Chapter: 39

Adrenocorticosteroids & Adrenocortical Antagonists
Introduction

• The adrenal cortex synthesizes three classes of steroids:
  – the glucocorticoids, (fasciculata)
  – Mineralocorticoids (glomerulosa)
  – and the androgens (reticularis)

• Glucocorticoids, those having important effects on:
  – intermediary metabolism
  – and immune function,

• Mineralocorticoids, those having principally:
  – salt-retaining activity

• and those steroids having androgenic or estrogenic activity
Introduction

• In humans,
  – cortisol (hydrocortisone) is the main glucocorticoid
  – and aldosterone is the main mineralocorticoid
  – Quantitatively, dehydroepiandrosterone (DHEA) is the major adrenal androgen (20 mg) secreted daily
    • .....very weak androgens

• Adrenal androgens constitute the major endogenous precursors of estrogen in women:
  – after menopause
  – and in younger patients in whom ovarian function is deficient or absent
Introduction

• The **adrenal gland synthesizes steroids** from cholesterol,
  – which is derived from plasma **lipoproteins**

• **Some of the reactions** in the **biosynthetic pathway** can be **inhibited** by **drugs** …..
  
  – **Ex:** **Metyrapone** prevents the **β-hydroxylation** at C11, and thus the formation of:
    • hydrocortisone and corticosterone
Introduction

- Both natural and synthetic corticosteroids are used
  - for the diagnosis and treatment of a variety of inflammatory and immunological disorders

- Secretion of the adrenocortical steroids is controlled by the pituitary release of corticotropin (ACTH)

- Secretion of the salt retaining hormone aldosterone is primarily under the influence of angiotensin

- Inhibitors of the synthesis or antagonists of the action of adrenocortical steroids are important in the treatment of several conditions
Regulation of glucocorticoid hormone Secretion

- Are synthesised under the influence of circulating ACTH secreted from the anterior pituitary gland

- **ACTH** stimulates the adrenal cortex to secrete glucocorticoids, mineralocorticoids, and the androgen precursor dehydroepiandrosterone (DHEA) that can be converted peripherally into more potent androgens

- **ACTH secretion** itself (also pulsatile in nature) is regulated by:
  - CRH released from the hypothalamus
  - and vasopressin from the posterior gland
Glucocorticoids
Glucocorticoids

• The adrenal secretes a mixture of glucocorticoids; the main hormone in humans is hydrocortisone (also called cortisol)

• It exerts a wide range of physiologic effects, including
  – regulation of intermediary metabolism,
  – CV function,
  – growth,
  – and immunity

• Rate of secretion follows circadian rhythm governed by irregular pulses of ACTH that:
  – peak in the early morning hours
  – followed by a decline
  – and then a secondary, smaller peak in the late afternoon
Fluctuations in plasma ACTH and glucocorticoids throughout the day in a normal girl (age 16). The ACTH was measured by immunoassay and the glucocorticoids as 11-oxysteroids (11-OHCS). Note the marked ACTH and glucocorticoid rises in the morning, before awakening from sleep. (Reproduced, with permission, from Krieger DT et al: Characterization of the normal temporal pattern of plasma corticosteroid levels. J Clin Endocrinol Metab 1971;32:266.)
Regulation of adrenocortical hormone Secretion

• Three characteristic modes of regulation of the HPA axis:

  a) **Diurnal rhythm in basal steroidogenesis**

  b) Marked **increases in steroidogenesis** in response to **stress**
     - injury,
     - hemorrhage,
     - severe infection,
     - major surgery,
     - hypoglycemia,
     - cold,
     - pain,
     - and fear

  c) **Negative feedback** regulation by **adrenal corticosteroids**
The role of the HPA in the regulation of glucocorticoid hormone synthesis and release
Adrenocorticotropic hormone (ACTH, corticotropin)

- ACTH, binding to MC2R (a GPCR),
  - activates the Gs-adenylyl cyclase-cAMP-PKA pathway

- ACTH stimulates the synthesis and release of adrenocortical hormones

- Mutations in MC2R account for 25% of the cases of familial glucocorticoid deficiency,
  - a rare syndrome of familial resistance to ACTH
Adrenocorticotropic hormone (ACTH, corticotropin)

- **ACTH** currently has **only limited utility** as a therapeutic agent
  - Therapy with **ACTH** is **less predictable** and **less convenient** than therapy with **corticosteroids**

