Pharmacology - 2

Dr. Yousef Abusamra. Ph.D.

Assistant professor of pharmacology and pharmacognosy

Faculty of Pharmacy

Philadelphia University – Amman - Jordan

yabusamra@philadelphia.edu.com

Adrenocorticosteroids & Adrenocortical Antagonists

Faculty of pharmacy
Philadelphia University
Amman -JORDAN

Learning outcomes:

After studying this chapter, the student should be able to:

- Summarize the pathophysiological aspects of the adrenal gland hormones.
- Recognize the most commonly prescribed drugs as substitutional therapy, and the cases (diseases) where these drugs are prescribed.
- Numerate some of the most commonly prescribed corticosteroid antagonistic drugs and the diseases prescribed for.
- Explain the mechanisms of action of these drugs either agonistic or antagonistic.
- Numerate the most remarkable side effects, precautions, interactions and certain clinical considerations, if exist, of these medications.
- Recognize the most prominent pharmacokinetic and pharmacodynamic features of these prescribed drugs.

- The natural adrenocortical hormones are steroid molecules produced and released by the adrenal cortex.
- Deficiency of the adrenocortical hormones results in the signs and symptoms of Addison's disease.
- Excess production causes Cushing's syndrome.
- Both natural and synthetic corticosteroids are used for the diagnosis and treatment of disorders of adrenal function.
- Secretion of adrenocortical steroids, especially the glucocorticoids, is controlled by the pituitary release of corticotropin (ACTH).
- Secretion of the salt-retaining hormone aldosterone is primarily under the influence of circulating angiotensin and potassium.

ADRENOCORTICOSTEROIDS:

The hormonal steroids may be classified as:

- **Glucocorticoids:** those having important effects on intermediary metabolism and immune function.
- **Mineralocorticoids:** those having principally salt-retaining activity.
- Those having androgenic or estrogenic activity.

- ✓ In humans, the major glucocorticoid is cortisol and the most important mineralocorticoid is aldosterone.
- ✓ Quantitatively, dehydroepiandrosterone (DHEA) in its sulfated form (DHEAS) is the major adrenal androgen.
- ✓ Androstenediol is a potent estrogen.
- ✓ Androstenedione can be converted to testosterone and estradiol in extra-adrenal tissue.

THE NATURALLY OCCURRING GLUCOCORTICOIDS; CORTISOL (HYDROCORTISONE):

- Its synthesis and secretion are tightly regulated by the central nervous system, which is very sensitive to negative feedback by the circulating cortisol and exogenous (synthetic) glucocorticoids.
- The rate of secretion is governed by pulses of ACTH that peak in the early morning hours and after meals.
- In plasma, cortisol is bound to circulating proteins.
- Corticosteroid-binding globulin (CBG), an α2 globulin synthesized by the liver, binds about 90% of the circulating hormone under normal circumstances. The remainder is free.

- Synthetic corticosteroids such as dexamethasone are largely bound to albumin rather than CBG.
- The half-life of cortisol in the circulation is normally about 60–90 minutes.

Mechanism of Action:

- Cellular mechanism of action of corticosteroids in the inhibition of inflammation. Three anti-inflammatory mechanisms are originated by corticosteroids:

I. Increasing anti-inflammatory mediators.

II. Decreasing inflammatory mediators. and

III. Increasing anti-inflammatory messengers through membrane-associated receptors.

EFFECTS OF GLUCOCORTICOIDS:

1. Promote intermediary metabolism:

- Increase amino acids intake by the liver and kidney.
- They stimulate protein catabolism (except in the liver) and lipolysis, thereby providing the building blocks and energy that are needed for glucose synthesis.
- Glucocorticoid insuffciency may result in hypoglycemia (for example, during stressful periods or fasting).

2. Increase resistance to stress:

- By raising plasma glucose levels, glucocorticoids provide the body with energy to combat stress caused by trauma, fright, infection, bleeding, or debilitating disease.

3. Alter blood cell levels in plasma:

- Glucocorticoids cause a **decrease** in eosinophils, basophils, monocytes, and lymphocytes by redistributing them from the circulation to lymphoid tissue {diminish immunity}.
- Glucocorticoids also **increase** hemoglobin, erythrocytes, platelets, and polymorphonuclear leukocytes.

4. Have anti-inflammatory action:

- The most important therapeutic properties of the glucocorticoids are their potent anti-inflammatory and immunosuppressive activities.
- They lower circulating lymphocytes.
- They inhibit the ability of leukocytes and macrophages to respond to mitogens and antigens.

