بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | FINAL 5

Pharmacology of the Adrenal gland pt. 2

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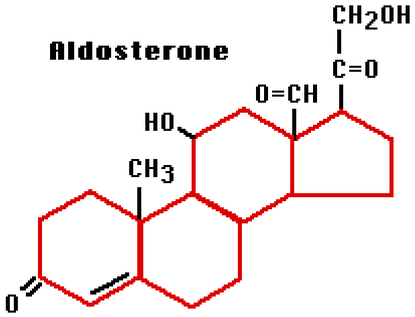
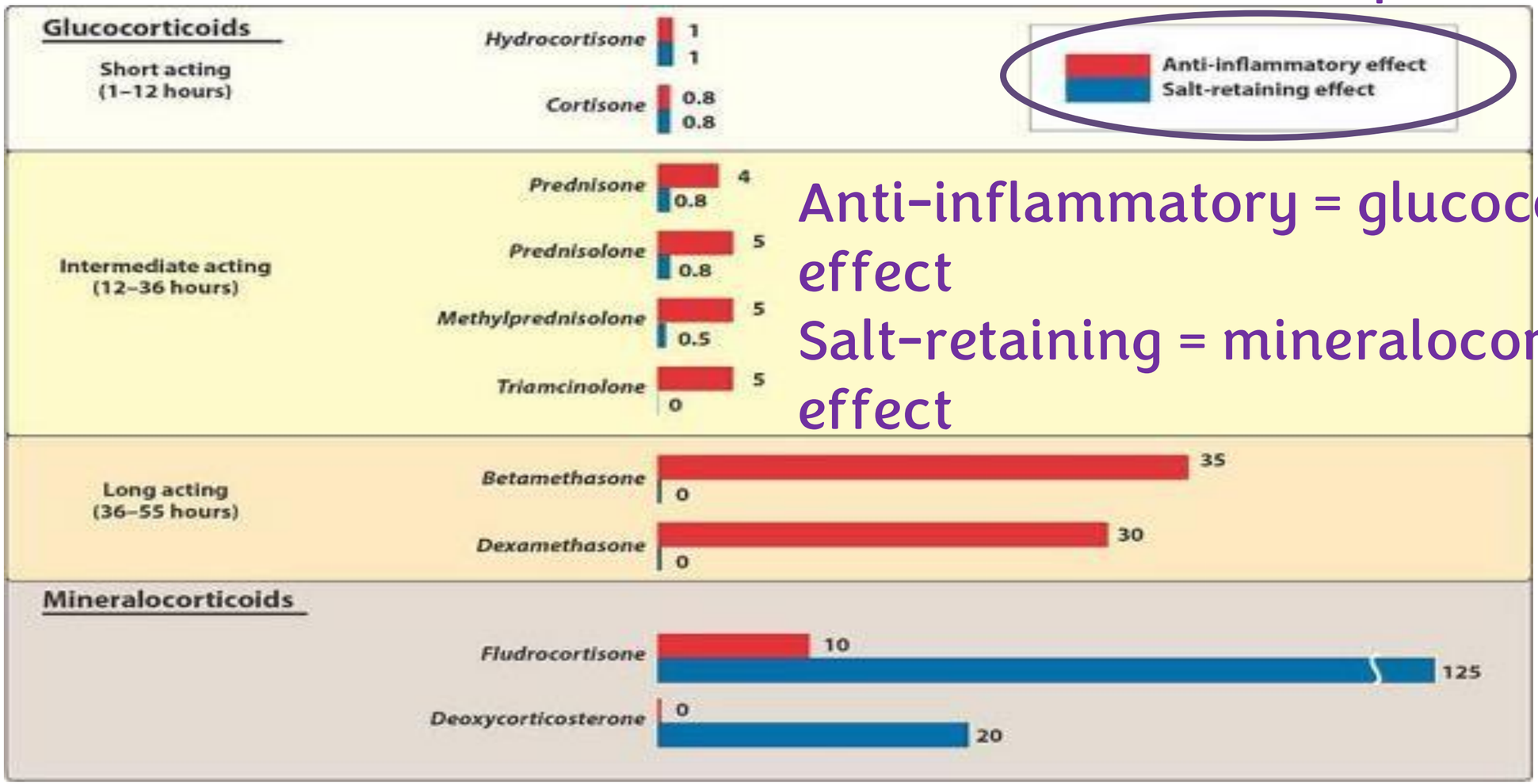
Mineralocorticoids



- Mineralocorticoids help to control the body's **water volume** and **concentration of electrolytes**, especially sodium and potassium.
- Aldosterone acts on kidney tubules and collecting ducts, causing a reabsorption of sodium, bicarbonate, and water.
- Conversely, aldosterone decreases reabsorption of potassium, which, with H+, is then lost in the urine.
- Elevated aldosterone levels may cause alkalosis and hypokalemia.
- Retention of sodium and water leads to an increase in blood volume and blood pressure.

