Adrenocorticosteroids (2)

Dr. Entisar Al-Mukhtar

Corticosteroids therapeutic uses:

1. Replacement therapy:

a. Primary adrenocortical insufficiency (Addison disease):

Caused by adrenal cortex dysfunction. **Hydrocortisone** (identical to natural cortisol), is given to correct the deficiency. 2/3 of **hydrocortisone** daily dose is given in the morning and 1/3 is given in the afternoon. **Fludrocortisone**, (potent synthetic mineralocorticoid with some glucocorticoid activity), may also be given.

b. Secondary or tertiary adrenocortical insufficiency:

Caused by a defect in the production of CRH or ACTH. **Hydrocortisone** is used for treatment of these deficiencies (**note**: synthesis of mineralocorticoids in the adrenal cortex is less impaired than that of glucocorticoids).

c. Congenital adrenal hyperplasia (CAH):

Group of diseases resulting from an enzyme defect in the synthesis of one or more of the adrenal steroid hormones. CAH may lead to virilization in females due to overproduction of adrenal androgens.

Note: The choice of replacement hormone depends on the specific enzyme defect. The corticosteroids administration suppress CRH and ACTH release, thus decreases production of adrenal androgens.

2. Diagnosis of Cushing syndrome:

Cushing syndrome is caused by a hypersecretion of glucocorticoids (hypercortisolism) due to excessive release of ACTH or an adrenal tumor.

Cortisol levels (urine, plasma, and saliva) and the dexamethasone suppression test are used to diagnose Cushing syndrome. Dexamethasone (synthetic glucocorticoid) suppresses cortisol release in normal individuals, but not those with adrenal tumor induced-Cushing syndrome (note:iatrogenic Cushing syndrome is caused by chronic treatment with high doses of glucocorticoid).

3. Relief of inflammatory symptoms:

Glucocorticoids dramatically reduce the manifestations of inflammation (eg. rheumatoid arthritis and inflammatory skin conditions). They are also important for

maintenance of symptom control in persistent asthma, as well as management of asthma exacerbations and active inflammatory bowel disease. In noninflammatory disorders such as osteoarthritis, intra-articular corticosteroids may be used for treatment of a disease flare.

4. Allegies:

Allergic rhinitis & drug, serum & transfusion allergic reactions can be treated with glucocorticoids. Inhalation of fluticasone, beclomethasone, triamcinolones & others can minimize systemic effects.

5. Acceleration of lung maturation:

Fetal cortisol regulates lung maturation. A dose of dexamethasone or beclomethasone is given I.M to the mother 48 hours prior to premature delivery, followed by a 2nd dose 24 hours before delivery can be used to prevent the development of respiratory distress syndrome in premature infants.

Pharmacokinetics:

- All glucocorticoids can be administered orally (readily absorbed from GIT).
- Selected agents can also be given I.V, I.M, intra-articularly (into arthritic joints), topically or via inhalation or intranasal delivery.
- All topical and inhaled glucocorticoids are absorbed to some extent and, therefore, have the potential to cause hypothalamic–pituitary–adrenal (HPA) axis suppression.
- Hepatic dysfunction may dramatically increase glucocorticoids half- lives.
- **Prednisone** is preferred in pregnancy, it is a prodrug that is not converted to the active compound **prednisolone** in the fetal liver. Also any **prednisolone** formed in the mother is biotransformed to **prednisone** by the placental enzymes.

Note: glucocorticoids can be given I.M (cortisone, desoxycorticosterone, triamcinolone), I.M or I.V (betamethasone, dexamethasone, hydrocortisone, methylprednisolone & prednisone), as inhaler & nasal sprays (beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone & triamcinolone), intra-articularlly (methylprednisolone & triamcinolone) & betamethasone, hydrocortisone, mometasone & triamcinolone can be used topically.

