Respiratory Therapy Drugs

Jennifer McDaniel, BS, RRT-NPS
Anti-Asthma Drugs

- Bronchodilators
  - Adrenergic Agents
  - Anti-Muscarinics
  - Methylxanthines

- Maintenance Drugs
  - Corticosteroids
  - Antiallergics
  - Antileukotrienes
Another Classification

- 1995 Global Initiative for Asthma
- 1997 NAEPP Guidelines
  - Long-term control
  - Quick relief
Long-Term Control

- Inhaled corticosteroids
- Cromolyn sodium
- Nedocromil
- Long-acting $\beta_2$ agonists
- Methylxanthines
- Leukotriene antagonists
- Systemic corticosteroids
Quick-Relief

• Short-acting inhaled $\beta_2$ agonists
• Anticholinergic
• Systemic corticosteroids
Mucokinetic Agents

- Bland aerosols
- Acetylcysteine
- Propylene glycol
- Sodium bicarbonate
- Dornase alfa
Adrenergic Agents - Actions

- Agents - Vasoconstriction
  - Used topically to decrease edema
  - Used systemically to increase blood pressure

- Agents - Increase heart rate and contractility - Increase cardiac output
Adrenergic Agents - Actions

- **$\beta_2$ Agents**
  - Relaxation of bronchial smooth muscle
  - Increase in mucociliary action
  - Some inhibition of inflammatory mediator release
  - Relaxation of vascular smooth muscle
  - Relaxation of other smooth muscle (e.g. uterine)
  - Useful as a tocolytic agent (terbutaline)
Classes of Adrenergic Agents

- Catecholamines
- Resorcinols
- Saligenins
- Ultra-long acting
- Mucosal vasoconstrictors
Catecholamines

- L-Epinephrine (Adrenalin): \(\leq 1, \leq 1, \leq 2\)
  - potent
  - given SC for asthma attack (esp. pediatrics)

- D, L-Epinephrine or Racemic Epinephrine (Vaponefrin, MicroNefrin): \(\leq 1, \leq 1, \leq 2\)
  - not as potent as L-Epinephrine
  - used to reduce airway edema
Catecholamines

- **Isoproterenol (Isuprel):** \( (\beta_1, \alpha_1, \alpha_2) \)
  - Nonspecific \( \alpha \) agonist
  - Very high potency
  - Relatively short acting (1-2)

- **Isoetharine (Bronkosol):** \( (\alpha_1, \alpha_2) \)
  - first \( \alpha_2 \) selective drug (1-3)

- **Bitolterol (Tornalate):** \( \alpha_2 \)
  - actually a prodrug (inactive) that is converted to colterol (a \( \alpha_2 \) specific catecholamine) (5-8)
Resorcinols

• Metaproterenol (Alupent, Metaprel): \( \text{\textbullet} (1), 2 \)
  – low potency
  – relatively long acting (3-6)

• Terbutaline (Bricanyl, Brethine): \( \text{\textbullet} 2 \)
  – high potency
  – relatively long acting (3-6)
Saligenins

- Albuterol (Ventolin, Proventil): \( \text{long acting (3-8)} \)
- Pirbuterol (Maxair): \( \text{long acting (5)} \)
- Levalbuterol (Xopenex): \( \text{fewer side effects} \)
- long acting
Ultra-Long Acting

- Salmeterol (Serevent): \( \text{\textregistered} \)
  - very long acting (12)
  - slow onset
  - not useful in acute attack, a maintenance bronchodilator
- Formoterol (Foradil): \( \text{\textregistered} \)
  - very long acting (12)
  - faster onset
  - greater efficacy than albuterol
  - not recommended for rescue due to cumulation
- Arformoterol (Brovana)
  - nebulized solution (12)
Mucosal Vasoconstrictors

- Phenylephrine (Neo-Synephrine): $\leq_1$, $(\leq_1)$, $(\leq_2)$
Belladonna alkaloids (tertiary amines) : botanical derivatives from *Atropa belladonna* (Nightshade), *Datura spp* (Family: Solanaceae)

**Atropine sulfate**
- Not widely used anymore because of
  - drying effect on secretions
  - CNS effects
  - Other side effects

**Scopolamine**
- preanesthetic agent
- motion sickness
Anti-Muscarinics

- Quaternary amines
  - Ipratropium bromide (Atrovent)
    - potent bronchodilator
    - less drying effect on secretions
    - does not readily cross blood:brain barrier - reduced CNS and ocular effects
  - Glycopyrrolate (Robinul)
  - Tiotropium bromide (Spiriva)
Combination Drugs

- Ipratropium & albuterol
  - Combivent (MDI)
  - DuoNeb (SVN)
Methylxanthines

• Found in many beverages
  – Theophylline: tea
  – Caffeine: coffee, cocoa, cola
  – Theobromine: cocoa

