The Endocrine System

PHARMACOLOGY

☑ Sheet ☐ Slide ☐ Handout

Number:	11
Subject:	Adrenocorticosteriods
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Price:

System under the title 'Adrenocorticosteroids'. Finally!!

- This sheet was deigned by copying all the slides for this lecture within it, followed by the doctor's notes; so NO need to go through the slides if you study it! It is long because it has all the slides written within it !
- If you are one of the few people who actually will study this sheet, then you already know it will be a bit long, yet some-how easy! Lol.
- One way to go through this sheet easily; is for you to already have the appropriate knowledge about the physio. for the adrenal gland.

-YOUR GUIDE: ***In Bold, the slide's number** **In Italics, the slide's content*

*Followed by this symbol $, are the doctor's notes.

Good Luck =D ..

SLIDE 1

Divided into those having:

1.Important effects on intermediary metabolism and immune function = glucocorticoids (cortisol).

2.Salt-retaining activity = mineralocorticoids (aldosterone).

3.Androgenic or estrogenic activity. Dehydroepiandrosterone (DHEA) sulfate and androstenedione, respectively.

$ Androgenic and estrogenic are functioning in males and females in their own respective roles.

SLIDE 2

Secretion of adrenocortical steroids is controlled by the pituitary release of corticotropin (ACTH).

Secretion of the salt-retaining hormone aldosterone is primarily under the influence of angiotensin.

$ Mainly the glucocorticoids are regulated through the hypothalamic-pituitary axis, through CRH from the hypothalamus that stimulates the ACTH. That's unlike the mineralocorticoids, especially aldosterone, that depend on the Angiotensin system. (Renin , Angiotensinogen , Angiotensin I , by ACE becomes Angiotensin II).

SLIDE 3

Cortisol

•A naturally occurring glucocorticoid.

•Also called hydrocortisone.

•In the absence of stress, 10-20 mg are secreted daily, which follows a circadian rhythm with a pulse of secretion that peaks in the early morning hours and after meals.

$ You should know that Cortisone is very similar to Cortisol; with the addition of a ketone group and a bit less potency.

$ The 10-20 mg is your daily requirement under no stress.

SLIDE 4

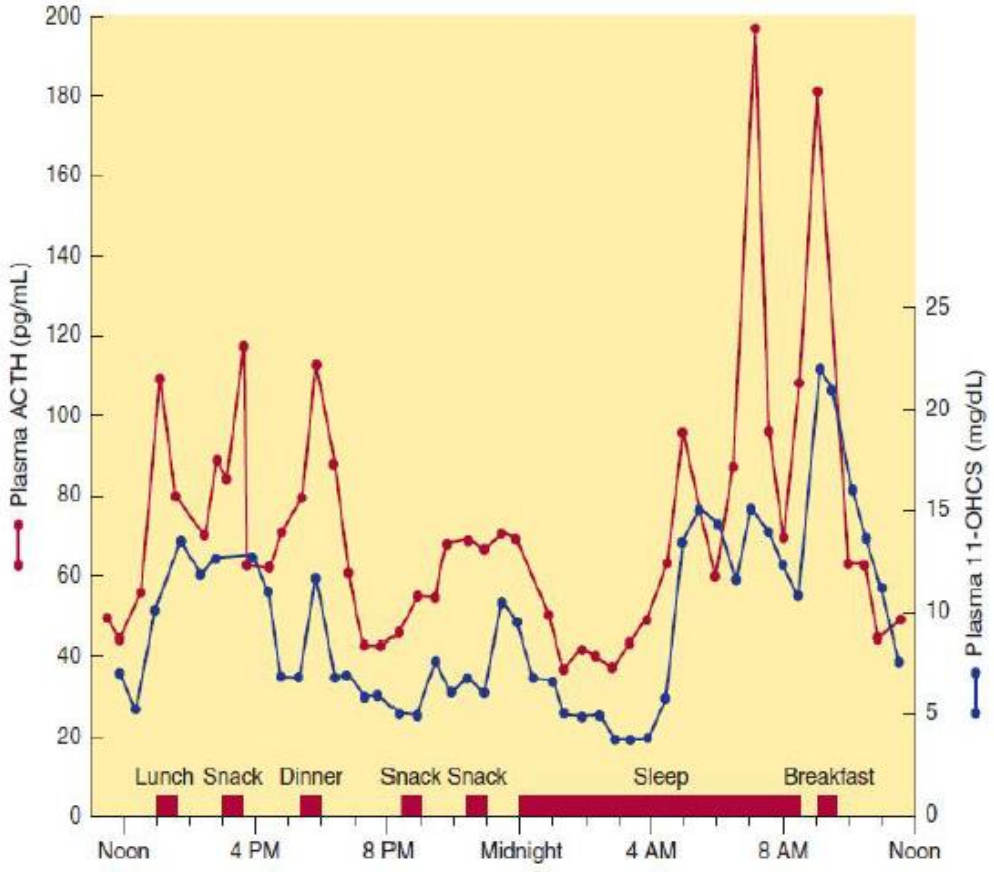

FIGURE 39–2 Fluctuations in plasma ACTH and glucocorticoids throughout the day in a normal girl (age 16). The ACTH was measured by immunoassay and the glucocorticoids as 11-oxysteroids (11-OHCS). Note the marked ACTH and glucocorticoid rises in the morning, before awakening from sleep. (Reproduced, with permission, from Krieger DT et al: Characterization of the normal temporal pattern of plasma corticosteroid levels. J Clin Endocrinol Metab 1971;32:266.)

$ You should pay attention to your circadian rhythm , because any disturbance in it could cause much problems to you including in the secretion of many hormones and other psychiatric issues like depression.

$ Highest level is on the morning and the lowest is in the afternoon. After-meals cortisol level increases but not as high as on the morning .

