Endocrine System

PHARMACOLOGY 432 TEAM

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Slides

Female side

Male side

Explanation

CORTICOSTEROIDS

Learning Objectives:

1-Revise synthesis, regulations & dysregulations of corticosteroids

2- Classify available natural vs synthetic glucocorticoides; whether systemic or topical; expanding on their properties & indications

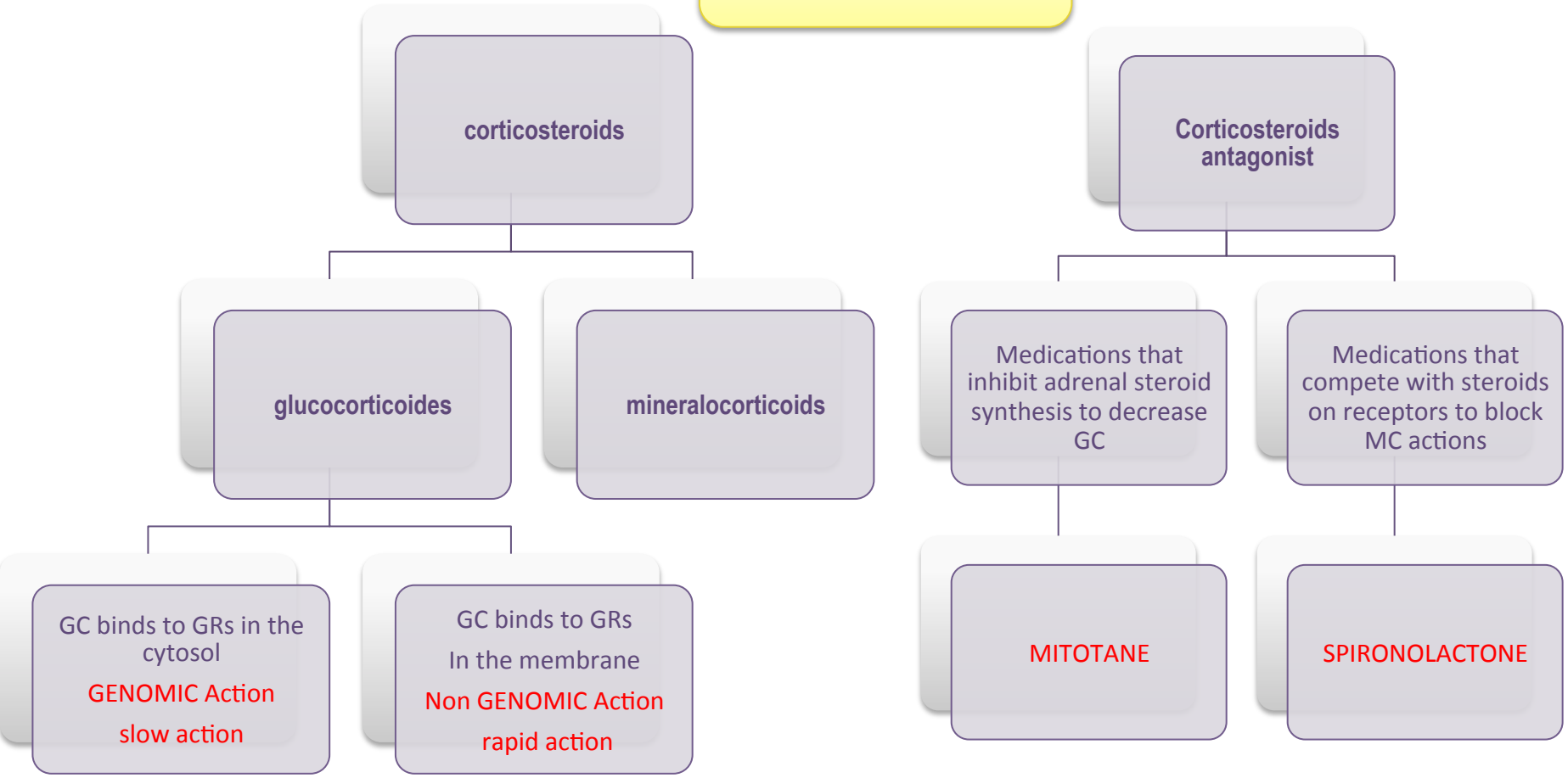
3- Contrast their different ADRs & methods of prevention or treatment

