

Pharmacology of Corticosteroids

By

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Slides are adopted and modified from **Dr. Alia Alshanawani**

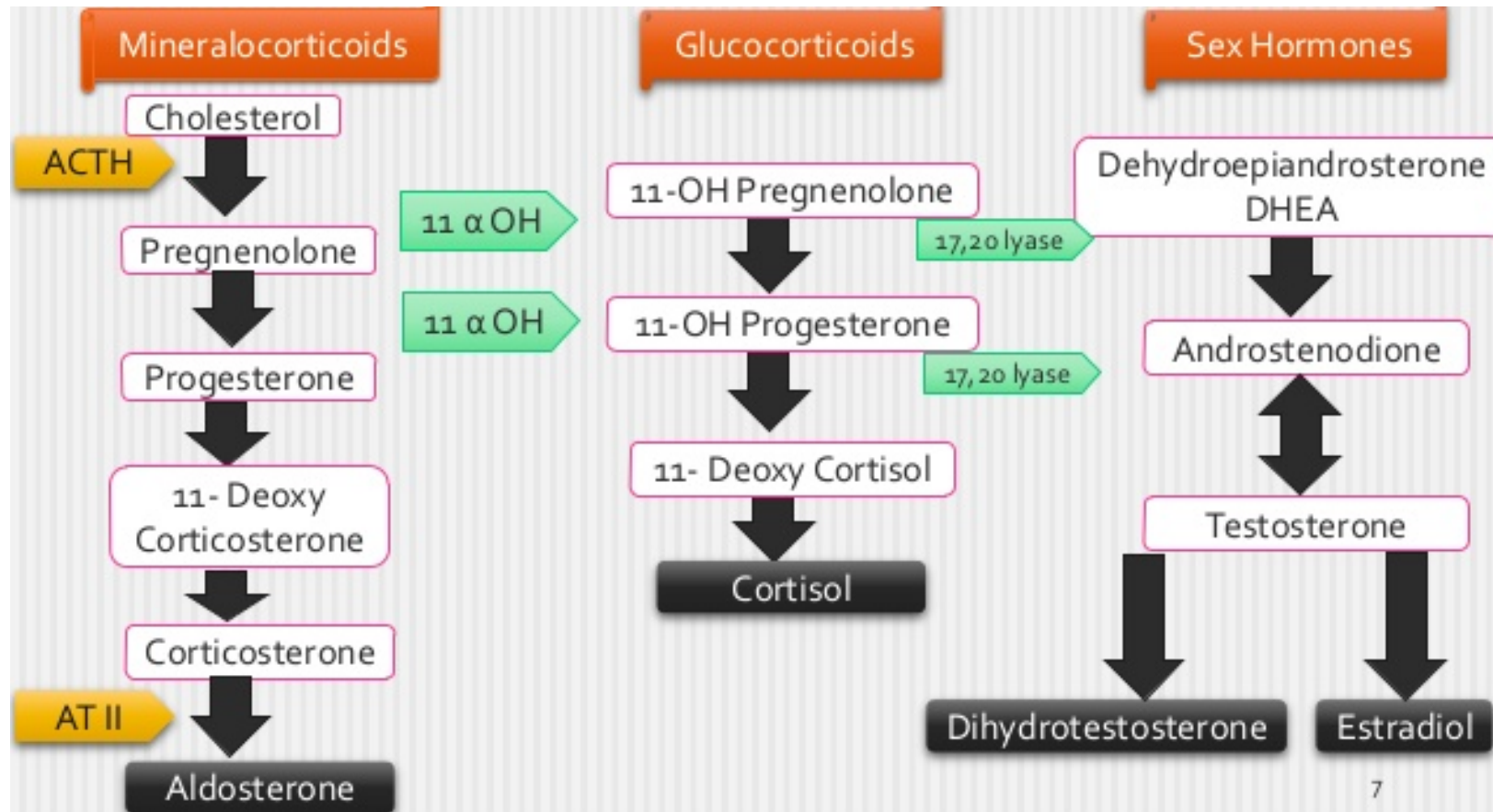
Objectives

- By the end of this lecture, the student will be able to Know Corticosteroids: glucocorticoids (GCs) and mineralocorticoids (MCs) from different perspectives:
 - Their synthesis
 - Their Mechanism of actions
 - Their Metabolic, catabolic, anti-inflammatory and immunosuppressive effects
 - Some examples of GCs and MCs
 - Some of their clinical uses
 - Toxicity
 - GCs and MCs antagonists

