Pharmacology of corticosteroids

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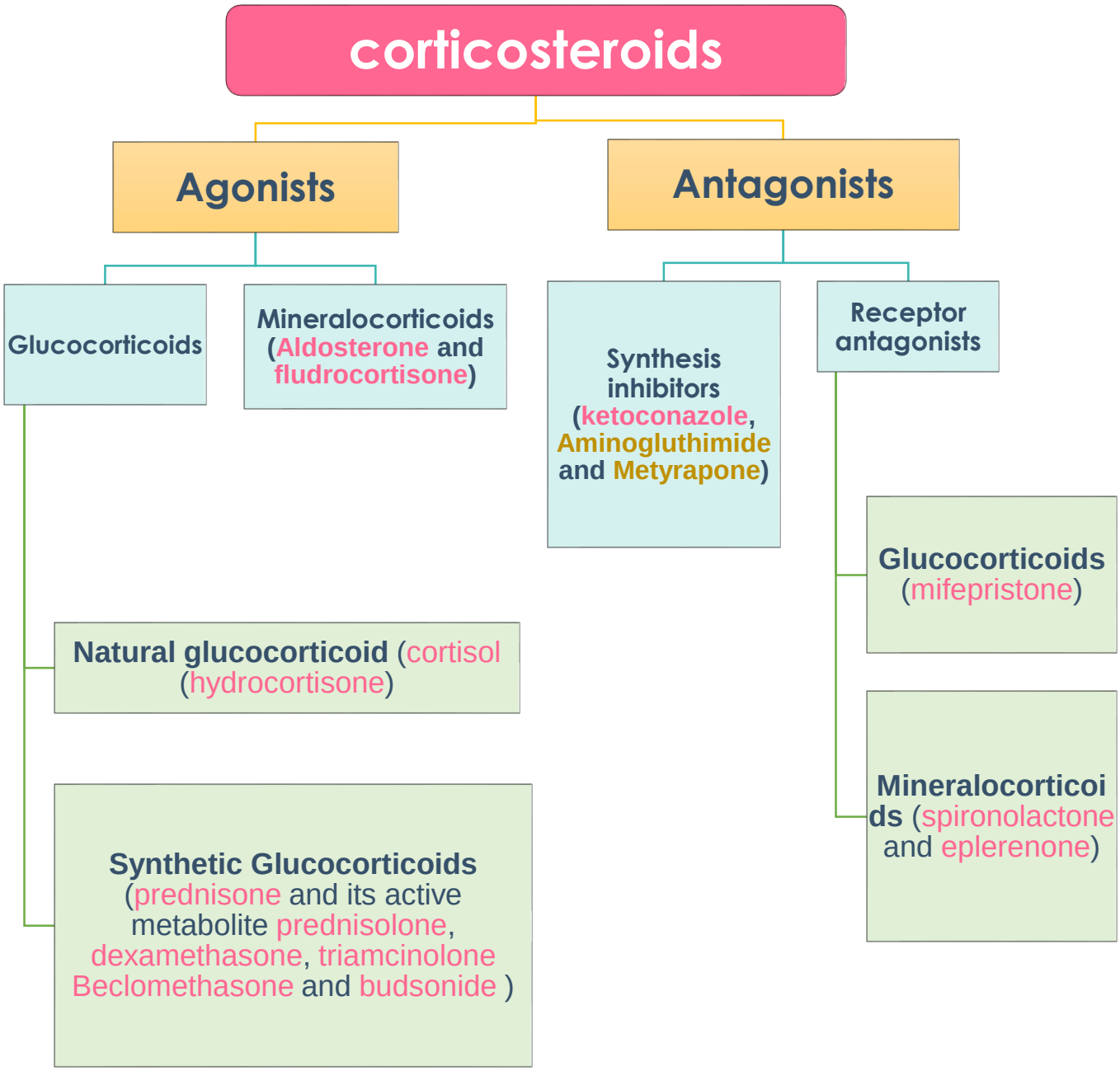
Drug's name | Doctors' notes | Important | Extra