4-Focus on therapeutic roles of mineralocorticoids &relevant mechanism of action

5- Hint on drugs antagonizing corticosteroid action

Gray: not important

Mind Map

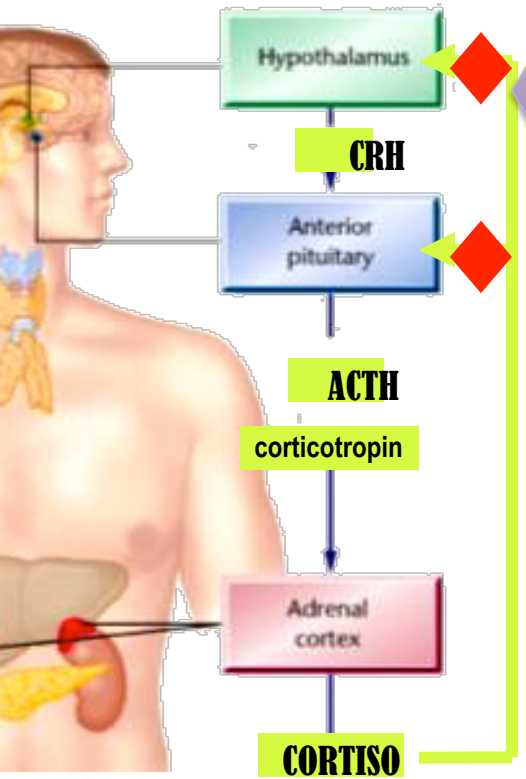

corticosteroids
glucocorticoides
mineralocorticoids
GC binds to GRs in the cytosol
GENOMIC Action
slow action
GC binds to GRs
In the membrane
Non GENOMIC Action
rapid action
Corticosteroids antagonist
Medications that inhibit adrenal steroid synthesis to decrease GC
Medications that compete with steroids on receptors to block MC actions
MITOTANE
SPIRONOLACTONE

CORTICOSTEROIDS

Are a class of steroid hormones that are produced in the adrenal cortex:

✧**Glucocorticoids [GC]** ➔ **Released <u>from Zona Fasciculata</u>** ➔ as Cortisol , Cortisone & Corticosterone ➔ **<u>regulated by ACTH</u>** + cytokines (IL-1, IL-6, TNF), neuropeptides & catecholamines (stressors) Control carbohydrate, fat & protein metabolism. They are also anti-inflammatory & immunosuppressants

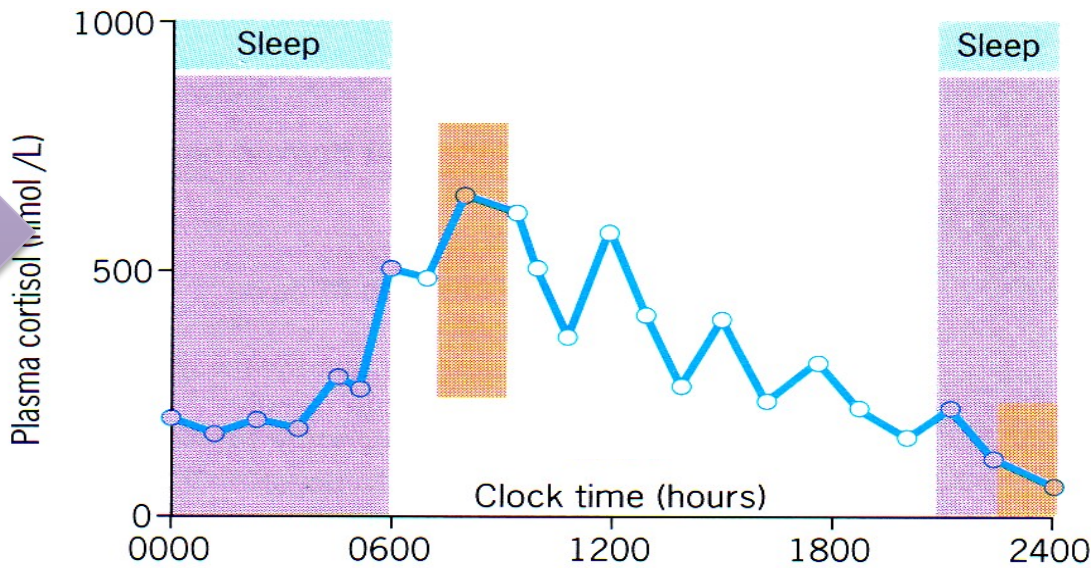
✧**Mineralocorticoids [MC]**′ Released from **<u>Zona Glomeruloza</u>** ➔ as Aldosterone ➔ **Regulated by <u>angiotensin II</u>**, potassium, and ACTH. In addition, dopamine, atrial natriuretic peptide (ANP) and other neuropeptides Control water & electrolyte homeostasis



