King Saud University

College of Medicine

2nd Year, Endocrine Block

PHARMACOLOGY 433

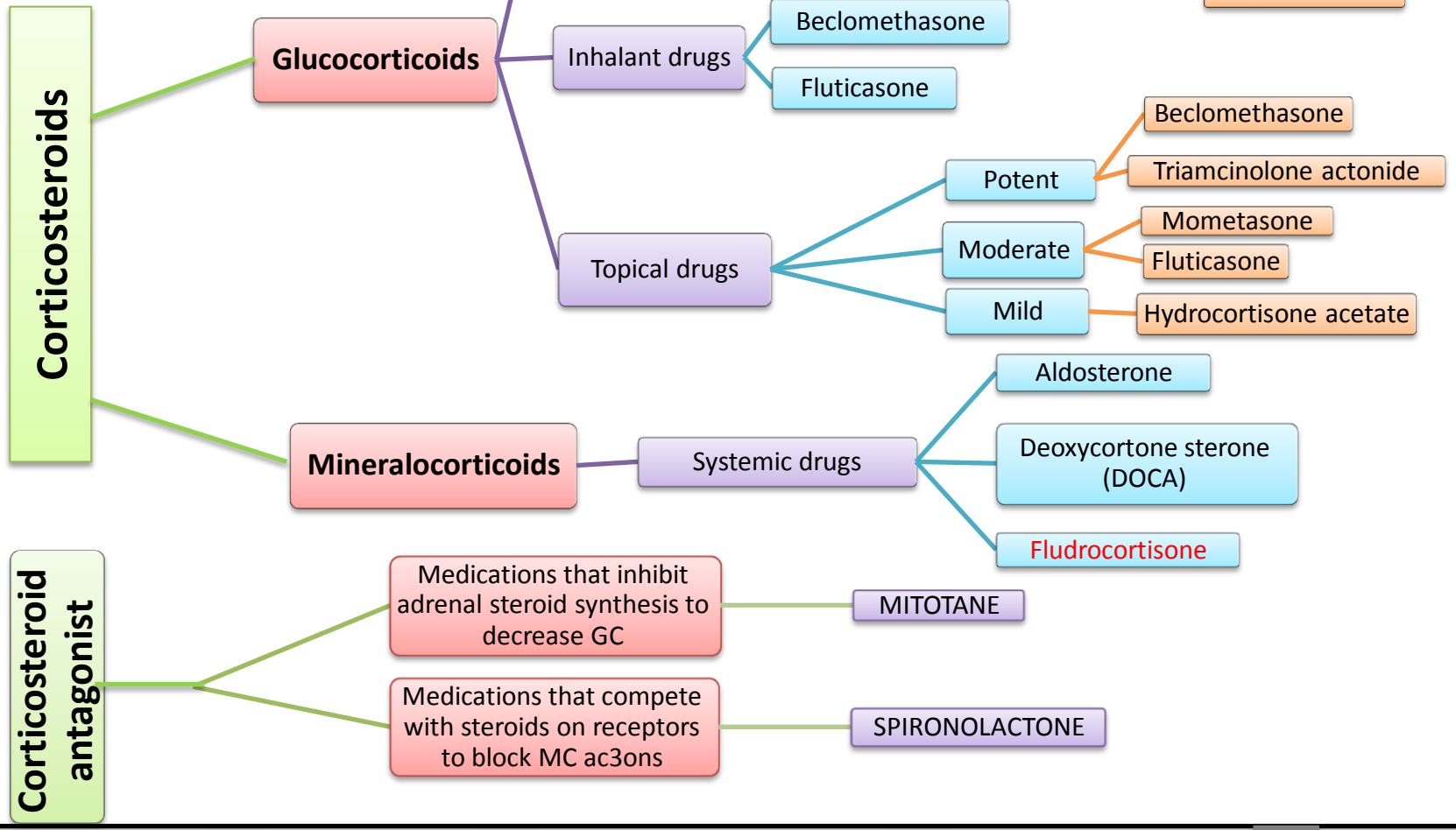
MED 433 Teams

L5- Corticosteroids

Objectives

- ✓ **Revise synthesis, regulations & dysregulations of corticosteroids.**
- ✓ **Classify available natural vs synthetic glucocorticoides; whether systemic or topical; expanding on their properties & indications .**
- ✓ **Contrast their different ADRs & methods of prevention or treatment Focus on therapeutic roles of mineralocorticoids & relevant mechanism of action.**
- ✓ **Hint on drugs antagonizing corticosteroid action.**