Classification of corticosteroids

Explained below



Anti-inflammatory = glucocorticoidal effect

Salt-retaining = mineralocorticoidal effect

Several **semisynthetic** derivatives of the glucocorticoids have been developed that vary in:

1. Their anti-inflammatory potency
2. Degree to which they cause sodium retention
3. Duration of action

The previous slide is the most important slide according to the doctor.

- Explanation:

We have a problem administering cortisol, which an endogenous glucocorticoid, because of its very short half-life meaning it's rapidly destroyed in the body.

Alright so how did we overcome this? We came up with semisynthetic derivatives (chemically modified cortisol to solve some problems, most important of which is the duration of action), these chemical modifications not only increased the duration of action but also changed/affected some of cortisol's proberties.

Semisynthetic glucocorticoids can be divided depending on the duration of action into 3 subclasses:

1. Short acting
2. Intermediate acting
3. Long acting

- Keep in mind that short acting drugs have a very rapid onset of action, intermediate acting drugs have a slightly delayed onset of action compared to short acting drugs and long acting drugs have the most delayed/slowest onset of action.

Example: in the case of an anaphylactic shock-which is an emergency-one of the drugs that should be administered is a glucocorticoid,but what subclass should it be? Your choice would definitely be a short acting glucocorticoid (Hydrocortisone is the most important one) due to the extremely fast onset of action which is exactly what we need in such emergencies.

On contrast a long acting glucocorticoid would be your choice in managing certain conditions (for instance autoimmune diseases) where we prefer a low frequency of administration.

Take a quick look at the classification above and pay attention to the red and blue bars, what can you see? We can simply say that modifying cortisone has led to changing its anti-inflammatory (red) : salt-retaining (blue) ratio.

-note:

Hydrocortisone resembles cortisol the most in structure and function that's why it's prescribed in case of adrenocortical deficiency (primary, secondary or tertiary), although it's short acting and the dosing will be frequent it's still our choice to be more specific this is exactly why it's the drug of choice. (explained below)

- It might sound contradictory to choose a short acting drug knowing the frequent dosing can negatively affect patients compliance so why do we choose it then?

Remember how cortisol's secretion rate isn't constant throughout the day, which in turn affects the circadian rhythm?we use hydrocortisone to mimic it so that the patient's sleep wake cycle isn't messed up for instance the pateint could take a large dose in the early morning, a smaller dose at noon and a very small dose at evening, see how its quick clearance turned into quite an advantage in this case?

Remember in primary adrenocortical deficiency both cortisol and aldosterone are deficient thus hydrocortisone alone won't be enough so we need to add fludrocortisone (important as it's most commonly prescribed) for its high mineralocorticoidal activity, however this is not the case for secondary and tertiary adrenocortical deficiency since aldosterone won't be affected hydrocortisone alone will be enough. (this is an important exam question)

Long acting glucocorticoids like betamethasone and dexamethasone are most commonly used for managing chronic inflammatory diseases.

Let's take an example:

Antihistamine pills are usually used for managing spring allergies but there are far more superior drugs that could be taken as oily injections* once every spring instead of let's say an antihistamine pill a day. You probably guessed right these powerful drugs are long acting glucocorticoids since glucocorticoids decrease the activity of mast cells which are responsible for releasing histamine.

-There are two types of injections: watery and oily.

*Oily injections refer to medications suspended in an oily base and are only be administered intramusculary. Never ever administer oily injections intravenously!

-Oily injections MOA:

Let's go back to one basic pharmacology principle; absorption which refers to the movement of the drug from the site of administration to the circulation this will help us understand how could one single injection provide protection for months.

Once the drug is injected into the muscle it forms some kind of an oily puddle and given that blood is water based they'll never mix and a physical rebelling force will develop. --->

Now the drug (lipophilic) has to move from that oil puddle to the plasma, passing the capillaries; simplifying the path:

Oil ---> phospholipid bilayer ---> water.