Glucocorticoids regulation

We have to know this to know when to take the medicati on

CIRCADIAN pattern of CORTISOL secretion

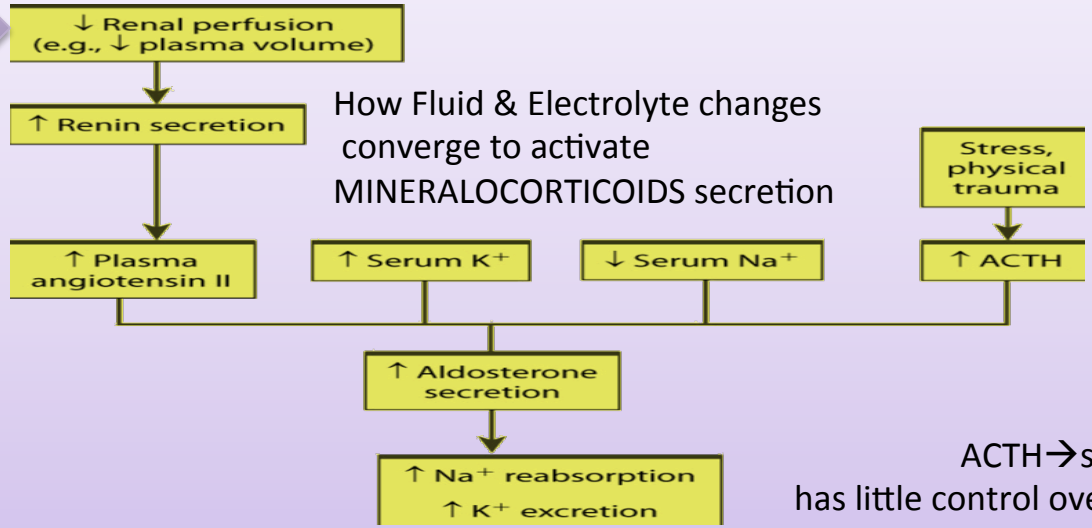


Pathology they will not ask about it you can skip this slide

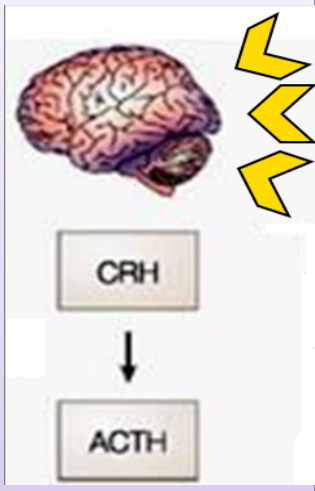
REGULATION

Mineralocorticoids

FLUID LOSS



How Fluid & Electrolyte changes converge to activate MINERALOCORTICOIDS secretion



ACTH→specifically stimulates GC & has little control over secretion of aldosterone

DYSREGULATION :

1- **Deficiency in corticosteroids →[Addison's disease]**

Hyponatremia, hyperkalemia, hypoglycemia, progressive weakness & fatigue, low blood pressure, depression, anorexia & loss of weight, skin hyperpigmentation (not emergency)

If subjected to stresses → [Addisonian Crisis]→↑↑ symptoms → + fever, confusion sever vomiting, diarrhea, abdominal pain & shock (emergency)

2-Deficiency of mineralocorticoids, seldom alone→ Hyponatremia, hyper kalemia, acidosis & wasting + ↓ ECF volume, hypotension & shock .

3-Increased **production of glucocorticoids → Cushing's syndrome**

4-Increased **production of mineralocorticoids → Conn's syndrome**

symptoms :(Hyperaldosteronism ,Hypernatremia,Hypervolemia ,Hypertension ,Hypokalemia)

PHARMACOLOGY OF EXOGENOUS GLUCOCORTICOIDS

Cortisol, Cortisone, Hydrocortisone, Prednisone, Prednisolone, Methylprednisolone, Triamcinolone, Dexamethasone, Betamethasone, Beclomethasone, Fluticasone, Budesonide, Mometasone, ...etc.

MECHANISM

GLUCOCORTICOIDS binds to G receptors → A) In the cytosol B) On cell membrane

1. Cytosolic GLUCOCORTICOIDS receptors > mediates GENOMIC Action > slow process needs→ **hrs-days**

Expression of proteins → Anti-inflammatory Effects	**Repression of proteins → Pro-inflammatory Effects**
➢Binding & Activation ➢ Nuclear translocation ➢Dimerization on GRE ➢Gene Transcription ➢mRNA Translation ➢**New Protein Formatione.g. Lipocortin→ –ve PLA2 -ve COX-2** (plA2 =phospholipase A2)	➢Binding & Activation ➢Nuclear translocation ➢**Prevent other transcription factors (AP-1)from binding to their RE** (ap-1=activator protien 1) ➢No Gene Transcription ➢No mRNA Translation ➢No new Protein Formation e.g. No proinflammatory cytokines (IL-2)& chemokines

.2- Membranous GLUCOCORTICOIDS receptors→mediates NON-GENOMIC Action → cross talks with GP coupled receptors
→alter Ca, cAMP, their downstream kinases (PKA & PKC)
→ rapidly exert anti-inflammatory effects & shut down proinflammatory effects
→ rapid process needs minutes-hrs

Not important you can skip this slide (physiology)

1. On Metabolism

: CHO ↓glucose utilization.

