc.  
**Clinical Uses:**  
• Routine management of 3rd stage of labour, i.m. +/- oxytocin  
• High Risk postpartum haemorrhage, i.v. after delivery of the shoulders  
• Post-partum atony of the uterus - oral  
**Myometrium:**  
• Increases tone  
• Prolonged series of contractions  
**Blood Vessels:**  
• Constriction of umbilical and placental vessels  
**Ergot derived from fungus Clariceps Purpurea**  
**Contra-Indications:**  
• Pregnancy prior to 3rd stage of labour  
• Pre-eclampsia and other vascular diseases  
**Pharmacokinetics:**  
• Administration  
  o i.v., i.m. or oral  
• Distribution  
  o Well Distributed  
• Metabolism  
  o Hepatic  
  o Duration 3-4 hours  
**Unwanted Effects:**  
• Abdominal Pain  
• Hypertension  
• Anginal Pain  
• Nausea/Vomiting  
**Endocrinology Lecture 6** |
| **Prostaglandins** | Dinoprostone (PGE2 Vasodilator)  
Gemeprost (PGE1 Derivative)  
**Clinical Uses:**  
• Induction of abortion – dinoprostone – intravaginally as a gel or tablet  
• Induction of cervical ripening (at term: dinoprostone, prior to abortion: gemeprost vaginal pressaries)  
**Prostaglandins:**  
• Stimulate contractions **throughout** pregnancy  
• Induce cervical ripening – i.e. softening of the tissue  
**Unwanted Effects:**  
• Potentiation of actions of oxytocin  
• Nausea, vomiting and diarrhoea  
• Hypertension (PGF2α), Hypotension (PGE2)  
• Pyrexia (fever)  
**Endocrinology Lecture 6** |
| **Carboprost** (15methyl PGF2α – Vasoconstrictor) | • Post-partum haemorrhage in those resistant to oxytocin and ergometrine (carboprost, i.m.) |  |  |
| (Oxytocics – Increase motility) | Prostaglandins are also abortifacients (induce abortion) |  |  |

| **Progesterone Receptor Blockers** (e.g. Mifepristone) | Clinical Uses:  
- Early therapeutic abortion (<63 days)  
- Softening and dilation of cervix prior to suction abortion  
- Therapeutic abortion (13-20 weeks) with gemeprost | Competitive antagonist of progesterone at the progesterone receptor with weak agonist activity | Mechanism of early therapeutic abortion:  
- Blockade of uterine progesterone receptors  
- Detachment of blastocyst  
- Reduced hCG production  
- Reduced progesterone production by ovarian corpus luteum  
- Causing:  
  - Accenuated decidual breakdown  
  - Increased uterine prostaglandin production  
| **Abortifacients** (induce abortion) |  |  | Endocrinology Lecture 6 |

| **Tocolytics** (reduce motility)  
- β-adrenoceptor agonists | Receptor activation increases intracellular cAMP  
This causes relaxation of the uterine muscle |  |  | Endocrinology Lecture 6 |
| **Dexamethasone** | **Low Dose Dexamethasone Suppression Tests - Confirming Cushing’s Syndrome** | **Dexamethasone is a steroid hormone which affects the Hypothalamo - Adenohypophysial - Adrenal Axis** | **Low Dose:**  
Give 0.5mg Dexamethasone every 6h for 48h  
In normal patients: Cortisol levels fall to 0 (suppressed)  
In Cushing’s patients: 680 (any cause of Cushing’s will fail to suppress) | **Endocrinology Lecture 7** |
|----------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| **High Dose Dexamethasone Suppression Tests – Differentiating Cushing’s Disease from other causes** | It causes negative feedback inhibition of ACTH release by the adenohypophysis (similar to Cortisol) | **High Dose:**  
Give 2.0mg Dexamethasone every 6h for 48h  
In pituitary Cushing’s, cortisol levels fall from ~680 to ~235nM  
In other causes (e.g. Ectopic ACTH or adrenal tumouts), still high ~680. | | |
| **Metyrapone** | Treats Cushing’s Syndrome (Reduces production of Cortisol)  
Enzyme Inhibitor | **Inhibits the 11β-Hydroxylase Enzyme which converts:**  
11deoxycortisol $\rightarrow$ cortisol  
11deoxycorticosterone $\rightarrow$ corticosterone | **Key Effects of Metyrapone:**  
- Cortisol Synthesis blocked  
- ACTH secretion increased  
- Plasma deoxycortisol increased  
  
