CORTICOSTEROIDS

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ISMAIL RASLAN

حاولنا جاهدين بأن نجعلها مبسطة قدر استطاعتنا . . .

نأمل أن تجدوها كذلك . . . ^_^

((,, it will be easy en sha2 Allah))

ولأن هذا آخر عمل نقدمه إليكم . . كل ما نود قوله :

اعذرونا إن بدر منا تقصير أو أخطأنا يوما في معلومة كتبناها إليكم

فالجهد جهد بشري . . فجلّ من سلم عن كل نقص وعيب . . .

تمنياتنا لكم بالتوفيق دنيا وآخرة . .

دعواتكم لكل من قام على فارما تيم لهذا العام . . . (:

PHARMACOLOGY OF EXOGENOUS GLUCOCORTICOIDS:

- **Example:**

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

- **MoA:**

- **They bind to glucocorticoid receptor, found in two locations:**
  - **In the cytoplasm: *GENOMIC Action***
    - **Mediate actions by genomic effect which takes long time (hours to days)**
    - **The action will be one of two :**

1- expression of proteins that will lead to :

anti-inflammatory effect ((New Protein Formation))

- **Example : . Lipocortin → inhibit COX-2 and PLA_2**

2- repression of proteins that lead to:

prevent AP-1 from binding to Rs and pro-inflammatory effects ((there will be no protein formation)) :

- **Example : . No proinflammatory cytokines (IL-2) & chemokines**

Lipocortins :An enzyme that inhibits the activity of phospholipase A2. Lipocortins are activated by glucocorticoids. This is the mechanism by which glucocorticoids (primarily cortisol) inhibits inflammation.

Repression = no inflammation (inhibit primary steps of inflammation) " Remember NO with repression "
Expression= increase protein formation >> inhibit progressing of inflammation

- **On the cell membrane (membranous receptor): *NON-GENOMIC Action***

1. **Mediate actions by second messenger effects which take rapid effects (minutes to hours)**
2. **Utilizes both Calcium and cAMP as second messengers activating protein kinase A and protein kinase C**
3. **rapidly exert anti-inflammatory effects & shut down proinflammatory effects**

3- Pharmacokinetics:

a. **Some preparations transform to active form in liver:**

Cortisone → Hydrocortisone
Prednisone → Prednisolone

The imp. Point in Pharmacokinetic is the 1st one ..

b. **Hydrocortisone & its synthetic analogues are effective orally ,, and Available in parental forms**
c. **also absorbed systemically when given from sites of local administration**

1. **skin, synovial spaces, respiratory tract,etc..**

d. **90% or more of cortisol in plasma is reversibly bound to Corticosteroids Binding Globulin (CBG) & to albumin**
e. **Corticosteroids compete with each other for binding sites on CBG, which have relatively, have:**

i. **high affinity to cortisol & most of its synthetic derivative**
ii. **low affinity for aldosterone**

- **Only the unbound free form can enter cells by diffusion**

f. **Metabolized by the liver**
g. **t ½ is variable [short, intermediate & long acting]**

i. **For hydrocortisone → 90 min & biological effects → after 2-8 hrs**

h. **They are excreted as soluble sulphates in the urine.**

CLASSIFICATION ACCORDING TO T 1/2 & METHOD OF ADMINISTRATION

SYSTEMIC Drugs :

A) Short Acting Preparations (t1/2 < 12 h)

Cortisol In EMERGENCY Cortisone *not in liver disease*	less effective as anti-inflammatory And have high Na/H2O retention activity..

B) Intermediate Acting Preparations ($t_{1/2}$ = 12 -36 h):

Prednisolone

Triamcinolone

C) Long Acting Preparations (t1/2 > 36 h)

-Dexamethasone *[Fluorinated]* -Betamethasone *[Fluorinated]*	More potent as anti-inflammatory And have less Na/H2O retention activity..