↑gluconeogenesis →hyperglycaemia

Fats: fat deposition on shoulders, face and abdomen

Proteins: ↓ anabolism & ↑ catabolism leading to:

Negative nitrogen balance with muscle wasting + ↑ uric a. production

Osteoporosis.

Retardation of growth in children.

Skin atrophy + capillary fragility → bruising and stria.

Calcium metabolism: ↑ urinary excretion & ↓ absorption from intestine (antivitamin D action).

2. On INFLAMMATORY & IMMUNE RESPONSE

↓vascular permeability; so → ↓ edema & redundancy of soft tissues

↓ release & synthesis of inflammatory mediators; so -ve PLA2 → -ve AA & LTs pathways….

↓antigen antibody reaction→↓ mast cell degranulation & transmitter release

↓infiltration & activity of inflammatory cells (eosinophilic, lymphocytic, …etc) by → ↓cytokines & chemokine production

↓ Complement formation

3. ON HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

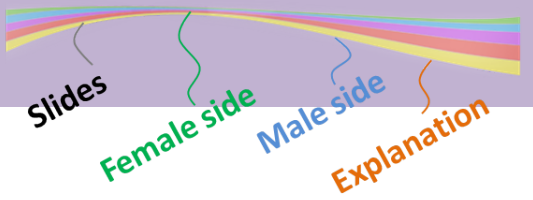
Occurs with high doses & long periods of treatment.

Sudden withdrawal of corticosteroids→

produce a state of adrenocortical insufficiency

4. Others

Euphoria or psychotic states: may occur (probably due to CNS electrolyte changes



Pharmacokinetics

Absorption	Distribution;	Metabolism;	t 1⁄2
;(from every where), **Most preparations are >>effective orally. Parentral forms are also available. Can get absorbed systemically when given at local sites (e.g. skin, respiratory tract, conjunctival sac, synovial spaces etc.)**	90% or more of cortisol in plasma is transported by reversible binding to Corticosteroids Binding Globulin (CBG) & to albumin * Corticosteroids compete with each other on CBG; **Glucocorticoids bind with high affinity** **Mineralocorticoids bind with low affinity** • Only the unbound free form is active & can enter cells by diffusion	are metabolized by the liver * Some preparations transform to active form in liver ▶ Cortisone Hydrocortisone ▶ Prednisone Prednisolone long use will cause liver cancers	is variable [short, intermediate & long acting] Excretion; as soluble sulphates in the urine.

Classification according to half life and methods of administration

Systemic drugs	T 1/2	Anti_inflam E.	Na retention	Notes
Cortisol *	Short(rapid) Less 12 H	low	High	I.m/I.V Emergency(addisons' crisis)
Cortisone *				Not in liver disease
*Prednisolone**	Intermediate 12-36 H	High	Low	Tablet, (IM, intrarticular)
Triamcinolone *				Tablet,(IM & intrarticular)
*Deamethasone (fluorinated)**	Long more than 36 H	Very high	0 (hardly do Na retention bcuz of flurination)	
Betamethasone [Fluorinated]				

Inhalant drugs	***Budesonide*** **and** ***Fluticasone*** (rapid first pass metabolism in liver if is given in high doses and then will cause systemic effects)	
TOPICAL DRUGS	**Preparation**	**Potency**
Beclomethasone	**cream**	**Potent**
Triamcinolone actonide	**ointment**	**Potent**
Mometasone	**cream, ointment**	**Moderate**
Fluticasone	**cream**	**Moderate**
Hydrocortisone acetate	**ointment**	**Mild**

Mild-moderate topical steriods are applied on the face as creams only

N.B.