**NB:** 11-deoxycortisol has no negative feedback effect on pituitary / hypothalamus so ACTH levels climb.  
**Uses:**  
- To treat some cases of Cushing’s Syndrome:  
  - E.g. bronchial tumours that are inaccessible to surgery  
  - Doses (oral) may be tailored to corticosteroid production.  
  - Corticosteroid replacement therapy may be required with high doses (as corticosterone production is also stopped in addition to cortisol)  
- Control of Cushing’s symptoms prior to surgery.  
**Unwanted Actions:**  
- Nausea, vomiting and dizziness  
- Sedation, hypoadrenalism  
  **Caution:** against impaired performance of skilled tasks (e.g. driving, operating heaving machinery)  
- Hypertension on long term administration  
  As deoxycorticosterone accumulates in the zona glomerulosa, it has aldosterone like effects (increased salt retention and hypertension) | **Endocrinology Lecture 7** |
| **Trilostane** | Treats Cushing’s Syndrome (Reduces production of Cortisol) | Inhibits 3β-Hydroxysteroid dehydrogenase (3β-HSD)  
  
  Pregnenalone → Progesterone  
  17α-Hydroxypregnenalone → 17α-Hydroxyprogesterone | Key Effects of Trilostane:  
  o Blocks synthesis of: Aldosterone, corticosterone, cortisol and androstenedione (testosterone/17β-Oestradiol)  
  o Blocks glucocorticoids, mineralocorticoids and sex steroid production.  
  Uses:  
  • Cushing’s Syndrome  
  • Primary Hyperaldosteronism  
  o Not easy to tailor dose to corticosteroid production.  
  Monitor circulating corticosteroids and plasma electrolytes and replace with glucocorticoids and mineralocorticoids when necessary.  
  • Reduction of sex steroid hormone production  
  o E.g. post menopausal breast cancer which has relapsed after initial surgery with anti-oestrogens.  
  Unwanted Actions:  
  o Nausea, vomiting, diarrhoea, flushing | Endocrinology Lecture 7 |
|---|---|---|---|---|
| **Ketoconazole** | Treats Cushing’s Syndrome (Reduces production of Cortisol) | Blockage of Cytochrome P450 | Key Effects of Ketoconazole:  
  o Blocks synthesis of: Aldosterone, corticosterone, cortisol and androstenedione (testosterone/17β-Oestradiol)  
  o Blocks glucocorticoids, mineralocorticoids and sex steroid production.  
  Uses (Similar to Metyrapone):  
  • Cushing’s Syndrome  
  • Treatment and control of symptoms prior to surgery  
  • Orally Active  
  Unwanted Actions:  
  o Nausea, vomiting, abdominal pain  
  o Alopecia  
  o Gynecomastia  
  o Oligospermia  
  o Ventricular Tachycardias  
  o (Possibly fatal) Liver Damage (monitor liver function) | Endocrinology Lecture 7 |
| **Aminolutethamide** | Treats Cushing’s Syndrome (Reduces production of Cortisol)  
Enzyme Inhibitor | Inhibits conversion of cholesterol into pregnenalone (very toxic) | Key Effects of Aminolutethamide:  
- Blocks synthesis of: Aldosterone, corticosterone, cortisol and androstenedione (testosterone/17β-Oestrodol)  
- Blocks glucocorticoids, mineralocorticoids and sex steroid production.  
Uses:  
- Adrenocortical carcinoma (malignant)  
- Prostatic cancer (malignant)  
- NB – Replace corticosteroids  
Pharmacokinetics: Orally Active | Endocrinology Lecture 7 |
| **Spironolactone** | Treats Conn’s Syndrome (Primary Hyperaldosteronism)  
Also used for treatment of oedema, congestive heart failure, nephrotic syndrome and cirrhosis of the liver. | Spironolactone is a **prodrug** rapidly metabolised into **canrenone** (competitive antagonist of mineralocorticoid receptor) | Key Effects of Spironolactone:  
- Blocks Na+ resorption and K+ excretion in kidney tubules (K+ sparing diuretic)  
Pharmacokinetics:  
- Orally Active  
- Given in single/divided doses daily  
- Highly protein bound and metabolised in the liver  