If the medication was suspended in water there'd be no force impeding the drug from moving towards the plasma but since this is not the case and the drug is in an oily medium, an opposing force will develop, slowing the drug's movement towards the circulation=slow rate of absorption=sustained release, this way we are able to create a resvoir of the drug within the body.

Middle Easterners have deficient vitamin B12 absorption and pills barely help that's why we start by 10 watery injections- one injection a day, why watery? To reach the targeted level quickly then to maintain this level we switch to oily injections once a week then once every two weeks and finally once a month.

-note:

Watery injections don't hurt unlike oily injections which are painful since they stretch the muscle fibers.

All this to conclude that a dexamethasone injection for instance could provide protection against spring allergies for 3 months due to two reasons: being long acting and oily.

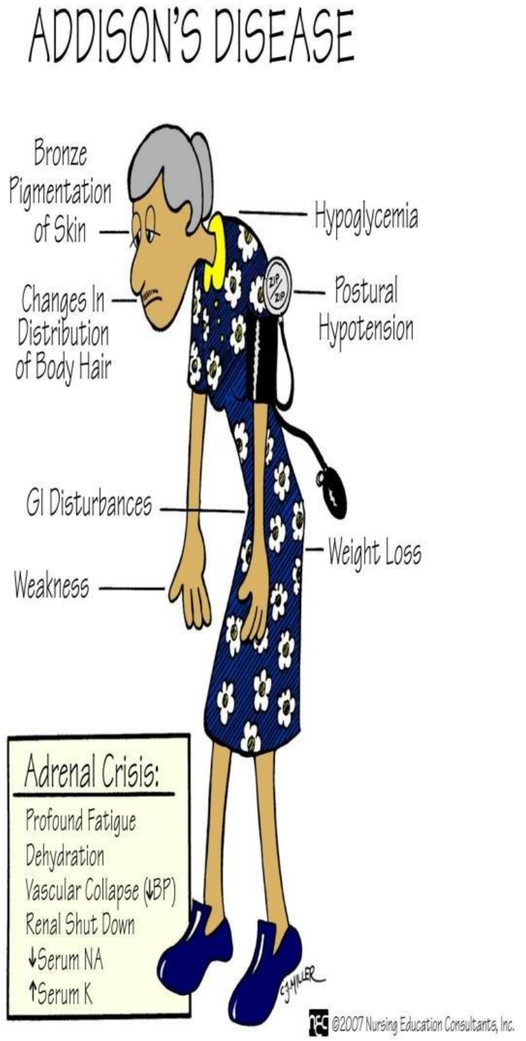
- Intermediate acting glucocorticoids (Trimcinolone) can be used as topical creams to manage immune/inflammatory skin conditions like eczema and psoriasis.
- Acne in definition is an inflammation but we can't really prescribe glucocorticoid creams to treat acne this is because acne vulgaris in the first place develops due to increased sebum secretion which is an ideal environment for the bacterial microorganism Cutibacterium acnes (previously known as P. acnes) to thrive thus prescribing glucocorticoids will get rid of the redness -which is a result of the irritants produced by the anaerobic microorgansim- but won't treat the underlying cause, in fact it'll only make things worse because of their immuno-suppressing properties.
- Our target is to decrease sebum production, this could be achieved by a vitamin A derivative like accutane (Roaccutane), we also add antibacterials to reduce the bacterial load.
- Intermediate glucocorticoids formulated as oral inhalators are used in the management of asthma since it's an inflammatory disease. Why oral inhalators though? for their fast and local effect since acting locally will prevent unwanted systemic effects.
- What is the difference between prednisone and predinsolone (both intermediate acting)?

Prednisone is a prodrug which needs to be activated in the liver unlike prednisolone which is already active. So in case of liver impairment or skin conditions we'd go for prednisolone as it's already active.

Therapeutic uses of the adrenal corticosteroids

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

- Hydrocortisone (cortisol), is given to correct the deficiency.
- The dosage of hydrocortisone is divided so that two-thirds of the normal daily dose is given in the morning and one-third is given in the afternoon. (why?!!)
- Administration of **fludrocortisone**, a potent synthetic mineralocorticoid with some glucocorticoid activity, may also be necessary to raise the mineralocorticoid activity to normal levels.



Therapeutic uses of the adrenal corticosteroids

2.Replacement therapy for secondary or tertiary adrenocortical insufficiency: The adrenal cortex responds to corticotropin (ACTH) administration by synthesizing and releasing the adrenal corticosteroids. Hydrocortisone is also used for these deficiencies.