INHALANT DRUGS:

Fluticasone (very potent)

Budesonide

TOPICAL DRUGS

TOPICAL DRUGS	Potency
Beclomethasone	Potent
Triamcinolone actonide	Potent
Mometasone	Moderate
Fluticasone	Moderate
Hydrocortisone acetate	Mild

N.B. Mild-moderate topical steroids are applied on the face as creams only

N.B. with Change in basic cortisol molecule we can get compounds with : ↓mineralocorticoid activity,, ↑greater potency,, ↑duration of action

4- Dosage:

a. The dosage method should follow the normal circadian rhythm especially on prolonged use. Why?

i. to minimize hypothalamo-pituitary-adrenal axis impairment

b. so given early in the morning and better if alternate days

((normal circadian rhythm= in morning ... because normally , the GCs produced more on morning))

5- indications :

a. Adrenal insufficiency

i. Acute : addisonian crisis:

1. This is an emergency situation
2. **Parental hydrocortisone** ➔ IV / every 6-8hrs until patient is stable. Dose ➔ gradually reduced until you reach maintenance dosage in 5 dys
3. Fluids and electrolytes should be corrected
4. Treatment of precipitating factors

ii. Chronic: Addison's disease:

1. **Hydrocortisone** is used (orally) + small amount of mineralocorticoid **(fludrocortisone, orally)**

   ((given together to correct Both mineralocorticoida + glucocortecoids))
2. Doses must be increased **in stress** to prevent development of Addisonian crisis
3. Should follow circadian rhythm

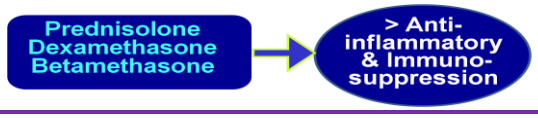
   N.B. Cortisol ➔Drug of choice in acute replacement ,, but: dexamethasone could be given on prolonged use in Addison's Disease

b. Cushing syndrome:

i. **Cortisol** given; In Diagnoses and Treatment ➔ During & AFTER surgical removal of pituitary / adrenal / corticosteroid secreting tumors

You may ask ,, how to give cortisol in cushing where there is high level of glucocortecoids ??
The ans. is : because when you remove the cuz of this disease such as remove the tumor ,, there will be a sudden suppression of endogenous secretion ((the body not yet adapt for its own secretion)). So the pt given cortisol until stabilization of his case occur...
Using in diagnosis : as in Dexamethasone suppression test

c. Anti-inflammatory and immunosuppressant:



imp to know the name of these drugs AS potent Anti-inflammatory !!!

i. Prednisolone, Dexamethasone and Betamethasone are the most potent in this action

ii. Severe allergic reactions
   1. e.g. serum sickness and angioneurotic edema... etc.

iii. Diseases of allergic origin;
   1. bronchial asthma, rhinitis, conjunctivitis,eczema & many other atopic & proliferative skin diseases

iv. Autoimmune disorders;
   1. rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythrematosus, nephrotic syndrome,...

v. Organ transplantation;
   1. kidney, cardiac, bone marrow (↓rejection)

vi. Blood dyscrasias; hemolytic anemia, thrombocytopenic purpura, agranulocytosis ... etc.

vii. Acute gout (resistant) to other drugs

To get it easily :
Remember : they are used in
Any Autoimmune OR inflammatory disorders

d. Other indications:

When decrease Na retention is needed Use Dexamethasone or Betamethasone in :

i. Raised intracranial pressure

ii. In neoplastic diseases
   1. With cytotoxic drugs ➔ as in Hodgkin's disease, acute lymphocytic leukaemia
   2. Primary or secondary neoplasms in the brain & postoperative to brain surgery➔ to decreaseedema
   3. In antiemetic regimens ➔prevent / cure emesis of chemotherapy

iii. Suppress excess ACTH production

6- ADR's

a. Suppression of hypothalamic pituitary adrenal axis imp !!!

How to avoid this ADR?

1. **If the drug is used for less than a week :**
    1) **no big doses then no fear**
    2) **big doses dose you may ↓ 2.5-5 mg prednisolone → at an interval of 2-3 days**
2. **If longer periods & high dose : ↓ halve dose weekly until 25 mg prednisolone or equivalent is reached Then ↓ by about 1mg every 3-7 days**

b. Dose and time related ADR: IATROGENIC CUSHING's SYNDOME imp !!!

i. **Increased serum cortisol and decreased ACTH**

How to treat this ADR?

1. **If possible → slow withdraw to allow body to slowly resume its normal balance of ACTH & cortisol**
2. **If not possible to stop because of underlying disease→↓ treat concurrent symptom separately**
    a. *** Antidiabetic for hyperglycaemia**
    b. *** Bisphosphonates for osteoporosis**
    c. *** H_2 blocker or proton pump inhibitors for peptic ulcer**

C. inflammation :

- Wanted: healing of tissue injury due to : viruses , fungus ....