Unwanted Actions:  
- Menstrual irregularities  
- Gynaecomastia (androgen receptor binding)  
- GI Tract Irritation  
Contraindications:  
- Renal/Hepatic Disease | Endocrinology Lecture 7 |
<table>
<thead>
<tr>
<th>Compound</th>
<th>Test for Addison’s Disease</th>
<th>Administration of these drugs can be:</th>
<th>Clinical Uses of Glucocorticoids</th>
<th>Lecture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synacthen</td>
<td>Give 250 µg synthetic IM and measure cortisol response.</td>
<td><strong>Oral</strong>&lt;br&gt;<strong>Parenteral (I.V. or I.M.)</strong></td>
<td>1. <strong>Anti-Inflammatory (Immunosuppressive Therapy)</strong>&lt;br&gt;• Asthma&lt;br&gt;• Inflammatory conditions of the skin, nasal mucosa, ear, eye, joints&lt;br&gt;• Autoimmune / Inflammatory disease e.g. rheumatoid arthritis&lt;br&gt;• Other autoimmune disease e.g. myasthenia gravis&lt;br&gt;• Prevent rejection following organ/bone marrow transplant.</td>
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<tr>
<td>synACTHen</td>
<td><strong>Typical Addison’s patient response:</strong>&lt;br&gt;Cortisol at 9AM → 100 (270-900 normal)</td>
<td><strong>Metabolism and Excretion – Hepatic:</strong>&lt;br&gt;• Reduction of A Ring&lt;br&gt;• Other modifications&lt;br&gt;• Conjugation&lt;br&gt;• Excretion via Bile and Urine</td>
<td>2. <strong>Neoplastic Disease</strong>&lt;br&gt;• In combination with cytotoxic drugs in specific</td>
<td></td>
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<tr>
<td>Synthetic ACTH</td>
<td>Administration of IM synacthen (injection):&lt;br&gt;Cortisol at 9.30AM → 150 (&gt;600 normal)</td>
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<tr>
<td>Hydrocortisone</td>
<td>1. <strong>Anti-Inflammatory (Immunosuppressive Therapy)</strong>&lt;br&gt;2. Neoplastic Disease&lt;br&gt;3. Pregnancy</td>
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<td>Lecture 9 + 10</td>
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<tr>
<td>(Cortisol)</td>
<td><strong>Glucocorticoid with mineralocorticoid activity at high doses.</strong>&lt;br&gt;Distribution: 90-95% Bound to Plasma Protein (CBG)&lt;br&gt;Duration/Excretion: t₁/₂=1h, Duration=8h</td>
<td><strong>Administration of these drugs can be:</strong>&lt;br&gt;• Oral&lt;br&gt;• Parenteral (I.V. or I.M.)</td>
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<td>Prednisolone</td>
<td><strong>Glucocorticoid with weak mineralocorticoid activity.</strong>&lt;br&gt;Distribution: Binds to CBG&lt;br&gt;Duration: 12h</td>
<td><strong>Metabolism and Excretion – Hepatic:</strong>&lt;br&gt;• Reduction of A Ring&lt;br&gt;• Other modifications&lt;br&gt;• Conjugation&lt;br&gt;• Excretion via Bile and Urine</td>
<td></td>
<td>Lecture 9 + 10</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td><strong>Synthetic glucocorticoid with no mineralocorticoid activity.</strong>&lt;br&gt;Distribution: Binds weakly to albumin&lt;br&gt;Duration: 36h</td>
<td><strong>Clinical Uses of Glucocorticoids</strong>&lt;br&gt;1. <strong>Anti-Inflammatory (Immunosuppressive Therapy)</strong>&lt;br&gt;• Asthma&lt;br&gt;• Inflammatory conditions of the skin, nasal mucosa, ear, eye, joints&lt;br&gt;• Autoimmune / Inflammatory disease e.g. rheumatoid arthritis&lt;br&gt;• Other autoimmune disease e.g. myasthenia gravis&lt;br&gt;• Prevent rejection following organ/bone marrow transplant.</td>
<td></td>
<td>Lecture 9 + 10</td>
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</tbody>
</table>
malignancies e.g. acute lymphocytic leukaemia
  • To reduce cerebral oedema in patients with brain tumours
  • As a component of anti-emetic treatment with chemotherapy
  • To elevate mood in terminally ill patients.