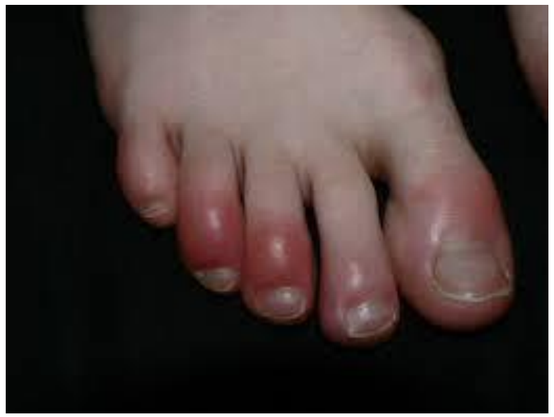
3. Diagnosis of Cushing's syndrome: Dexamethasone suppression test is used to diagnose the cause of an individual's case of Cushing's syndrome.

Dexamethasone can be used to help differentiate between pituitary and ectopic ACTH-dependent Cushing syndrome. Ectopic ACTH production means that ACTH is secreted by cells outside the pituitary that do not normally produce it. First, the ACTH level is measured to determine whether the Cushing syndrome is ACTH-dependent. Then, dexamethasone is administered. If ACTH is produced by a pituitary adenoma (Cushing disease), a high dose of dexamethasone may suppress ACTH secretion and consequently reduce cortisol levels because the pituitary tumor may retain some sensitivity to glucocorticoid negative feedback. In contrast, if ACTH is produced ectopically, the ectopic tumor usually does not respond to this negative feedback, so ACTH and cortisol remain elevated.

Therapeutic uses of the adrenal corticosteroids

3.Replacement therapy for congenital adrenal hyperplasia: Treatment requires administration corticosteroids to normalize hormone levels by suppressing release of CRH and ACTH>>>> This decreases production of adrenal androgens.

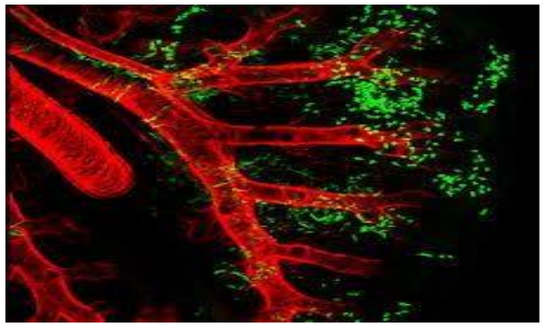
4.Relief of inflammatory symptoms: Glucocorticoids reduce rheumatoid and osteoarthritic inflammations, as well as inflammatory conditions of the skin.



Therapeutic uses of the adrenal corticosteroids

6. Treatment of allergies: Glucocorticoids are beneficial in the treatment of asthma, allergic rhinitis, and allergic reactions. Beclomethasone, triamcinolone, and others are applied through inhalation.

7. Acceleration of lung maturation: Respiratory distress syndrome is a problem in premature infants. Cortisol enhances lung maturation. A dose of beclomethasone is administered intramuscularly to the before delivery.



Dexamethasone in fetal Lung Maturation

- The lungs are among the last organs to achieve functional maturation in the fetus, particularly because adequate production of surfactant develops relatively late in pregnancy. Surfactant is produced by type II pneumocytes and is essential for reducing surface tension within the alveoli and preventing their collapse during expiration. Cortisol plays an important role in fetal lung maturation and stimulates surfactant production. Therefore, when preterm delivery is expected, such as delivery around the seventh month of pregnancy, the fetal lungs may still be immature with insufficient surfactant production, increasing the risk of neonatal respiratory distress syndrome (RDS). To accelerate fetal lung maturation, a corticosteroid such as dexamethasone is administered to the mother before delivery, rather than directly to the fetus. Dexamethasone is a potent glucocorticoid with strong anti-inflammatory activity and minimal mineralocorticoid (salt-retaining) activity. Importantly, it can cross the placenta, reach the fetal lungs, and promote their maturation and surfactant production, thereby reducing the risk of respiratory complications after premature birth.