$ The circadian rhythm is very important in our practice! Q: If you were to give your patient a corticosteroid for a specific disease, when will you give it to him ? A: At night, when there are low levels of the corticosteroids in the body and the receptors are up-regulated, for a better response (explained later).

SLIDE 5

•Bound in plasma (90%) to an α2-globulin, corticosteroid-binding globulin (CBG).

•CBG is saturable above 20-30 μg/dL cortisol.

•CBG is increased during pregnancy, estrogen therapy and in hyperthyroidism; and decreased in hypothyroidism, genetic defects of synthesis and protein deficiency states.

$ Very High doses of cortisol, means too much free cortisol as its binding is saturable at 20-30 μg/dL.

$ During pregnancy and high estrogen concentration , High CBG concentration , High binding , Low amount of the free cortisol , Low degree of action and elimination (Recall that the free hormone is the one capable of doing action and being eliminated).

SLIDE 6

•Albumin has a large capacity but low affinity for cortisol.

•Synthetic steroids like dexamethasone are largely bound to albumin rather than to CBG.

•t½ ~ 60-90 min. It may be increased when hydrocortisone is administered in large amounts or when stress, hypothyroidism, or liver disease is present.

•Mostly inactivated in the liver, 20% converted to cortisone.

SLIDE 7

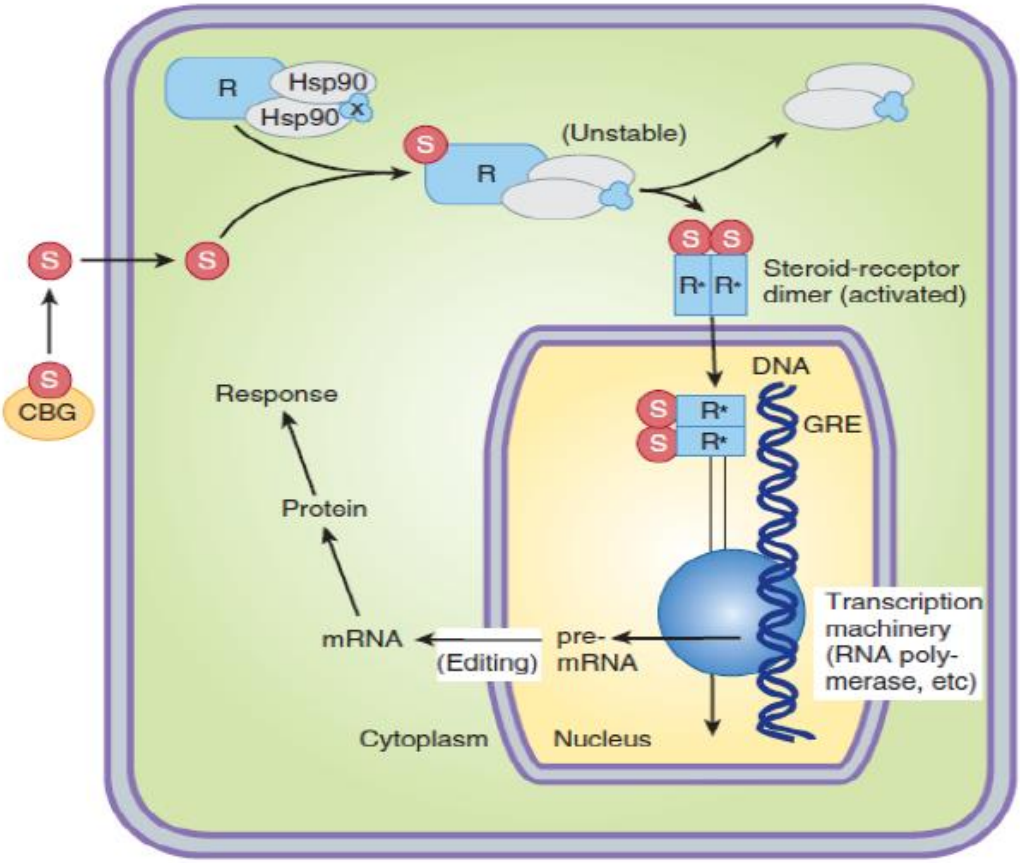

FIGURE 39–4 A model of the interaction of a steroid, S (eg, cortisol), and its receptor, R, and the subsequent events in a target cell. The steroid is present in the blood in bound form on the corticosteroid-binding globulin (CBG) but enters the cell as the free molecule. The intracellular receptor is 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.

$ READ THE FIGURE DISCREPTION ABOVE! VERY IMPORTANT!

$ Don't mix it with the thyroid hormone mechanism; as the thyroid hormone binds to its receptor in the nucleus.

$ The receptor for the corticosteroids is Intracelluer Cytoplasmic receptor.

$ For fast actions with no need to inter the nucleus; we need plasma membrane receptor. Some receptors are found near the plasma membrane with regions on

them that are called palmitoylation motifs (sites on the receptor that can bind fatty acids; like palmitic acid). Binding of the fatty acid to this receptor makes it hydrophobic; making it possible for the receptor to bind onto the plasma membrane and to function from there. This explains the fast suppression ACTH ,within minutes, unlike the mRNA pathway that could take days to synthesize the proteins needed! (The fast effect that cortisol puts on are not through protein synthesis, but by other means that were not mentioned)

SLIDE 8

Mechanism of Action:

•In addition to GREs, other transcription factors also bind to and are activated by the ligand-bound receptor such as activator protein 1 (AP1) and nuclear factor KB (NF-KB).

•AP1 and NF-KB act on non-GRE-containing promoters, to contribute to the regulation of transcription of their responsive genes.

SLIDE 9

•These transcription factors play a role in regulation of growth factors and proinflammatory cytokines, and to a greater extent, mediate antigrowth, antiinflammatory and immunosuppressive effects of glucocorticoids.