3. Pregnancy
  • Mature foetal lungs before preterm birth.

Prolonged Glucocorticoid use in excess can lead to Iatrogenic Cushing’s Syndrome

<table>
<thead>
<tr>
<th>Fludrocortisone</th>
<th>Used as an aldosterone substitute</th>
<th>Aldosterone Analogue</th>
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<tr>
<td></td>
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<td>Distribution: Binds weakly to albumin only.</td>
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<td>If less is administered, more bioavailability.</td>
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<td>Cross placenta, and also secreted in milk.</td>
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<td>Fludrocortisone is used instead of aldosterone, as aldosterone is not as clinically effective when given orally.</td>
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<td>Administration – Oral</td>
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Endocrinology Lecture 10
| **17β-Oestriol (and its esters)** | Well absorbed, but undergo extensive first pass metabolism, so usually given **i.m. in oil vehicle**. This:  
- Delays absorption  
- Maintains plasma levels over extended periods  
- Prolongs duration of action  
Conjugation is mainly as sulphates, and is excreted in the bile and urine.  
Types:  
- **Oestriol** – *a naturally, orally active oestrogen*  
- **Oestrone Sulphate** – ‘Conjugated’ oestrogen (*natural and Premarin*)  
  - Orally active, hydrolysed to (more active) oestrogen in peripheral tissue.  
- **EthinyI Oestriol** – *A semi-synthetic oestrogen. An oestriol with an ethinyl group at C17.*  
  - Resistant to metabolism and orally active. So the **drug of choice.**  
- **Transdermal Skin Patches**  
  - Oestrogens readily cross membranes  
  - This route avoids first pass metabolism  
Bioavailability:  
- 70% of circulating oestrogens are bound to plasma proteins – sex steroid hormone binding globulin and albumin.  
Physiological Actions:  
- **Increase negative and positive feedback** (LH Surge and ovulation)  
- **Increase smooth muscle contractility** (Uterus and fallopian tubes) | **Endocrinology Lecture 11** |
<table>
<thead>
<tr>
<th>Effects</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cervical secretions – Decreased viscosity</td>
<td>(favours penetration of sperm)</td>
</tr>
<tr>
<td>• Stimulates endometrial proliferation and glandular secretions.</td>
<td></td>
</tr>
<tr>
<td>Unwanted Effects:</td>
<td></td>
</tr>
<tr>
<td>• Blood clotting factors <strong>Increase</strong></td>
<td></td>
</tr>
<tr>
<td>o Increased incidence of thromboembolic disease</td>
<td>(chronic usage at high doses)</td>
</tr>
<tr>
<td>• Endometrium Proliferation</td>
<td></td>
</tr>
<tr>
<td>o Increased risk of endometrial cancer</td>
<td></td>
</tr>
<tr>
<td>o Reduce by co-administration of progestogens</td>
<td></td>
</tr>
<tr>
<td>• On the breast</td>
<td></td>
</tr>
<tr>
<td>o Breast discomfort</td>
<td></td>
</tr>
<tr>
<td>o Increased risk of breast cancer (controversial)</td>
<td></td>
</tr>
<tr>
<td>• <strong>Increase</strong> salt and water retention in the kidneys</td>
<td>Can cause oedema and accentuate oedema due to other causes (e.g. cardiac failure, kidney disease)</td>
</tr>
<tr>
<td>o Can cause oedema and accentuate oedema due to other causes (e.g. cardiac failure, kidney disease)</td>
<td></td>
</tr>
<tr>
<td>o Contributes to hypertension and weight gain</td>
<td></td>
</tr>
<tr>
<td>• Chemoreceptor trigger zone and vomiting centre of the brain</td>
<td></td>
</tr>
<tr>
<td>o Nausea</td>
<td></td>
</tr>
<tr>
<td>• Headaches</td>
<td></td>
</tr>
<tr>
<td>• <strong>Increased weight</strong> due to fat deposition</td>
<td></td>
</tr>
</tbody>
</table>
| Progestogens (Two types) | Progesterone (natural progestogen) and its analogues e.g. medroxyprogesterone acetate | • Poorly absorbed  
• Rapidly metabolised in the liver  
• Give I.M. in oily vehicle (depot preparation)  