Corticosteriod Use During Pregnancy

- The first trimester is the most sensitive period for the use of these drugs because corticosteroids can cross the placenta, and this period is characterized by organogenesis, during which the fetal organs are being formed. Therefore, exposure to these drugs during the first trimester may increase concern about possible fetal developmental abnormalities or congenital malformations. For this reason, when possible, we prefer to avoid unnecessary exposure during the first trimester and use them later in pregnancy when clinically indicated

Pharmacokinetics

- The only glucocorticoid that has **no** effect on the fetus in pregnancy is prednisone.

- Prednisone is a prodrug that is not converted to the active compound, **prednisolone**, in the fetal liver.

- **Prednisone is an inactive prodrug that must be converted in the liver to its active form, prednisolone. Since the fetal liver has very limited capacity to perform this conversion, prednisone has no direct effect on the fetus. Therefore, prednisone is generally preferred during pregnancy when a glucocorticoid is required.**

Dosage:

- When large doses of the hormone are required over an extended period of time (**more than 2 weeks)** >>>>> suppression of the hypothalamic-pituitary-adrenal (HPA) axis occurs. (important!)

- **Tapering** means gradually decreasing the glucocorticoid dose when the patient no longer needs the treatment and we want to stop it safely. This is necessary after prolonged glucocorticoid therapy because the exogenous steroid suppresses the HPA axis (CRH → ACTH → cortisol), so gradual dose reduction gives the hypothalamus, pituitary, and adrenal cortex time to recover and resume normal cortisol production.

- For example, the dose may be reduced from 10 mg daily → 7.5 mg daily → 5 mg daily → 2.5 mg daily → stop. In contrast, **alternate-day administration (ADA)** is mainly used when the patient still needs long-term glucocorticoid therapy, but we want to reduce HPA-axis suppression and some adverse effects. Instead of giving the drug every day, it can be given every other morning, for example 10 mg daily may be changed to an appropriate equivalent regimen given every other morning. The steroid-free day allows some recovery of ACTH and endogenous cortisol secretion. Therefore, the main difference is that tapering is used when the goal is to discontinue the drug safely, whereas ADA is used when treatment is still needed but we want to minimize HPA-axis suppression during long-term therapy.

Pharmacokinetics

- To prevent this adverse effect, a regimen of alternate-day administration of the adrenocortical steroid may be useful. This schedule allows the HPA axis to recover/function on the days the hormone is not taken.

- Withdrawal from corticosteroids can be a serious problem (WHY?!), because if the patient has experienced HPA suppression.

- Abrupt removal of the corticosteroids causes an acute adrenal insufficiency syndrome that can be lethal >>>>> So, the dose must be tapered gradually.

Adverse effects

- The common side effects of **long-term** corticosteroid therapy are:

1. Osteoporosis is the due to

A. The ability of glucocorticoids to suppress intestinal Ca2+ absorption
B. Inhibit bone formation
C. Decrease sex hormone synthesis

Alternate-day dosing does not prevent osteoporosis. Patients are advised to take calcium and vitamin D supplements.

2. Cushing-like syndrome may result from either exogenous glucocorticoid administration or endogenous cortisol excess

3.Increased frequency of cataracts. Continuous glucocorticoid administration also increases the risk of cataracts, in which the lens becomes opaque due to glucocorticoid-induced changes in lens proteins, including protein aggregation, which contributes to loss of lens transparency.

4.Hyperglycemia may develop and lead to diabetes mellitus

5. **Hypokalemia** may occur when high glucocorticoid levels exert mineralocorticoid effects, leading to increased sodium reabsorption and water retention together with increased renal potassium excretion; therefore, potassium increases in the urine and decreases in the blood.

6. **Decreased growth in children.** In children, prolonged glucocorticoid administration may cause decreased growth. Glucocorticoids can decrease GH secretion and decrease GH binding to its receptors in the liver by reducing GH receptor expression and responsiveness, resulting in decreased production of IGF-1 (somatomedin). They may also decrease the response of peripheral tissues to somatomedin by interfering with the IGF-1 (somatomedin) receptor pathway, further contributing to growth suppression. However, in severe or life-threatening conditions, the benefit-risk ratio must be considered; if glucocorticoid therapy is necessary to save or adequately treat the patient, it should be prescribed despite its potential negative effect on growth

7. **Increased appetite.**Glucocorticoids increase appetite centrally, leading to increased food intake and weight gain.

8.Increased risk of infection because of their immunosuppressive effect.

9.Peripheral edema due to sodium and water retention.