« لو أن الناس كلما استصعبوا أمرًا تركوه؛ ما قام للناس دنيا ولا دين! »

عمر بن عبدالعزيز

Mind Map



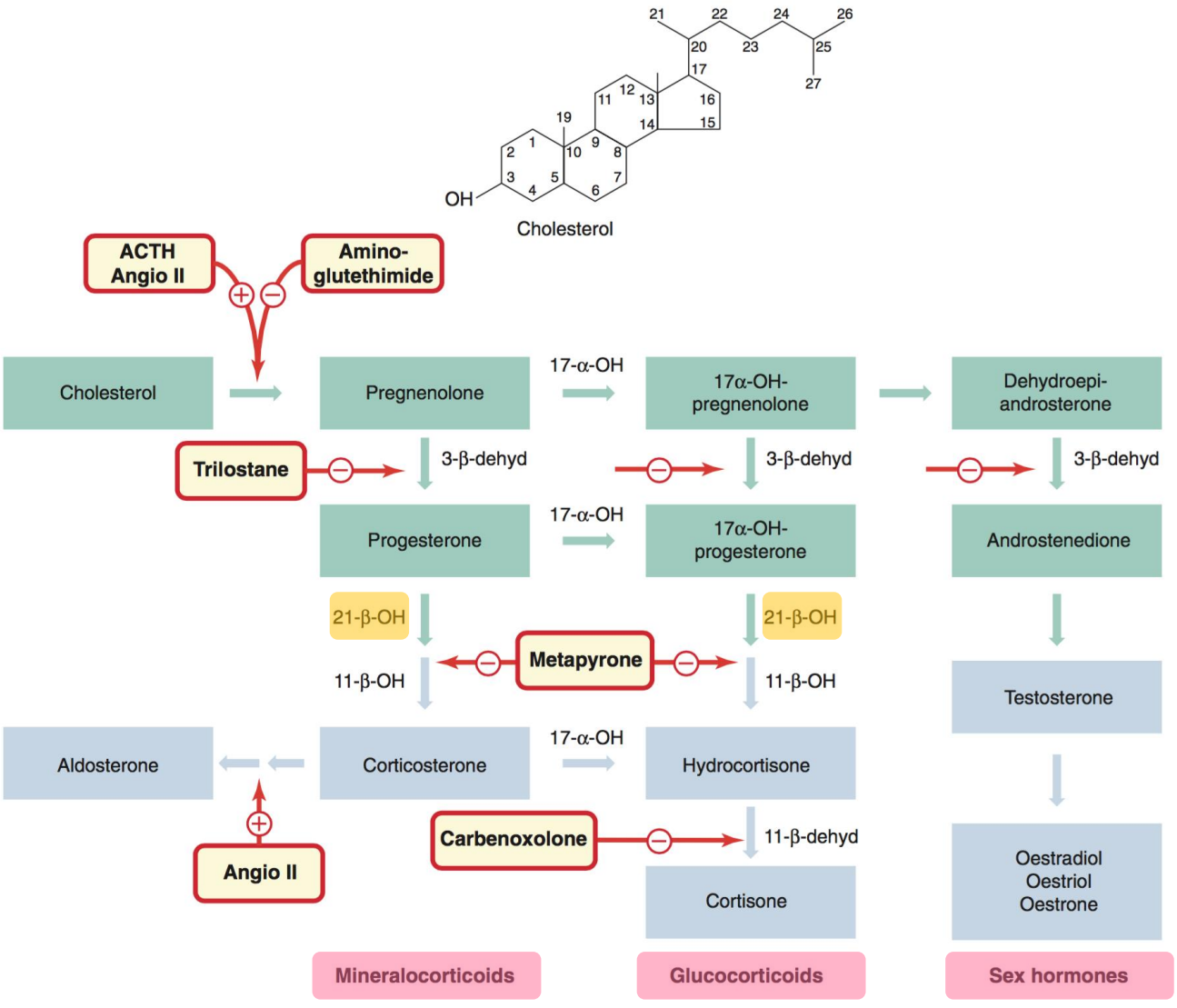
If you do not have time, the most imp. slides are: 6-10

Comic!