- All proven **therapeutic effects** of **ACTH** can be achieved with **appropriate doses** of **corticosteroids**
  - with a **lower** risk of **side effects**

- **ACTH** stimulates **mineralocorticoid** and **adrenal androgen secretion**
  - and may therefore cause **acute retention** of **salt and water**, as well as **virilization**
Therapeutic Uses and Diagnostic Applications of ACTH

1) Testing the Integrity of the HPA Axis
   • A 250 µg of cosyntropin (Cortrosyn, Synacthen) is administered either IM or IV,
     - with cortisol measured just before administration (baseline) and 30-60 minutes after cosyntropin administration
   • An increase in the circulating cortisol to a level greater than 18-20 µg/dL indicates a normal response
Therapeutic Uses and Diagnostic Applications of ACTH

2) CRH Stimulation Test

- **Ovine CRH** (corticotropin-releasing hormone) and **human CRH** are available for diagnostic testing of the HPA axis.

- CRH testing may help **differentiate** between a pituitary source (i.e., Cushing's disease) and an ectopic source of ACTH.

  - Patients with Cushing's disease respond to CRH with either a **normal** or an exaggerated **increase** in ACTH,

  - whereas ACTH levels **generally do not increase** in patients with ectopic sources of ACTH.
Glucocorticoids mechanism of action

• Most of the known **effects** of the glucocorticoids are mediated by **widely distributed glucocorticoid receptors** (**nuclear receptors**)

• As a consequence of the **time** required to **modulate gene expression** and **protein synthesis**,  
  – most **effects** of corticosteroids are **not immediate** but become **apparent** after several hours
Glucocorticoids Mechanism of action

- In the absence of the hormonal ligand,
  - glucocorticoid receptors (GR) are primarily cytoplasmic,
    - in oligomeric complexes with heat-shock proteins (hsp)

- After ligand binding,
  - the GR dissociates from its associated proteins and translocates to the nucleus
  - In the nucleus, it interacts with specific DNA sequences (glucocorticoid responsive elements, GRES) and provide specificity contribute to the regulation of transcription of their responsive genes
Glucocorticoids Mechanism of action

• Some of the effects of glucocorticoids can be attributed to their binding to aldosterone receptors (ARs);
  – ARs bind aldosterone and cortisol with similar affinity

• A mineralocorticoid effect of cortisol is avoided in some tissues by expression of 11β-hydroxysteroid dehydrogenase type 2, the enzyme responsible for biotransformation to its 11-keto derivative (cortisone),
  – which has minimal affinity for aldosterone receptors
Glucocorticoids Pharmacokinetics

• More than 90% of cortisol in plasma is reversibly bound to protein under normal circumstances corticosteroid-binding globulin (CBG; also called transcortin)
  – and albumin (5–10% is free or loosely bound to albumin)

• CBG is increased:
  – in pregnancy
  – and with estrogen administration
  – and in hyperthyroidism

• CBG is decreased by:
  – hypothyroidism,
  – genetic defects in synthesis,
  – and protein deficiency states

• Most cortisol is metabolized in the liver
Physiologic effect

1. Metabolic effects
   • The glucocorticoids have important **dose-related** effects on **CHO, protein, and fat metabolism**
   • Glucocorticoids **stimulate** and are **required** for **gluconeogenesis** and glycogen synthesis in the fasting state
   • They stimulate:
     – phosphoenolpyruvate carboxykinase, *(gluconeogenesis)*
     – glucose-6-phosphatase, *(gluconeogenesis)*
     – and glycogen synthase *(glycogen synthesis)*
   • They stimulate the **release of amino acids** in the course of **muscle catabolism** *(substrate for gluoneogenesis)*
Physiologic effect

1. Metabolic effects
   • Glucocorticoids **increase serum glucose** levels and **thus stimulate insulin** release
   • and **inhibit the uptake of glucose** by **muscle cells**, 
   • while they **stimulate hormone sensitive lipase** and **thus lipolysis**

   • The **increased insulin** secretion stimulates **lipogenesis** and to a **lesser degree inhibits lipolysis**,
     – leading to a net increase in **fat deposition combined** with increased **release of fatty acids and glycerol** into the circulation