*Changes in basic cortisol molecule >> ′compounds with

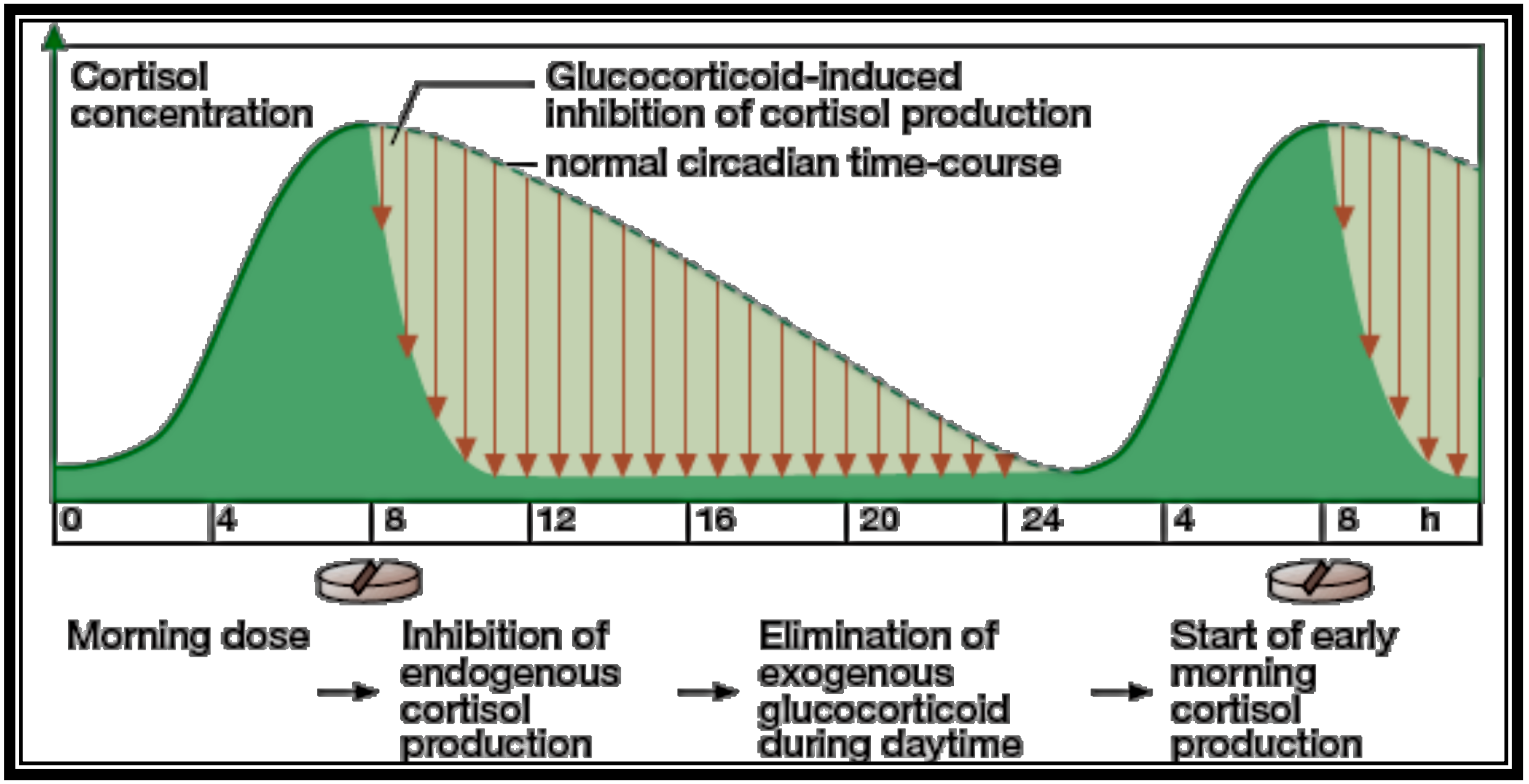
increase mineralocorticoid activity ,greater potency,increase duration of action

*Mild-moderate topical steroids are applied on the face as creams only

Potent and intermediate are given in non exposed area of the body) and not given in delicate tissues (such as axilla , face , around the sex organs and children skin)could be used at any time,but for the exposed areas at night to prevent the pigmentation due to photosensitivity.

Mild and cream preparations (not ointment which is lipophilic and rapidly absorbed) are used in delicate tissues, if potent preparations used>> sloughing and ulceration occur.

Time of administration of GCs>> specially on prolonged use follows natural circadian rhythm i.e. early morning >>to minimize hypothalamo-pituitary-adrenal axis impairment. Better if administered on alternate days



Systemic drugs are given at the morning cuz in the evening the cortisol level is already high while tropical or spray drugs could be given at night (produce local actions not systemic)

Indication in hormone replacement therapy

Hormone replacement therapy

1_Adrenal insufficiency

Acute(Addisonian Crisis)

Parental Cortisol (hydrocortisone)ER 100 mg IV / every 6-8 hrs until patient is stable.

Dose gradually reduced reach maintenance dosage in 5 dys

→ Fluids and electrolytes should be corrected.

