Pathophysiology of Adrenal Disorders and Clinical Use of Corticosteroids

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Adrenal Glands

- Located on upper poles of both kidneys

Adrenal cortex (90% gland wt)
- Zona Glomerulosa: **Aldosterone**
- Zona Fasciculata: **Cortisol**
- Zona Reticularis: **Testosterone** and **estradiol** production from cholesterol

Adrenal medulla: Catecholamines
Corticosteroid Physiology

1. Hypothalamus (Corticotropin releasing factor)
2. Pituitary (Corticotropin/ACTH)
3. Adrenals
   - Cortisol (Hydrocortisone)
     - (12-25 mg/day; 300 mg with stress)
     - (Plasma level = 5-20 μg/dL; >60 μg/dL with stress)
   - Aldosterone
     - (50-250 mg/24 hr)

Regulate via negative feedback
Diurnal Cycle of Release

- ACTH peaks midnight to 2 AM
- Cortisol peaks at 6-8 AM
- Varies with sleep cycle
  - Night shift workers
  - Consider consequence of multiple shift or changing shift workers
Stress Related Cortisol Increase

- Surgery
- Trauma
- Sepsis
- Hypoglycemia
- Mediators
  - CNS release of CRF
  - Cytokines: IL-1, IL-2, IL-6, TNF, platelet aggregating factor
Prostaglandins and Leukotrienes

Cell Membrane Destruction

\[ \text{phospholipase } A_2 \]

\[ \text{Arachidonic Acid} \]

Lipooxygenase \[ \rightarrow \] Leukotrienes

cyclooxygenase \[ \rightarrow \] Prostaglandins

Leukotrienes

- Inflammation
- Bronchospasm

Prostaglandins

- PGE
  - Vasodilate
  - Edema
  - Bronchodilate
  - Pain sensitization

- Prostacyclin (vascular)
  - Vasodilate
  - Inhibit platelets

- Thromboxane (platelets)
  - Vasoconstrict
  - Platelet aggregation

- PGF
  - Vasocostric
Glucocorticoid Actions

- Decrease inflammatory response
  - Inhibit phospholipase A$_2$ → ↓ production of arachidonic acid → indirect inhibition of both prostaglandins and leukotrienes.
  - Inhibit activity of T lymphocytes (especially TH$_2$)
  - Suppress IL-1, IL-3, IL-4, IL-5; ↓ chemotraction of eosinophils and macrophages
  - Vasoconstrict, ↓ edema, ↓ fever
  - Stabilize neutrophilic (granulocyte) lysosomes to ↓ lysosomal enzyme release
White Blood Cell Effects

• **Increase neutrophils** without “shift to left”
  – Demargination (↓ adherence to vascular endothelium)
  – ↓ neutrophil egress from intravascular space
  – Stimulate marrow release of **mature** WBCs
    (not immature **band** cells as in infection)

• **Decrease lymphocytes, eosinophils, and basophils**
  – Decrease B and T lymphocyte function
  – Basis for role in treatment of lymphomas and lymphocytic leukemia
Other Glucocorticoid effects

- ↓ protein synthesis and protein movement out of vessels
- ↑ Gluconeogenesis (hyperglycemia)
- Fat Redistribution: suppress lipolysis and lipogenesis via insulin inhibition.
- ↑ beta adrenergic responses (note value in asthma)
Mineralocorticoid actions

• Sodium retention
• Potassium loss
Clinical Use of Corticosteroids

- Goal of treatment: symptomatic, not curative
  - Topical or oral: contact dermatitis or allergic rxn
  - Allergic rhinitis and asthma
  - Arthritis
  - Psoriasis
  - Autoimmune (lupus, polymyalgia rheumatica, non-viral hepatitis)
  - Inflammatory bowel disease
  - Lymphoma, leukemia
  - Transplant surgery: post-op/maintenance, rejection prevention
  - Prophylaxis of “dry socket” with dental surgery
  - Brain and spinal cord tumors (“cerebral edema”)
  - PCP infection in AIDS patients, ARDS, sepsis
  - Hypercalcemia- multiple myeloma, bone mets, sarcoid
Choice of Agent