   • The **net results** of these actions are most apparent in **the fasting state** which contribute to maintenance of an adequate **glucose supply to the brain**
2. Catabolic and Antianabolic Effects

- Glucocorticoids have **catabolic** and **antianabolic** effects in:
  - lymphoid and connective tissue,
  - muscle,
  - peripheral fat,
  - and skin

- **Supraphysiologic amounts** of glucocorticoids lead:
  - decreased muscle mass and weakness
  - and **thinning of the skin**

- Catabolic and antianabolic effects **on bone** are the cause of **osteoporosis** in Cushing's syndrome

- **In children**, glucocorticoids **reduce growth**.
  - This effect may be partially prevented by administration of **growth hormone** in high doses
3. Anti-inflammatory & Immunosuppressive Effects

- Glucocorticoids dramatically reduce the manifestations of inflammation
  - They inhibit both the early and the late manifestations of inflammation

- They reverse virtually all types of inflammatory reaction, whether caused by:
  - invading pathogens,
  - by chemical or physical stimuli,
  - or by inappropriately deployed immune responses such as are seen in hypersensitivity or autoimmune disease
Physiologic effect

2. Anti-inflammatory & Immunosuppressive Effects

• This is due to:
  – their **profound effects** on the:
    • concentration,
    • distribution,
    • and function of *peripheral leukocytes*
  – and to their **suppressive effects** on the:
    • inflammatory *cytokines* and *chemokines*
    • and on other *mediators of inflammation*
<table>
<thead>
<tr>
<th>Cell type</th>
<th>Factor</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophages and monocytes</td>
<td><strong>Arachidonic acid</strong> and its metabolites</td>
<td>Mediated by glucocorticoid <em>inhibition of COX-2</em> and <em>PLA₂</em>.</td>
</tr>
<tr>
<td></td>
<td>(prostaglandins and leukotrienes)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Cytokines</strong>, including:</td>
<td><em>Production and release are blocked</em>. The cytokines exert multiple</td>
</tr>
<tr>
<td></td>
<td>interleukin (IL)-1, IL-6,</td>
<td>effects on inflammation (e.g., activation of T cells, stimulation of</td>
</tr>
<tr>
<td></td>
<td>and tumor necrosis factor- (TNF-)</td>
<td>fibroblast proliferation).</td>
</tr>
<tr>
<td></td>
<td>Acute phase reactants</td>
<td>These include the third component of complement.</td>
</tr>
<tr>
<td>Endothelial cells</td>
<td>ELAM-1 and ICAM-1</td>
<td>ELAM-1 and ICAM-1: critical for <em>leukocyte localization</em>.</td>
</tr>
<tr>
<td></td>
<td>Acute phase reactants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cytokines (e.g., IL-1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arachidonic acid derivatives</td>
<td></td>
</tr>
<tr>
<td>Basophils</td>
<td>Histamine, LTC₄</td>
<td>IgE-dependent release inhibited by glucocorticoids.</td>
</tr>
<tr>
<td>Fibroblasts</td>
<td>Arachidonic acid metabolites</td>
<td>Same as above for macrophages and monocytes. Glucocorticoids also</td>
</tr>
<tr>
<td></td>
<td></td>
<td>suppress growth factor–induced DNA synthesis and fibroblast proliferation.</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Cytokines (IL-1, IL-2, IL-3, IL-6, TNF-,</td>
<td>Same as above for macrophages and monocytes.</td>
</tr>
<tr>
<td></td>
<td>GM-CSF, interferon-)</td>
<td></td>
</tr>
</tbody>
</table>
4. Other physiologic effects

- **CNS effects**: Indirect and direct effects on:
  - mood,
  - behaviour,
  - and brain excitability

- **Lipid metabolism**: promote fat redistribution in the body, with increase of:
  - visceral,
  - facial,
  - nuchal,
  - and supraclavicular fat

- **GIT**: Large doses of glucocorticoids have been associated with the development of peptic ulcer, possibly by suppressing the local immune response against *Helicobacter pylori*
Physiologic effect

3. Other physiologic effects

- Glucocorticoids exert effects on fluid and electrolyte balance, largely due to permissive effects on tubular function and actions that maintain GFR

- Decreased total body Ca$^{2+}$ stores:
  - interfere with Ca$^{2+}$ uptake in the gut
  - and increase Ca$^{2+}$ excretion by the kidney

- Chronically suppress the pituitary release of ACTH, GH, TSH, and LH
Physiologic effect

3. Other physiologic effects

• Development of the fetal lungs:
  – stimulates the production of surfactant required for air breathing during development of fetal lungs
Synthetic glucocorticoids

• **Chemical modifications** to the **cortisol** molecule have generated **derivatives** with:
  – greater **separations** of **glucocorticoid** and **mineralocorticoid** activity.