Mind map



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Corticosteroids		Are a class of steroid hormones that are produced in the adrenal cortex	
		Glucocorticoids [GC]	**Mineralocorticoids [MC]**
Synthesis in		Zona Fasciculata	Zona Glomeruloza
Released as		-Cortisol -Cortisone -Corticosterone	Aldosterone
Regulated by		ACTH - cytokines, neuropeptides & catecholamines.	Potassium - ACTH (little control) dopamine- atrial natriuretic peptide (ANP) – Angiotensin II – neuropeptides .
Function		-Control carbohydrate, fat & protein metabolism. -anti-inflammatory & immunosuppressants	Control water & electrolyte homeostasis (acute function)
Dysregulation	Deficiency	Addison's disease	Hyponatremia, hyperkalemia, acidosis, wasting, hypotension & shock.
	Increased	Cushing's syndrome	Conn's syndrome: Hyperaldosteronism, Hypernatremiam, Hypervolemiam Hypertension & Hypokalemia.

INTRODUCTION +IMP

Notes

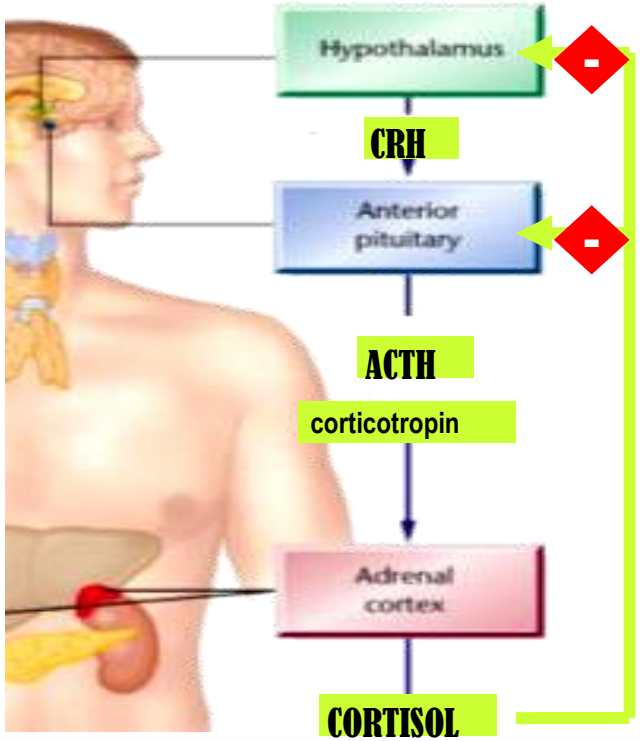
1-Addison's disease

Hyponatremia, hyperkalemia, hypoglycemia, progressive weakness & fatigue, low blood pressure, depression, anorexia & loss of weight, skin hyperpigmentation.