- Glucocorticoids also decrease the production and release of proinflammatory cytokines.
- They inhibit phospholipase A2 {causes the release of arachidonic acid (the precursor of the prostaglandins and leukotrienes) from membrane-bound phospholipid. The decreased production of prostaglandins and leukotrienes is believed to be the core of the anti-inflammatory action.
- They influence the inflammatory response by stabilizing mast cell and basophil membranes, resulting in decreased histamine release.

5. Other effects:

- They serve as feedback inhibitors of ACTH production and affect the endocrine system by suppressing further synthesis of glucocorticoids and thyroid-stimulating hormone.

- Adequate cortisol levels are essential for normal glomerular filtration.

SYNTHETIC CORTICOSTEROIDS:

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

[1]Potency relative to hydrocortisone.
[2]Outside USA.
[3]Triamcinolone acetonide: Up to 100.

Some commonly used natural and synthetic corticosteroids for general use.

- The synthetic corticosteroids are in most cases rapidly and completely absorbed when given by mouth.
- Alterations in the glucocorticoid molecule influence the pharmacodynamic and pharmacokinetic profile of these agents.
- For example, halogenation, unsaturation and methylation at certain sites prolong the half-life by more than 50%.
- In some cases, the agent given is a **prodrug**; for example, prednisone is rapidly converted to the active product prednisolone by the liver {clinical consideration}.
- The actions of the synthetic steroids are similar to those of cortisol.
- They bind to the specific intracellular receptor proteins and produce the same effects but have different ratios of glucocorticoid to mineralocorticoid potency.

Therapeutic uses of the corticosteroids:

1. Replacement therapy for primary adrenocortical insufficiency (Addison disease):

- Addison disease is caused by adrenal cortex dysfunction (diagnosed by lack of response to ACTH administration).
- **Hydrocortisone**, which is identical to natural cortisol, is given to correct the deficiency. Failure to do so results in death.
- Two-thirds of the daily dosage of hydrocortisone (20-30 mg) is administered in the morning and one-third in the afternoon, mimicking the normal diurnal (of day) variation in cortisol levels.
- Administration of **fludrocortisone**, a potent synthetic **mineralocorticoid**, may also be necessary to correct mineralocorticoid deficiency (e.g. replacing aldosterone).

2. Replacement therapy for secondary or tertiary adrenocortical insufficiency:

- These disorders are caused by a defect in CRH production by the hypothalamus (3°) or in ACTH production by the pituitary (2°).
- Hydrocortisone is used for treatment of these deficiencies.

3. Diagnosis of Cushing syndrome:

- Cushing syndrome is caused by hypersecretion of glucocorticoids (**Hypercortisolism**) that results from excessive release of ACTH by the anterior pituitary or an adrenal tumor.
- Chronic treatment with high doses of glucocorticoids is a frequent cause of iatrogenic Cushing syndrome.