•The interaction of glucocorticoid receptors with GREs or other transcription factors is facilitated or inhibited by several families of proteins called steroid receptor coactivators and corepressors (coregulators).

SLIDE 10

•The coregulators do this by serving as bridges between the receptors and other nuclear proteins, and by expressing enzymatic activities such as histone acetylase or deacetylase that alter the conformation of the nucleosome and the transcribability of genes.

•Between 10-20% of expressed genes in a cell are regulated by glucocorticoids.

$ Their regulation covers any kind of cells.

$ Their regulation covers bigger degree and diversity than the thyroid hormones.

SLIDE 11

*•The number and affinity of receptors for hormone, the complement of transcription factors and coregulators, and posttranscription events determine the relative **specificity** of hormone action in various cells.*

•The effects of glucocorticoids are mainly due to proteins synthesized from mRNA transcribed by their target genes.

SLIDE 12

•Some of the effects can be attributable to binding to aldosterone receptors (ARs). ARs bind aldosterone and cortisol with similar affinity, while cortisone has minimal affinity for ARs.

$ Cortisol can do the same function as aldosterone when it binds to ARs, so be careful of hypertension, edema and heart failure.

SLIDE 13

•The GR also interacts with other regulators of cell function.

•One such molecule is CLOCK/BMAL-1, a transcription factor dimer expressed in all tissues and generating the circadian rhythm of cortisol secretion at the suprachiasmatic nucleus of the hypothalamus.

SLIDE 14

•CLOCK has an acetyltransferase activity that acetylates the hinge region of the GR, neutralizing its transcriptional activity and thus rendering target tissues resistant to glucocorticoids.

•The glucocorticoid target tissue sensitivity rhythm is in reverse phase to that of circulating cortisol concentrations, explaining the increased sensitivity of the organism to evening administration of glucocorticoids.

$ The doctor again emphasized on the example we mentioned above relating to 'SLIDE 4' about the best time to give your patient Cortisol especially if it was only one dose , linking that to the sensitivity of the receptors (much sensitive and up-regulated at night).

SLIDE 15

•The GR also interacts with NF-ΚB, a regulator of production of cytokines and other molecules involved in inflammation.

SLIDE 16

•Feedback suppression of pituitary ACTH occurs in minutes and is too rapid to be explained on the basis of gene transcription and protein synthesis.

•Proposed mechanisms include a direct effects on cell membrane receptors for the hormone or nongenomic effects of the classic hormone-bound glucocorticoid receptor.

•The putative membrane receptors might be entirely different from the known intracellular receptors.

SLIDE 17

•All corticosteroid receptors have palmitoylation motifs that allow enzymatic addition of palmitate and increased localization of the receptors near the plasma membranes, making them available for direct interactions with and effects on various membrane-associated or cytoplasmic proteins without the need for entry into the nucleus and induction of transcriptional actions.

SLIDE 18

Physiological Actions:

•Widespread actions affecting most cells of the body.

I. Permissive actions (In the absence of glucocorticoids, these functions become deficient):

1.The response of vascular and bronchial smooth muscle to catecholamines is diminished in the absence of cortisol and is restored by physiological amounts of it.

$ These permissive actions are the actions that are done better with the presence of Cortisol , and are not done well in its absence.

$ Therapeutically, giving the corticosteroids along with catecholamines for patients with bronchial asthma overcomes the down-regulation for the receptors of these catecholamines.

SLIDE 19

2. Lipolytic responses of fat cells to catecholamines, ACTH and GH are attenuated in the absence of glucocorticoids.

3. In the absence of cortisol, glomerular filtration is impaired, vasopressin (ADH) secretion is augmented and the ability to excrete water load is abolished. (So cortisol increases dieuresis)

$ Be sure to know that these actions are not facilitated directly by Cortisol ! Yet Cortisol is needed for these actions to be done well by the other hormones.

$ Relating to the glomerular filtration, some consider the cortisol action as a direct pharmacological/physiological action rather than being permissive with glomerular filtration.

$cortisol also inhibits the release of ADH . (According to Wikipedia)

SLIDE 20

II. Dose-dependant Actions:

A.Metabolic effects:

1.Stimulate and are required for gluconeogenesis and glycogen synthesis in the fasting state. They stimulate phosphoenolpyruvate carboxykinase, glucose-6-phosphatase and glycogen synthase.

2.Stimulate the release of amino acid during muscles catabolism.

$ The first point gives a net increase in the concentration of glucose. Remember that cortisol counteracts insulin. When an individual goes through hypoglycemia, two systems in his body respond to that; one is fast which is the Catecholamines and the other is slow which is the Cortisol, both aim to increase the blood-glucose level.

$ You should expect some weakness in the muscles due to its catabolic effect .

SLIDE 21

3.Increase serum glucose levels and thus insulin release.

4.Inhibit glucose uptake by muscles.

5.Stimulate lipase and thus lipolysis.

•The increase in insulin stimulates lipogenesis and to a lesser degree lipolysis is inhibited leading to a net increase in deposition of fat, combined with increased release of fatty acids and glycerol into the circulation.

$ Over secretion in Cortisol causes fat re-distribution(lipolysis in a place and lipogenesis in somewhere else), marked by Buffalo hump, central obesity and Moon face.

SLIDE 22

•The net results of these actions are most apparent in the fasting state, when:

1.the supply of glucose from gluconeogenesis,

2.the release of amino acids from muscle catabolism,

3.the inhibition of peripheral glucose uptake,

4.and the stimulation of lipolysis

all contribute to maintenance of an adequate glucose supply to the brain.

*$ Brain is very dependent on Glucose to function***.** As only in extreme fasting cases it may then be able to metabolize another compound than glucose. And

that's why hypoglycemia is very dangerous on the brain.