Introduction

- The **Corticosteroids** are steroid hormones produced by the adrenal cortex.
- **They consist of two major groups:**
 1. Glucocorticoids [Major cortisol (Hydrocortisone)]
 2. Mineralocorticoids (most important Aldosterone)

Biosynthesis of Adrenal Hormones



GCs and MCs Effects:

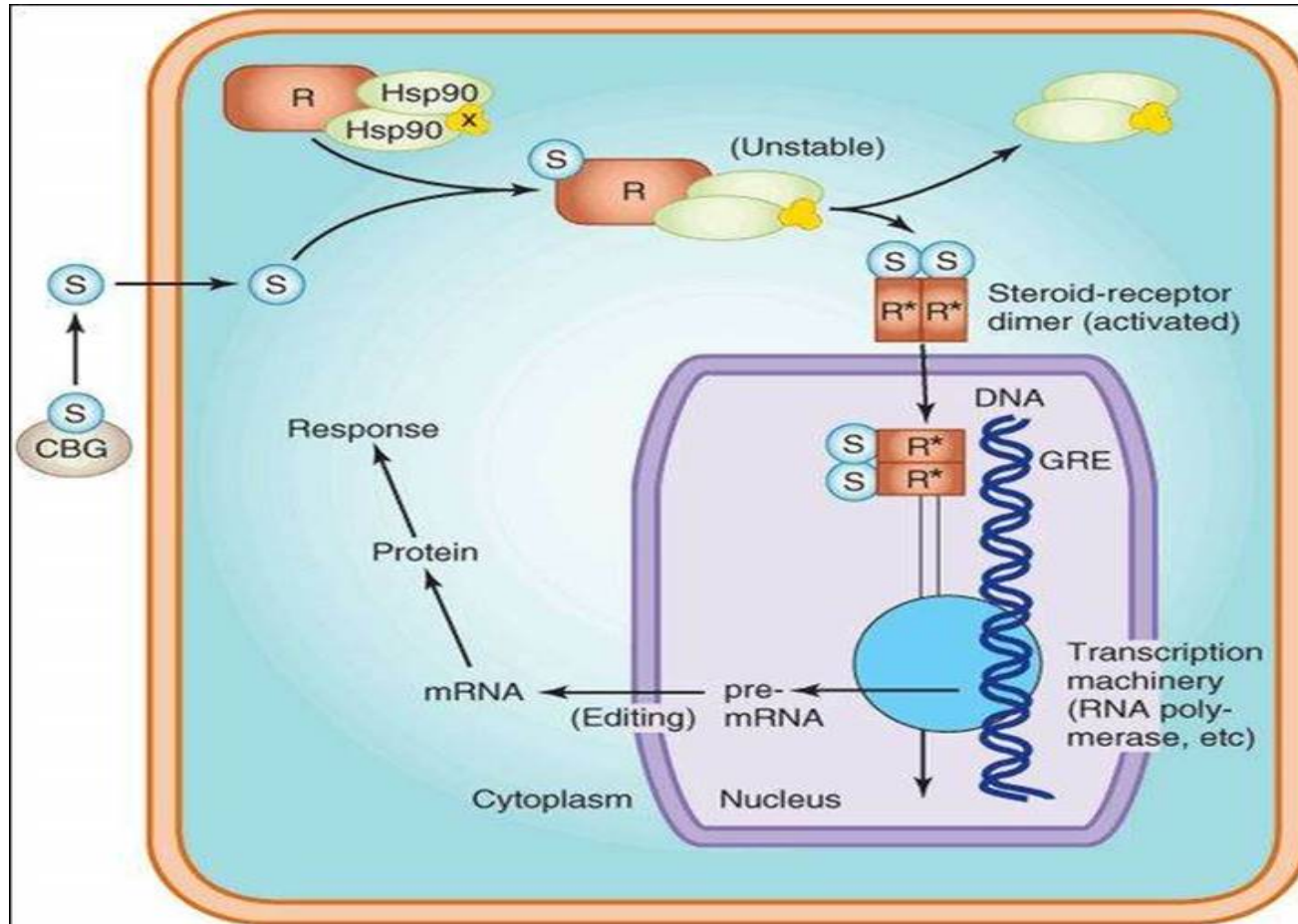
- **Glucocorticoids:**

They have important effects on intermediary **metabolism, catabolism, immune responses, growth** and **inflammation**.

- **Mineralocorticoids:**

They have **salt-retaining activity** which **regulate sodium & potassium reabsorption** in the collecting tubules of the kidney.