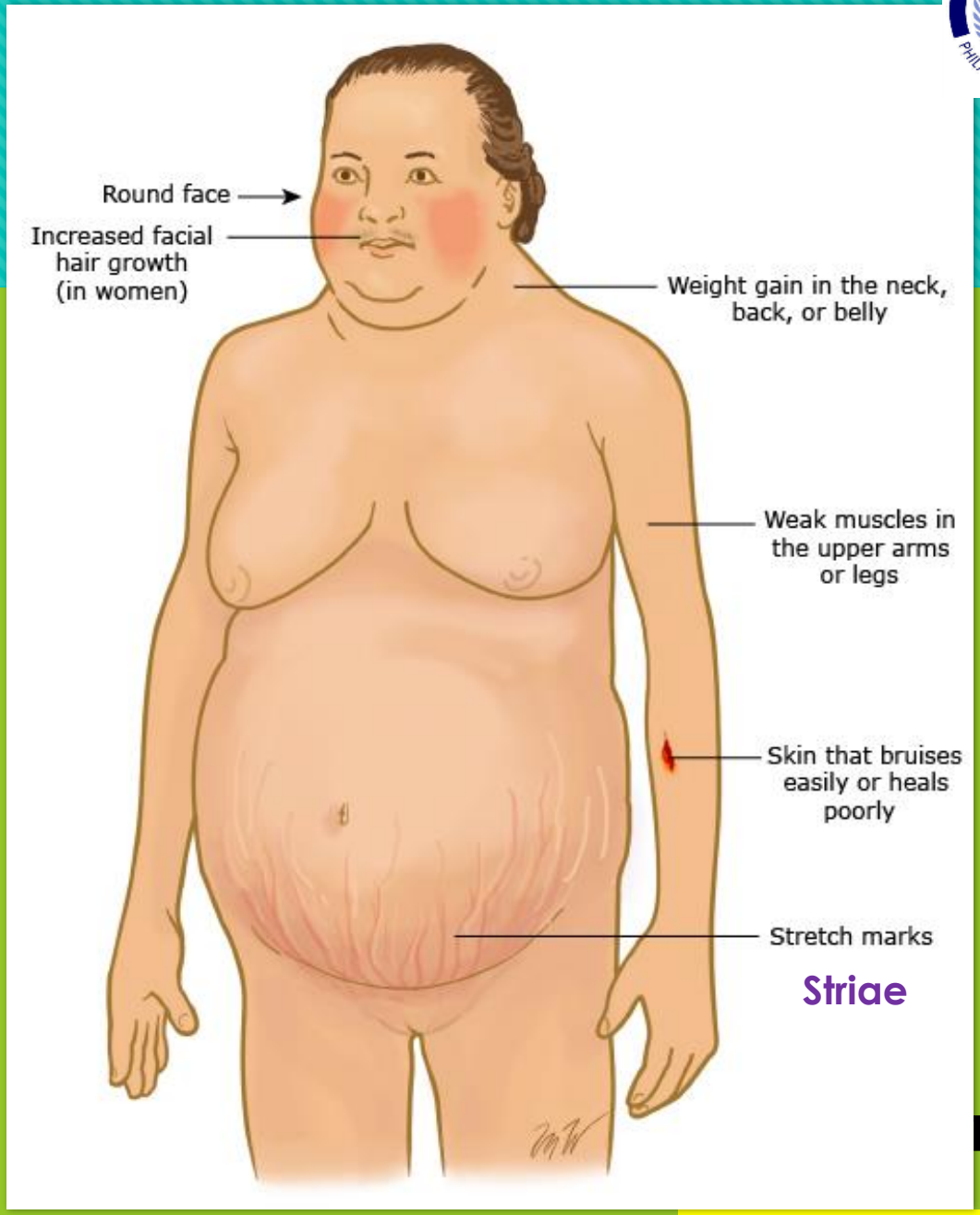
Diagnosis of Cushing syndrome:

- Cortisol levels (urine, plasma, and saliva).
- Dexamethasone suppression; dexamethasone suppresses cortisol release in normal individuals, but not those with Cushing syndrome.
- Dexamethasone will exert a negative feed-back on the pituitary gland, therefore, and suppression occurs if the tumor is in the pituitary gland (2°) not in the adrenal gland (1°)

Symptoms:

- A rounded, plethoric (thick) face and trunk obesity.
- Protein loss including muscle wasting; thinning, purple striae, and easy bruising of the skin. Poor wound healing; and osteoporosis.
- Mental disorders, hypertension, and diabetes.

