Chapter 6

Adrenergic (Sympathomimetic) Bronchodilators
Clinical Indications for Adrenergic Bronchodilators

- Relaxation of smooth airway muscle in the presence of reversible obstruction
  - Asthma
  - Bronchitis
  - Emphysema
  - Bronchiectasis
Indication for Short-acting Agents

- *Acute* reversible airflow obstruction
- Short-acting agents:
  - a.k.a. “rescue” agents
  - Albuterol
  - Levalbuterol
  - Pirbuterol
Indication for Long-acting Agents

- Maintenance bronchodilation, control of bronchospasm, and control of nocturnal symptoms
  - Salmeterol
  - Formoterol
Indications for Racemic Epinephrine

- To control airway bleeding during endoscopy
- To reduce airway swelling
  - Postextubation
  - Epiglottitis
  - Croup
  - Bronchiolitis
Specific Adrenergic Agents and Formulations

● Ultrashort acting
  ➢ Duration < 3 hours
  ➢ Epinephrine, racemic epinephrine, isoetharine

● Short acting
  ➢ Duration of 4 to 6 hours
  ➢ Albuterol, levalbuterol, metaproterenol, pirbuterol

● Long acting
  ➢ Duration of 12 hours
  ➢ Salmeterol, formoterol, arformoterol
Catecholamines

- Sympathomimetic bronchodilators are either catecholamines or derivatives of catecholamines
- Catecholamines mimic epinephrine
  - Tachycardia
  - Elevated BP
  - Smooth muscle relaxation (bronchioles and skeletal muscle blood vessels)
  - Glycogenolysis
  - Skeletal muscle tremor
  - CNS stimulation
Adrenergic Bronchodilators as Stereoisomers

- Nonsuperimposable molecular mirror images
  - (R)-Isomer (right isomer)
  - (S)-Isomer (left isomer)
- Similar physical and chemical properties
- Different physiological effects
- Example: levalbuterol
Epinephrine

- Potent catecholamine bronchodilator
- Stimulates both α and β receptors
- High prevalence of side effects
  - Tachycardia
  - Increased BP
  - Tremor
  - Headache
  - Insomnia
- Available as a synthetic racemic mixture
Isoproterenol

- Potent catecholamine bronchodilator
  - Stimulates both $\beta_1$ and $\beta_2$ receptors
- No longer manufactured as a nebulizer solution
- Available parenterally
Isoetharine

- One of first $\beta_2$-specific adrenergic bronchodilators
- Short duration, rapid onset
- Minimal $\beta_1$ stimulation
Keyhole Theory of $\beta_2$ Specificity

- The larger the catecholamine side chain, the more $\beta_2$ specific
  - Epinephrine
    - Equal $\alpha$ and $\beta$
  - Isoproterenol
    - Strong $\beta$, little $\alpha$
  - Isoetharine
    - $\beta_2$ preferential
Metabolism of Catecholamines

- Rapidly inactivated by COMT
  - Duration of action is limited
  - 1.5 to 3 hours
- Unsuitable for oral administration
  - Inactivated in gut and liver
- Also inactivated by:
  - Heat
  - Light
  - Air
Resorcinol Agents

- Better for maintenance therapy
- Significantly longer duration of action
  - 4 to 6 hours
- Slower peak effect
  - 30 to 60 minutes
- Examples:
  - Terbutaline
  - Metaproterenol
Saligenin Agents

- Example:
  - Albuterol

- Available as:
  - MDI
  - Syrup
  - Nebulizer
  - Extended-release tablets
Saligenin Agents

**Benefits:**
- $\beta_2$ Preference
- Effective by mouth
- Peak effect in 30 to 60 minutes
- Duration of up to 6 hours
Pirbuterol

- Noncatecholamine adrenergic agent
- Available as breath-actuated MDI
- Onset: 5 to 8 minutes
- Peak effect: At 30 minutes
- Duration of action: 5 hours
Levalbuterol: The (R)-Isomer of Albuterol

- Pure (R)-isomer of racemic albuterol
- Available as HFA MDI and nebulizer solution
- Available in four doses:
  - 0.31 mg/3 mL
  - 0.63 mg/3 mL
  - 1.25 mg/3 mL
  - 1.25 mg/0.5 mL concentrate
Long-acting β-Adrenergic Agents

- Offer less frequent dosing and nocturnal protection
  - Extended-release albuterol
  - Salmeterol
  - Formoterol
  - Arformoterol
Extended-release Albuterol

- Available as Vospire ER
- 4-mg or 8-mg oral tablet
- Activity time, 8 to 12 hours
Salmeterol

- Available as DPI (Diskus inhaler)
- Bronchodilator effect
  - Slower onset than albuterol
  - Time to peak bronchodilating effect, 3 to 5 hours
  - Duration, 12 hours
**Formoterol**