LOL SORRY FOR BUCKTING OL-L
WILL HYDROCORTISONE BE OKAY FIGHTING ADDISON ON HIS OWN?
NO ONE HOLDS THEIR CBG (HUMOR ME AND PRETEND IT SOUNDS LIKE SWORD) AS WELL AS HIM
AN AGONIST LIKE HIM IS OUR BEST CHOICE
BUT EVEN IF HE CAN GET BLOOD FREELY USING CBG, HE STILL HAS BIND A RECEPTOR TO FREE ALL 90 HOSTAGES (HSP90)
I KNOW HE CAN PIERCE THE TARGET'S NUCLEUS,
TIME EFFECTIVE MODE: ACTIVATED!
STE REC
ROID EPTOR
COMPLET!
TOUCHING THEIR GRE, HE CAN REGULATE THEIR GENE TRANSCRIPTION BUT...
IF HE STAYS THERE FOR 2 WEEKS...
HE WILL DEFINITELY FACE THE MOON'S CURSE
WHEN THAT TIME COMES
YOU WILL BE THE ONE TO END HIM, MIFEPRISTONE
THANK YOU FOR READING THIS FAR!
-SHADOW
@435kid

To Understand Better

Biosynthesis of adrenal hormones:



أهم شيء أبغاكم تعرفونه إنه تصنيع الهرمونات يبدأ بالكولسترول.

Introduction to corticosteroids

Corticosteroids:

❖ Are steroid hormones produced by the adrenal cortex. They consist of two groups:

1- Glucocorticoids	2- Mineralocorticoids
They have important effects on intermediary metabolism, catabolism, immune responses, growth & inflammation.	They have salt-retaining activity which regulate sodium & potassium reabsorption in the collecting tubules of the kidney.

Mechanism of action:

Mechanism of action and effects
9:09 min

Corticosteroid is present in the blood bound to the corticosteroid binding globulin (CBG) and enters the cell as the free molecule.

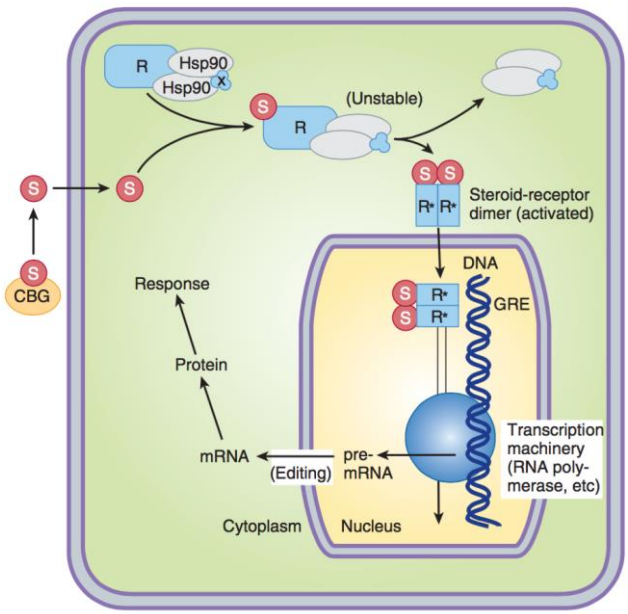
The intracellular receptor is bound to the stabilizing proteins, including **heat shock protein 90 (Hsp90)** and several others (X). When the complex binds a molecule of steroid, the Hsp90 and associated molecules are **released**.

The Steroid – receptor complex enters the nucleus as a **dimer**, binds to the **glucocorticoid response element (GRE)** on the gene, and regulates gene transcription by RNA polymerase2 and associated transcription factors.