Coadministration of medications that induce or inhibit the hepatic mixed-function oxidases may require adjustment of the glucocorticoid dose (WHY?!) because they are metabolized by liver P450s

Drugs That Inhibit Endogenous Cortisol Synthesis in Cushing Syndrome

- In Cushing syndrome, there is excessive endogenous cortisol production.
- One therapeutic approach is to inhibit cortisol synthesis.

- The major adrenal steroid hormones are derived from the same building block, cholesterol:

1.Cortisol

2.Aldosterone / mineralocorticoids

3. Androgen

Drugs used to inhibit cortisol synthesis Three important drugs are:

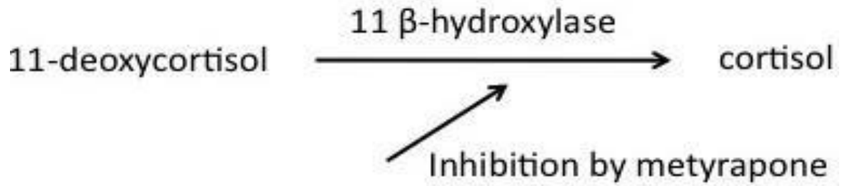
1. Metyrapone

2. Aminoglutethimide

3.Ketoconazole

Inhibitors of adrenocorticoid biosynthesis

Metyrapone



- Is used for tests of adrenal function
- Can be used for the treatment of pregnant women with Cushing's syndrome.
- It interferes with corticosteroid synthesis by blocking the final step (11-hydroxylation) in glucocorticoid synthesis, leading to an <u>increase</u> in 11-deoxycortisol as well as adrenal androgens and the potent mineralocorticoid 11-deoxycorticosterone. (why?! This inhibition stimulates ACTH secretion)

The adverse effects

1. Salt and water retention (WHY?!)
2. Hirsutism (WHY?!)
3. Transient dizziness
4. Gastrointestinal disturbances

Metyrapone

- Metyrapone interferes with corticosteroid synthesis by blocking the final step (11-hydroxylation) in glucocorticoid synthesis
- Specifically, it inhibits 11β-hydroxylase, which normally converts: 11-deoxycortisol → cortisol
- Therefore, metyrapone causes ↓ cortisol production.
- When cortisol decreases, there is less negative feedback on the pituitary: ↓ Cortisol → ↓ negative feedback → ↑ ACTH
- The increased ACTH stimulates the adrenal cortex and drives steroid synthesis, but because the final step toward cortisol is blocked, the precursors before the block accumulate.
- Therefore, metyrapone leads to an increase in 11-deoxycortisol as well as adrenal androgens and the potent mineralocorticoid 11-deoxycorticosterone (DOC).

- **Why do adrenal androgens increase?**
- Because ↓ cortisol causes ↑ ACTH, the increased ACTH stimulates adrenal steroid synthesis and increases the availability of precursors for the androgen pathway: ↓ Cortisol → ↑ ACTH → ↑ adrenal androgens → hirsutism .**Therefore, hirsutism is one of the adverse effects of metyrapone.**

Why does 11-deoxycorticosterone (DOC) increase?

- Although aldosterone itself is mainly regulated by RAAS and serum K^+ rather than ACTH, increased ACTH drives adrenal steroid synthesis upstream of the metyrapone block. This causes increased production and accumulation of 11-deoxycorticosterone (DOC). DOC has potent mineralocorticoid activity: ↑ DOC → ↑ Na^+ and water retention → salt and water retention .**Therefore, salt and water retention is another adverse effect of metyrapone.**

- **Uses:**
- Is used for tests of adrenal function.
- Can be used for the treatment of pregnant women with Cushing's syndrome.

- **Adverse Effects :**
- Salt and water retention → due to increased 11-deoxycorticosterone (DOC) and its mineralocorticoid activity.
- Hirsutism → due to increased adrenal androgens secondary to increased ACTH.
- Transient dizziness.
- Gastrointestinal disturbances

