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

- Hypothalamus (Corticotropin releasing factor)
- Pituitary (Corticotropin/ACTH)
- 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

- phospholipase A₂

Arachidonic Acid

Lipooxygenase

Leukotrienes

- Inflammation
- Bronchospasm

- Edema
- Bronchodilate
- Pain sensitization

cyclooxygenase

Prostaglandins

- PGE
  - Vasodilate
  - Vasoconstrict
  - Platelet aggregation
  - Platelet

- Prostacyclin (vascular)
  - Vasodilate
  - Pain sensitization

- Thromboxane (platelets)

- PGF
  - Vasoconstrict

Phospholipase A₂
Glucocorticoid Actions

- Decrease inflammatory response
  - Inhibit phospholipase $A_2 \rightarrow \downarrow$ production of arachidonic acid $\rightarrow$ indirect inhibition of both prostaglandins and leukotrienes.
  - Inhibit activity of T lymphocytes (especially TH$_2$)
  - Suppress IL-1, IL-3, IL-4, IL-5;
    $\downarrow$ chemotraction of eosinophils and macrophages
  - Vasoconstrict, $\downarrow$ edema, $\downarrow$ fever
  - Stabilize neutrophilic (granulocyte) lysosomes to $\downarrow$ 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>
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</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>
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</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?