→ Treatment of precipitating factors

Chronic (Addison's Disease),long and intermediate acting drugs

Cortisol (20-30 mg/day orally) + (fludrocortisone (0.1 mg orally)

→ Dexamethasone could be given on prolonged use

→ Doses must be increased in stress to prevent development of Addisonian crisis

→ Doses should follow circadian rhythm

2_Cushing's syndrome

In Diagnoses Dexamethasone suppression test(one injection to diffrentiate the cause

In Treatment (replacing therapy) Cortisol; Temporally administred AFTER surgical removal of pituitary / adrenal / corticosteroid secreting tumors(till adjusted)

Indication> I. ANTI-INFLAMMATORY & IMMUNOSUPPRESSANT

Severe allergic reactions e.g. serum sickness, angioneurotic edema... etc.
Diseases of allergic origin; bronchial asthma, rhinitis, conjunctivitis, eczema & many other atopic & proliferative skin diseases
Autoimmune disorders; rheumatoid arthritis, inflammatory bowel disease systemic lupus erythrematosus, nephrotic syndrome,...
Organ transplantation; kidney, cardiac, bone marrow (rejection)
Blood dyscrasias; hemolytic anemia, thrombocytopenic purpura, agranulocytosis ... etc.
Acute gout (resistant) to other drugs

Predisolone
Dexamethasone
Betamethasone
Give the fluronide forum

→ **>>anti –inflammatory and immunosuppression**

Indication >> Other

Raised intracranial pressure.
In neoplastic diseases.
With cytotoxic drugs >>as in Hodgkin's disease, acute lymphocytic leukaemia
Pry or 2ndry neoplasms in the brain & postoperative to brain surgery to disease **edema**
In antiemetic regimens >prevent / cure emesis of chemotherapy
Suppress excessACTHproduction

Dexamethasone
Betamethasone

→ If water retention is undesirable

ARDS

SUPPRESSION OF HYPOTHALAMIC PITUITARY ADRNAL AXIS

1]Withdraw Corticosteroids Regimens

If less than 1 week (7 – 10 days)

If longer periods

not used in big doses = no fear.

big dose you may 2.5-5 mg prednisolone at an interval of 2-3 days

& high dose : halve dose weekly until 25 mg prednisolone or equival-ent is reached Then by about 1mg every 3-7 days.

& Small dose = I have to stop it (gradually)

So , in SYSTEMIC treatment & from 7 to 10 days = ok to stop it without gradual withdrawal.
Also, in TOPICAL treatment like (cream) , ok to stop it without gradual withdrawal what ever the duration .

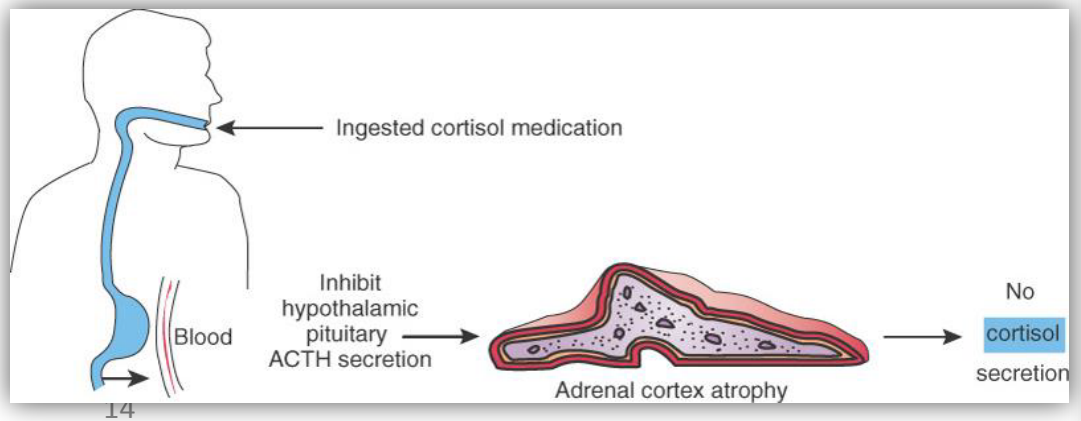
If longer period more than 7 – 10 days, I've to stop it gradually whatever the dose!
In case cortisol is taken as long life treatment I adjunctive therapy is given like (vit.D , insulin, Proton pump inhibitors ..etc) see next slide