- Relative glucocorticoid and mineralocorticoid potency (see table)
- Relative duration of action: Not correlated to half life
- Organ specificity
  - Methylprednisolone in asthma
  - Dexamethasone for cerebral edema
- Lack of systemic absorption if topical
  - Consider skin thickness, surface area to be covered
  - Also nasal and pulmonary inhalation applications
- Cost
- Who sponsored the original clinical trials
  - Dexamethasone for cerebral edema
  - Methylprednisolone in asthma, sepsis
## Relative potencies

<table>
<thead>
<tr>
<th>Name</th>
<th>Equivalent dose</th>
<th>Anti-inflam</th>
<th>Na retention</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>20-25 mg</td>
<td>1</td>
<td>2+</td>
<td>8-12 hr</td>
</tr>
<tr>
<td>Pred</td>
<td>5 mg</td>
<td>3.5</td>
<td>1+</td>
<td>18-36 hr</td>
</tr>
<tr>
<td>Methyl pred</td>
<td>4 mg</td>
<td>5</td>
<td>0.5+</td>
<td>18-36 hr</td>
</tr>
<tr>
<td>Dexa</td>
<td>0.75 mg</td>
<td>30</td>
<td>0</td>
<td>36-54 hr</td>
</tr>
<tr>
<td>Fludro</td>
<td></td>
<td></td>
<td>125</td>
<td></td>
</tr>
</tbody>
</table>
Dosing

• Acute:
  – Moderate to high dose for rapid resolution of symptoms; high dose “bursts” x 7-14 days
  – E.g., 60-80 mg prednisone or equivalent “burst therapy” for asthma in ER
  – 60-120 mg methylprednisolone QID for hospitalized patient
  – 4 mg QID dexamethasone for brain tumor

• Chronic (maintenance)
  – Minimum dose for shortest duration possible. Prefer to avoid all together.
  – Morning doses preferred
  – Every other day in some cases (next slide)
Every other day dosing

• Theory: use drug that works 36 hours (prednisone, methylprednisolone) every other day to allow HPA to function every other night
  – Fewer side effect and HPA suppression possible
  – Concern over loss of therapeutic effect on evening of day 2
  – E.g. 10 mg QD slowly converted to 20 mg QOD
Tapering Principles

• Less than 10 – 14 days, with no prior exposure
  – Rapid taper acceptable, even with high doses
  – Major considerations are disease exacerbation, mild flu like symptoms, mild depression

• Longer term exposure, even with low doses
  – Slow taper mandatory, especially as approach physiologic dose equivalent.
  – Physiologic withdrawal effects may be observed (see next slide)

• Short term exposure to high doses in patient with chronic use of high doses.
  – Rapid taper from high dose may be acceptable, but do not go below the chronic dose
  – E.g. patient on 10 mg prednisone per day for 3 months. Physiologic for this person is 10 mg. Then even slower taper if trying to remove drug entirely.
Physiologic Withdrawal Signs

• Time and dose dependent.
  – Unlikely if duration less than 10-14 days
  – Avoid night time doses if >5-7 days
• CNS depression
• Flu-like symptoms
• Muscle and joint pain
• Tremor
• Hypotension (not necessarily hyponatremic)
• Hyperkalemia, arrhythmias
Timing considerations

• Takes 7-14 days, even with very high doses to suppress pituitary ACTH release and adrenal cortisol release.

• With prolonged dosing (>30 days?) HPA suppression is evident, but dose dependent.
  – 9-12 months to fully restore HPA axis after slow withdrawal and complete removal.
  – Pituitary response recovers before adrenal gland
  – May need to cover with prednisone bursts during times of stress after complete withdrawal.
Example tapering dose

- Methylprednisolone 60 mg IV QID x 3 days
- Day 4: change to prednisone 60-80 mg/ day
  - QD or split into 2-3 doses?
  - Compare to physiologic dose of 5 mg prednisone or 4 mg methylprednisolone
- Then 60 mg x 3 days, 40 mg x 3 days, 30 mg x 3 days, 20 mg x 3 days, 15 mg x 3 days, 10 mg x 5 days, 5 mg x 5 days, 2.5 mg x 5 days, then stop
- Increase dose or slow taper rate if symptoms worsen
- What if patient was taking 10 mg per day at home before exacerbation?
- What if patient is using inhaled steroids?
Another example