• Mode of action
  – Unknown, but once proposed to be a phosphodiesterase inhibitor
  – May work by combining with adenosine receptors
Methylxanthines

- Pulmonary effects
  - bronchial smooth muscle relaxation
  - inhibit glandular secretions
  - inhibit release of allergic mediators
  - respiratory stimulant - increasing CO₂ sensitivity of medullary respiratory centers
  - increase diaphragmatic contractility
Methylxanthines

- Extrapulmonary effects
  - Cardiac effects
    - positive inotropic effect
    - positive chronotropic effect
    - increases myocardial oxygen demands
    - may cause arrhythmias
Methylxanthines

- Extrapulmonary effects
  - Vascular effects
    - dilation of pulmonary blood vessels
    - dilation of coronary blood vessels
    - dilation of renal blood vessels, increase urine
    - constriction of cerebral blood vessels
Methylxanthines

- Extrapulmonary effects
  - Other effects
    - mild CNS stimulation
    - stimulation of ventilatory, cardiac, and vasomotor centers of brainstem
    - skeletal muscle stimulation
    - Indirect diuretic effect
    - Increased glandular secretion and increased motility of G. I. tract smooth muscle
Methylxanthines

- Serum levels and therapeutic index
  - fairly low therapeutic index
  - therapeutic serum level 10-20 $\text{mg/mL}$
- Toxicities
  - nausea and vomiting: >20 $\text{mg/mL}$
  - cardiac arrhythmias & seizures: >40 $\text{mg/mL}$
Methylxanthines

- Metabolized by liver (hepatic microsomal enzymes)
  - cigarette smoking induces enzymes - decreasing 1/2 life of theophylline
  - cirrhosis, CHF, etc. decrease hepatic blood flow & increase 1/2 life
  - Drugs that damage liver (e.g. erythromycin, rifampin) increase 1/2 life
Methylxanthines

- Aminophylline (theophylline ethylenediamine): Aminophyllin, Somophyllin
- Oxtriphylline: Choledyl
- Dyphylline: Aerophylline
Corticosteroids

- Adrenal cortex produces:
  - glucocorticoids (hydrocortisone or cortisol)
  - mineralocorticoids (aldosterone)
  - gonadocorticoids (anabolic steroids)
Adrenal cortex dysfunction - Hypersecretion

- Mineralocorticoids: $\uparrow \text{Na}^+ , \downarrow \text{K}^+$, fluid accumulation $\rightarrow$ "moon face"
- Glucocorticoids: gluconeogenesis $\rightarrow$ $\uparrow$ glucose
  - diabetes
  - fat redistribution
  - immunosuppression $\rightarrow$ $\uparrow$ infection
  - weight gain
Adrenal cortex dysfunction - Hypersecretion

- Gonadoocorticoids: Masculinization
  - hirsutism
  - ↑ muscle mass
  - voice change
  - disruption of menstrual cycle
Adrenal cortex dysfunction - Hyposcretion

- Mineralocorticoids: ↓ Na\(^+\), ↑ K\(^+\), rapid diuresis → renal suppression, ↓ blood pressure, arrhythmias, death
- Glucocorticoids: ↓ glucose, usually compensated
- Gonadocorticoids: muscle weakness
Comparison: Hypersecretion vs Hyposcretion

<table>
<thead>
<tr>
<th>Cushingoid Effects</th>
<th>Addisonian Effects</th>
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<tr>
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<td>Diuresis, fluid loss</td>
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<tr>
<td>Hypertension</td>
<td>Hypotension</td>
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<tr>
<td>Hyponatremia</td>
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<tr>
<td>Diabetes</td>
<td>Renal suppression</td>
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<tr>
<td>Immunosuppression</td>
<td>↓ resistance to stress</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Weight loss</td>
</tr>
</tbody>
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Chronic Systemic Steroid Therapy

• General Effects
  – Hypothalamic suppression
  – Adenohypophyseal suppression
  – Adrenocortical suppression
Chronic Systemic Steroid Therapy

- Mineralocorticoid Effects
  - Hypernatremia
  - Edema
  - Hypertension
  - Hypokalemia
Chronic Systemic Steroid Therapy

• Glucocorticoid Effects
  – Fat and protein mobilization
  – Immunosuppression
  – Connective tissue destruction
  – Hyperglycemia
  – Adrenocortical diabetes
  – Glaucoma
Chronic Systemic Steroid Therapy

• Gonadocorticoid Effects
  – Protein anabolism
  – Masculinization
Chronic Systemic Steroid Therapy