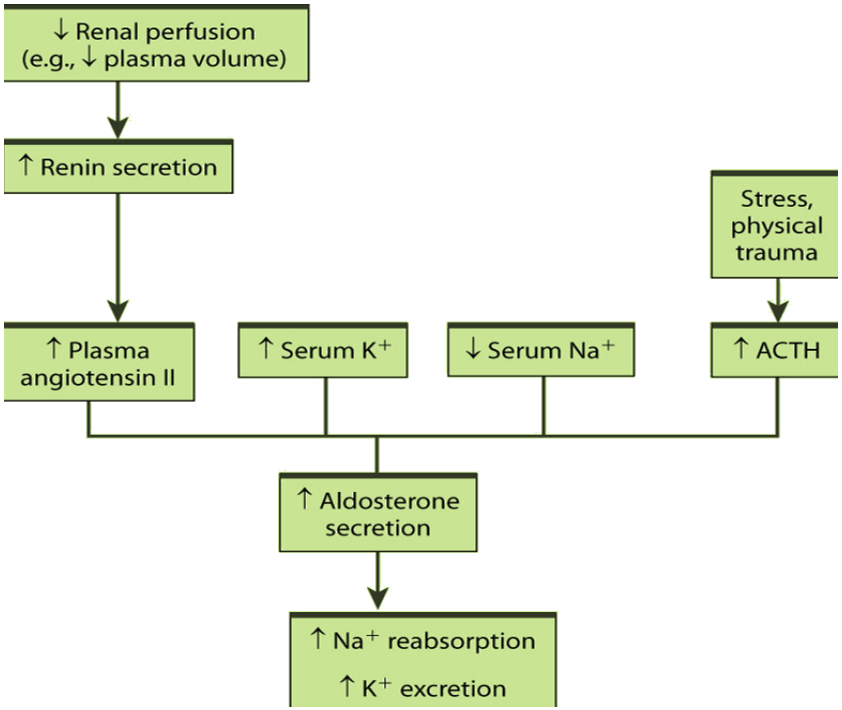
2-Addisonian Crisis (EMERGENCY)

↑↑ symptoms →fever, confusion sever vomiting, diarrhea, abdominal pain & shock.

Regulation of Glucocorticoids



Regulation of Mineralocorticoid



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Pharmacology Of Exogenous Glucocorticoids

*Many types of Exogenous Glucocorticoids but most important are:

-Cortisol, Cortisone, Hydrocortisone

*Mechanism:

-Glucocorticoids binds to its receptor on by two ways :

1-Cytosolic Glucocorticoids receptor:

Mediates Genomic Action (Slow Process)

A-Expression of proteins ➔ Anti-inflammatory Effects

e.g. Lipocortin ,which suppress phospholipase A2 >> inhibit PG & leukotiene.

B-Repression of proteins ➔ Pro-inflammatory Effects

prevent (AP-1) from binding to it's receptor >> no pro-inflammatory mediators (IL-2,6...ECT) .

2-Membranous Glucocorticoids receptor:

mediates NON-GENOMIC Action (rapid process) ➔ 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

Pharmacological actions

1. On METABOLISM

CHO	Proteins	Fats	Calcium
↓glucose utilization. ↑gluconeogenesis leading to (hyperglycaemia)	↓ 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)	fat deposition on shoulders, face and abdomen.	↑ 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 so ↓ mast cell degranulation & transmitter release
↓ infiltration & activity of inflammatory cells 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. (-ve feed back mechanism)

4. Others

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

Pharmacokinetics

1. Absorption

- Most preparations are effective orally and Parentral forms are also available.
- Can get absorbed systemically when given at local sites (e.g. skin, respiratory tract, conjunctival sac, synovial spaces etc.)

2. Distribution

- 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

3. Metabolism & Excretion

- are metabolized by the liver & excreted as soluble sulphates in the urine
- Some preparations transform to active form in liver

Cortisone → Hydrocortisone

Prednisone → Prednisolone

4. Dosage Schedule

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

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Classification According To t 1/2 & Method Of Administration

Systemic drugs

Short Acting (t1/2 < 12h) .	Intermediate Acting (t1/2=12 -36h)	Long Acting (t1/2 >36h)
↑ Na retaining property .	↑ anti-inflammatory action, with some Na retaining .	Anti-inflammatory , **No** Na retention .
1-**Cortisol** *IM / IV * (***EMERGENCY***) 2-**Cortisone** *IM* (***not in liver disease***)	1-**Prednisolone** *IM, intrarticular* 2-**Triamcinolone** *IM, intrarticular* (No Na retention) 3-Prednisone 4-Methyl- ″	**1-Dexamethasone [Fluorinated]** * IM / IV * **2-Betamethasone [Fluorinated]** * IM / IV *