GCs Mechanism of Action



GCs Mechanism of Action

- Corticosteroid is present in the blood bound to the **corticosteroid binding globulin (CBG)** & enters the cell as the free molecule.
- The intracellular receptor (R) is bound to the stabilizing proteins, including heat shock protein 90 (Hsp90) & several others (X). When the complex binds a molecule of steroid, the Hsp90 & associated molecules are released.

GCs Mechanism of Action

- The Steroid– R complex enters the nucleus as a dimer, binds to the **glucocorticoid response element** (GRE) on the gene & regulates gene transcription by RNA polymerase II & associated transcription factors.
- The resulting mRNA is edited & exported to the cytoplasm for the production of protein that brings about the final hormone response.

GCs Metabolic effects

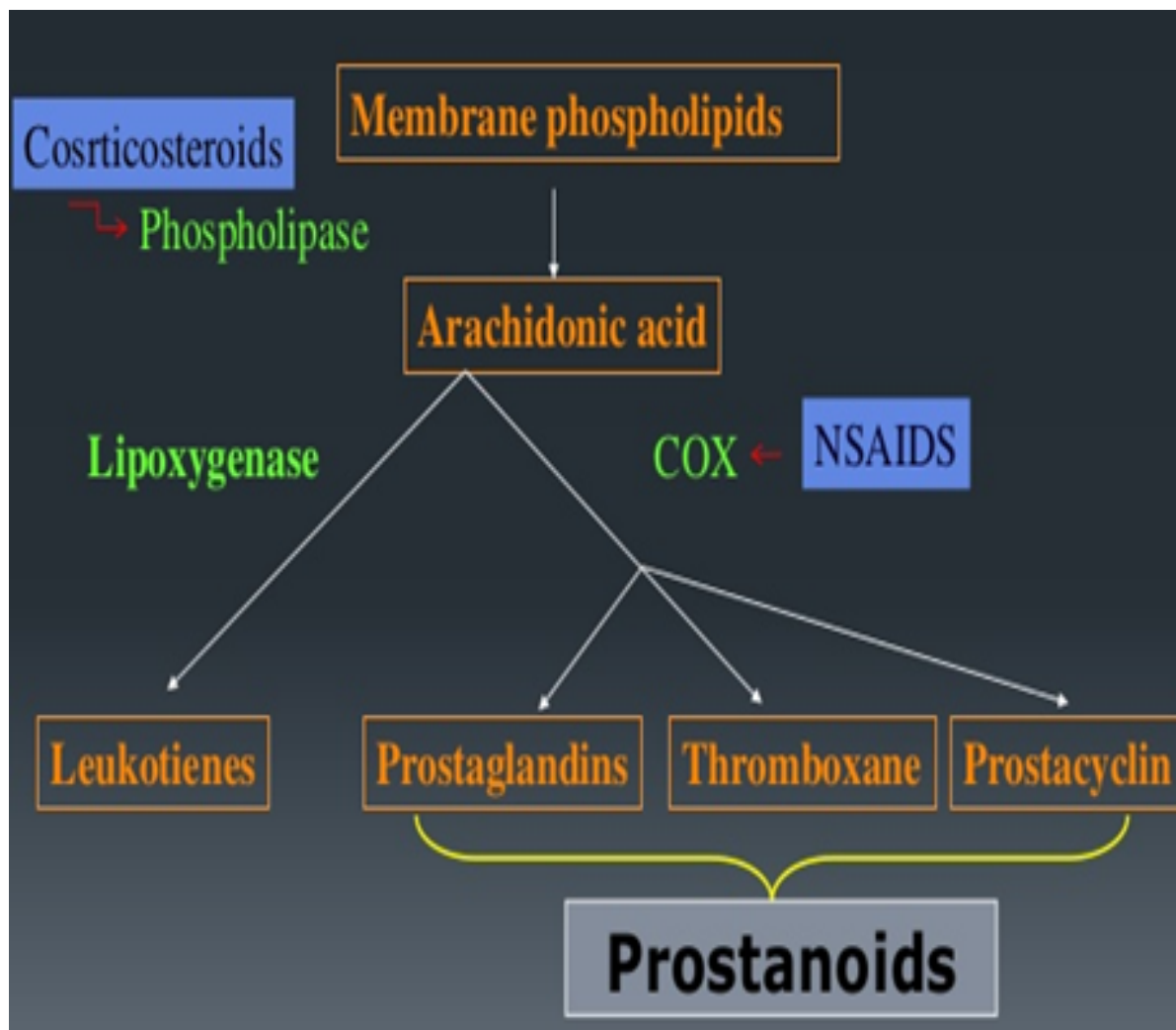
- **Glucocorticoids stimulate gluconeogenesis, as a result:**
 - Blood glucose rises
 - Insulin secretion is stimulated
 - Stimulate lipolysis & lipogenesis (due to increased insulin)
- With a net increase of fat deposition in certain areas e.g, the face (moon faces) and shoulder & back (buffalo hump).
- These effects occur when the patient is treated with 100 mg of hydrocortisone or > for longer than 2 weeks.

