

PHARMACOLOGY OF ADRENAL CORTEX

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ADRENAL CORTEX

I. PENDAHULUAN

Adrenal gland adl organ kecil yg terletak disamping ginjal.

Cortical substance of the adrenal gland:

1. Medula (sumsum) → neurohormon, yi adrenalin, sbg neurotransmitter.
2. Cortex (kulit=lap luar) dari kel adrenal, dsb Adrenal cortex, menghasilkan 3 jenis hormon, a.l :
 - a. Glucocorticoid: cortisol (hydrocortisone), berpengaruh terhadap:
 - metabolisme carbohydrat
 - protein
 - lemak dan inflamation
 - b. Mineralocorticoid: aldosteron (precursor corticosteron & desoxicorton), berpengaruh terhadap, garam (Na^+ ; K^+) dan air
 - c. Sex hormon, menghasilkan:
 - testosteron, aldosteron, DHEA (Dehidro-epi-androsteron)
 - estrogen dan progesteron

Sintesa hormon ini berlangsung di dlm **Adrenal cortex** (Cortisol, glucocorticoid) melalui:

- kolesterol,
- sintesa sex hormon dalam testes dan ovaria.

Cortisol, glucocorticoid zat alami utama,

Zat ini mempengaruhi metabolisme:

- glucosa,
- protein dan lemak
- mempunyai aktivitas mineralokortikoid (mis. Hydrocortison, prednisone).

Effect of the adrenocortical hormones & physiology of the pituitary adrenal system are described. The distinct clinical syndromes produced by:

- hypofunction or hyperfunction of the adr. cortex.

Adrenal hypofunction:

Disease Chronic adrenal cortical insufficiency, chronic hypoadrenocorticism

The adrenal cortex synthesizes three classes of hormones:

1. Mineralocorticoids (e.g aldosteron)
2. Glucocorticoids (e.g cortisol)
3. Androgens (e.g sex hormones)

ADRENOCORTICOSTEROID

- ◆ Glucocorticoid:
 - cortisol (hydrocortisone) intermediate in metabolism process
- ◆ Mineralocorticoid
 - aldosterone, Na & water retention & Influenced by angiotensin
- ◆ Testosterone & estrogen secretion (sex hormones, steroids)

Histologically, the adrenal cortex is divided into three regions:

1. Zone glomerulosa --- synthesizes aldosterone & regulated by circulating levels of angiotensin II & K
2. Zone fasciculata/reticularis → {11 β hydroxylase, 17 α hydroxylase} --→ cortisol, androgen.

Etiologi and incidence:

About 70% of cases are due to adrenal cortical atrophy of unknown cause. The remainder are a result of partial destruction of the gland by granuloma (e.g. tuberculosis), rarely by neoplasm, amyloidosis, or inflammatory necrosis. The incidence is about 4: 100,000 Addison's disease occurs in all age groups and about equally in both sexes. It becomes clinically apparent under conditions of metabolic stress or trauma.

Pathophysiologi:

The biologically important products of the human adrenal cortex:

1. **Cortisol** deficiency produces disturbances in intermediate:

- carbohydrate, fat and protein metabolism,
- severe insulin sensitivity.

In the absence of cortisol:

- insufficient carbohydrate is formed from protein,
- little fat, too much carbohydrate are broken down;
- Hypoglycemia and diminished liver glycogen result.
- Weakness, due in part to deficient
- Neuromuscular function, ensues.
- Resistance to infection, trauma, other stress is diminished because of reduced adrenal output.

2. Aldosteron

Deficiency result in transfer of sodium from extracellular to intracellular compartment and its replacement by potassium.

There is increased excretion of sod & decreased excretion of potassium in the urine sweat, saliva and GI tract.

Low blood concentrations of sodium and chloride and high serum potassium result. The changes in electrolyte balance produce increased increased Water ecreation with severe dehydration, increased plasma concentration, decreased circulatory volume. Hypotensi, and circulatory collapse.