Inhalant Drugs

1-Fluticasone
2-Budesonide
3-Beclomethasone

Topical Drugs

Potent	Moderate	Mild
1-Beclomethasone *cream* **2-Triamcinolone actonide** *ointment* 3-Betamethasone	**1-Mometasone** *ointment* **2-Fluticasone** *cream* 3-Fluocinolone actonide 4-Hydrocortisone acetate	**1-Hydrocortisone acetate** *ointment*

On sensitive skin (**face, babies**) only apply **milde-moderate** steroid as **creams**

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INDICATIONS

1. Hormone replacement therapy

1. ADRENAL INSUFFECIENCY

Addisonian Crisis *acute* (shock)

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

Dose ➔ gradually reduced

2-Fluids and electrolytes should be corrected.

3-Treatment of precipitating factors.

Addison's Disease *chronic*

1-Cortisol (orally) + fludrocortisone (orally)

And Dexamethasone could be given on prolonged use

2-**Doses must be increased in stress to prevent development of Addisonian crisis**

3- **Doses should follow circadian rhythm**

2. CUSHING'S SYNDROME

1-in **Diagnoses** Dexamethasone suppression test.

2-in **Treatment** Cortisol **Temporally administered** AFTER **surgical removal** of **pituitary / adrenal / corticosteroid secreting tumors.**

2. Anti-inflammatory & immunosuppressant

We use :

1-Prednisolone

2-Dexamethasone

3-Betamethasone

As anti inflammatory drugs

1-Severe allergic reactions e.g. serum sickness,angioneurotic edema

2-Diseases of allergic origin bronchial asthma, rhinitis, conjunctivitis, eczema & many other atopic & proliferative skin diseases

3-Autoimmune disorders; rheumatoid arthritis, inflammatory bowel disease systemic lupus erythrematosus, nephrotic syndrome

4-Organ transplantation; kidney, cardiac, bone marrow (↓rejection) **5-Acute gout (resistant) to other drugs**

5-Blood dyscrasias hemolytic anemia, thrombocytopenic purpura, agranulocytosis

3. Others

We use :

1-Dexamethasone

2-Betamethasone

If water retention is undesirable

1-Raised intracranial pressure

2-In neoplastic diseases With cytotoxic drugs ➔ as in Hodgkin's disease, acute lymphocytic leukemia /// 1ry or 2ndry neoplasms in the brain & postoperative to brain surgery➔ ↓edema /// In antiemetic regimens ➔prevent / cure emesis of chemotherapy

3-Suppress excess ACTH production

Adverse effects:

1. ↓ HYPOTHALAMIC PITUITARY ADRNAL AXIS

Withdrawal of Corticosteroids Regimens

(Next slide)