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B. Catabolic effects:

•Although glucocorticoids increase protein and RNA synthesis in the liver, they have catabolic and antianabolic effects in lymphoid and connective tissue, muscle, peripheral fat and skin, leading to:

1.Decreased muscle mass weakness.

2.Thinning of the skin.

3.Osteoporosis.

4.Reduced growth in children.

$ Don't mix ! Protein synthesis here is just a part of the mechanism of action for the cortisol that leads then to protein lysis in the muscles.

$ Its effects on the lymphoid and connective tissue is part of the immune suppression and anti-inflammatory action, and on the peripheral fat is for the fat re-distribution action.

$ Osteoporosis, is due to the catabolic effect on the bones. (Remember, it antagonizes vit.D)

$ Reduced growth is very important to pay careful of when your patient is a child. To reduce(not abolish) the systemic effect on your patient from the cortisol; we give it by inhalation.

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C.Antiinflammatory and immunosuppressive effects:

•Glucocorticoids dramatically reduce the manifestations of inflammation.

•This is due to their profound effects on the concentration, distribution, and function of peripheral leukocytes and to their suppressive effects on the inflammatory cytokines and chemokines and on other mediators of inflammation.

SLIDE 25

•After a single dose of a short-acting glucocorticoid, the concentration of neutrophils in the circulation increases while the lymphocytes (T and B cells), monocytes, eosinophils, and basophils decrease.

•The increase in neutrophils is due both to the increased influx into the blood from the bone marrow and to the decreased migration from the blood

vessels(due to suppression of adhesion molecules), leading to a reduction in the number of cells at the site of inflammation and higher concentration of them in the circulation .

$ In addition to the neutrophils; RBCs and platelets number do increase too.

$ If experimentally you gave corticosteroids to an individual who has an enlargement of lymph nodes, you could notice after 2 days that it shrinks due to the corticosteroids effect.

$ Only in some cases of thrombocytopenia and anemia, you could give corticosteroids as part of the treatment.

$ Neutrophils number gets re-distributed only, while RBCs and platelets number increases for real.

$ Eosinophils are prominent in bronchial asthma, that's why we give corticosteroids to these patients; to reduce their number.

SLIDE 26

•The reduction in circulating lymphocytes, monocytes, eosinophils, and basophils is primarily the result of their movement from the vascular bed to lymphoid tissue.

•Glucocorticoids also inhibit the functions of tissue macrophages and other antigen-presenting cells. The ability of these cells to respond to antigens and mitogens is reduced.

$ Antigen-presenting cells (a type of macrophages) process the antigen so that the response by immune system by its two divisions (Innate and Adaptive'two divisions; Cell-mediated & Humoral') can take place.

SLIDE 27

•The effect on macrophages is particularly marked and limits their ability to phagocytose and kill microorganisms and to produce tumor necrosis factor-α, interleukin-1, metalloproteinases, and plasminogen activator.

•Both macrophages and lymphocytes produce less interleukin-12 and interferon-γ, important inducers of TH1 cell activity, and cellular immunity.

SLIDE 28

•Inhibit phospholipase A2 and thus synthesis of prostaglandins, leukotrienes and platelet activating factor, thus influencing the inflammatory response.

•Reduce expression of cyclooxygenase-2, the inducible form, during

inflammatory reactions.

•Reduces mast cell degranulation and histamine release → Reduction of capillary permeability, and Vasoconstriction in the skin when applied locally.

$ Cyclooxygenase (COX) is an enzyme responsible for the synthesis of prostaglandins and thromboxanes, and is of two forms; COX-2 which is the inducible form that acts upon the presence of inflammation, and COX-1 which is the house-keeping enzyme; meaning it is constitutive.

$ An example to clarify the COX-1 function; it synthesizes prostaglandin E which causes vasodilation in the mucosa of the stomach for better nutrition for the cells, and stimulates the formation of the mucous to line up the mucosa and protect it from the acid plus, it increases the concentration of HCO_3^- to neutralize the acid.

$ We aim to suppress COX-2 not COX-1 as an anti-inflammatory action. So, most of the side effects that arises from NSAIDs, comes from the inhibition of COX-1 due to low selectivity.

$ We can use glucocorticoids for treatment of Histamine manifestations. As Subcutaneous Epinephrine is used as an immediate reverse for Histamine action; Glucocorticoids are used for prevention of further action. H-1 & H-2 blockers can be used too.

SLIDE 29

•In humans complement activation is unaltered but its effects are inhibited. (So it has an indirect effect on the complement system)

•Reduces antibody production at large doses but not affected by moderate dosage (~ 20 mg/day of prednisone).

•The anti-inflammatory and immunosuppressive effects of these agents are widely useful therapeutically but are also responsible for some of their most serious adverse effects.

$ Immunosuppressive effect can lead to viral or bacterial infection as a side effect.

SLIDE 30

•Control of transplant rejection, may be due to:

a. Reduction of antigen expression from grafted tissue.

b. Interference with sensitization of cytotoxic T lymphocytes.

c. Interference with the generation of primary antibody forming cells. (At high doses)

d. Delay of revascularization.

$ In the old days, Glucocorticoids along with anti-cancerous drugs were used in organ transplantation for their known immunosuppressive effect, but especially due to the anti-cancer drugs which are known to be toxic by definition, fears circles these organ transplantation operations.

$ Now with the revolution, Cyclosporines family are used, which made these operations more safe. It lowered the dose needed to reach the needed action; meaning less side effects!

$ Cytotoxic T lymphocytes are the cells responsible for the rejection of that new organ.

$ We need that delay in the revascularization to delay the deliver of the immune cells to the new organ.