• Other Effects
  – thin, fragile, dry, parchment-like skin
  – osteoporosis & vertebral compression
  – cataracts
  – peptic ulcers
  – behavioral changes

• Abrupt withdrawal → Addisonian crisis
Therapeutic Systemic Agents

- Short-Acting (8-12 hours)
  - Hydrocortisone (Cortisol): Solu-Cortef
  - Cortisone: Cortone
Therapeutic Systemic Agents

• Intermediate-Acting (12-36 hours)
  – Methylprednisolone: Medrol (Oral), Solu-Medrol (IV)
  – Prednisolone: Delta-Cortef
  – Prednisone: Colisone, Deltasone, Winpred (Oral)
  – Triamcinolone Azmacort (oral MDI), Aristocort (Oral, IM), Kenacort (Oral)
Therapeutic Systemic Agents

- Long-Acting (36-72 hours)
  - Betamethasone: Celestone (IM)
  - Dexamethasone: Decadron (Oral, IM, IV, Nasal MDI), Hexadrol (Oral, IM, IV), Dexasone (Oral)
Therapeutic Nonsystemic Agents

- **Beclomethasone**: Beclovent, Vanceril (Oral MDI & DPI); Beconase, Vancenase (Nasal MDI)
- **Flunisolide**: Bronalide, AeroBid (Oral MDI); Nasalide (Nasal spray)
- **Budesonide**: Pulmicort (Oral MDI)
- **Fluticasone**: Flovent (Oral MDI), Flonase (Nasal spray)
Reducing/Eliminating Systemic Steroids

- Alternate day therapy
- Add inhaled corticosteroids
- Use other maintenance drugs
- Tapered withdrawal
Antiallergic Drugs: Cromolyn

- **Trade names:** Intal, Aarane
- **Action:** stabilizes mast cells, preventing mediator release
- **Route of administration:** inhalation
- **Other cromolyn drugs**
  - Nasalcrom: nasal solution for prophylaxis of seasonal rhinitis
  - Opticrom: seasonal allergic conjunctivitis
Antiallergic Drugs: Cromolyn

- **Uses**
  - No role in treatment of acute bronchospasm
  - Prophylaxis of asthma (esp. allergic); 6 to 12 weeks for peak effectiveness
  - Prevention of cold air and exercise-induced bronchospasm
  - Adverse effects - with DPI
    - Throat irritation: dryness, hoarseness, coughing
    - Bronchospasm: wheezing
Antiallergic Drugs: Nedocromil

- **Action:** blocks production of inflammatory mediators
- **Uses:** similar to cromolyn
Antileukotrienes: Zileutin

- Trade name: Zyflo
- Action: inhibits formation of leukotrienes
- Uses:
  - asthma maintenance
  - not useful for acute bronchospasm
- Dosage: 600 mg QID 100 = $62.50
Antileukotrienes: Zafirlukast

• Trade name: Accolate
• Action: competitive, reversible antagonist of the leukotriene D4 receptor
• Uses:
  – asthma maintenance
  – exercise-induced asthma
  – not useful for acute bronchospasm
• Dosage: 20 mg BID  100 = $84.67
Antileukotrienes: Montelukast

- Trade name: Singulair
- Action: competitive, reversible antagonist of the leukotriene D4 receptor
- Uses:
  - asthma maintenance
  - exercise-induced asthma
  - not useful for acute bronchospasm
- Dosage: 5 mg or 10 mg QD
- Approved for use in children
Mucokinetics: Bland Aerosols

- Physiologic saline (0.9%)
- Sterile distilled water
- Hypertonic saline (>0.9%)
- Hypotonic saline (4.5%)
Mucokinetics: Acetylcysteine

- Trade name: Mucomyst
- Action: ruptures disulfide bonds of glycoproteins
- Effectiveness: best when given by direct instillation, especially via bronchoscope.
- Adverse effects: bronchospasm, “rotten egg” odor and taste, nausea and vomiting
- Precautions: administer with a bronchodilator
- 10% and 20% solutions
Mucokinetics: Propylene glycol

- Action: hygroscopic agent - absorbs water & ruptures hydrogen bonds
- Bacteriostatic: not suitable for sputum induction for sputum induction intended for C & S
Mucokinetives: Sodium bicarbonate

- Action: weakens saccharide side chains of glycoproteins
Mucokinetics:  Dornase alfa

• Trade name:  Pulmozyme
• rhDnase
• Effective against infected sputum in cystic fibrosis
• Expensive
• Usually, by inhalation once daily
• Stored refrigerated (2-8°C)
Combination Drugs

- Advair
  - salmeterol (5mcg)
  - fluticasone (100, 250, or 500 mcg)
- Symbicort
  - formoterol (4.5 mcg)
  - Budesonide (80 or 160 mcg)