The resulting mRNA is edited and exported to the cytoplasm for the **production of protein that brings about the final hormone response.**

Extra:

FIGURE 39–4 A model of the interaction of a steroid, S (eg, cortisol), and its receptor, R, and the subsequent events in a target cell. The steroid is present in the blood in bound form on the cortico-steroid-binding globulin (CBG) but enters the cell as the free molecule. The intracellular receptor is bound to stabilizing proteins, including two molecules of heat-shock protein 90 (hsp90) and several others, denoted as "X" in the figure. This receptor complex is incapable of activating transcription. When the complex binds a molecule of cortisol, an unstable complex is created and the hsp90 and associated molecules are released. The steroid-receptor complex is now able to dimerize, enter the nucleus, bind to a glucocorticoid response element (GRE) on the regulatory region of the gene, and regulate transcription by RNA polymerase II and associated transcription factors. A variety of regulatory factors (not shown) may participate in facilitating (coactivators) or inhibiting (corepressors) the steroid response. The resulting mRNA is edited and exported to the cytoplasm for the production of protein that brings about the final hormone response. An alternative to the steroid-receptor complex interaction with a GRE is an interaction with and altering the function of other transcription factors, such as NF-κB in the nucleus of cells.



Effects of steroids

1- Metabolic effects

- Glucocorticoid stimulate **gluconeogenesis**, as a result:
  - Blood glucose rises → gluconeogenesis through increasing amino acid uptake by the liver and kidney and elevating activities of gluconeogenic enzymes.
  - Insulin secretion is stimulated → Lipolysis and lipogenesis are stimulated → Lipolysis results as a consequence of the glucocorticoid augmenting the action of growth hormone on adipocytes
- With a net increase of fat deposition in certain areas (e.g., the face (moon facies), shoulder and back (buffalo hump) → Redistribution of fat.
- These effects occur when the patient is treated with 100 mg of hydrocortisone or > for longer than 2 weeks.

2- Catabolic effects

- Glucocorticoids cause **muscle protein catabolism** → thereby providing the building blocks and energy that are needed for glucose synthesis. → results in muscle wasting.
- Lymphoid and connective tissue **fat** and skin undergo wasting.
- **Catabolic effects on bone lead to osteoporosis**
- In children growth is inhibited → عشان كذا يفضل عدم استخدامهم بشكل كبير عند الأطفال عشان ما يتأثر النمو عندهم

3- 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.

4- Anti-inflammatory effect

- Glucocorticoids have important effects on the distribution and function of leukocytes → The most important therapeutic property.
- Suppressive effect on the inflammatory **cytokines & chemokines**.
- These drugs **increase** neutrophils and **decrease** lymphocytes, eosinophils, basophils and monocytes. The migration of leukocytes is also inhibited → important in the treatment of leukemia.
- **Inhibit phospholipase A2 & Prostaglandins synthesis.**

5- 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). → Adrenal insufficiency causes marked slowing of the alpha rhythm of the electroencephalogram and is associated with depression. Increased amounts of glucocorticoids often produce behavioral disturbances in humans: initially insomnia and euphoria and subsequently depression. Large doses of glucocorticoids may increase intracranial pressure (pseudotumor cerebri).
- **GIT**: Large doses also **stimulate gastric acid secretion** and decrease resistance to ulcer formation.

Important Glucocorticoids

Cortisol:

- The major natural glucocorticoid is cortisol (hydrocortisone) → Drug of choice for replacement therapy (cortisol)
- The physiologic secretion of cortisol is regulated by adrenocorticotropic hormone (ACTH) and varies during the day (circadian rhythm).
- The peak occurs in the morning and the trough occurs about midnight.

TABLE 39–1 Some commonly used natural and synthetic corticosteroids for general use.

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.