GCs Catabolic effects

- Glucocorticoids cause muscle **protein** catabolism (muscle mass)
- Lymphoid & connective tissue, **fat** & skin undergo wasting
- Catabolic effects on **bone** lead to osteoporosis
- In **children**, **growth** is inhibited.

GCs Anti-inflammatory effects

- Glucocorticoids have important inhibitory effects on the distribution, function & migration of **leukocytes**
- Suppressive effect on the inflammatory **cytokines & chemokines**
- These drugs increase neutrophils & decrease **lymphocytes, eosinophils, basophils & monocytes**
- MOA: Inhibit **phospholipase A2** & **Prostaglandins** synthesis.



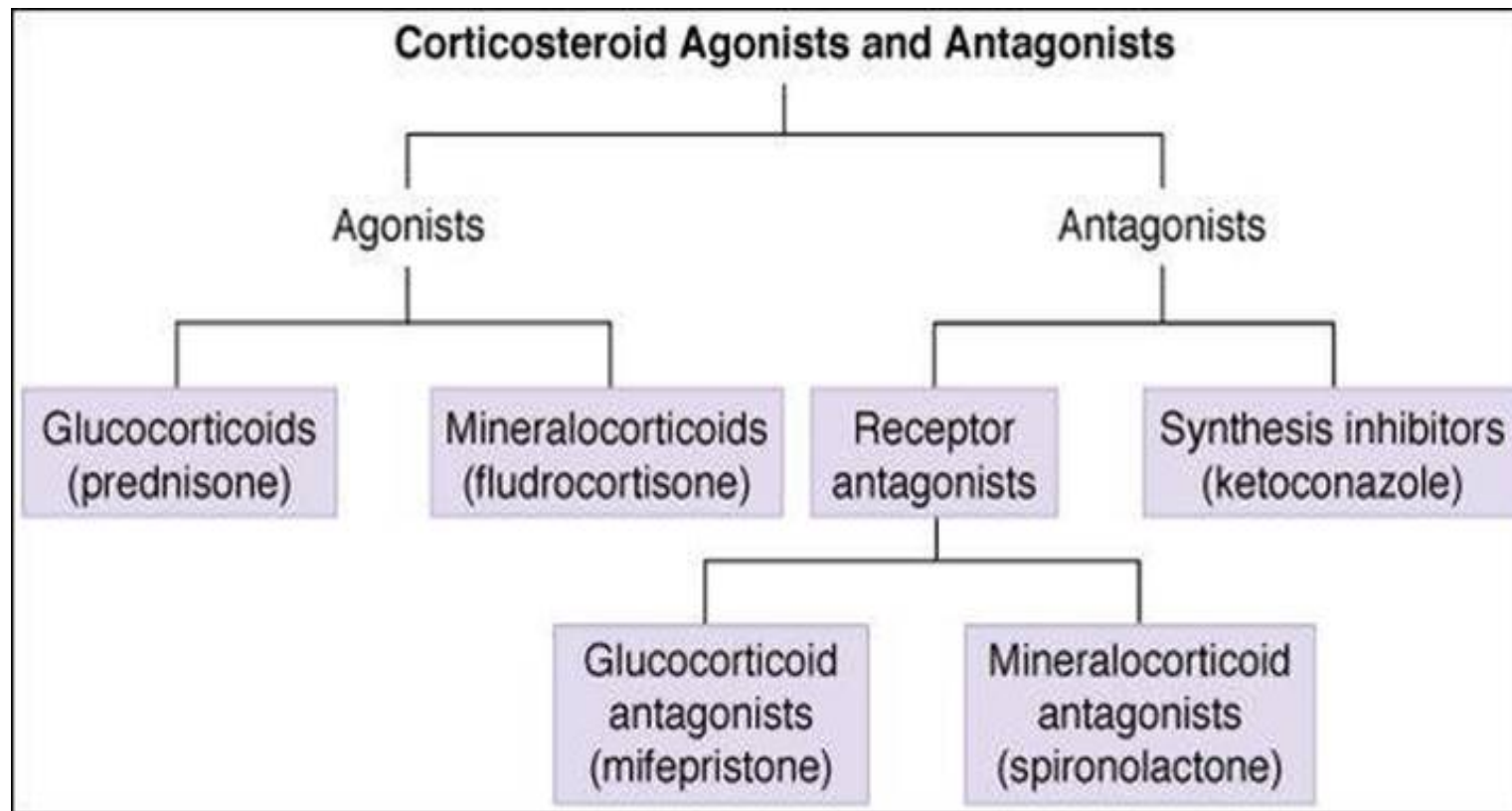
GCs Immunosuppressive effects

- Glucocorticoids **inhibit** cell-mediated immunologic functions, especially dependent on **lymphocytes** & decrease **interleukins** secretion.
- Glucocorticoids do not interfere with the development of normal acquired immunity but delay rejection reactions in patients with organ transplants.

GCs Other effects

- Glucocorticoids such as **cortisol** are required for normal **renal excretion of water** loads.
- **CNS**: When given in large doses these drugs may cause profound behavioral changes (first insomnia & euphoria then depression).
- **GIT**: Large doses also stimulate **gastric acid secretion** & decrease resistance to ulcer formation.

Examples for Corticosteroids: Agonists vs. Antagonists



Examples for Glucocorticoids

- **Cortisol (hydrocortisone)**
- The major natural glucocorticoid
- The physiologic secretion of cortisol is regulated by adrenocorticotropin hormone (ACTH) & secretion rate varies during the day (circadian rhythm), peaks in the early morning & declines about midnight.

Cortisol Pharmacokinetics

- Given **orally**, cortisol is well absorbed from GIT
- Cortisol in the plasma is 95% bound to **CBG**
- It is metabolized by the **liver** & has **short** duration of action compared with the synthetic congeners