• Steroid naïve patient receives 80 mg of prednisone in the emergency room
  – Should IV drug have been used instead of oral?
  – Assuming the symptoms resolve over 4 hours, why does the patient need a prednisone prescription for outpatient use?
  – How long should treatment continue?
  – Should the dose be tapered?
    • E.g. 20 mg qd x 7-14 days without taper
    • E.g. 40 mg x 2-3 days, 30 mg x 2-3 days, 20 mg x 2-3 days, 10 mg x 2-3 days, 5 mg x 2-3 days
Acute side effects

- Dose dependent, low risk
- Endocrine: hyperglycemia. Diabetic?
- Elevated white count: demargination vs. infection
- GI: Bleeding, “stress ulcers”
  - mucous production, local vasoconstriction
- Na retention (caution re edema, HTN, CHF)
- Hypokalemia, metabolic acidosis
- Jitteriness, euphoria, confusion (steroid psychosis)
Longer term side effects

- Continuation of short term side effects
- HPA axis suppression after 2 weeks
- Cushingoid features: fat redistribution to face and back, striae
- Muscle weakness, myopathy, protein wasting
- Thinning of skin, capillary fragility with petechiae, bruising, acne
- Osteoporosis in adults with compression fractures; aseptic necrosis of hip, growth retardation in children
- Cataracts, glaucoma
- Decreased immune response; TB activation, poor wound healing
Buffalo Hump: 
Accumulation of fat on back of neck and upper back

Moon Facies: 
Fat deposition in face

Central obesity and striae
Striae (stretch marks)
Drug Interactions

- Steroids increase aspirin clearance. Risk of ASA toxicity when steroids stopped.
- Barbiturates, phenytoin, rifampin increase steroid clearance/metabolism
- Cimetidine: decreased steroid metabolism?
- Ketoconazole: decreased cortisol production
- Hypoglycemics: steroid induced glucose increase
- Additive hypokalemia to potassium wasting diuretics
- Additive ulcerogenic property to NSAIDS?
Precautions

- Sodium retention in patients with hypertension or heart failure
- Effects on electrolytes in patients with arrhythmias or renal disease
- Hepatic failure: lack of conversion of prednisone to prednisolone.
  - Clinical significance debated
Hyperfunctioning Adrenal Gland

• Cushing’s Disease (60-70%)
  – Overactive pituitary gland (85% via adenomas)
  – Excess ACTH production with secondary bilateral adrenal hyperplasia
  – Primary (via pituitary) or secondary (via hypothalamus)

• Cushing’s Syndrome
  – Adrenal adenoma (benign)
  – Adrenal carcinoma
  – Ectopic ACTH syndrome (e.g., oat cell lung carcinoma, pancreas)

• Iatrogenic: overuse of exogenous corticosteroids. Mimics hyperfunctioning gland, but actually underactive gland
Clinical Features of Cushing’s Disease

- Central obesity and facial rounding – 90%
  - “moon face”, “buffalo hump”, central obesity
- Hypertension - 75-80% via Na retention
- Glucose intolerance - 80%
- Menstrual dysfunction, hirsutism - 76%
  - Androgen excess
- Abdominal striae (red-purple)
- Muscle weakness, myopathy, compression fractures – 50-60%; osteoporosis 20%
- Anxiety, tremor, mood elevation, psychosis - 50%
Buffalo Hump:
Accumulation of fat on back of neck and upper back

Moon Facies:
Fat deposition in face

Central obesity and striae
Workup of patient

- Suspect Cushing’s based on symptoms
- Screening serum or urine cortisol level
  - Should be high. If not, look for other disease.
  - Exception: low if taking exogenous steroids as cause of Cushing’s syndrome
- If cortisol level is high, measure ACTH level to differentiate pituitary vs adrenal cause.
  (see next slide)
- To differentiate pituitary origin vs adrenal origin: conduct dexamethasone suppression test. (details on another slide)
Adrenal Lab Tests

- **24 hour urine cortisol**
  - Nl: 20-90 mcg per 24 hr.
  - Increase 2-3x with Cushings

- **Plasma cortisol**
  - Nl: 12-20 mcg/100 ml @ 8AM; 4-8 mcg/100 mL @ 11 PM
  - Cushings: higher (up to 50 mcg/100 mL) and not circadian
  - Low if taking exogenous steroids

- **Plasma ACTH**
  - Nl 150 pcg/mL
  - High (up to 500 pcg/mL) if pituitary or hypothalamic origin
  - Low (<50 pcg/mL) if adrenal adenoma or carcinoma
More Adrenal Tests