• Alterations in the glucocorticoid molecule influence its:
  – **protein-binding** affinity,
  – side **chain stability**,
  – rate of **elimination**,
  – and **metabolic products**

• The relative **anti-inflammatory potency** of each of the **synthetic analogues** is **compared** with cortisol and is roughly **correlated** with its **biological half-life**.
<table>
<thead>
<tr>
<th>Glucocorticoids</th>
<th>Anti-inflammatory effect</th>
<th>Salt-retaining effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short acting</strong> (1-12hrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cortisone</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Intermediate acting</strong> (12-36hrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>4</td>
<td>0.8</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
<td>0.8</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td><strong>Long acting</strong> (36-55hrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betamethasone</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>30</td>
<td>0</td>
</tr>
</tbody>
</table>
Fludrocortisone

Desoxycorticosterone

Mineralocorticoids

Anti-inflammatory effect  Salt-retaining effect

125

10

0

30
Synthetic glucocorticoids

• All of the other undesirable side effects of supraphysiological concentrations of hydrocortisone have been observed with the synthetic analogues

• Available in a wide range of preparations:
  – orally,
  – IV,
  – IM,
  – intra-articularly,
  – topically,
  – or as an aerosol for inhalation
## Route of administration of glucocorticoids

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>All can be administered orally</td>
</tr>
<tr>
<td>IM</td>
<td>Cortisone, deoxycorticosterone, triamcinolone</td>
</tr>
<tr>
<td>IV, IM</td>
<td>Dexamethasone, hydrocortisone, methylprednisolone, prednisolone</td>
</tr>
<tr>
<td>Aerosol</td>
<td>Beclomethasone, flunisolide, triamcinolone</td>
</tr>
<tr>
<td>Topical</td>
<td>Beclomethasone, dexamethasone, hydrocortisone, triamcinolone</td>
</tr>
</tbody>
</table>
TABLE 39-1 Some commonly used natural and synthetic corticosteroids for general use.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Activity(^1)</th>
<th>Equivalent Oral Dose (mg)</th>
<th>Forms Available</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-Inflammatory</td>
<td>Topical</td>
<td>Salt-Retaining</td>
</tr>
<tr>
<td><strong>Short- to medium-acting glucocorticoids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone (cortisol)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cortisone</td>
<td>0.8</td>
<td>0</td>
<td>0.8</td>
</tr>
<tr>
<td>Prednisone</td>
<td>4</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
<td>4</td>
<td>0.3</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5</td>
<td>5</td>
<td>0.25</td>
</tr>
<tr>
<td>Meprednisone(^2)</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Intermediate-acting glucocorticoids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>5</td>
<td>5(^3)</td>
<td>0</td>
</tr>
<tr>
<td>Paramethasone(^2)</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fluprednisolone(^2)</td>
<td>15</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td><strong>Long-acting glucocorticoids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betamethasone</td>
<td>25–40</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>30</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td><strong>Mineralocorticoids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>10</td>
<td>0</td>
<td>250</td>
</tr>
<tr>
<td>Desoxycorticosterone acetate(^2)</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
</tbody>
</table>

\(^1\)Potency relative to hydrocortisone.

\(^2\)Outside USA.

\(^3\)Triamcinolone acetonide: Up to 100.
Therapeutic uses of adrenal corticosteroids

1. Replacement therapy in adrenocortical insufficiency

- Adrenal insufficiency can result from:
  
a) Structural or functional lesions of the adrenal cortex (primary adrenal insufficiency, or Addison's disease 80%)
  
b) Structural or functional lesions of the anterior pituitary or hypothalamus
     a) secondary adrenal insufficiency
Therapeutic uses of adrenal corticosteroids

a. **Chronic adrenocortical insufficiency** (Addison's disease):

- Characterized by:
  - weakness,
  - fatigue,
  - weight loss,
  - hypotension,
  - hyperpigmentation,
  - and inability to maintain blood glucose during fasting