- It diffuses **poorly** across normal skin & mucous membranes
- The cortisol molecule also has a small but significant mineralocorticoid effect. This is an important cause of **hypertension** in patients with **cortisol** secreting **adrenal** tumor or a **pituitary** ACTH secreting tumor (Cushing's syndrome).

Examples for Glucocorticoids

- **Synthetic Glucocorticoids**

Large number are available for use:

Prednisonone & its active metabolite prednisolone

Dexamethasonone

Beclomethasonone

Budesonide

Synthetic Glucocorticoids

- **Their properties (compared with cortisol) include:**
 - Longer half life & duration of action
 - Reduce salt retaining effect
 - Better penetration of lipid barriers for topical activity.

| Agent | Activity ¹ | | | Equivalent Oral Dose (mg) | Forms Available |
|--|-----------------------|----------------|----------------|---------------------------|---------------------------|
| | Anti-Inflammatory | Topical | Salt-Retaining | | |
| Short- to medium-acting glucocorticoids | | | | | |
| Hydrocortisone (cortisol) | 1 | 1 | 1 | 20 | Oral, injectable, topical |
| Cortisone | 0.8 | 0 | 0.8 | 25 | Oral |
| Prednisone | 4 | 0 | 0.3 | 5 | Oral |
| Prednisolone | 5 | 4 | 0.3 | 5 | Oral, injectable |
| Methylprednisolone | 5 | 5 | 0.25 | 4 | Oral, injectable |
| Meprednisone ² | 5 | | 0 | 4 | Oral, injectable |
| Intermediate-acting glucocorticoids | | | | | |
| Triamcinolone | 5 | 5 ³ | 0 | 4 | Oral, injectable, topical |
| Paramethasone ² | 10 | | 0 | 2 | Oral, injectable |
| Fluprednisolone ² | 15 | 7 | 0 | 1.5 | Oral |
| Long-acting glucocorticoids | | | | | |
| Betamethasone | 25–40 | 10 | 0 | 0.6 | Oral, injectable, topical |
| Dexamethasone | 30 | 10 | 0 | 0.75 | Oral, injectable, topical |
| Mineralocorticoids | | | | | |
| Fludrocortisone | 10 | 0 | 250 | 2 | Oral |
| Desoxycorticosterone acetate ² | 0 | 0 | 20 | | Injectable, pellets |

¹Potency relative to hydrocortisone.

²Outside USA.

³Triamcinolone acetonide: Up to 100.