Physiological actions of progesterone:  
1. **Changes in mucosal secretions in fallopian tubes** (important for the nourishment of the fertilized ovum)  
2. **Thickens cervical mucus** (Hostile to sperm)  
3. **Decreases myometrial contractility** (Favours implantation and embryo development)  
4. **Stimulates mammary tissue development (primed by oestrogen)** (Prepares breasts for lactation)  
   
   *(In breast, stimulates development of lobules and alveoli in mammary tissue prepared by oestrogens)*  

**Progesterone only contraceptives:**  
• May be used when oestrogen-only contraceptives are contraindicated:  
  o CVS Problems  
  o History of Thrombosis  
  o Prior to major surgery  
  o During lactation  
• Administer:  
  o Orally  
  o I.M. depot preparation (e.g. Depot-Provera-Medroxyprogesterone for long acting contraception use) | Endocrinology Lecture 11 |
| **Testosterone Analogues**  
e.g. norethisterone | • Orally active  
• Metabolised to other biologically active steroids e.g. testosterone, oestrogen  

Bind to SHBG and Albumin in the circulation |
|---|---|
| Combined Oral Contraceptives  
(Orally active oestrogen e.g. ethinyl oestriodiol + Progesterone e.g. norethisterone) | Efficacy at minimal drug concentrations to suppress fertility  

• **Feedback actions of progesterone in hypothalamus and pituitary** → suppresses menstrual cycling  
• **Progesterone thickens cervical mucus** → provides environment inhospitable to sperm  
• **Oestrogen upregulates progesterone receptors** → enhances sensitivity to progesterone  
• **Oestrogen counteracts the androgenic effects of synthetic progesterone** → prevents masculanisation  
• **Oestrogen also contributes to negative feedback at hypothalamus and pituitary** → synergises with progesterone |
| ‘Emergency’ Contraception  
(Post-Coital-Pill / Morning After Pill) | • Combined oestrogen and progesterone (prescription only) or progesterone only (over the counter)  
• Emergency contraception has doses higher than that used for COC’s  

**Administration:**  
• 2 Doses 12 hours apart  
• Beginning ASAP and within 72 hours of intercourse  
• Single, double-dose tablet also available over the counter (Levonorgestrel ‘Levonelle’)  
• May cause nausea & vomiting:  
  o Repeat the dose if necessary, may require co-administration with an anti-emetic. |
<table>
<thead>
<tr>
<th>Effectiveness:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prevents 75-85% of pregnancies that might otherwise occur after unprotected intercourse</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• If unsuccessful, there are no harmful effects to the woman, the course of her pregnancy or her foetus.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Caution:</th>
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</thead>
<tbody>
<tr>
<td>• Ineffective in terminating an established pregnancy – do not use with a known/suspected pregnancy.</td>
</tr>
</tbody>
</table>

Use progesterone only when there is a history of stroke, blood clots or migraine.
### Calcium Salts e.g. Calcium Chloride, Calcium Gluconate

**Uses:**
1. **Osteoporosis**
   - From (postmenopausal oestrogen deficiency, age related deficiency in bone homeostasis, raised glucocorticoid levels)
2. **Hypocalcaemias**
   - Dietary deficiency of calcium, malabsorption of Ca2+, hypoparathyroidism, hypocalcaemic tetany (i.v.)
3. **Cardiac Dysrhythmias**
   - caused by severe hypokalaemia (i.v.)

**Pharmacokinetics – Calcium Chloride**
- Administer i.v. Slow Infusion
- Can cause peripheral vasodilation, cutaneous burning sensation and a moderate fall in blood pressure.
- **DO NOT USE ORALLY** – as it is a gastric irritant, and do not inject any Ca2+ salt directly into tissues (e.g. IM) as it can cause tissue necrosis.

**Pharmacokinetics – Calcium Gluconate**
- Orally active – does not cause gastric irritation
- Administer i.v. for severe hypocalcaemic tetany

### Bisphosphonates / Diphosphonates (analogues of pyrophosphate)
- e.g. sodium etidronate, alendronate

**Uses:**
1. **Treating Paget’s Disease**
2. **Management of hypercalcemia**
   - associated with malignancies
3. **Cancer**
   - treatment to delay bone metastases
4. **Osteoporosis induced by high pharmacological**

**Inhibits recruitment, and promotes apoptosis of osteoclast cells (favouring bone resorption)**

**i.e. reduced bone turnover**

Indirectly stimulates osteoblast activity (cells which lay down bone matrix)

**Pharmacokinetics:**
- Orally active but poorly absorbed (take on an empty stomach – food especially milk decreases drug absorption)
- Accumulates at the site of bone mineralisation and remains part of the bone until resorbed (months, years)
- Excreted in the urine **unmetabolised**.