Mineralocorticoids

Aldosterone is the naturally occurring mineralocorticoid. It is secreted by the zona glomerulosa of adrenal cortex. Secretion of aldosteron is increased by angiotensin II & K^+ , especially when serum Na^+ is low. The physiologic action of aldosteron is increase Na^+ reabsorption in distal convoluted tubule & cortical colecting tubule via the amiloride-sensitive Na^+ channel. As Na^+ is reabsorbed, K^+ or H^+ is secreted into the urine and water is retained.

Cardiac output is reduced & circulatory failure can occur even when the blood volume is not unduly low. Pituitary ACTH (Adrenocorticotrophic hormone, corticotropine) & melanocyte-stimulating hormone (MSH) secretion is increased in response to the decrease in cortisol production. The excess of MSH causes hyperpigmentation of the skin and mucous membranes.

Adrenal steroids and their synthetic analogues:

Hormones normally produced by the adrenal cortex include:

- hydrocortisone (cortisol),
- Androgens and oestrogens,

the synthesis and release of which is controlled by the hypothalamic-pituitary system, aldosterone, whose biosynthesis is largely dependent on the renin-angiotensin system.

When the adrenal cortex fails:

Adrenocortical steroids are available for replacement therapy, but their chief use in medicine is for their anti-inflammatory & immunosuppressive effect. These are obtained only when the drugs are given in doses far above

☞ Stress control

Hipothalamus ; CRH



Pituitary : ACTH



Adrenal gland ; Cortisol

II. ADRENAL STEROID

Sec normal memproduksi:

- cortisol (hydrocortison)
- androgen dan oestrogen

The synthesis and release of which is controlled by hypothamic-pituitary system, and aldosterone, whose biosynthesis is largely dependent on the renin-angiotensin system. When the adrenal cortex fails, adrenocortical steroid are available for replacement therapy.

Action of hydrocortisone:

Plainly, there is distinction between replecement therapy (physiological effects) & higher doses of pharmacotherapy.

On inorganic metabolism (mineralocorticoid effects):

-increased retention of Na^+ by the renal tubule, and increase K^+ excretion in the urine

On organic metabolism (glucocorticoid effects):

-carbohydrate metabolism: gluconeogenesis is increased & peripheral glucose utilisation (transport across cell membranes) may be decreased (insulin antagonism) so that hyperglycaemia & sometime glucosuria result (diabetes).

-protein metabolism: anabolism (conversion of amino acids to protein) is decreased, but catabolism continues unabated or even faster, so that there is a negative nitrogen balance with muscle wasting.

-osteoporosis (reduction of bone protein matrix) occurs, growth slows in children, the skin atrophies and this with increased capillary fragility, cause bruising and striae.

-healing of peptic ulcer.

-fat deposition: this increased on shoulders, face and abdomen.

-inflammatory response is depressed, regardless of its cause or excessive inflammation.

-antibody production is reduced by heavy doses.

- Lymphoid tissue is reduced (Including leukaemic lymphocytes).
- Renal excretion of urate is increased.
- Blood eosinophils are reduced in number.
- Euphoria or psychotic state may occur, perhaps due to CNS electrolyte changes
- Anti-vit D action
- Reduction of hypercalcaemia
- Urinary Ca excretion is increased & renal stone may form.
- Growth reducing (In children).
- Suppression of hypothalamic/pituitary/ adrenalcortical feedback system (with delayed recovery).

Normal daily secretion of hydrocortisone is 10 – 30 mg. the exogenous daily dose that completely suppresses the cortex is hydrocortisone 40-80mg, or prednisolone 10-20mg.