SLIDE 31

D. Other effects:

1.Adrenal insufficiency causes marked slowing of the alpha rhythm of the electroencephalography (EEG) and is associated with depression.

2.Increased amounts of glucocorticoids often produce behavioral disturbances: initially insomnia and euphoria and subsequently depression.

$ Hyper-Adrenal also causes Depression. (Because cortisol is important in the balance of factors in the brain , so a decrease or increase disrupts this balance)

SLIDE 32

3.Large doses of glucocorticoids may increase intracranial pressure (pseudotumor cerebri).

4.Glucocorticoids given chronically suppress the pituitary release of ACTH, growth hormone, thyroid-stimulating hormone, and luteinizing hormone.

5.Redistribution of fat increases visceral, facial, nuchal and supraclavicular fat.

$ They can cause edema in the brain due to the retention of Na+ and water.

$ Nuchal refers to the neck.

$ Visceral obesity is the most dangerous type of obestiy. It is associated with many cardiovascular problems.

SLIDE 33

6. Peptic ulceration, possibly by suppressing:

a. Prostaglandin synthesis

b. Immune response against Helicobacter pylori.

7.Antagonizes the effects of vitamin D on Ca2+ absorption.

8.Increases the number of platelets and RBCs.(Remember, can be used in some cases of thrombocytopenia and anemia)

9.Development of fetal lung and formation of surfactant.

$ Peptic ulceration is due to the inhibition of phospholipase A2 that gives rise to arachidonic acid that produces prostaglandins. Helicobacter pylori were found in 99% of individuals with peptic ulcer.

$ If a pregnant women comes to you with an expected early delivery at her ,for example, 36th week of pregnancy and the child is thought to live; you should give her a dose of beta-methasone of the glucocorticoids; which will increase the surfactant substance in the alveoli of the lungs. The surfactants are important for the alveoli to expand in order to breath well, in its absence it will cause Respiratory Distress Syndrome; failure of adequate respiration! One dose or two is all what is needed to be given to the mom in order for the infant to develop these surfactants in the alveoli.

SLIDE 34

10. Cortisol deficiency results in impaired renal function (particularly glomerular filtration), augmented vasopressin secretion, and diminished ability to excrete a water load , leading to dilution of the electrolytes which is dangerous .

SLIDE 35

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.

$ THIS SLIDE IS VERY IMPORTANT ! THE DOCTOR MADE IT CLEAR THAT ONE OF THE Qs ON THIS LECTURE WILL BE ABOUT IT !

$ You need to memorize the two columns; anti-inflammatory and salt-retaining. Why ? cause these doses could be critical and you need to know them, as you may have no time to look for them in your practice if it was an urgent case.

$ How to deal with these numbers ? before we talk about that, remember that cortisol acts on the ARs(Aldosterone receptors) , so it increases sodium and water and decreases hydrogen ion and potassium in the blood. Plus, these numbers represent the potencies of these synthetic corticosteroids relatively to Cortisol !

$ Anti-inflammatory : Q1: If you were to give your patient Prednisolone a dose

that corresponds to a 20 mg of Cortisol, what is the dose ? A1: You know that the potency for Predisolone is relatively 5 times bigger than Cortisol; so you divide the 20 mg dose of Cortisol on 5, meaning that the answer is 4 mg of Prednisolone! Q2: How much is the dose of Prednisone that applies the same effect as 12mg of Cortisol? A2: From your memorizing; 12 divided by 4 equals 3mg of Prednisone! Q3: (I do not think the doctor would bring such one but just to be cautious) The dose from Methylprednisone that would exert a similar effect that 20mg of Paramethasone does; is ? A3: 20mg of Paramethasone corresponds to 200mg of Cortisol ! 200mg of Cortisol corresponds to 40mg of Methylprednisone ! So all these numbers are important to know the doses between these synthetic corticosteroids relatively to the Cortisol.

$ Salt-retaining : If your patient came to you with adrenal insufficiency, then you should give him a synthetic corticosteroid with a salt-retaining activity cause he is having an Aldosterone deficiency as well as cortisol, like Fludrocotisone & Deoxycoticosterone acetate. But what if he is having a problem with the glucocorticoids receptor ? It wouldn't be wise to give him a synthetic corticosteroid with salt-retaining activity over a long period of time for the treatment to occur; why? Cause he will develop hypertension; as the aldosterone hormone is already functioning well and you just simply have increased its net effect by giving a drug that does the same action ! So, the right thing to do is for you to give him a corticosteroid with no salt-retaining effect, like Meprednisone, Triamcinolone, Paramethsone .. ! So simply, know the ones that don't exert salt-retaining effect to differentiate them from those who do.

$ Cortisone's relative potency is too close to the cortisol making the 0.2 difference negligible ! Dose of Cortisone = Dose of Cortisol !

$ Deoxycoticosterone acetate is the precursor of Aldosterone. And both have a 0 relative potency as Anti-inflammatory corticosteroids.

$ Aldosterone has the same salt retaining effect of cortisol (=1) .

SLIDE 36

Therapeutic Uses:

1. Diagnosis and treatment of disturbed adrenal functions:

1. Adrenocortical insufficiency:

a. acute

b. chronic (Addison's disease)

•Replacement therapy with hydrocortisone + a mineralocorticoid (fludrocortisone).

$ Therapeutic uses represents pharmacological effect that arises from the ACTH suppression.

$ Diagnosis is represented by the suppression tests that aim to locate the lesion's place in the endocrine system and to identify the problem.

$ The most common cause of death in Adrenocortical insufficiency is due to hyperkalemia and hyponatremia, due to the failure of retention of Na+ and water and the excretion of K+! Adrenocortical insufficiency is fatal and is an urgent case.

SLIDE 37

•Synthetic glucocorticoids that are long-acting and devoid of salt-retaining activity should not be administered to these patients.