Synthetic Glucocorticoids

- **Beclomethasone & budesonide** have been developed for use in **asthma** & other conditions in which good surface activity on **mucous membrane or skin** is needed & systemic effects are to be avoided.
- These drugs **rapidly** penetrate the **airway mucosa** but have very short half lives after they enter the blood, so that systemic effects & toxicity are greatly **reduced**.

Clinical uses of corticosteroids

❖ Adrenal disorders:

- Addison's disease (**chronic** adrenal cortical insufficiency)
- **Acute** adrenal insufficiency associated with life threatening shock, infections or trauma
- Congenital adrenal hyperplasia (in which synthesis of **abnormal forms** of corticosteroids are stimulated by ACTH).

Clinical uses of corticosteroids

❖ Non-adrenal disorders:

- Allergic reactions (e.g. bronchial asthma, angioneurotic edema, drug reactions, urticaria, allergic rhinitis)
- Collagen vascular disorder (e.g; rheumatoid arthritis, systemic lupus erythematosus, giant cell arteritis, polymyositis, mixed connective tissue syndrome)
- Organ transplants (prevention & treatment of rejection – immunosuppression).

Clinical uses of corticosteroids

- **Non-adrenal disorders:**
 - GI disorders such as inflammatory bowel disease
 - Hematologic disorders (leukemia, multiple myeloma, acquired hemolytic anemia, acute allergic purpura)
 - Infections (acute respiratory distress syndrome, sepsis)
 - Neurologic disorders (to minimize cerebral edema after brain surgery, multiple sclerosis).

Clinical uses of corticosteroids

❖ Non-adrenal disorders:

- Pulmonary diseases (e.g.; aspiration pneumonia, bronchial asthma, sarcoidosis).
- Thyroid diseases (malignant exophthalmos, subacute thyroiditis)
- Renal disorders (nephrotic syndrome)
- Miscellaneous (hypercalcemia, mountain sickness).

Corticosteroids Toxicity (Adverse effects)

- Cushing's syndrome (iatrogenic, by higher doses > than 100 mg hydrocortisone daily for > than 2 weeks characterized by moon shape face & buffalo hump)
- Increased growth of fine hair on face, thighs & trunk. Myopathy, muscle wasting, thinning of skin, Diabetes Mellitus
- Osteoporosis & aseptic necrosis of the hip
- Wound healing is impaired

Corticosteroids Toxicity (Adverse effects)

- Peptic ulcer
- Acute psychosis, depression
- Subcapsular cataracts
- Growth suppression
- Hypertension
- Adrenal suppression.

Methods for minimizing these toxicities include

- Local application (e.g, aerosol for asthma)
- Alternate day therapy (to reduce pituitary suppression)
- Tapering the dose soon after achieving a therapeutic response
- To avoid adrenal insufficiency in patients who have had long term therapy, **additional stress doses** may need to be given during serious illness, or before major surgery.

Examples for Mineralocorticoids:

- **Aldosterone:**

- The major **natural** mineralocorticoid in human.
- Aldosterone is the main salt-retaining hormone, promotes Na reabsorption, K excretion, in the distal convoluted tubule & thus it is very important in the regulation of blood volume & blood pressure. Its secretion is regulated by ACTH & by the renin-angiotensin system.
- Aldosterone has short half life & little glucocorticoid activity.

Examples for Mineralocorticoids:

- **Aldosterone Mechanism of action:**

- Same as that of glucocorticoids.

- **Fludrocortisone** is favored for replacement therapy after adrenalectomy & in other conditions in which mineralocorticoid therapy is needed.

Examples for Corticosteroids Antagonists:

- **Receptor Antagonists:**
- **Spironolactone** (mineralocorticoid antagonist & K-sparing diuretic)
 - antagonists of aldosterone at its receptor, used in the treatment of primary aldosteronism (**Conn's syndrome**).
- **Mifepristone:**
 - A competitive inhibitor of glucocorticoid receptors & useful in the treatment of Cushing's syndrome.

Examples for GCs Antagonists:

Synthesis inhibitors:

- **Ketoconazole (anti fungal)**
- **Clinical uses:**
- **Adrenal cancer**, when surgical therapy is impractical or unsuccessful because of metastasis.

Examples for GCs Antagonists:

- **Mechanism of Action of Ketoconazole:**
- It inhibits the cytochrome p450 enzymes necessary for the synthesis of all steroids & is used in a no. of conditions in which reduced steroid level are desirable such as:
 1. Adrenal carcinoma
 2. Hirsutism
 3. Breast cancer
 4. Prostate cancer.

Questions ???