- About *20–30 mg of hydrocortisone* must be given daily,
  - with *increased* amounts during *periods of stress*
Therapeutic uses of adrenal corticosteroids

a. Chronic adrenocortical insufficiency (Addison's disease):
   • In an effort to mimic the normal diurnal rhythm of cortisol secretion, these glucocorticoids generally have been given in divided doses:
     • with two-thirds of the dose given in the morning
     • and one-third given in the afternoon

• Although some patients with primary adrenal insufficiency can be maintained on hydrocortisone and liberal salt intake,
  • most of these patients also require mineralocorticoid replacement; fludrocortisone acetate
Therapeutic uses of adrenal corticosteroids

b. **Acute adrenal insufficiency**

- This **life-threatening** disease is **characterized** by:
  - GI symptoms (nausea, vomiting, and abdominal pain),
  - dehydration,
  - hyponatremia,
  - hyperkalemia,
  - weakness,
  - lethargy,
  - and hypotension

- It sometimes follows **abrupt withdrawal** of glucocorticoids used **at high doses** or **for prolonged periods**
b. Acute adrenal insufficiency
   • When **acute** adrenocortical insufficiency is **suspected**, **treatment** must be instituted **immediately**.

   - **Hydrocortisone** sodium succinate or phosphate in doses of
     - 100 mg IV is given every 8 hours

   • As the **patient stabilizes**, the hydrocortisone dose may be **decreased** to 25 mg every 6-8 hours

   • **Thereafter**, patients are treated in the **same fashion** as those with **chronic adrenal insufficiency**
Therapeutic uses of adrenal corticosteroids

2. Congenital Adrenal Hyperplasia (CAH)

• This group of disorders is characterized by specific defects in the synthesis of cortisol.

• In 90% of patients, CAH results from mutations in CYP21 (P450c21=21β-hydroxylase):
  – this would lead to a reduction in cortisol synthesis and thus produce a compensatory increase in ACTH release.
  – the gland becomes hyperplastic
  – and produces abnormally large amounts of precursors such as 17-hydroxyprogesterone that can be diverted to the androgen pathway, leading to virilization
Therapeutic uses of adrenal corticosteroids

2. Congenital Adrenal Hyperplasia (CAH)
   - **All patients** with classical CAH require replacement therapy with hydrocortisone or a suitable congener,
   - and **those** with salt wasting also require mineralocorticoid replacement (fludrocortisone acetate)

   - **The goals of therapy** are to normalize the patient hormone level by:
     - suppressing the release of CRH and ACTH (decrease production of adrenal androgens)
3. Acceleration of Lung Maturation

- Reduces the incidence of respiratory distress syndrome in premature infants

- When delivery is anticipated, IM betamethasone is commonly used 48hrs prior to birth and repeated 24hrs before delivery

- Betamethasone:
  - maternal protein binding
  - & placental metabolism is less than that of cortisol
    - (transfer across placenta to fetus)
Clinical Pharmacology

3. Cushing’s syndrome

- Is usually the result of bilateral adrenal hyperplasia secondary to an ACTH-secreting pituitary adenoma (Cushing’s disease) or of the adrenal gland or ectopic production of ACTH

- The manifestations are those associated with the chronic presence of excessive glucocorticoids

- The disorder is treated by
  - surgical removal of the tumor,
  - irradiation of it,
  - or resection of one or both adrenals

- These patients must receive large doses of hydrocortisone during and after surgery
  - which is then reduced slowly to normal replacement therapy
Therapeutic uses of adrenal corticosteroids

4. Nonendocrine Diseases

• The synthetic analogs of cortisol are useful in the treatment of a diverse group of diseases unrelated to any known disturbance of adrenal function

• The usefulness of corticosteroids in these disorders is a function of their ability to suppress inflammatory and immune responses and to alter leukocyte function
4. Nonendocrine Diseases

- Glucocorticoids dramatically reduce the manifestations of inflammations, for example,
  - Rheumatoid,
  - osteoarthritic inflammations,
  - as well as inflammatory conditions of the skin,

- The manifestations include the:
  - redness,
  - swelling,
  - heat,
  - and tenderness

that are commonly present at the inflammatory site.
Therapeutic uses of adrenal corticosteroids