Symptoms of Cushing syndrome



4. Replacement therapy for congenital adrenal hyperplasia (CAH):

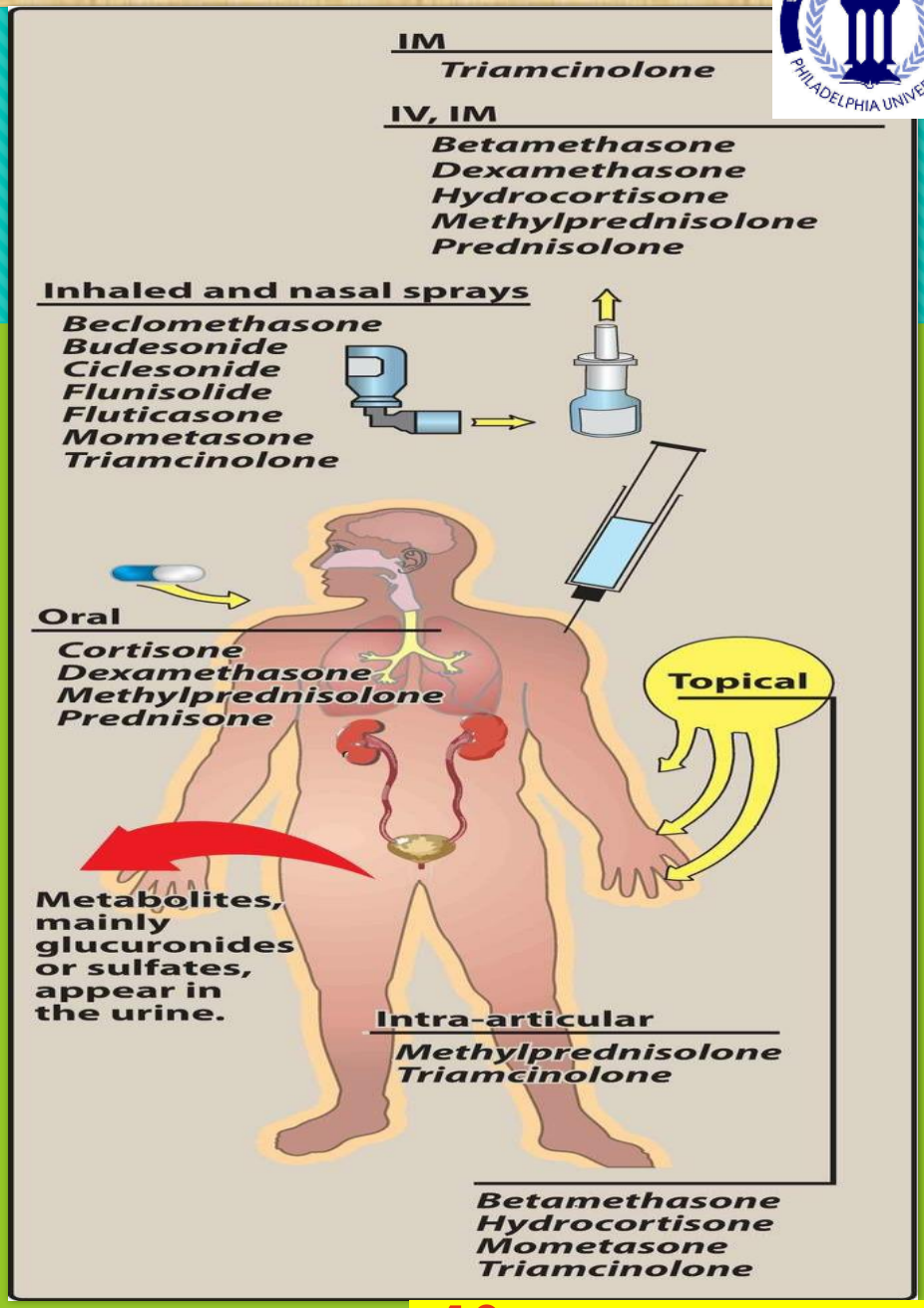
- CAH is a group of diseases resulting from an **enzyme defect** in the synthesis of one or more of the adrenal steroid hormones.
- CAH may lead to virilization {having male physical traits} in females due to overproduction of adrenal **androgens**.
- Treatment requires administration of sufficient corticosteroids to **suppress release of CRH and ACTH** and **normalize hormone levels.**
- This decreases production of adrenal androgens.
- The choice of replacement hormone depends on the specific enzyme defect.
- Infants and children usually take a form of cortisol called hydrocortisone. Adults take hydrocortisone, prednisone, or dexamethasone, which also replace cortisol.

5. Relief of inflammatory symptoms:

- Corticosteroids significantly reduce inflammation associated with rheumatoid arthritis and inflammatory skin conditions, including redness, swelling, heat, and tenderness.
- These agents are important for symptom control in persistent asthma, as well as treatment of exacerbations of asthma and inflammatory bowel disease.
- In osteoarthritis, intraarticular corticosteroids may be used for treatment of a disease flare {an exacerbation of a chronic disease}.
- Corticosteroids are not curative in these disorders.

6. Treatment of allergies:

- Corticosteroids are beneficial in the treatment of allergic rhinitis, as well as drug, serum, and transfusion allergic reactions.
- In the treatment of allergic rhinitis and asthma, fluticasone and others are inhaled into the respiratory tract from a metered dose dispenser.
- This minimizes systemic effects, reducing or eliminating the use of oral corticosteroids.



7. Acceleration of lung maturation:

- **Fetal** cortisol is a regulator of lung maturation. Consequently, a regimen of betamethasone or dexamethasone administered intramuscularly to the mother within 48 hours proceeding (prior to) premature delivery (before 34 weeks) can accelerate lung maturation in the fetus and prevent respiratory distress syndrome [RDS].
- Betamethasone, or dexamethasone, is chosen because maternal protein binding and placental metabolism of this corticosteroid is less than that of cortisol, allowing increased transfer across the placenta to the fetus.
- MECHANISM: It stimulates the synthesis and release of surfactant, which lubricates the lungs, allowing the air sacs to slide against one another without sticking when the infant breathes.