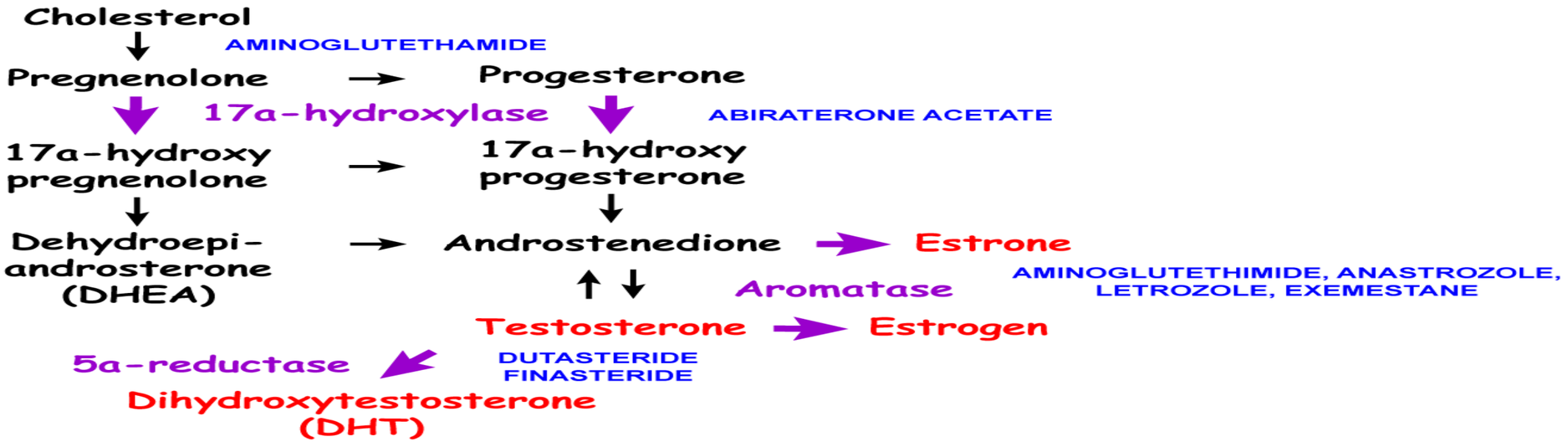
Inhibitors of adrenocorticoid biosynthesis

Aminoglutethimide

- This drug acts by inhibiting the conversion of cholesterol to pregnenolone (the first step)
- As a result, the synthesis of **all** hormonally active steroids is reduced.
- Aminoglutethimide has been used therapeutically in the treatment of:

1. Breast cancer to reduce or eliminate androgen and estrogen production.
2. Useful in the treatment of malignancies of the adrenal cortex to reduce the secretion of steroids.

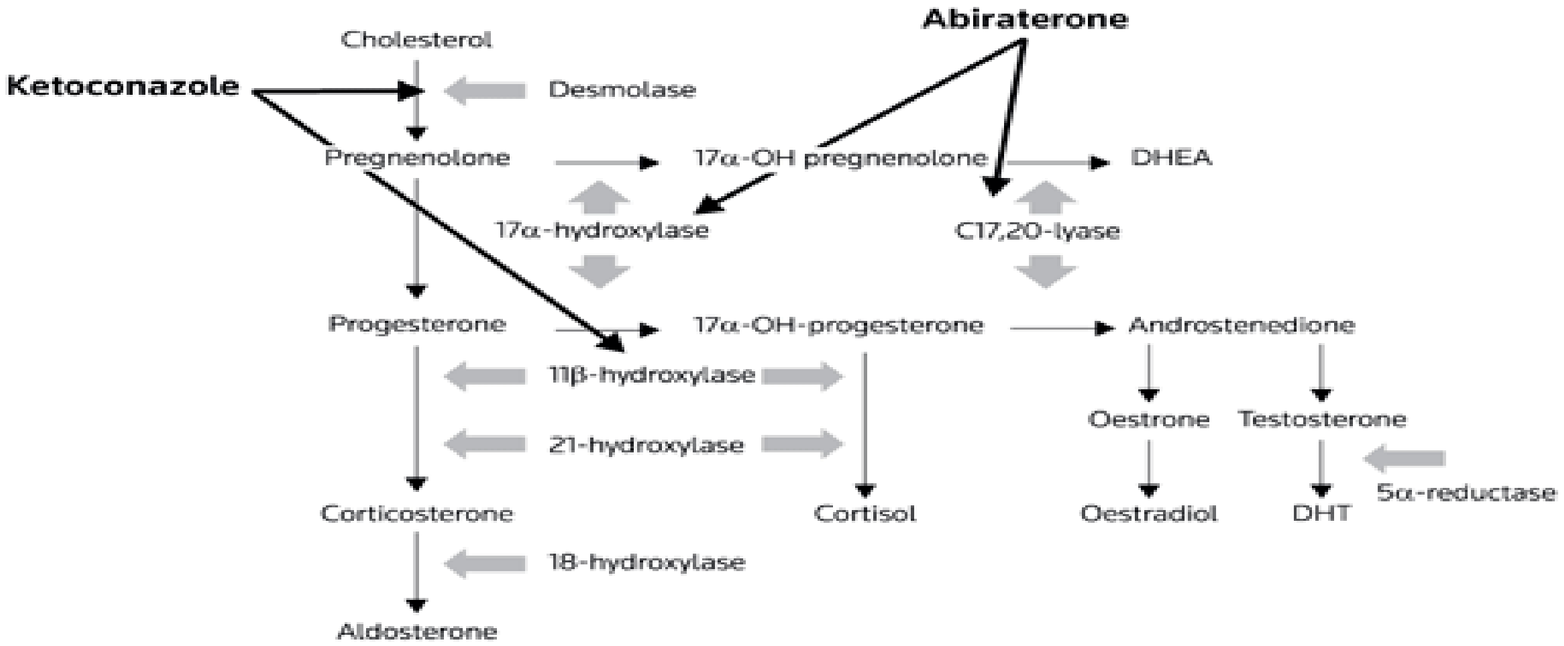
- Recent studies indicate it is an aromatase inhibitor.