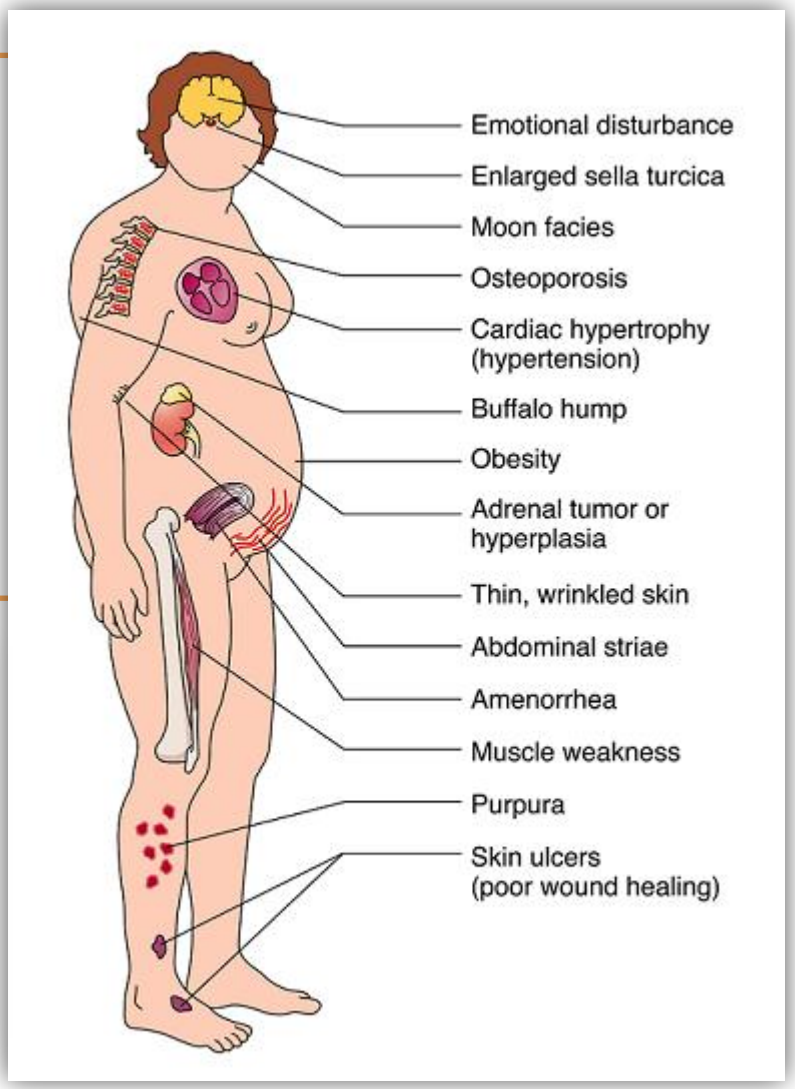
2] In case of IATROGENIC CUSHING's SYNDOME:

If possible : slow withdraw to allow body to slowly resume its normal balance of ACTH & .cortisol

↓ If not possible to stop because of underlying disease: treat concurrent symptom separately

- *** Antidiabetic for hyperglycaemia**
- *** Bisphosphonates for osteoporosis**
- *** H2 blocker or proton pump inhibitors for peptic ulcer**





ARDS

Hyperglycemia , glycosuria, diabetes mellitus > fluorinated preparations
→Growth retardati >>premature closure of epiphysis >> short stature(I've to take care when I give it to children)
→Muscle wasting >>-ve nitrogen balance > fluorinated preparations
→Fat redistribution & abnormal deposition
→Hypertension, oedema, Na retention
→vertebral compression & fractures
Hypokalaemia
→Osteoporosis >>-ve of osteoblasts / +ve osteoclasts &/decrease Ca absorption increase Ca excretion
Avascular necrosis of head of femur ? (there are theories about it , but it's Very common) Coagulation / apoptosis?
→Menstrual irregularities
→Psychiatric disorders; depression, euphoria,…
→Impairment of defense mechanisms >>serious infections, flare of dormant T.B., activate hepatitis, increase reaction to live vaccines
→Delayed wound healing
→Peptic ulcer specially if with NSAIDs
→Skin, acne, striae, hirsutism
→Ocular toxicity glaucoma & cataract
* Delayed wound healing
* Peptic ulcer specially if with NSAIDs
* Skin, acne, striae, hirsutism
• Ocular toxicity :glaucoma & cataract

Local ARDS

Local Toxicity:
- Skin: infection, atrophy, bruising.
- Eye : viral infection(if large dose), cataract, glaucoma. (Always hydro cortisol for eyedrops i Have to give It with antibiotic)due to immune suppression
- Inhalation: fungal infection, hoarseness
- Intrarticular : infection, necrosis

No need to memorize it work by word >> relate it with the physiology

Contraindications &Precautions :

Contrandications	Precautions
* Diabetes mellitus. * Hypertension or heart failure * History of mental disorders or Epilepsy. * Osteoporosis * Peptic ulcer *Presence of infection or Tuberculosis :requires chemotherapy before administration (Same as ARDS)	* Patients receiving GCs and is subjected to stress : double the dose * In children receiving : take care of live attenuated vaccines Children & live attenuated vaccine , I've 2 options: - If I have to give the glucocorticoids: give it in Reduced dose - If I can stop the glucocorticoids, so stop during the vaccination time \^^/ * In pregnant women; better avoid fluorinated GCs : because of Teratogenicity It crosses the placenta ,Pregnant lady in the first 3 months : short acting are life saving ,it's ok to give her any one EXCEPT Fluorinated GCs , in the last 3 months>> suppresion of hypothalamic pituatry axis (addison crises) thus you have to check cortisol level of the baby and replace it ig it's low * Neo-born to mothers taking high dose GCs : -ve HPA axis.