الدكتورة قالت بس شوفوا الدرقز اللي أخذناهم في هذي المحاضرة،
والهدف من هذا الجدول إنه يبين لك كيف إن ال Synthetic glucocorticoids تتميز عن الكورتيزول الطبيعي في جسمنا (اللي هو hydrocortisone) في عدة خصائص
فلو نلاحظ إن الموجود في جسمنا طبيعي عنده الsalt-retaining effect كثيرة، بينما Synthetic glucocorticoids عندها low salt-retaining effect وهو شيء جيّد

glucocorticoids

Drug	Cortisol (hydrocortisone) - **natural**	Synthetic glucocorticoids
notes	○ It's the major **natural** glucocorticoid. ○ The physiologic secretion of cortisol is regulated by adrenocorticotropic (ACTH) and varies during the day (Circadian rhythm). ○ Peaks in the morning and trough in midnight.	**Prednisone** & its active metabolite **prednisolone**. **Dexamethasone**, **Triamcinolone**
P.K	○ Given **orally**, cortisol is well absorbed from GIT. ○ Cortisol in the plasma in 95% **bound** to CBG (corticosteroid binding globulin). ○ It is metabolized by the **liver** and has **short duration of action** compared with the synthetic congeners. ○ It **diffuses poorly** across normal skin and mucous membranes.	❖ Their properties (compared with cortisol) include: ○ **Longer half life** ○ Longer duration of action. ○ **Reduce salt retaining effect** ○ **Better penetration** of lipid barriers for topical activity.
ADRs	○ The cortisol molecule also has a small but **significant salt-retaining** (**mineralo-corticoid**) effect. This is an important cause of **hypertension** in patients with cortisol secreting adrenal tumor or a **pituitary ACTH secreting tumor** (chushing's syndrome)	**Beclomethasone** & **Budsonide** ○ Have been developed for use in **asthma** and other condition in which good surface activity on **mucous membrane or skin** is needed and systemic effects are to be avoided. ○ Rapidly **penetrate the airway mucosa**. ○ **Very short half lives** after they enter the blood, so that systemic effects and toxicity are greatly **reduced**.

ADRs (toxicity)

○ **Cushing's syndrome** (iatrogenic (as a result of corticosteroid treatment) , by higher doses more than 100mg **hydrocortisone** daily for more than 2 weeks characterized by moon shape face and buffalo hump)
○ Increase growth of fine hair on face, thighs and trunk.
○ Myopathy, muscle wasting, thinning of skin, Diabetes Mellitus (bc of ↑ gluconeogenesis, so be careful when using these drugs in case of DM pt)
○ **Osteoporosis** and aseptic necrosis of the **hip** → Glucocorticoid-induced osteoporosis is attributed to inhibition of calcium absorption as well as bone formation.
○ Wound healing impaired.
○ In general pts treated with corticosteroids should be on high protein and potassium enriched diet.

Illustrated corticosteroid ADRs

○ Peptic ulcer → possibly by suppressing the local immune response against H. pylori.
○ **Adrenal suppression** → bc exogenous corticosteroid give –ve feed back to HPA axis result in adrenal suppression (no ACTH to stimulate it)
○ Acute psychosis, depression → in ↑ dose)
○ Sub-capsular cataracts نادر، بس لما يصير المريض مصاب بالسكر فهو معرض أصلاً إنه يصاب بالcataract فننتبه له
○ Growth suppression → avoid its use in child
○ Hypertension → bc of H_2O & salt retention.

Clinical uses of glucocorticoids

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.)

Non-adrenal disorders

- **Allergic reactions** (e.g; bronchial asthma, angioneurotic edema, drugs reactions, urtecaria, allergic rhinitis)
- Collagen vascular disorders (e.g; rheumatoid arthritis, systemic lupus erythematous, giant cell arteritis, poly myositis, mixed connective tissue syndrome)
- **Organ transplant** (prevention and treatment of rejection-immunosuppression).
- GIT disorders (inflammatory bowel disease, non-tropical sprue).
- **Hematologic disorders** (leukemia, multiple myeloma, acquired hemolytic anemia, acute allergic purpura) → they give them chemotherapy + corticosteroids (to **minimize autoimmune** disorders e.g. anemia)
- Infections (acute respiratory distress syndrome, sepsis)
- **Neurologic disorders** (to minimize **cerebral edema** after brain surgery, multiple sclerosis)
- **Pulmonary disease** (e.g; aspiration pneumonia, bronchial asthma, sarcoidosis) → to minimize the inflammation.
- Thyroid diseases (malignant exophthalmos (Graves), subacute thyroiditis)
- Renal disorders (nephrotic syndrome)
- Miscellaneous (**hypercalcemia** "corticosteroid increase the excretion of Ca^{2+} & decrease reabsorption from intestine" , mountain sickness)
- autoimmune disorders في النهاية هو أكثر شيء يستخدم لأغلب الأمراض اللي يصاحبها التهاب أو الـ