4. Nonendocrine Diseases

• Glucocorticoids are beneficial in the treatment of the symptoms of:
  – bronchial asthma,
  – allergic rhinitis,
  – and drug, serum, and transfusion allergic reactions

• Glucocorticoids are:
  – not curative
  – and pathologic process may progress
  – while clinical manifestations are suppressed

• Preferably used in conjunction with specific therapy (eg, antibiotic, antifungal, antiTB)
## Therapeutic Indications for the Use of Glucocorticoids in Nonadrenal Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reactions</td>
<td>Angioneurotic edema, asthma, bee stings, contact dermatitis, drug reactions, allergic rhinitis, serum sickness, urticaria</td>
</tr>
<tr>
<td>Collagen-vascular disorders</td>
<td>Giant cell arteritis, lupus erythematosus, mixed connective tissue syndromes, polymyositis, polymyalgia rheumatica, rheumatoid arthritis, temporal arteritis</td>
</tr>
<tr>
<td>Eye diseases</td>
<td>Acute uveitis, allergic conjunctivitis, choroiditis, optic neuritis</td>
</tr>
<tr>
<td>Gastrointestinal diseases</td>
<td>Inflammatory bowel disease, nontropical sprue, subacute hepatic necrosis</td>
</tr>
<tr>
<td>Hematologic disorders</td>
<td>Acquired hemolytic anemia, acute allergic purpura, leukemia, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, multiple myeloma</td>
</tr>
<tr>
<td>Systemic inflammation</td>
<td>Acute respiratory distress syndrome (sustained therapy with moderate dosage accelerates recovery and decreases mortality)</td>
</tr>
<tr>
<td>Infections</td>
<td>Acute respiratory distress syndrome, sepsis</td>
</tr>
<tr>
<td>Inflammatory conditions of bones and joints</td>
<td>Arthritis, bursitis, tenosynovitis</td>
</tr>
<tr>
<td>Neurologic disorders</td>
<td>Cerebral edema (large doses of dexamethasone are given to patients following brain surgery to minimize cerebral edema in the postoperative period), multiple sclerosis</td>
</tr>
<tr>
<td>Organ transplants</td>
<td>Prevention and treatment of rejection (immunosuppression)</td>
</tr>
<tr>
<td>Pulmonary diseases</td>
<td>Aspiration pneumonia, bronchial asthma, prevention of infant respiratory distress syndrome, sarcoidosis</td>
</tr>
<tr>
<td>Renal disorders</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Skin diseases</td>
<td>Atopic dermatitis, dermatoses, lichen simplex chronicus (localized neurodermatitis), mycosis fungoides, pemphigus, seborrheic dermatitis, xerosis</td>
</tr>
<tr>
<td>Thyroid diseases</td>
<td>Malignant exophthalmos, subacute thyroiditis</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Hypercalcemia, mountain sickness</td>
</tr>
</tbody>
</table>
4. Non-endocrine Diseases

- When prolonged therapy is anticipated, it is helpful to obtain chest x-rays and a tuberculin test. GC can reactivate dormant TB.

- The presence of diabetes, peptic ulcer, osteoporosis, and psychological disturbances and CV function should be taken into consideration.

- Tx. for transplant rejection: reduce antigen expression from the grafted tissue, and interfere with the sensitization of cytotoxic T lymphocytes and the generation of primary antibody-forming cells.
c. Dexamethasone suppression test

- Used to differentiate among the different causes of Cushing's syndrome

- As a screening test (low dose test) (supression is normal)
  - 1 mg dexamethasone is given orally at 11 PM,
  - and a plasma sample is obtained the following morning
  - In normal individuals, the morning cortisol concentration is usually less than 3 mcg/dL,
  - whereas in Cushing's syndrome the level is usually greater than 5 mcg/dL (no suppression)
c. Dexamethasone suppression test

- In patients in whom the diagnosis of Cushing's syndrome has been established, ….