Pharmacokinetics:

- Corticosteroids are readily absorbed after oral administration.
- May be administered intravenously, intramuscularly, intra-articularly, topically, or via inhalation or intranasal delivery.
- All topical and inhaled glucocorticoids are absorbed to some extent and, therefore, have the potential to suppress the hypothalamic–pituitary–adrenal (HPA) axis.
- **90%** bound to plasma proteins, mostly corticosteroid-binding globulin or albumin.
- Corticosteroids are metabolized by the liver microsomal oxidizing enzymes.
- The metabolites are excreted by the kidney.

- Prednisone is preferred in pregnancy because it minimizes steroid effects on the fetus.

1. It is a prodrug that is **not** converted to the active compound, prednisolone in the fetal liver.
2. Moreover, any prednisolone formed in the mother is biotransformed to prednisone by placental enzymes.

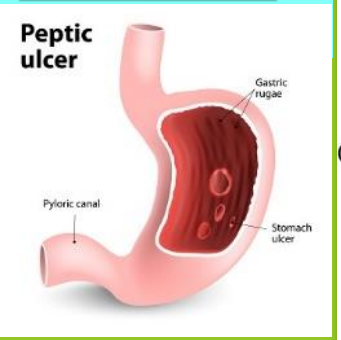
- When large doses of corticosteroids are required for more than **2 weeks**, suppression of the HPA axis occurs.
- **Alternate-day** administration of corticosteroids may prevent this adverse effect by allowing the HPA axis to recover/function on days the hormone is not taken.

Adverse effects:

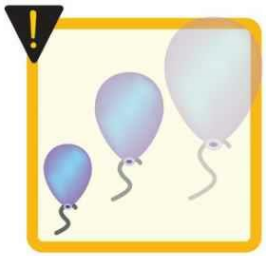
- **Osteoporosis** is the most common adverse effect due to the ability of glucocorticoids to {1} suppress intestinal Ca2+ absorption, {2} inhibit bone formation (inhibit osteoblasts; formation of bone matrix), and {3} decrease sex hormone synthesis (which prolong the life span of osteoblasts).
  - Patients are advised to take calcium and vitamin D supplements.
  - Bisphosphonates: for the treatment of glucocorticoid-induced osteoporosis; inhibit osteoclast-mediated bone resorption.
- **Increased appetite (?)**: is not necessarily an adverse effect; in fact it is one of the reasons of the use of **prednisone** in cancer chemotherapy.
- The classic Cushing-like syndrome (**redistribution of body fat**, **puffy face**, **hirsutism**, and **increased appetite**). **See the figure** ➡

Adrenocorticosteroids & Adrenocortical Antagonists

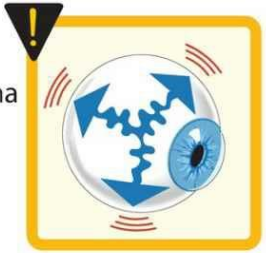
Cataracts
Hyperglycemia
atrophy, ecchymosis, and purple stria
PEPTIC ULCERS



Decreased growth in children



Glaucoma



Centripetal distribution of body fat

Negative calcium balance

Osteoporosis

Impaired wound healing

Increased risk of infection

Increased risk of diabetes

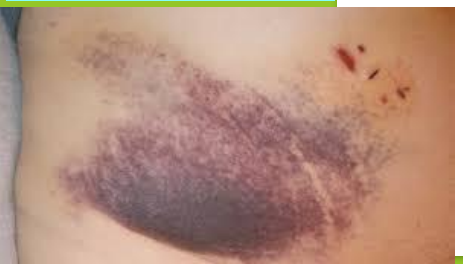
Increased appetite

Euphoria
Depression

Emotional disturbances

Hypokalemia

Ecchymosis:
Blood under the skin



Hypertension

Peripheral edema

Discontinuation:

- **Sudden** discontinuation of these drugs can cause serious consequences if the patient has suppression of the HPA axis.
- In this case, abrupt removal of corticosteroids causes acute adrenal insufficiency that can be fatal.
- This risk, coupled with the possibility that withdrawal could exacerbate the disease, means that the dose must be tapered slowly according to individual tolerance.
- The longer the duration of therapy, the slower the withdrawal period should be.
- The patient must be monitored carefully.