Methods for minimizing corticosteroid toxicities include:

1. Local application (e.g; aerosol for asthma)
   يعني إذا المريض عنده pneumonia ما نعطيه local نعطيه oral or I.V
2. Alternate day therapy (to reduce pituitary suppression)
   يعني يوم وراء يوم، مب لازم كل يوم عشان ما يصير فيه pit & adrenal suppression
3. Tapering the dose soon after achieving a therapeutic response.
   يعني بمجرد ما نوصل للي نبيه من الإفكت حق الدواء، نبدأ نقلل الدوز
4. To **avoid adrenal insufficiency** in pts who have had long term therapy, **additional stress doses** may need to be given during serious illness or before major surgery.
   اللي ياخذون long term therapy نتوقع إنه عندهم أصلا adrenal suppression عشان كذا لما يصيرون مريضين مرة، أو بيسوون عملية.. أعطيهم دوز أكثر من العادة من الكورتيكوستيرويدز لأننا عارفين إنه عنده adrenal suppression!

Mineralocorticoids

Drug	Aldosterone - (the major **natural** mineralocorticoid)	Fludrocortisone
notes	○ Aldosterone is the **main salt-retaining hormone**, promotes Na^+ reabsorption, K^+ excretion (by enhancing Na^+\K^+ ATPase) , 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** and little **glucocorticoid** activity. not used as a drug.	○ Its is **mineralocorticoid** has a **long duration** of action and significant glucocorticoid activity.
MOA	○ Is same as the glucocorticoids.	-
indications	-	Fludrocortisone is **favored for replacement therapy** after adrenalectomy and in other conditions in which mineralocorticoid therapy in needed → the only agonist for aldosterone

Corticosteroid antagonists

A- Receptor antagonist

Drug	Spironolactone & Eplerenone	Mifepristone
MOA	○ **Mineralocorticoid** antagonist & K-sparing diuretic. ○ Antagonists of aldosterone at its receptor.	○ Is a competitive inhibitor of **glucocorticoid** receptors as well as progesterone receptors.
uses	○ Treatment of **primary** aldosteronism. ○ Useful in the treatment of hirsutism in women, probably due to interference at the androgen receptor of the hair follicle	○ Useful in the treatment of Cushing's syndrome.

B- Synthesis inhibitors

Drug	Ketoconazole (antifungal in ↓ dose, corticosteroid antagonist in very ↑ dose)
MOA	○ It **inhibits the cytochrome p450** enzymes necessary for synthesis of all steroids and is used in a number of conditions in which **reduced steroid** level are desirable.
Clinical use	○ **Adrenal carcinoma** → When surgical therapy is not useful as in case of metastasized cancer. ○ Hirsutism ○ Sex related cancer: ○ Breast cancer ○ Prostate cancer (لأن بيصير عندهم الsex hormones كثيرة، فنبي نثبطها) ○ Cushing syndrome. ○ **Adrenal cancer,** when surgical therapy is impractical or unsuccessful because of metastasis.