- Differentiation test (high-dose test):
  - suppression with large doses of dexamethasone will help to distinguish patients with:
    - Cushing's disease
    - steroid-producing tumors of the adrenal cortex
    - or with the ectopic ACTH syndrome

- Dexamethasone is given in a dosage of:
  - 0.5 mg orally every 6 hours for 2 days, followed by
  - 2 mg orally every 6 hours for 2 days
c. Dexamethasone suppression test

- Patients with pituitary-dependent Cushing's syndrome (i.e., Cushing's disease)
  - generally respond with decreased cortisol levels

- In patients in whom suppression does not occur,
  - the ACTH level will be low in the presence of a cortisol-producing adrenal tumor
  - ACTH is elevated in patients with an ectopic ACTH-producing tumor
Dosage

• In determining the dosage of adrenocortical steroids many factors need to be considered:

1) Glucocorticoid: mineralocorticoid activity
2) Duration of therapy
3) Seriousness of the disease
4) Amount of drug likely to be required to obtain the desired effect
5) Type of preparation
6) Time of day when the steroid is administered
Dosage

- **Given** the number and severity of potential SEs, the decision to institute therapy with glucocorticoids
  - always requires a careful consideration of the relative risks and benefits in each patient

- **Except** in patients receiving replacement therapy,
  - CSs are not curative,
  - pathologic process may progress
  - while clinical manifestations are suppressed
Dosage

• For any disease and in any patient, the appropriate dose to achieve a given therapeutic effect must be determined by trial and error and must be re-evaluated periodically
  – as the activity of the underlying disease changes
  – or as complications of therapy arise

• A single dose of glucocorticoid, even a large one, is virtually without harmful effects,

• and a short course of therapy (up to 1 week), in the absence of specific contraindications, is unlikely to be harmful
Dosage

- As the *duration* of glucocorticoid therapy is increased beyond 1 week, there are *time- and dose-related* increases in the incidence of *disabling* and *potentially lethal effects*.

- Therefore **chronic therapy**:  
  - should be undertaken with *great care*  
  - & only when *seriousness of disorder* warrants CS use
Dosage

• When **large doses** are required for **prolonged periods** of time,
  – alternate-day therapy should be utilized to prevent suppression of the hypothalamic-pituitary-adrenal (HPA) axis
  – Therapy **should not** be **reduced** or **stopped abruptly**;
  – treatment should be **tapered slowly**

• as it may take **2-12 months** for the HPA axis to function properly,

• & cortisol levels may **not return to normal** for another 6-9 mths
### Guidelines for pharmacological glucocorticoid therapy

<table>
<thead>
<tr>
<th>Instruction</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiate only if there is published evidence of objective therapeutic benefit</td>
<td></td>
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<tr>
<td>Use only after other specific therapies fail</td>
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<tr>
<td>Identify a specific therapeutic objective</td>
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<tr>
<td>Use objective criteria of response</td>
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<tr>
<td>Administer sufficient glucocorticoid for a sufficient time to achieve the desired response</td>
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<tr>
<td>Administer glucocorticoid for no longer than is necessary to achieve the desired response</td>
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<tr>
<td>Terminate if objective therapeutic benefit is not observed when expected, if complications arise, or if maximum benefit has been achieved</td>
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</tbody>
</table>
ADEs

- Two categories of toxic effects result from the therapeutic use of corticosteroids:
  
a) Those resulting from withdrawal of steroid therapy

b) Those resulting from continued use at supraphysiological doses
ADEs

1) **Continued Use** of Supraphysiological Glucocorticoid Doses
   a) Osteoporosis
   b) Cushing-like syndrome
   c) Suppression of the response to infection or injury
   d) Metabolic: Hyperglycemia with glycosuria

   e) Fluid and Electrolyte Handling:
      a) hypokalemic alkalosis and hypertension:
         a) use synthetic non-salt-retaining steroids,
         b) Na$^+$ restriction,
         c) & K$^+$ supplements
   f) In children, inhibition of growth (>6 months)
ADEs

1) Continued Use of Supraphysiological Glucocorticoid Doses

  g) CNS: euphoria, depression and psychosis

h) Other effects:
   – glaucoma (in genetically predisposed persons),
   – raised intracranial pressure
   – and an increased incidence of cataracts

i) Muscle wasting and proximal limb muscle weakness
Euphoria
(though sometimes depression or psychotic symptoms, and emotional lability)

Buffalo hump
(Hypertension)

Thinning of skin

Thin arms and legs: muscle wasting

Also:
Osteoporosis
Tendency to hyperglycaemia
Negative nitrogen balance
Increased appetite
*Increased susceptibility to infection*
Obesity

(Benign intracranial hypertension)
(Cataracts)

Moon face, with red (plethoric) cheeks

Increased abdominal fat

(Avascular necrosis of femoral head)