- Dose selection is affected by many factors, including glucocorticoid versus mineralocorticoid activity, duration of action, type of preparation & time of day of the drug administration. Large doses of the hormone administered for more than 2 weeks cause suppression of the HPA axis. The alternate-day administration is a useful regimen that can allows the HPA axis to recover/ function on days the hormone is not taken.

Adverse effects:

Long- term corticosteroid therapy can cause:

1. Osteoporosis (most common) because glucocorticoids inhibit intestinal absorption of Ca^{2+}, inhibit bone formation & decrease sex hormone synthesis (patient is advised to take calcium & vitamin D supplements). Bisphosphonates may also be useful in the treatment of glucocorticoid-induced osteoporosis.

2. Increased appetite, but it is one of the reasons for the use of **prednisone** in cancer chemotherapy.

3. Cushing – like syndrome (redistribution of body fat, puffy face, hirsutism, acne, HT, insomnia & increased appetite) is observed in excess corticosteroid replacement.

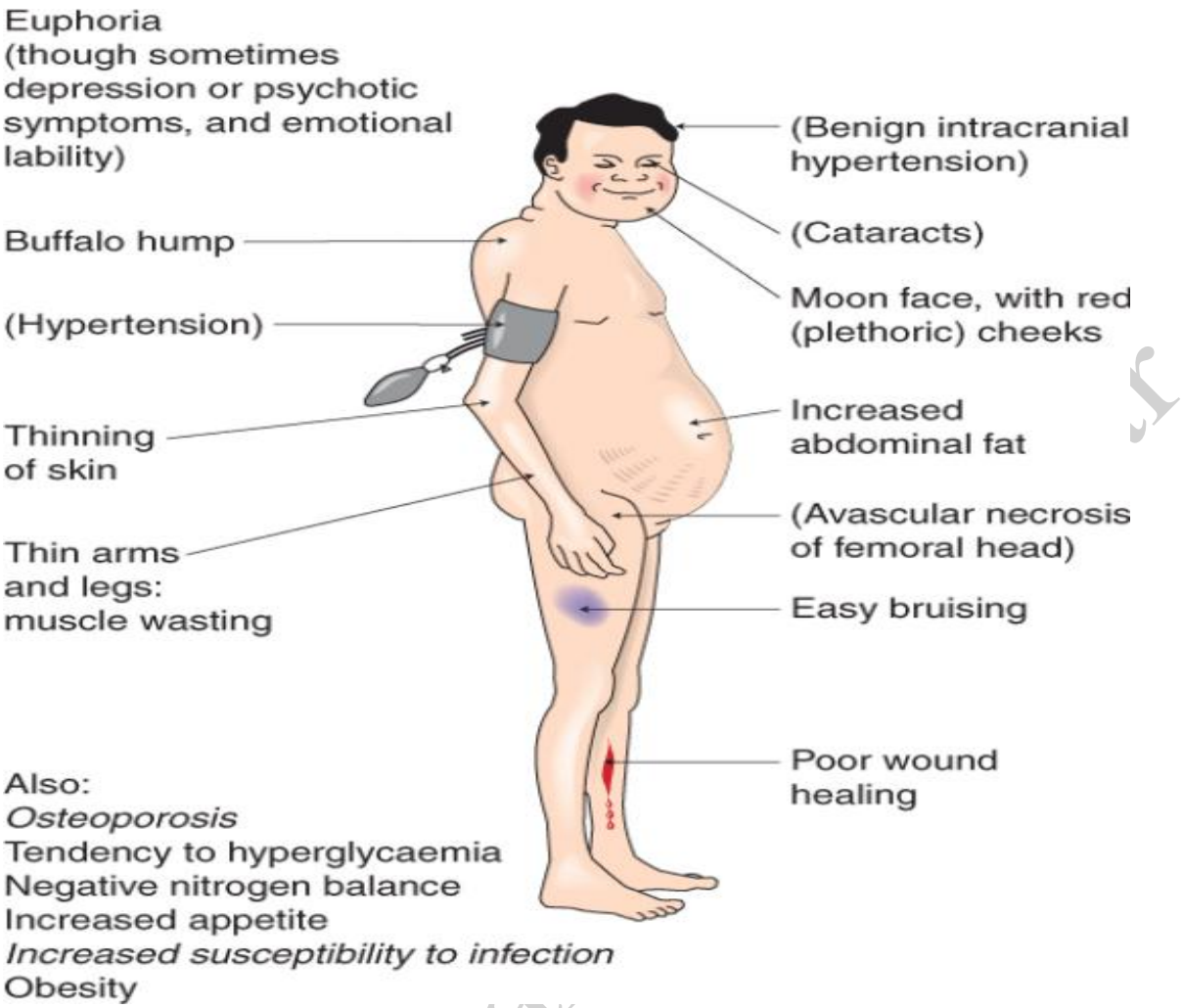
4. Decreased growth in children, impaired wound healing & increased risk of infection.
5. Emotional disturbances (euphoria, depression).