2. IATROGENIC CUSHING's SYNDOME

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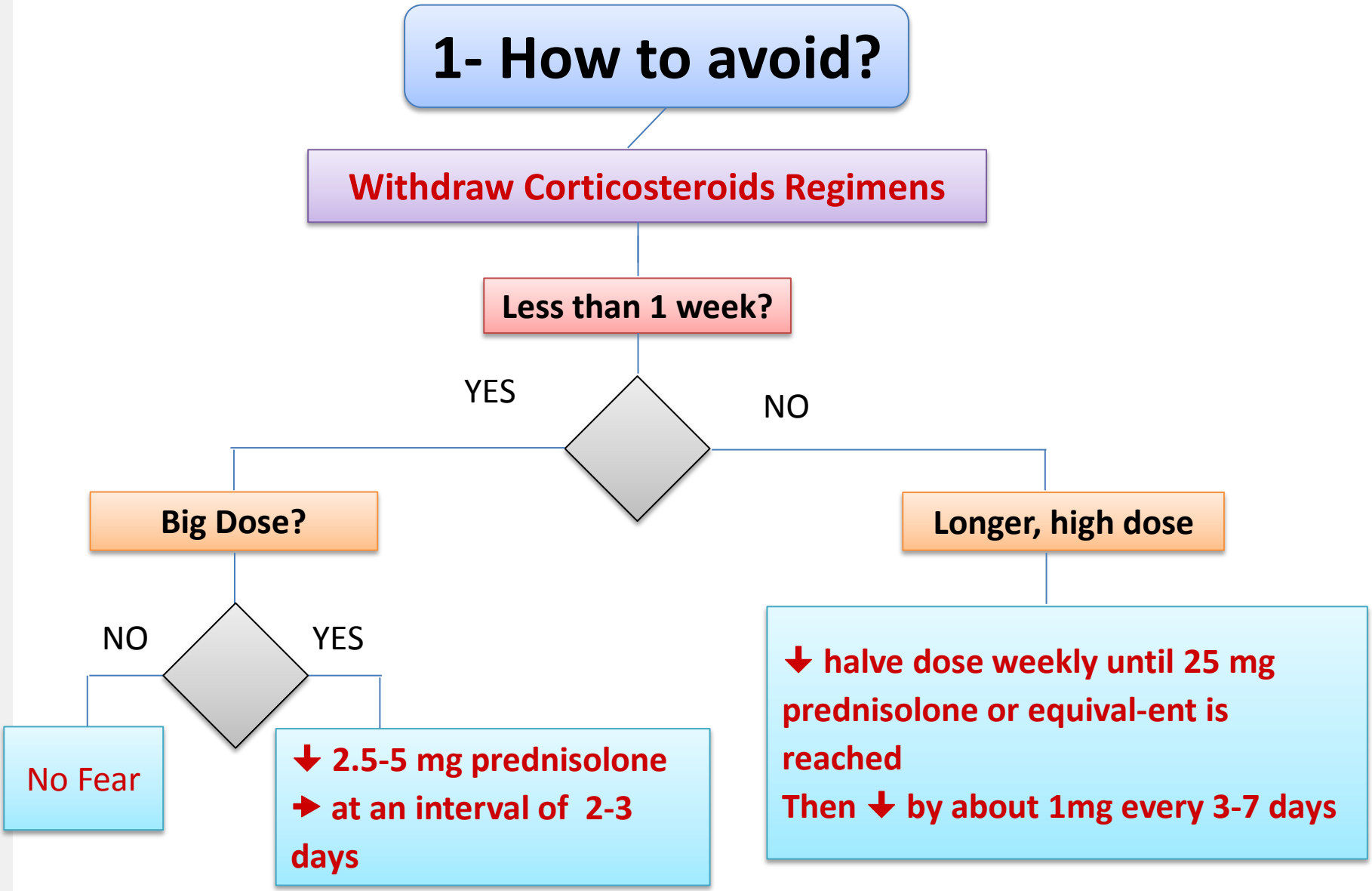
3.Inflamation:

Unwanted: e.g. allergy, autoimmune disease, transplant rejection.

Wanted: healing of tissue injury due to bacteria, viruses, fungi, trauma.

1- How to avoid?



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2- IATROGENIC CUSHING's SYNDOME

How to treat

Stopping the drug ?

- **possible**
  - slow withdraw to allow body to slowly resume its normal balance of ACTH & cortisol
- **not possible due to the underlying disease**
  - ↓ treat concurrent symptom separately

hyperglycaemia	Antidiabetic
osteoporosis	Bisphosphonates
peptic ulcer	H_2 blocker or proton pump inhibitors

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	3-Others ADRs	Notes
Systemic	-Hyperglycemia , glycosuria, diabetes mellitus , Muscle wasting .	use better fluorinated preparations
	-Growth retardation ➔ short stature. -Fat redistribution & abnormal deposition. -Hypertension, oedema, Na retention, Hypokalaemia . -Osteoporosis . -Menstrual irregularities. -Psychiatric disorders. -Impairment of defense mechanism. -Peptic ulcer specially if with NSAIDs. -Skin, acne, striae, hirsutism.	
	-Avascular necrosis of head of femur. -Ocular toxicity ➔glaucoma & cataract.	Specific to glucocorticoid.
Local Toxicity	-Skin➔ infection, atrophy, bruising. -Eye ➔ viral infection, cataract, glaucoma. -Inhalation ➔ fungal infection, hoarseness. -Intrarticular ➔ infection, necrosis.	
CONTRAINDICATIONS	-Diabetes mellitus. -Hypertension or heart failure. -History of mental disorders or Epilepsy. -Osteoporosis. -Peptic ulcer. -Presence of infection or Tuberculosis ➔ requires chemotherapy before administration.	