2. Adrenocortical hypo- and hyperfunction:

a. Congenital adrenal hyperplasia: The aim is to suppress ACTH production. It can be due to deficiency of any of the following: 21-β-hydroxylase, 11-β-hydroxylase, 17-α-hydroxylase, 3-β-dehydrogenase.

$ Adrenocortical hyperfunction is treated by suppression of ACTH secretion. But if there were a tumor; then we need surgical removal (until then we suppress ACTH) .

SLIDE 38

↓ leading to reduction of cortisol formation ↑ ACTH release ↑ accumulation of precursors ↑ a variety of forms of the disorder.

SLIDE 39

$ The doctor didn't ask us to memorize this but didn't say don't :p ; just get the general idea of it and understand it. (Remember, a problem in an enzyme leads to accumulation of its substrates)

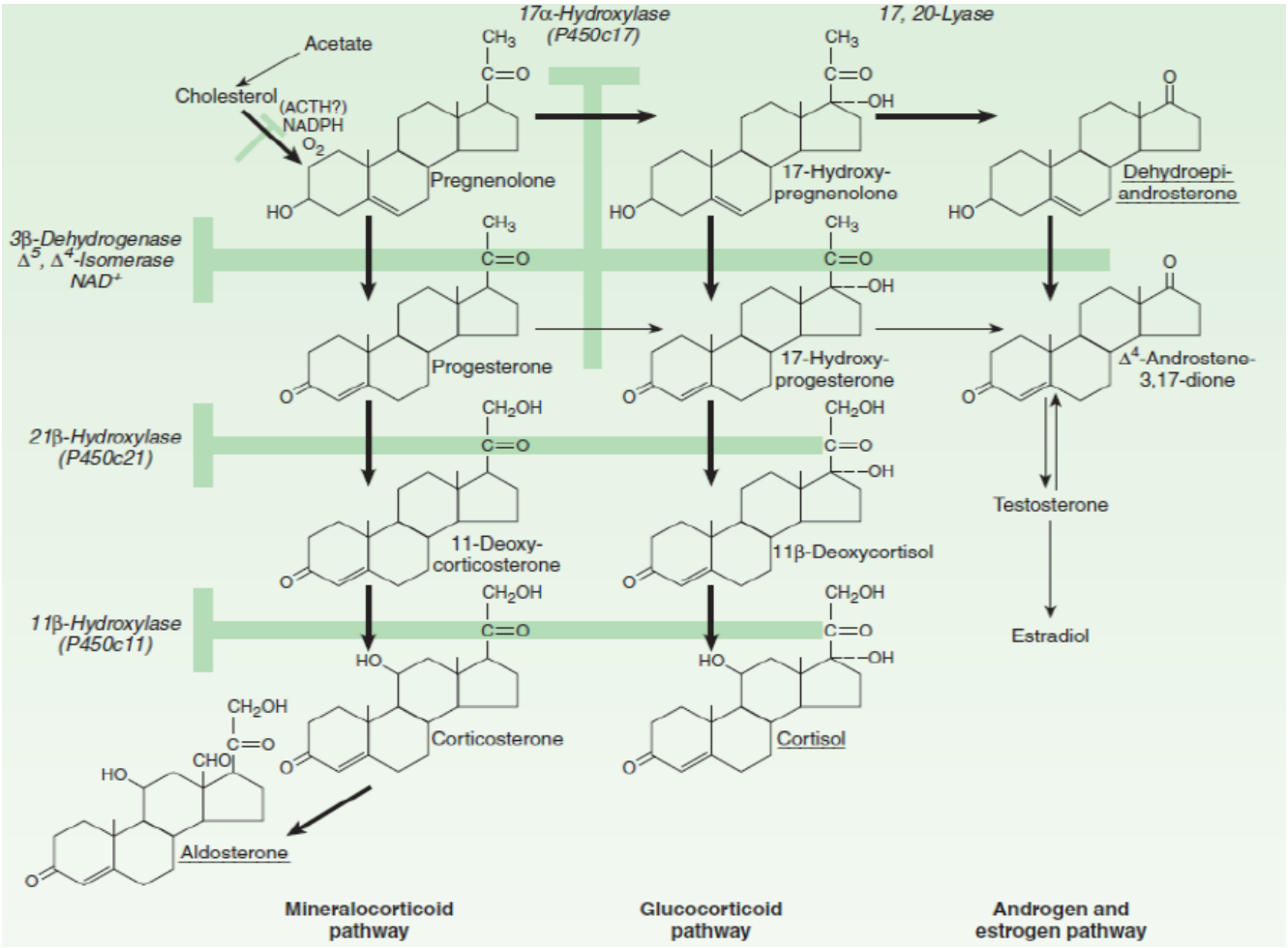

FIGURE 39-1 Outline of major pathways in adrenocortical hormone biosynthesis. The major secretory products are underlined. Pregnenolone is the major precursor of corticosterone and aldosterone, and 17-hydroxypregnenolone is the major precursor of cortisol. The enzymes and cofactors for the reactions progressing down each column are shown on the left and across columns at the top of the figure. When a particular enzyme is deficient, hormone production is blocked at the points indicated by the shaded bars. (Modified after Welikey et al; reproduced with permission, from Ganong WF: *Review of Medical Physiology*, 17th ed. Originally published by Appleton & Lange. Copyright © 1995 by The McGraw-Hill Companies, Inc.)

SLIDE 40

b. Cushing's syndrome:

•Cushing's syndrome is the result of bilateral adrenal hyperplasia secondary to an ACTH-secreting pituitary adenoma (Cushing's disease), and occasionally is due to tumors or nodular hyperplasia of the adrenal gland or ectopic production of ACTH by other tumors. (ACTH ↑ excess glucocorticoids).