- Dexamethasone suppression test
  - 1 mg dexamethsone @ 11 PM
  - Nl:  suppressed plasma cortisol at 8 AM; < 5 mcg/100 mL
  - Cushings:  fail to suppress
  - May repeat times 2 days
  - May use higher doses
    (4 mg Q 11 PM times 2 days)
- Nuclear scanning, CT scans, MRI
Treatment of Cushings

- Surgical removal or radiation of adrenal, pituitary, or hypothalamus
  - Replace cortisol and fludrocortisone (Florinef) 0.1 mg QD x (6-12 months if one adrenal only involved)
  - Replace other pituitary hormones as indicated (thyroid, sex hormones)
- Ketoconazole (Nizoral) for refractory cases
  - Inhibits 11-hydroxylase and 17-hydroxylase
- Metapyrone (Metopirone) and/or aminoglutethamide (Cytadren) for ectopic ACTH syndrome
- Mitotane (o,p’DD, Lysodren) for adrenal carcinoma. Inhibits 11 hydroxylation
- RU 486 (mifepristone): progesterone and glucocorticosteroid receptor antagonist
Hormone Synthetic Pathways

From figure 76-2, Chapter 76, Pharmacotherapy
Hypofunctioning Adrenal Gland

- Addison’s Disease
- Primary
  - Autoimmune-70%
    (may involve other organs: thyroid, ovary, pancreas)
  - Tuberculosis, AIDS, other infections
  - Vascular obstruction, bleeds
- Secondary (low ACTH)
  - Hypopituitarism
  - Corticosteroid administration
Clinical Features of Addison’s

- Weakness-100%
- Weight loss-100%
- *Increased pigmentation-95%
  (via ACTH stimulation of melanocyte stimulating hormone; absent in secondary forms)
- Hypotension-90%
- Vitiligo-20%
- Diuresis (analogy to spironolactone)
  Hyponatremia/hyperkalemia
  note: aldosterone (mineralocorticoid function) may be spared in secondary cases
Vitiligo
Vitiligo
Workup of patient

• Suspect Addison’s based on symptoms
• Screening serum or urine cortisol level
  – Should be low. If not, look for other disease.
• If cortisol level is low, measure ACTH level to differentiate pituitary vs adrenal cause. (see next slide)
• To differentiate pituitary origin vs adrenal origin: conduct ACTH or Cosyntropin stimulation test. (details on another slide)
Lab Tests for Adrenal Insufficiency

- Serum cortisol low in both primary and secondary Addison’s
- Serum ACTH above normal in primary Addison's, but low or absent in secondary
ACTH Stimulation Test

• Administer 25-40 units ACTH (Acthar) in early morning.
  – Measure serum cortisol pre-ACTH and 30 minutes post
  – Cortisol level should double.
    Lack of response if Addison’s

• Cosyntropin
  – Synthetic polypeptide of ACTH
    (24 of 39 amino acids present)
  – Dose = 0.25 mg
  – 1 mg cosyntropin = 100 mg ACTH

• Lack of cortisol response in primary, possibly in secondary.
Metyrapone Test

- To verify secondary Addison’s (hypopituitarism)
- Metyrapone blocks conversion of desoxycortisol to cortisol
- As cortisol levels fall, there should be a reflex increase in ACTH production.
- ACTH levels do not rise if pituitary is hypofunctioning
Hormone Synthetic Pathways

Cholesterol → Prenenolene → Progesterone → 17-hydroxyprogesterone → 11-deoxy cortisol → Cortisol

18-hydroxy pregnenolone → Dehydroepiandrosterone → Androstenedione → Testosterone

18-hydroxyprogesterone → Corticosterone → 18-hydroxy Aldosterone

corticosterone

From figure 76-2, Chapter 76, Pharmacotherapy
Treatment of Addison’s

• Prednisone or hydrocortisone to mimic normal diurnal rhythm
  – Prednisone 5 mg AM, 2.5 mg PM
  – Cortisol 25 mg AM, 12.5 mg PM
  – Hydrocortisone 20 mg /10 mg

• Extra doses for stressful situations

• Fludrocortisone (Florinef)
  0.05-0.2 mg Q AM
  (to minimize hyperkalemia)

• Monitor hyperpigmentation

• IV HC, Florinef, epinephrine for acute adrenal insufficiency