PHARMACOLOGY OF MINERALOCORTICOIDS

Form : Aldosterone (Not used because it metabolized and excreted rapidly) , Deoxycorticosterone (Not good because it's strongly increase the Blood pressure), Fludrocortisonee (Good) (diffrentate between it and fluticanazole>> cortisol like effect)

Mechanism :

Bind to mineralocorticoid receptors [MC R] " Binds GC > MC, in MC responsive cells i.e. distal nephron

GC is destroyed, enzymatically in MC responsive cells , so MC will bind to its receptor alone without any competition from GC.

1.Cytosolic MC R : mediates GENOMIC Action , lead to Expression of proteins .

In distal & collecting tubules:

***Na pumps: ↑ Na retention**
*** Na channels: Na reuptake from lumen**
***K simporters: excretion of K & H**

N.B. Actions also on (colon, sweat & salivary glands)(has distribution in uncommon areas)

2. Membranous GC R : mediates NON-GENOMIC Action

Interact with GP coupled receptors & channels to mediate rapid adaptive changes to fluid depletion

2] EFFECTS / USES / PREPARATIONS

Net effect is to conserve body sodium >> osmotic effect >> water follows >> expansion of extracellular fluid > increase renal excretion of potassium & decrease Intracellular potassium.

In excess >> hypertension, atherosclerosis , fibrosis >> vascular & cardiac remodeling >> cerebral hemorrhage / stroke & or .cardiomyopathy

SYSTEMIC Drugs	Anti-inflam.	Na retention	Preparations & doses
Aldosterone	0.3	300	**Natural / Not used clinical**
Deoxycortone sterone[DOCA]	0	100	**2.5 mg sublinual, ineffective orally ? Inactive in liver**
Fludrocortisone **Dr said memorize this drug only**	10	150	**100mcg oral tablets / duration of 36-72hrs / Drug of Choice in Replacement Therapy**

PHARMACOLOGY OF CORTICOSTEROID ANTAGONIST

Medications that inhibit adrenal steroid synthesis to ↓GC:

Mitotane :

-ve 11 b-hydroxylase

↓ Corticosteroid production → ↓ its peripheral metabolism & plasma & urine levels Used in Cushing syndrome; whether iatrogenic, or to alleviate severe symptoms till removal by surgery Safe in pregnanc

So, it inhibit the Synthesis of GC by inhibit 11B-hydroxylase (use it in case of high GC)

Medications that compete with steroids on receptors to block MC actions:

SPIRONOLACTONE :

Is a competitive aldosterone antagonist Is a K+ sparing diuretic (weak, slow onset & prolonged effect) Used in hypertension (alternation with others), in heart failure In Hyperaldosteronism (Conn's)

Decrease Na and water retention

So, it inhibit the (Receptor) of MC .

1. **Osteoporosis is a major adverse effect caused by the GC. It's due to their ability to:**
   A. Increase the excretion of Ca
   B. Inhibit absorption of Ca
   C. Stimulate the hypothalamic – pituitary – adrenal axis
   D. Decrease production of prostaglandin

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

3. **All of the following adverse effects commonly occur in GC therapy except:**
   A. Osteoporosis
   B. Increased risk of infection
   C. Hypotension.
   D. Emotional Disturbance

Answers: B – C – C

4. 4. A pregnant - 10 week -women came to the doctor of with
5. ulcerative collitis , which of the following I should avoid :

A. Fluorinated Dexamethasone
B. Fludrocortisone
C. Mitotane
D. Pridnisone

5) A 56-yr-old woman with systemic lupus erythematous had been maintained on a moderate daily dose of prednisone for 9 mo. Her disease has finally gone into remission and she now wishes to gradually taper and then discontinue the prednisone. Gradual tapering of a glucocorticoid is required for recovery of which of the following?

(A) Depressed release of insulin from pancreatic B cells
(B) Hematopoiesis in the bone marrow.
(C) Normal osteoblast function.
(D) The control by vasopressin of water excretion.
E) The hypothalamic-pituitary-adrenal system.

Answers: A - E

6. 25 years old patient has eczema on the face, which of the following suits her condition?

A. Mometasone ointment
B. Hydrocortizone acetate ointment
C. Beclomethasone
D. Hydrocortizone acetate cream

7. Pregnant lady with cushing syndrome which drug is safe for her?

A. Mitotane
B. Spironolactone
C. Predinselone
D. Beclomethasone

Answers: D - A

Endocrine System

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