Precaution

1- Patients receiving GCs and is subjected to stress ➔double the dose, because it may lead to addisonian crisis .

2- In children receiving GCs ➔ stop live attenuated vaccines, due to low immunity.

3- In pregnant women; better avoid fluorinated GCs (long acting GCs) ➔ teratogenicity.

4- Neo-born to mothers taking high dose GCs ➔ -ve HPA axis → give the neo-born low dose of GCs the reduce it gradually to avoid adrenocortical insufficiency .

PHARMACOLOGY OF MINERALOCORTICOIDS

Aldosterone Natural (not given) , Deoxycorticosterone (DOCA) , Fludrocortisone

M.O.A	-Bind to mineralocorticoid receptors [binds GC>MC] ⇨in Mineralocorticoids 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 Mineralocorticoids receptor ➔mediates GENOMIC Action ➔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)) 2. Membranous GC R ➔ mediates NON-GENOMIC Action. -Interact with GP coupled receptors & channels to mediate rapid adaptive changes to fluid depletion.
Effects & uses	-Fludrocortisone Drug of choice in replacement thereby -DOCA given Sublingual , ineffective orally. -Net effect is to conserve body sodium ➔ osmotic effect ➔ water follows ➔ expansion of extracellular fluid . -↑renal excretion of potassium &↓ intracellular potassium- -In excess ➔ hypertension, atherosclerosis , fibrosis ➔ vascular & cardiac remodeling ➔ cerebral hemorrhage, stroke & or cardiomyopathy.

Corticosteroid antagonist

DRUG	M.O.A.	INDICATIONS	NOTES
METOTANE	**Inhibit β-hydoxylase → inhibit corticosteroid synthesis ➔↓** its peripheral metabolism & plasma & urine levels	**Cushing syndrome:** • **To reduce the symptoms before the surgery.** • **If the surgery can't be performed.**	**Safe in pregnancy.**
SPIRONOLACTONE Aldosterone ntagonist	• **K sparing diuretic.** • **Compete with steroid on receptors to block MC action.**	*** Hypertension & heart failure in hyperaldosteronism (Conn's)**	-

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SUMMARY

GLUCOCORTICOIDS

Short Acting (< 12 h)		Intermediate Acting (12 - 36 h)	Long Acting (> 36 h)
Cortisol {emergency Adisonian crisis}	Cause salt and water retention	Prednisolone	Dexamethasone
Cortisone		Triamcinolone	Betamethasone

TOPICAL DRUGS	Potency	Notes
Beclomethasone, Triamcinolone actonide	Potent	–
Mometasone, Fluticasone	Moderate	Mild-moderate topical steroids are applied on the face as creams only
Hydrocortisone acetate	Mild	

INHALANT DRUGS	Notes
Fluticasone, Budesonide	No systimic effects

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SUMMARY

Replacment thrapy		
Used in	**Drugs**	**Notes**
Addison's crisis	**Cortisol (hydrocortisone)**	Cause salt and water retention
Addison's disease	**Cortisol**	Given orally
	fludrocortisone	Minralocorticoid
	Dexamethasone	
Cushing syndrome	**Dexamethasone suppression test**	In Diagnoses
	Cortisol	Temporally AFTER surgical removal of tumors

ANTI-INFLAMMATORY & IMMUNOSUPPRESSANT	
Drugs	**uses**
Prednisolone	Severe allergic reactions Diseases of allergic origin, Autoimmune disorders, Organ transplantation, Blood dyscrasias, Acute gout
Dexamethasone	
Betamethasone	
OTHERS	**uses**
Dexamethasone	Raised I.C.P, neoplastic diseases, With cytotoxic drugs
Betamethasone	