Easy bruising

Poor wound healing

-Decreased growth in children

-Peripheral edema

-Hirsutism

-Peptic Ulcer

-Hypokalemia
ADEs

2. Withdrawal of Therapy

• Characterized by:
  – flare-up of the **underlying disease** for which steroids were prescribed
  – and **acute adrenal insufficiency**, results from overly rapid withdrawal of corticosteroids after prolonged therapy has suppressed the HPA axis

• A characteristic **glucocorticoid withdrawal syndrome** consists of:
  • fever,
  • myalgia,
  • arthralgia,
  • and malaise,
  • which may be **difficult to differentiate** from some of the **underlying diseases** for which steroid therapy was instituted
Contraindications

- Peptic ulcer
- Heart disease
- Hypertension
- Infections
- Psychoses
- Heart failure
- Osteoporosis
- Glaucoma
Mineralocorticoids

• The **most important** mineralocorticoid in humans is **aldosterone**

• **Fludrocortisone**, a **synthetic** corticosteroid, is the **most commonly** used mineralocorticoid

• **Control** depends mainly on:
  – the **electrolyte composition** of the plasma
  – and on the **angiotensin II system**
Mechanism of action

• The interaction of aldosterone with its receptor (MR) initiates transcription and translation of specific proteins, resulting in:
  – an increase in the number of sodium channels in the apical membrane of the cell,
  – and subsequently an increase in the number of Na+/K+ ATPase molecules in the basolateral membrane

• Aldosterone and other steroids with mineralocorticoid properties:
  – promote the reabsorption of Na+ from:
    • the distal part of the distal convoluted tubule
    • and from the cortical collecting renal tubules,
  – loosely coupled to the excretion of K+ and H+
Aldosteronism/ hyperaldosteronism

• Primary results from excessive production of aldosterone by adrenal adenoma. Primary features:
  – HTN,
  – weakness,
  – tetany due to hypokalemia,
  – alkalosis,
  – increases in plasma Na+ concentration

• Patients have low (suppressed) levels of plasma renin activity & angiotensin II

• Patients are generally improved when treated with spironolactone, & response to this agent is of diagnostic & therapeutic value
Mineralocorticoid Deficiency

• Leads to:
  – hypotension
  – and vascular collapse,
  – Na+ wasting
  – and contraction of the extracellular fluid volume,
  – hyponatremia,
  – hyperkalemia,
  – and acidosis

• Oral fludrocortisone is used in the treatment of adrenocortical insufficiency associated with mineralocorticoid deficiency
Antagonists of Adrenocortical agents

1) *Synthesis inhibitors*: mitotane, etomidate, ketoconazole, metyrapone

2) *Receptor Antagonist*: mifepristone, spironolactone & eplerenone
1. Synthesis Inhibitors: Metyrapone

- Interferes with corticosteroid synthesis by blocking the final step (11-hydroxylation) in glucocorticoid synthesis, leading to an increase in:
  - 11-deoxycortisol
  - adrenal androgens
  - and the potent mineralocorticoid 11-deoxycorticosterone

- It can be used in:
  - diagnostic tests of adrenal function
  - and can be used to treat pregnant women with Cushing’s syndrome

- ADEs:
  - water retention,
  - hirsutism,
  - transient dizziness,
  - & GIT disturbances
2. Receptor antagonists

1) Mifepristone (RU 486)
   - At high doses, it is a potent glucocorticoid antagonist as well as an antiprogestin
   - It forms a complex with the glucocorticoid receptor (stabilization of the Hsp-glucocorticoid receptor complex),
     - but the rapid dissociation of the drug from the receptor leads to a faulty translocation into the nucleus
   - Its use can only be recommended for:
     - inoperable patients with ectopic ACTH secretion
     - or adrenal carcinoma who have failed to respond to other options
2. Receptor antagonists

2) Spironolactone
   • **Competes** for the MR and thus **inhibits sodium reabsorption** in the kidney
   
   • It can also **antagonize aldosterone and testosterone synthesis**
   
   • It is effective **against hyperaldosteronism**.
   
   • It is also **useful in the treatment of hirsutism** in **women**,
     – probably due to interference at the **androgen receptor of the hair follicle**
   
   • **ADEs:**
     – hyperkalemia,
     – gynecomastia,
     – menstrual irregularities,
     – and skin rash