Inhibitors of adrenocorticoid biosynthesis or function:

1. Ketoconazole:

- Ketoconazole is an **antifungal** agent that strongly and non-selectively inhibits **all** gonadal and adrenal steroid hormone synthesis; [anti-steroidogenesis].
- Mechanism of action: It inhibits the cholesterol side-chain cleavage and thee enzymes required for steroid hormone synthesis.
- The sensitivity of the P450 enzymes to this compound in mammalian tissues is much lower than that needed to treat fungal infections, so that its inhibitory effects on steroid biosynthesis are seen only at **high** doses.
- It is used in the treatment of patients with Cushing syndrome (200-1200 mg/d).

- Hepatotoxic; start with a dose of 200 mg/d and increase slowly.

2. Etomidate:

- Etomidate is used for induction of general anesthesia and sedation (off-label: is the use of pharmaceutical drugs for an unapproved indication or in an unapproved age group, dosage, or route of administration; uses are not approved by the FDA. Health providers have approved that use).
- Off-labeled use: to inhibit steroidogenesis.
- At subhypnotic doses (of 0.1 mg/kg per hour), this drug inhibits adrenal steroidogenesis.
- It has been used as the only parenteral medication available in the treatment of severe Cushing's syndrome (off-label).

3. Spironolactone:

- This antihypertensive drug competes for the mineralocorticoid receptor and, thus, inhibits sodium reabsorption in the kidney.
- Spironolactone also antagonizes aldosterone and testosterone synthesis.
- It is effective for:
  1) Hyperaldosteronism.
  2) Hepatic cirrhosis.
  3) Heart failure (among the standard therapy).
  4) Hirsutism in women; probably due to antiandrogen activity on the hair follicle
- Adverse effects include hyperkalemia, gynecomastia (an enlargement or swelling of breast tissue in male), menstrual irregularities.

4. Eplerenone:

- Eplerenone **specifically** binds to the mineralocorticoid receptor, where it acts as an aldosterone antagonist.
- This specificity avoids the adverse effect of gynecomastia that is associated with spironolactone.
- It is approved for the treatment of hypertension and for heart failure with reduced ejection fraction.

5. Metyrapone:

- It interferes with cortisol and corticosterone synthesis by inhibiting steroid hydroxylation step.
- Metyrapone is the only adrenal-inhibiting medication that can be administered to pregnant women with Cushing's syndrome.

- It is used as a test in the diagnosis of Cushing syndrome.
- **Test basis:** in patients with Cushing's syndrome, a normal response to metyrapone {if an increase in the secretion of ACTH did not occur} indicates that the cortisol excess is **not** the result of a cortisol-secreting adrenal carcinoma or adenoma, since secretion by such tumors produces suppression of ACTH and atrophy of normal adrenal cortex.

6. Trilostane:

- Comparable to aminoglutethimide.
- Adverse effects with both drugs are GIT-related (in 50% patients).

7. Abiraterone:

- Abiraterone is the newest of the steroid synthesis inhibitors to be approved.
- It reduces synthesis of cortisol in the adrenal and gonadal steroids in the gonads.
- A compensatory increase occurs in ACTH and aldosterone synthesis, but this can be prevented by concomitant administration of dexamethasone.
- Abiraterone is an orally active steroid prodrug and is approved for the treatment of refractory prostate cancer.

8. Mifepristone:

- A glucocorticoid receptor antagonist with a high affinity to the receptor.
- It has a strong antiprogestin activity and initially was proposed as a contraceptive-contragestive agent (of gestation).
- The mean half-life of mifepristone is 20 hours. This is longer than that of many natural and synthetic glucocorticoid agonists (dexamethasone has a half-life of 4–5 hours).
- The long plasma half-life of mifepristone results from extensive and strong binding to plasma proteins.
- It causes generalized glucocorticoid resistance.
- Mifepristone can only be recommended for inoperable patients with ectopic ACTH secretion {nonpituitary tumors} or

adrenal carcinoma who have failed to respond to other therapeutic manipulations.

Uses:

- To cause an abortion during the early part of a pregnancy (up to week 10 of pregnancy). NOT used in ectopic pregnancy.
- Hypercortisolism in Cushing's syndrome where it is indicated to control hyperglycemia.
- Endometriosis.
- Certain brain tumors.
- At present, the drug is being investigated for psychotic depression.

THE END

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