Summary ☺

corticosteroid Agonist

groups	Glucocorticoids	Mineralocorticoids	
Mech. of action	1. Corticosteroid is present in the blood bound to the corticosteroid binding globulin(CBG) and enters the cell as the free molecule. 2. The intracellular receptor is bound to the stabilizing proteins, including heat shock protein 90(Hsp90) and several others(X). When the complex binds a molecule of steroid, the Hsp90 and associated molecules are released.(When the drug is 3. bound with the receptor the stable protein is detached from the receptor) 4. The Steroid – receptor complex enters the nucleus as a dimer, binds to the glucocorticoid response element(GRE) on the gene, and regulates gene transcription by **RNA polymerase2** and associated transcription factors. 5. The resulting mRNA is edited and exported to the cytoplasm for the production of protein that brings about the final hormone response		
P.D	• Metabolic effects • Catabolic effects • Immunosuppressive effects • Anti – inflammatory effects	-	
Drugs	**Cortisol**	**Aldosterone**	**Fludrocortisone**
Characteristic	○ The major natural glucocorticoid is cortisol(hydrocortisone). ○ The physiologic secretion of cortisol is regulated by adrenocorticotropic (ACTH) and varies during the day(circadian rhythm). ○ The peak occurs in the morning and the trough occurs about midnight (The drugs will be more beneficial if we use in the morning)	The Major natural mineralocorticoid in human. • Regulation: by ACTH and by the renin-angiotensin system and is very important in the regulation of blood volume and blood pressure. Aldosterone has short half life. little glucocorticoid activity.	Is a mineralocorticoid favored for replacement therapy after adrenalectomy and in other conditions in which mineralocorticoid therapy is needed **long duration of action** significant glucocorticoid activity
P.K & P.D	❖ **P.K & P.D for cortisols:** ○ Given **orally** ,cortisol is well absorbed from GIT ○ Cortisol in the plasma is 95% bound to CBG ○ It is metabolized by the liver and has **short duration of action** compared with the synthetic congeners. ○ It diffuses poorly across normal skin and mucous membranes ○ The cortisol molecule also has a small but significant salt – retaining (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).		

Synthetic Glucocorticoids

Prednisone and its active metabolite: (prednisolone, dexamethasone, triamcinolone).	**Beclomethasone and Budsonide**
○ Longer half life ○ Longer duration of action ○ Reduce salt retaining effect ○ Better penetration of lipid barriers for ○ Topical activity.	○ Have been developed for use in **Asthma** and other condition in which good surface activity on mucous membrane or skin is needed and systemic effects are to be avoided ○ These drugs rapidly penetrate the airway mucosa. ○ **Very short half lives** after they enter the blood, so that systemic effects and toxicity are greatly reduced.

Corticosteroid Antagonists

	Receptor Antagonists		Synthetic inhibitors	
Drugs	**Spironolactone eplerenone**	**Mifepristone**	**ketoconazole**	
Mech. of action	Antagonize aldosterone at its receptor. Spironolactone is a K^+-sparing diuretic.	competitive inhibitor of: • glucocorticoid receptors • progesterone receptors	**It inhibits the cytochrome p450** enzymes necessary for the synthesis of all steroids	
USES	So use it in conditions when we want less Aldosterone e.g.: hypertension, edema functioning adrenal adenoma involving zona glomerulosa.	useful in the treatment of Cushing's syndrome	• **Adrenal cancer**, when surgical therapy is impractical or unsuccessful because of metastasis.	
			Adrenocortical cancer (steroid producing tumor) in conjunction with other drugs.	Used in a no. of conditions in which reduced steroid level are desirable: Adrenal carcinoma, Hirsutism, Breast cancer, Prostate cancer.

Clinical uses of glucocorticoids

- Replacement therapy for patients with adrenal failure (*Addison's disease*).
- Anti-inflammatory/immunosuppressive therapy (see also Ch. 26):
  - in *asthma* (Ch. 27)
  - topically in various inflammatory conditions of skin, eye, ear or nose (e.g. *eczema*, *allergic conjunctivitis* or *rhinitis*)
  - *hypersensitivity states* (e.g. severe allergic reactions)
  - in miscellaneous diseases with autoimmune and inflammatory components (e.g. *rheumatoid arthritis* and other 'connective tissue' diseases, *inflammatory bowel diseases*, some forms of *haemolytic anaemia*, *idiopathic thrombocytopenic purpura*)
  - to prevent *graft-versus-host disease* following organ or bone marrow transplantation.
- In *neoplastic* disease (Ch. 55):
  - in combination with cytotoxic drugs in treatment of specific malignancies (e.g. *Hodgkin's disease*, *acute lymphocytic leukaemia*)
  - to reduce cerebral oedema in patients with metastatic or primary *brain tumours* (**dexamethasone**).