PHARMACOKINETICS

GLUCOCORTICOID :

Cortisol (hydrocortisone)

Pharmacokinetic :

- ✿ **Synthesized from cholesterol**
- ✿ **Cortisol is secreted 10-20 mg daily ("Circadian rhythm")**
- ✿ **75 % : Corticosteroid-binding globulin (α 2-globulin)**
25 % : free form & 5 %: loosely bound to albumin
(effect on target cells)

GLUCOCORTICOID (Cortisol : hydrocortisone)

Pharmacokinetic

- ✿ *ic*: Synthetic corticosteroid (dexamethasone) :
>>> bound to albumin
- ✿ $t_{1/2}$: 60 – 90 minutes, could be longer :
>>> cortisol administration,
stress, hypothyroidism & liver disease
- ✿ Only 1 % of cortisol is secreted
unchanged in the urine

III. PHARMACO-THERAPI

ADRENOCORTICOSTEROID

DIAGNOSTIC:
Adrenal gland dysfunction

- THERAPY:**
- ◆ Inflammation process
 - ◆ Disturbancies of immunologic process



Insufisiensi Adrenokortikal disebabkan oleh:

- a. Destruksi Adrenal cortex
- b. Cacat enzimatik pada sintesa hydrocortisone, aldosteron atau keduanya.
- c. Gangguan sekresi ACTH oleh pituitary
- d. Defisiensi aldosteron tersendiri.

Terapi bertujuan pengganti steroid yg adekuat & layak utk mencapai keadaan normal

Insufisiensi adrenal cortex kronik:

- Hydrocortisone, dosis dewasa: 30-40 mg/hari
- Hydrocortisone, dosis anak²: 20 mg/hari permeter persegi permukaan badan.

Insufisiensi adrenal cortex akut:

Merupakan keadaan darurat yg harus diterapi. Tujuan terapi, a.l:

1. Mengkoreksi dan mencegah hypoglycemia
2. Mengganti nkehilangan Natrium dan air
3. Mengkoreksi hypotensi dan mengusahakan tek darah normal
4. Mengobati penyakit lain spt. Infeksi dg antibiotika yg tepat.

Oleh karena itu penting diagnosa dan terapi sec tepat.

Relatif potences of adrenal steroids

| Compound (tablet strength, mg) | Approximate relative potency | | |
|--------------------------------|---|--|----------------------|
| | Anti-inflammatory Effect (glucocorticoid) | Sod-retaining effect (Mineralocorticoid) | Equivalent dosage mg |
| Cortisone | 0,8 | 1,0 | 25 |
| Hydrocortisone | 1,0 | 1,0 | 20 |
| Prednisolone | 4 | 0,8 | 5 |
| Meth. prednisolone | 5 | minimal | 4 |
| Triamcinolone | 5 | none | 4 |
| Dexamethasone | 30 | minimal | 0,75 |
| Betamethasone | 30 | negligible | 0,75 |
| Fludrocortisone | 15 | 150 | irrelevant |
| Aldosterone | none | 500 ³ | irrelevant |

COMMONLY USED ADRENOCORTICAL AGENTS

| Agen | Equivalent Dose (mg) | Glucocorticoid Potency | Mineralocorticoid Potency | Anti-inflammatory Potency |
|----------------------------|----------------------|------------------------|---------------------------|---------------------------|
| Cortisol | 20 | 100 | 1 | 1 |
| Cortisone (Hydrocortisone) | | | | |
| Prednisone | 5 | 100 | 0,4 | 4 |
| Met. prednisolone | 4 | 100 | 0,1 | 4 |
| Triamcinolone | 4 | 100 | 0,1 | 5 |
| Dexamethasone | 0,75 | 100 | 0,05 | 30 |
| Fludrocortisone | 2 | 100 | 250 | 10 |

SHORT TO MEDIUM ACTING GLUCOCORTICOIDS

| Agent | Activity | | | Eq. oral dose (mg) | Forms available |
|----------------|--------------|---------|--------------|--------------------|-----------------|
| | Anti-inflam. | Topical | Salt-retain. | | |
| Cortisol | 1 | 1 | 1 | 20 | oral, inj, tpcl |
| Cortisone | 0.8 | 0 | 0.8 | 25 | oral, inj, tpcl |
| Prednisone | 4 | 0 | 0.3 | 5 | oral |
| Prednisolone | 5 | 4 | 0.3 | 5 | oral, inj, tpcl |
| Flurocortolone | | | | 5 | oral, tpcl |
| M.prednisolone | 5 | 5 | 0 | 4 | oral, inj, tpcl |
| Meprednisone | 5 | | 0 | 4 | oral, inj |

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