- $\beta_2$-Selective agonist
- Short time to bronchodilatory effect (3 minutes)
- Duration of up to 12 hours
- Available as DPI
- Used for:
  - Asthma (5 yrs +)
  - Exercise-induced bronchospasm (5 yrs +)
  - COPD
Antiinflammatory Effects

- Salmeterol and formoterol inhibit mast cell activation
- *In vitro* results only; not clinically proven
Clinical Use

- Maintenance therapy of asthma not controlled by inhaled corticosteroids
- COPD needing daily bronchodilator
- *Not* recommended for rescue therapy
- *Not* recommended for treatment of breakthrough symptoms
Arformoterol

- $\beta_2$-Selective agonist
- Single isomer of formoterol
- Duration of up to 12 hours
- Available as nebulizer solution
- Approved for:
  - COPD
Mode of Action

- $\alpha$-Receptor stimulation
  - Vasoconstriction/vasopressor effect
- $\beta_1$-Receptor stimulation
  - Increased HR and contractile force
- $\beta_2$-Receptor stimulation
  - Relaxation of bronchial smooth muscle
β- and α-Receptor Activation

- β Receptor
  - Binds to β receptor, ultimately causing increased synthesis of cAMP

- α Receptor
  - Inhibits release of neurotransmitter from presynaptic neuron
  - *But*…may also lower synthesis of intracellular cAMP
α₁-Receptor Activation

- Agonists such as:
  - Phenylephrine
  - Epinephrine
- Results in vasoconstriction of peripheral blood vessels
Salmeterol, Formoterol, and Arformoterol: Mechanism of Action

**Salmeterol**
- Lipophilic
- Approaches β receptor *laterally*

**Formoterol**
- Also lipophilic
- Can also approach receptor from aqueous phase
Routes of Administration

- Inhalation
  - MDI
  - DPI
  - Nebulized
- Orally
  - Tablets
  - Syrup
- Parenterally
Inhalation Route

- Catecholamines are ineffective orally
  - Benefits of inhalation:
    - Rapid onset
    - Smaller doses
    - Reduced side effects
    - Drug delivered directly to target organ
    - Relatively safe and painless
Inhalation Route

- Limitations:
  - Time
  - Public embarrassment
  - Difficult to use correctly
Continuous Nebulization

- Used for management of asthma
- Reduces need for frequent therapist attendance
- Generally 10 to 15 mg/hour for adult
Continuous Nebulization

- Delivery methods
  - Refilling SVN
  - Volumetric infusion pump
  - Large-volume nebulizer

- Toxicity and monitoring
  - Potential complications
    - Cardiac arrhythmias, hypokalemia, hyperglycemia, tremor
Oral Route

- **Advantages**
  - Easy to use
  - Short administration time
  - Reproducibility and controlled dosage

- **Disadvantages**
  - Longer onset of action
  - More systemic side effects
  - Loss due to first pass through liver
Parenteral Route

- Used in the emergency management of acute asthma
- Thought to be useful when obstruction prevents penetration of aerosol to lung periphery
- Should be used as a last resort and requires:
  - Infusion pump
  - Cardiac monitor
  - Close attention for systemic side effects
Adverse Side Effects

- Side effect: Any effect other than intended therapeutic effect
  - Tremor
  - Cardiac effects
  - Tolerance to bronchodilator effect
  - Loss of bronchoprotection
  - CNS effects
  - Fall in PaO$_2$
  - Metabolic disturbances
  - Propellant toxicity and paradoxical bronchospasm
  - Sensitivity to additives
The β-Agonist Controversy

- The asthma paradox: Increasing evidence of asthma mortality and morbidity despite advances in treatment
  - Lack of steroid use?
  - Loss of bronchodilator effect?
  - Increase in bronchial hyperreactivity?
  - Exposure to triggers with no immediate symptoms?
The β-Agonist Controversy

● Increasing evidence of asthma mortality and morbidity despite advances in treatment (continued)
  ➢ Temporary relief leads to delay in seeking medical help?
  ➢ Poor patient compliance/education?
  ➢ Accumulation of (S)-isomer?
  ➢ Environmental pollution and lifestyle changes?
Respiratory Care Assessment of \( \beta \)-Agonist Therapy

- Assess effectiveness of drug based on indications for use
- Monitor peak flow rates
- Perform physical assessment before/after treatment
- Monitor HR for 20% increase
- Subjective reactions
Respiratory Care Assessment of β-Agonist Therapy

- ABGs
- Monitor glucose/K⁺
- PFTs
- Provide patient education
- Instruct/verify correct use of devices
Respiratory Care Assessment of β-Agonist Therapy

- For long-acting β agonists
  - Assess ongoing lung function
  - Assess use of rescue drug and nocturnal symptoms
  - Assess number of exacerbations
  - Assess days absent from work/school
  - Assess ability to reduce dose of inhaled corticosteroids