6. HT & peripheral edema.
7. Peptic ulcer.
8. Glaucoma & cataract may occur.
9. Hyperglycemia that may develop to D.M. (diabetic should monitor their blood glucose & adjust their medication accordingly).

10. Hypokalemia (counteracted by potassium supplementation).

11. Topical therapy can also cause skin atrophy, ecchymosis & purple striae.

Note: Coadministration of hepatic inducer or inhibitor drugs may require dose adjustment of glucocorticoids.


Euphoria
(though sometimes
depression or psychotic
symptoms, and emotional
lability)
Buffalo hump
(Hypertension)
Thinning
of skin
Thin arms
and legs:
muscle wasting
(Benign intracranial
hypertension)
(Cataracts)
Moon face, with red
(plethoric) cheeks
Increased
abdominal fat
(Avascular necrosis
of femoral head)
Easy bruising
Poor wound
healing
Also:
Osteoporosis
Tendency to hyperglycaemia
Negative nitrogen balance
Increased appetite
Increased susceptibility to infection
Obesity

Withdrawal

In patient who experienced HPA axis suppression the corticosteroids dose must be tapered, because abrupt removal of these drugs cause an acute adrenal insufficiency syndrome that can be lethal, in addition to the risk of the possible psychological dependence also the withdrawal might cause an exacerbation of the disease.

Inhibitors of adrenocorticoid biosynthesis or function:

INHIBITORS OF ADRENOCORTICOID BIOSYNTHESIS OR FUNCTION
Aminoglutethimide
Eplerenone
Ketoconazole
Metyrapone
Mifepristone
Spironolactone

1. **Metyrapone:**

- Inhibits glucocorticoid synthesis.
- Used to treats Cushing's syndrome during pregnancy.

2. **Aminoglutethimide:**

☒ Inhibits all corticosteroids synthesis.

☒ Used for treatment of breast cancer (it has largely replaced by tamoxifen) & adrenal cortex malignancies.

3. **Ketoconazole:**

- Antifungal agent that strongly inhibits all gonadal and adrenal steroid hormone synthesis. Used for the treatment Cushing's syndrome.

4. Mifepristone:

✓ At high doses it is a potent glucocorticoid antagonist as well as antiprogestin.

✓ Used treats ectopic ACTH syndrome in an inoperable patient.

5. **Spironolactone:**

- Competes on mineralocorticoid receptor.
- It antagonize aldosterone & testosterone synthesis.
- Used to treats HT, hyperaldosteronism, HF with reduced ejection fraction (along with other standard therapies), women hirsutism (competes on androgen receptor at hair follicle).
- Adverse effects → hyperkalemia, gynecomastia, irregular menses, skin rashes.

6. **Eplerenone:**

- Aldosterone antagonist, with no gynecomastia.
- Approved to treat HT and HF with reduced ejection fraction.