Inhibitors of adrenocorticoid biosynthesis

Ketoconazole

- Is an antifungal agent, **and causes hormonal imbalance**
- Strongly inhibits **all** gonadal and adrenal steroid hormone synthesis.
- It is used in the treatment of patients with Cushing's syndrome.



Inhibitors of adrenocorticoid biosynthesis

- Mifepristone

- At high doses, mifepristone is a potent **glucocorticoid antagonist** as well as an **antiprogestin**.
- Its use is presently limited to the treatment of inoperable patients with ectopic ACTH syndrome. (cancer with increased POMC)
- Mifepristone is different from the previous drugs. It does not inhibit cortisol synthesis. Instead, it acts as an antagonist of glucocorticoid receptors, so cortisol is still produced but cannot exert its normal effects through these receptors. Mifepristone also has another activity as a progesterone receptor antagonist. Progesterone is important for maintaining pregnancy, so blocking its receptors can interfere with pregnancy. Therefore, mifepristone may be misused for abortion and emergency contraception.

Inhibitors of adrenocorticoid biosynthesis

Spironolactone

- It competes for the mineralocorticoid receptor and, thus, inhibits sodium reabsorption in the kidney.
- It can also antagonize aldosterone and testosterone synthesis.
- It is effective against hyperaldosteronism.
- It is also useful in the treatment of hirsutism in women (WHY?!) probably due to interference at the androgen receptor of the hair follicle.
- Adverse effects include :
- Hyperkalemia, gynecomastia, menstrual irregularities, and skin rashes.

Spironolactone

- Drugs that act against aldosterone can be used in conditions associated with hyperaldosteronism, such as heart failure, liver cirrhosis, and hypertension. Normally, aldosterone acts in the kidney, particularly on the collecting duct, where it must bind to its mineralocorticoid receptor to produce its effects. Aldosterone therefore acts as an agonist at this receptor, promoting sodium and water retention and potassium excretion. Spironolactone acts as an antagonist of the aldosterone (mineralocorticoid) receptor in the collecting duct. It prevents aldosterone from binding to its receptor and therefore inhibits its effects. Spironolactone will also be discussed later as a diuretic. Spironolactone also acts as an androgen receptor antagonist, giving it an antiandrogenic effect. Therefore, prolonged use in men may reduce androgenic effects and lead to feminizing adverse effects such as gynecomastia. On the other hand, this antiandrogenic effect can be beneficial in women with hirsutism, because blocking androgen receptors reduces the effects of androgens

Inhibitors of adrenocorticoid biosynthesis

Eplerenone

- Eplerenone specifically acts as an aldosterone antagonist.
- **This specificity avoids the side effect of gynecomastia associated with spironolactone**.
- It is an antihypertensive.
- Eplerenone is similar to spironolactone in its main function. It acts as an aldosterone (mineralocorticoid) receptor antagonist, so it blocks the action of aldosterone in the collecting duct. However, unlike spironolactone, eplerenone has little to no antiandrogenic effect because it is more selective for the mineralocorticoid receptor. Therefore, it is much less likely to cause antiandrogen-related adverse effects such as gynecomastia.

Additional Resources:

رسالة من الفريق العلمي:

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			