SLIDE 41

•Replacement therapy with large doses of hydrocortisone following surgical treatment of Cushing's syndrome.

c. Primary generalized glucocorticoid resistance (Chrousos syndrome): A rare, genetic condition due to inactivating mutations of the glucocorticoid receptor gene.

SLIDE 42

•It is associated with increased production of ACTH leading to high circulating levels of cortisol and cortisol precursors such as corticosterone and 11-deoxycorticosterone with mineralocorticoid activity, as well as of adrenal androgens.

•Therapy of this syndrome is high doses of synthetic glucocorticoids such as dexamethasone with no inherent mineralocorticoid activity.

SLIDE 43

2.Dexamethasone suppression test for differential diagnosis of Cushing's syndrome.

3. Stimulation of lung maturation in the fetus by administration of betamethasone to the mother when premature delivery is anticipated ↑ reduce incidence of respiratory distress syndrome (RDS).

SLIDE 44

Treatment of Non-adrenal disorders:

•Due to antiinflammatory and immunosuppressive functions, and ability to alter leukocyte function .

•Corticosteroids are not usually curative, thus, the pathologic process may progress while clinical manifestations are suppressed.

SLIDE 45

•Glucocorticoid therapy can reactivate dormant tuberculosis.

•The presence of diabetes, peptic ulcer, osteoporosis, and psychological disturbances should be taken into consideration, and cardiovascular function should be assessed.

SLIDE 46

TABLE 39–2 Some therapeutic indications for the use of glucocorticoids in nonadrenal disorders.

Disorder	Examples
Allergic reactions	Angioneurotic edema, asthma, bee stings, contact dermatitis, drug reactions, allergic rhinitis, serum sickness, urticaria
Collagen-vascular disorders	Giant cell arteritis, lupus erythematosus, mixed connective tissue syndromes, polymyositis, polymyalgia rheumatica, rheumatoid arthritis, temporal arteritis
Eye diseases	Acute uveitis, allergic conjunctivitis, choroiditis, optic neuritis
Gastrointestinal diseases	Inflammatory bowel disease, nontropical sprue, subacute hepatic necrosis
Hematologic disorders	Acquired hemolytic anemia, acute allergic purpura, leukemia, lymphoma, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, multiple myeloma
Systemic inflammation	Acute respiratory distress syndrome (sustained therapy with moderate dosage accelerates recovery and decreases mortality)
Infections	Acute respiratory distress syndrome, sepsis
Inflammatory conditions of bones and joints	Arthritis, bursitis, tenosynovitis
Neurologic disorders	Cerebral edema (large doses of dexamethasone are given to patients following brain surgery to minimize cerebral edema in the postoperative period), multiple sclerosis
Organ transplants	Prevention and treatment of rejection (immunosuppression)
Pulmonary diseases	Aspiration pneumonia, bronchial asthma, prevention of infant respiratory distress syndrome, sarcoidosis
Renal disorders	Nephrotic syndrome
Skin diseases	Atopic dermatitis, dermatoses, lichen simplex chronicus (localized neurodermatitis), mycosis fungoides, pemphigus, seborrheic dermatitis, xerosis
Thyroid diseases	Malignant exophthalmos, subacute thyroiditis
Miscellaneous	Hypercalcemia, mountain sickness

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Adverse Effects:

•Affect every part of the body.

A.Major undesirable effect is iatrogenic Cushing's syndrome after 2 weeks of therapy.

B.Metabolic Effects:

1. Breakdown of protein – muscle wasting.

2. Gluconeogenesis: hyperglycemia, diabetes mellitus hyperinsulinemia and insulin resistance.

$ Iatrogenic means an effect produced by the treatment given to the patient by the doctor

SLIDE 48

3. Redistribution of fat

4. Osteoporosis (aseptic necrosis of the hip)

5. Impairment of wound healing.

C. Other complications:

1. Peptic ulceration and stress ulcers.

2. Masking of mycotic (diseases caused by mycobacteria e.x. tb) and bacterial infections.

3. Severe myopathy.

4. Acute psychosis, hypomania, depression, insomnia, and increased appetite.

$ Aseptic means with no infection, and its unknown why the hip in particular.

$ Don't do any surgery that requires cutting on the patient if he is taking corticosteroids, unless it is essential. (Because of the impairment of healing)

$ Psychosis is a different disease entity than depression. Psychosis is represented by an accelerated ideas flow that the patient loses contact with the external reality, and is associated with low dopamine. Depression is represented by extreme loss of hope in life for the patient, which makes his mind tend to the idea of committing suicide, and is associated with low catecholamines. Mania is the opposite of depression. Bipolar disorder represents the severe mind swings between Mania and Depression. Depression could be associated with psychosis.

SLIDE 49

5. Posterior subcapsular cataract.

6. Increased intraocular pressure (glaucoma).

7. Benign intracranial hypertension (pseudotumor cerebri).

8. Growth retardation in children.

9. Na+ and water retention and K+ , H+ and Cl- loss:

a. hypokalemic hypochloremic alkalosis.

SLIDE 50

b. hypertension in patients with normal cardiovascular and renal function.

c. edema in patients with hypoproteinemia, renal disease, hepatic disease.

d. congestive heart failure in patients with cardiovascular disease.

•Can be prevented by choosing synthetic, non-salt retaining steroids or Na+ restriction and K+ supplements.

SLIDE 51

D. Suppression of the hypothalamic-pituitary-adrenal axis (Adrenal suppression):

•Occurs when corticosteroids are used for more than 2 weeks.

•If corticosteroid therapy is to be terminated, this should be done gradually (tapering) to allow recovery of the axis.

$ Adrenal suppression is dose and duration(more than two weeks) dependent !