- Unwanted : transplant rejection , allergy autoimmune disease .

Plz,, try to study the physiology of GCs well .. this will help u to understand the ADRs easily ..(:

D. OTHERS:

c. **Hyperglycemia , glycosuria, diabetes mellitus >> fluorinated preparations**
d. **Growth retardation → premature closure of epiphysis →short stature**
e. **Muscle wasting →-ve nitrogen balance >> fluorinated preparations**
f. **Fat redistribution & abnormal deposition**
g. **Hypertension, oedema, Na retention**
h. **Hypokalaemia**
i. **Osteoporosis → -ve of osteoblasts / +ve osteoclasts & ↓ Ca absorption, ↑ Ca excretion → vertebral compression & fractures**
j. **Avascular necrosis of head of femur**
k. **Menstrual irregularities**
l. **Psychiatric disorders; depression, euphoria,…**
m. **Impairment of defense mechanism→ serious infections, flare of dormant T.B., activate hepatitis, ↑ reaction to live vaccines**
n. **Delayed wound healing**
o. **Peptic ulcer specially if with NSAIDs**
p. **Skin, acne, striae, hirsutism**
q. **Ocular toxicity →glaucoma & cataract**
r. **Local toxicity:**

- **Skin→ infection, atrophy, bruising.**
- **Eye → viral infection, cataract, glaucoma.**
- **Inhalation → fungal infection, hoarseness**
- **Intrarticular → infection, necrosis**

7- Contraindications:

a. Diabetes mellitus. << because GC raise blood sugar
b. Hypertension or heart failure
c. History of mental disorders or Epilepsy.
d. Osteoporosis
e. Peptic ulcer
f. Presence of infection or Tuberculosis ➔ requires chemotherapy before administration

8- precautions:

a. Patients receiving GCs and is subjected to stress ➔ double the dose (to avoid addisonian crisis)
b. In children receiving ➔ take care of live attenuated vaccines
c. In pregnant women; better avoid fluorinated GCs ➔ teratogenicity
d. Neoborn to mothers taking high dose GCs ➔ may inhibit the pituitary axis

PHARMACOLOGY OF MINERALOCORTICOIDS:

- **Example:**

  Aldosterone, Deoxycorticosterone, Fludrocortisone

- **MOA:** not imp as an exam Q

- Binds to mineralocorticoid receptors in mineralocorticoid responsive tissue
  - These receptors can bind to both Mineralocorticoid and glucocorticoid BUT GC is effectively destroyed, allowing MC to bind to its receptor without competition, they work in two ways:

- Cytosolic MineraloCorticoid Receptor ➔ mediates GENOMIC Action ➔ Expression of proteins :
  - Na pumps➔ ↑ Na retention
  - Na channels➔ ↑ Na reuptake from lumen
  - K simporters➔ ↑ excretion of K & H
    - This happens in In distal & collecting tubules
    - Sweat glands, colon and salivary glands

- Membranous Glucocorticoid Receptor ➔ mediates NON-GENOMIC
  - Interact with GP coupled receptors & channels to mediate rapid adaptive changes to fluid depletion

- **Effects \ uses \ preparations :**

- 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

SYSTEMIC Drugs	Anti-inflam.	Na retention	Preparations & doses
Aldosterone	0.3	3000 higher	Natural / Not used clinical
Deoxycortone sterone[DOCA]	0	100 lower	(Sublingual), ineffective orally ? B/c Inactive in liver
Fludrocortisone	10 higher	150	(Orally) **Drug of Choice in Replacement Therapy**

PHARMACOLOGY OF CORTICOSTEROID ANTAGONIST:

1. Medications that inhibit adrenal steroid synthesis :

MITOTANE (GCs antagonist)

a. MoA : inhibit 11 b-hydroxylase enzyme
   i. Effect on Corticosteroid production → ↓ its peripheral metabolism & plasma & urine levels
b. Used in Cushing syndrome; whether iatrogenic, or to alleviate severe symptoms till removal by surgery
c. Safe in pregnancy

2. Medications that compete with steroids on receptors :

SPIRONOLACTONE (MCs antagonist)

a. MoA: Is a competitive aldosterone antagonist
   i. Is a K sparing diuretic (weak, slow onset & prolonged effect)
b. Used in
   i. hypertension (alternation with others),
   ii. in heart failure
   iii. In Hyperaldosteronism (Conn's)