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SUMMARY

MINERALOCORTICOIDS

Drug	Therapeutic uses	Adverse effects
Aldosterone	Not used clinically	In excess → hypertension, atherosclerosis , fibrosis → vascular & cardiac remodeling → cerebral hemorrhage / stroke & or cardiomyopathy
Deoxycortone sterone[DOCA]	–	
Fludrocortisone	Drug of Choice in Replacement Therapy In Addison's disease	

CORTICOSTEROID ANTAGONIST

Drug	Therapeutic uses	Notes
MITOTANE	• Cushing syndrome	• ↓ Glucocorticoids • Safe in pregnancy
SPIRONOLACTONE	• hypertension • heart failure • Hyperaldosteronism (Conn's)	Block mineralocorticoids actions (aldosterone antagonist)

Quiz yourself

Q1: Typical features of topical corticosteroid use in dermatology include all of the following, except:
A) more potent corticosteroids should be preferred because of higher efficacy
B) Ointments are more potent than creams
C) occlusive dressing can help increase the potency of a topical corticosteroid
D) corticosteroid are best used in areas where the skin is thin,e.g. Face, scrotum, etc.
E) systemic absorption always leads to adrenals suppression with topical corticosteroid therapy

Q2: Which one of the following is wrong about lipocortin
A) lipocortin inhibits PLA2, cox-2
B) activated GRs prevent AP-1 from binding to RE and expressing pro-inflamatory mediators as lipocortin
C) activated GRs dimerize and bind to GRE allowing expression of anti-inflammatory mediators as lipocortin

Q3: child came to you with dermatitis in his face what is the topical treatment in this case?
A) Beclomethasone cream
B) Fluticasone cream
C) Hydrocortisone acetate ointment

Q4: Patient came to ER with hyponatremia, hyperkalemia, hypoglycemia, fever, confusion, sever vomiting, diarrhea and shock .
Which one of the following drugs is used in this case?
A) Betamethasone
B) Triamcinolone
C) Cortisol

Q5: A 34-yr-old woman with ulcerative colitis has required long-term treatment with pharmacologic does of a glucocorticoid agonist. Which of the following is a toxic effect associated with long-term glucocorticoid treatment?
A) A " lupus-like" syndrome
B) Adrenal gland neoplasm
C) Osteoporosis

Q6: Which one of the following is given with cortisol incase of chronic Addison's disease because it has a mineralocorticoid like action:
A) Hydrocortisone acetate
B) Beclomethason
C) Fludrocortisone

Q7: What would you do if you're treating your patient with Glucocorticoids and you know that he's subjected to stress:
A) You lower the dose
B) You ask the patient to not take the medication while he's in a bad mood
C) You double the dose

Q8: pregnant women came to you with moon face and high cortisol which diagnosed as Cushing syndrome. Which of the following is best drug in this case ?
A) Mitotane
B) spironolactone
C) Betamethasone

Explanation for Q1

Explanation: Traditionally, topical corticosteroids are divided into classes based on their potency. There is not much difference in safety and efficacy if one agent is compared over other. However, there may be significant difference in price. Although ointments are more oily, they are also more potent than creams. At least 4 hours of occlusive dressing (gloves, plastic wrap) can lead to several-fold increase in the potency of a topical corticosteroid. On areas of thin skin including vulva, skin folds, ear canal besides face and scrotum, topical corticosteroids must be used with caution. Topical corticosteroid use on the eyelids is known to cause glaucoma and cataract. The amount of topical corticosteroid to be used can be calculated be the same "rule of nines" as done in patients with burns. In general, about 20–30 g steroid is required to cover the body surface of an adult at one time. It is well-known that systemic absorption of topically applied steroids does occur, but adrenal suppression, and other systemic complications like osteoporosis, diabetes, hypertension, etc. appear to be rare.

Answers: 1-A+D+E, 2-B 3-B 4-C 5-C 6-C 7-C 8-A

PHARMACOLOGY
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We hope that we made this lecture easier for you
Good Luck !