SLIDE 52

•It may take 2-12 months for the axis to function properly and cortisol levels may not return to normal for a further 6-9 months. Treatment with ACTH does not reduce the time needed for the return of normal function.

•Reducing the dose slowly also:

1.Prevents acute hypoadrenalism which could be fatal.

$ To overcome this period of time and with no sudden stop of the drug in-take (this is very dangerous cause the disease can rise again); we do tapering of the dose. If the period of the treatment is over and I want to stop the drug, I lower the dose gradually; for example, 75mg on 1st week , 50mg on 2nd week , 25mg on 3rd week , 15 .. 10 .. 5 .. 2.5 .. then we stop the drug !

$ Through this way, we can have a good recovery for the axis. Another important thing, I can check if my patient is dependent on the steroid to control and prevent the disease from coming back again (this is not addiction). For example,

if through the tapering at 25mg dose you detected the disease again, you increase the dose again to the level at which the disease cannot develop again.

$ Another important method of tapering is the ' Every other day ' therapy. Yet not all patients are responsive to it, so be careful ! How is it done ? I start the treatment daily by let us say a dose of 50 mg, when I want to check if this method works for my patient I start reducing the dose for a day while increasing that loss for the next day; like this, on the first time I give him 40mg and the next day 60mg. The second time I give him 30mg and the next day 70mg. Third time; 20mg for the first day and 80mg for the next day. Fourth time , 10mg then 90mg. On the fifth time I get for no-dose day and the next day I give him the 100mg dose! If the response was stable, we can continue using this method. If not, I stop it.

SLIDE 53

2.Avoids exacerbation of the disease they were used to treat.

•Symptoms of hypoadrenalism in the presence of normal cortisol levels indicate glucocorticoid dependence.

•Alternate-day therapy can avoid suppression of the hypothalamic-pituitary-adrenal axis.

•Patients should receive supplementary therapy at times of stress.

SLIDE 54

Precautions:

•Monitor for the development of hyperglycemia, glycosuria, sodium retention with edema or hypertension, hypokalemia, peptic ulcer, osteoporosis, and hidden infections.

1.Need high K+ and low Na+ intake to prevent electrolyte disturbances and hypertension.

SLIDE 55

2.High protein intake to prevent breakdown of proteins.

3.With appropriate antacid therapy to prevent peptic ulceration in patients with epigastric distress.

4.Adequate Ca2+, vitamin D and bisphosphonates to prevent osteoporosis.

5.Dose should not be decreased or stopped abruptly (why?).

$ Ulcers caused due to steroids are called stress ulcers, and known to be multiple

(more than one in the stomach and duodenum).

$ Antacids are given when patient is thought to have epigastric distress, acid over secretion or derangement of the mucosa.

$ If the patient is old, you should give him bisphosphonates. If young, Ca2+ and vitamin D are enough.

SLIDE 56

Contraindications

1.Peptic ulcer

2.Heart disease

3.Hypertension with heart failure.

4.Diabetes mellitus

5.Infections, such as varicella and tuberculosis

6.Psychosis

7.Osteoporosis

8.Glaucoma, ... etc.

SLIDE 57

•Routes of administration:

1.Local therapy:

a. topical for skin disease and ophthalmic disease

b. intra-articular injections for joint disease.

c. inhalation for asthma (beclomethasone diproprionate, budesonide, flunisolide)

d. enemas for ulcerative colitis

2.PO and IV for other conditions.

SLIDE 58

1.Natural: Aldosterone, Deoxycorticosterone

2.Synthetic: Fludrocortisone

•Salt retaining hormones.

•Aldosterone is mainly under regulation by angiotensin and only partially by ACTH.

•Promotes the reabsorption of sodium from the distal part of the distal convoluted tubule and from the cortical collecting tubules, coupled to the excretion of potassium and hydrogen ion.

SLIDE 59

•Sodium reabsorption in the sweat and salivary glands, gastrointestinal mucosa, and across cell membranes in general is also increased.

•Excessive levels of aldosterone produced by tumors or overdosage with synthetic mineralocorticoids lead to hypokalemia, metabolic alkalosis, increased plasma volume, and hypertension.

•It is eliminated by metabolism.

SLIDE 60

•Aldosterone receptor has similar affinity for cortisol.

•The major effect of activation of aldosterone receptor is increased expression of Na+ / K+ ATPase and the epithelial sodium channel (ENaC).

•Deoxycorticosterone also serves as precursor of aldosterone. Its secretion is primarily under the influence of ACTH (in contrast to aldosterone).

SLIDE 61

•Fludrocortisone is the most commonly prescribed salt-retaining hormone. It is a potent steroid with both glucocorticoid and mineralocorticoid activity.

•Mineralocorticoids are indicated in the treatment of adrenocortical insufficiency associated with mineralocorticoid deficiency.

SLIDE 62

1.Spironolactone:

•Is an aldosterone receptor competitive antagonist.

•Is also an androgen antagonist, used in the treatment of hirsutism in women.

•Is used in the treatment of primary aldosteronism, and also in its diagnosis in hypokalemic patients with hypertension.

•Used as a diuretic in heart failure.

SLIDE 63

Adverse effects:

•Include hyperkalemia, cardiac arrhythmia, menstrual abnormalities, gynecomastia, sedation, headache, gastrointestinal disturbances, and skin rashes.

2.Eplerenone:

•Also aldosterone receptor antagonist for treratment of hypertension.

•It reduces mortality in heart failure like spironolactone.

SLIDE 64

•No effect on androgen receptors.

•The most common toxicity is hyperkalemia, but this is usually mild.

3.Drospirenone:

•Is a progestin used in oral contraceptives

•Antagonizes the effects of aldosterone.

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* Sorry for any mistakes that I may have done ..

'It is not impossible for the things

to end up beautifully .. !

Have some Faith .. ;) '