Pharmacokinetics and unwanted actions of the glucocorticoids

- Administration can be oral, topical or parenteral. Most naturally occuring glucocorticoids are transported in the blood by corticosteroid-binding globulin or albumen and enter cells by diffusion. They are metabolised in the liver.
- Unwanted effects are seen mainly after prolonged systemic use as anti-inflammatory or immunosuppressive agents but not usually following replacement therapy. The most important are:
  - suppression of response to infection
  - suppression of endogenous glucocorticoid synthesis
  - metabolic actions (see above)
  - osteoporosis
  - iatrogenic Cushing's syndrome (see Fig. 32.7).

Mineralocorticoids

Fludrocortisone is given orally to produce a mineralocorticoid effect. This drug:

- increases Na^+ reabsorption in distal tubules and increases K^+ and H^+ efflux into the tubules
- acts on intracellular receptors that modulate DNA transcription, causing synthesis of protein mediators
- is used together with a glucocorticoid in replacement therapy.

MCQs

1- Steroid receptor is found in which one of the following:
A- Nucleus
B- Cytoplasm
C- Cell membrane
D- Extracellular

2- Which one of the following drugs inhibits the synthesis of corticosteroids:
A- Spironolactone
B- Mifepristone
C- Ketoconazole
D- Prednisolone

3- Which one of the following is considered the major natural glucocorticoid:
A- Cortisol
B- Aldosterone
C- Budesonide
D- Ketoconazole

4- All of the following adverse effects commonly occur us glucocorticoids therapy except:
A- osteoporosis
B- increase risk of infection
C- hypotension
D- peripheral edema

5- A child with severe asthma is being treating oral prednisone. Which of the following adverse effects is of particular concern?
A- Hypoglycemia
B- Hirsutism
C- Growth suppression
D- Cushing syndrome

6- Osteoporosis is major side effect caused by the glucocorticoids. Its is due to their ability to:
A- Increase excretion of calcium
B- Inhibits absorption of calcium
C- Stimulate the hypothalamic-pituitary-adrenal axis.
D- Stimulating osteoblasts
E- Decrease collagen synthesis.

7- A 67-year-old man injures his shoulder in an ATV accident. Over-the-counter and prescription ibuprofen are unable to control the pain and swelling satisfactorily. The patient asks about glucocorticoid injections, so his doctor begins to explain the myriad effects of glucocorticoids in the body. How might glucocorticoids help this patient?
A- Decrease activity of phospholipase A2
B- Improve healing by enhanced collagen production
C- Increase blood flow by vasodilation
D- Stabilize the joint by causing skeletal muscle hypertrophy

8- A 63-year-old man with congestive heart failure comes to the cardiologist for a routine visit. He is doing well and has no complaints. He is taking digoxin, metoprolol, and spironolactone. What is the mechanism of action of spironolactone?
A- Carbonic anhydrase inhibitor
B- Inhibits NaCl reabsorption
C- Aldosterone receptor antagonist
D- Inhibits $Na^+/K^+/2Cl^-$ cotransport

Answers: 1-B 2-C 3-A 4-C 5-C 6-B 7- A 8- C

Thank you for checking our team!

Pharmacology 435

@ pharmacology435

Sources:

1. 435's slides.
2. Pharmacology (Lippincotts Illustrated Reviews Series), chapter 26, 5th edition.
3. Basic & Clinical Pharmacology by Katzung, chapter 39,12th edition.
4. Rang & Dale's pharmacology, chapter 32, 7th edition.