**Unwanted Actions:**
- Increase in non-mineral osteoid may predispose to fractures.
- Gastric Pains/GI Upsets
- Oesophagitis
- Bone Pain

### Endocrinology Lecture 14
<table>
<thead>
<tr>
<th>Oestrogen Receptor (ER) Ligands</th>
<th>Prevention of postmenopausal osteoporosis</th>
<th>Inhibits Osteoclast recruitment</th>
<th>Unwanted Actions of ER Ligands:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Oestrogens e.g. ethinyl estradiol (ER Agonist)</td>
<td></td>
<td>Opposes PTH</td>
<td>• Increased risk of endometrial cancer (aim for selective bone SERM)</td>
</tr>
<tr>
<td>2. Tissue selective ER antagonist/antiestrogen e.g. Tamoxigen</td>
<td></td>
<td></td>
<td>• (Controversial) increase in risk for breast cancer</td>
</tr>
<tr>
<td>(antagonises ER’s in breast, but has ER activity in bone)</td>
<td></td>
<td></td>
<td>• Minor GI problems</td>
</tr>
<tr>
<td>3. Tissue selective ER agonists e.g. Raloxifen</td>
<td></td>
<td></td>
<td>• Small increase in risk of venous thromboembolism and pulmonary embolism</td>
</tr>
<tr>
<td>(further selectivity on bone)</td>
<td></td>
<td></td>
<td>Endocrinology Lecture 14</td>
</tr>
</tbody>
</table>
| Calcitonin | 1) Paget’s Disease *(Relieves bone pain and neurological complications)*  
2) Osteoporosis *(Postmenopausal & glucocorticoid induced)*  
3) In treating Hypercalcaemias *(Primary Hyperparathyroidism – diseases of PTH excess)*  
   *(Vitamin D Intoxification/excess, Neoplasias, malignancies, osteolytic bone metastases)* | Released by thyroid gland parafollicular cells → calcitonin **decreases** plasma calcium by:  
1. Inhibiting Osteoclasts  
2. Inhibiting kidney a-hydroxylase | Pharmacokinetics:  
- Synthetic salmon and human calcitonin are available for clinical use.  
- Route of administration:  
  - s.c./i.m. injection (Paget’s Disease)  
  - Intranasally (Postmenopausal osteoporosis)  
- Resistance due to AB formation may develop after a few months.  
Unwanted Actions:  
- Inflammatory reaction at site of injection  
- Nausea / Vomiting  
- Facial Flushing  
- Tingling sensation in hands  
- Unpleasant taste in mouth |
**Vitamin D**  
(Fat soluble vitamin)

| **Physiological role in maintaining plasma calcium and regulating cell growth.** | **Ergocalciferol:**  
- Prevents osteomalacia (defects in bone mineralisation due to Vitamin D deficiency) and rickets (juvenile form of Vitamin D deficiency) and disorders of Vitamin D absorption.  
- To treat hypercalcaemias associated with hyperparathyroidism (preferable to PTH treatment → expensive, parenteral, more side effects)  

**Uses** – Treatment of diseases associated with hypocalcaemias.

**Calcitriol:**  
- To treat osteodystrophy arising as a result of decreased calcitriol production due to chronic renal failure.

**Actions/mechanisms:**

1. Calcitriol binds to its intracellular receptors which belong to the superfamily of nuclear receptors.

2. In the *small intestine*: *Enhances Transcription* of a Ca2+ transporter protein – intestinal absorption of Ca2+ phosphate are increased.

3. In the kidney it increases reabsorption of Ca2+ and phosphate.

4. In the bone – promotes healthy mineralization, growth and remodelling.

5. Role in cell growth and differentiation in many tissues especially the bone and marrow.

**Misc:**
- Nicotine – *increases* vasopressin secretion
- Alcohol and Glucocorticoids – *decrease* vasopressin secretion
- Chlorpropamide – is a cause for causing Syndrome of Inappropriate ADH (SIADH)