Learning Objective:
◆ Describe the current status of research on the actions, effects, indications and contraindications for bronchodilating agents, mucokinetic agents and anti-inflammatory agents.

Bronchodilator Agents

Beta-Agonists
◆ Short-acting
  ◆ racemic albuterol
  ◆ levalbuterol
◆ Long-acting
  ◆ salmeterol
  ◆ formoterol
  ◆ arformoterol (Brovana)

Beta-agonist bronchodilators
◆ Action- stimulate intracellular adenylate cyclase to increase levels of 3,5 cAMP

Adrenergic autonomic control
◆ Adrenergic receptors
  ◆ alpha, in vascular walls- vasoconstriction
  ◆ Beta1, in myocardium- cardiotonic effects
  ◆ Beta2, in vascular and bronchiolar smooth muscle- dilation
Activation of Beta2 receptors
- Catecholamine binds to receptor
- G protein in cell membrane activates adenylate cyclase

Activation of Beta2 receptors
- Adenylate cyclase catalyzes formation of 3,5 cyclic AMP (cAMP) => relaxation
- cAMP inactivated by phosphodiesterase

Short-acting beta-agonists
- Therapeutic effects:
  - Bronchodilation
  - Vasodilation
  - Stabilizes mast cells
  - Increase mucus secretion
  - Increase ciliary activity
  - Inhibits bronchial edema

Short-acting beta-agonists
- Therapeutic effects:
  - Bronchodilation
  - Vasodilation
  - Stabilize mast cells
  - Increase mucus secretion
  - Inhibits bronchial edema
  - Decrease airway hyper-responsiveness
  - Relax uterine muscle

Short-acting beta-agonists
- Therapeutic effects:
  - moderated by genetic differences
  - in beta receptors (polymorphism)
  - explains variability in response to beta agonists and beta blockers

Short-acting beta-agonists
- Indications
  - asthma- as a rescue medication
  - COPD
  - cystic fibrosis- regardless of PFT responsiveness
  - pulmonary edema??- may reduce edema by clearing lung water
  - ARDS/ALI??- may reduce edema and inflammation

Link to article on albuterol and ARDS/ALI
http://ajrccm.atsjournals.org/cgi/reprint/173/3/281
Short-acting beta-agonists

**Indications**
- Severe hyperkalemia - moves K+ into cells (dosage = 10 mg)
- Inhalational injury; e.g., smoke inhalation
- Anaphylaxis

Link to abstract on albuterol and hyperkalemia

**Adverse effects:**
- Skeletal muscle tremor - most common
- Tachyphylaxis (tolerance)
- Tachycardia, palpitation - B1 effects

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**Agents**
- Terbutaline
- Albuterol (racemic)
- Levalbuterol (Xopenex) - R isomer of albuterol

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Short-acting beta-agonists

**Adverse effects:**
- Sudden death
- Overusage == tachyphylaxis?
- Propellant??
- Hypoxemia, due to dilation of pulmonary vasculature increasing V/Q mismatch

**Adverse effects:**
- Hypokalemia - sometimes given to correct hyperkalemia for renal patients
- Hyperglycemia

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**Levalbuterol**

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Bad Guy
Short-acting beta-agonists

- **levalbuterol**
  - R isomer is therapeutically active
  - S isomer likely to produce adverse effects; levalbuterol has reduced adverse effects, such as tolerance
  - levalbuterol is more expensive
  - cost-effective if ordered appropriately

**Long-acting beta-agonists**

- **Salmeterol (Serevent)**
  - effective for asthma, COPD
- **Formoterol (Foradil)**
  - shorter onset than salmeterol
  - more cost-effective

Short-acting beta-agonists

- **levalbuterol**
  - indications
    - replace albuterol in event of adverse effects
    - emergency care for asthma

**Long-acting beta-agonists**

- **Action**—same as short-acting; but, binds with B2 receptor repeatedly
- **Indications**—maintenance therapy for:
  - moderate-to-severe persistent asthma
  - moderate-to-severe persistent COPD

**Controversy**—may increase risk of death from asthma

- desensitization of beta2 receptors
- decreased effective numbers of beta2 receptors
- bronchiolar hyperreactivity

**Cost per dose (SVN)**

- racemic albuterol (generic)-.75/dose
- levalbuterol-3.50/dose

**Cost per dose (MDI)**

- racemic albuterol (generic)-.09/puff
- levalbuterol-.29/puff
Long-acting beta-agonists

- Agents
  - Arformoterol (Brovana)
  - Recently approved and released for COPD
  - $R$ isomer (like Xopenex)
  - Shorter onset
  - Nebulizer solution
  - May not mix with other medications

Long-acting beta-agonists

- Agents on the horizon
  - Carmoterol- 30 H duration
  - Indacaterol- 24 H duration

Anticholinergics

- Actions
  - Block acetylcholine receptor sites
  - Inhibit guanylate cyclase, so reduce intracellular 3,5 cyclic GMP

- Therapeutic effects
  - Relax bronchial muscle in large airways- effective for COPD

Activation of M3 receptors

- Guanylyl cyclase catalyzes formation of 3,5 cyclic GMP (cGMP) $\Rightarrow$ contraction

Anticholinergics

- Adverse effects
  - Drying of mouth, pulmonary secretions- atropine
  - Tachycardia- atropine
  - Anisocoria- severe eye damage
  - Allergy to MDI

Adverse effects

- Cardiovascular events - greater than six months on drug
  - Myocardial infarction
  - Stroke
  - Cardiovascular death

Link to picture of anisocoria

Anticholinergics

**Indications**
- COPD maintenance and exacerbations
- Asthma exacerbations
- Requires multiple doses

**Ipratropium Bromide (Atrovent)**
- Not available in US
- Duration 8-12 H has been questioned

**Ioxitropium Bromide (Oxivent)**
- Dry powder inhaler
- Duration 24-36 H
- Effective for COPD
- Increased FEV1
- Slower decline in FEV1
- Increased exercise capacity
- Reduced exacerbations

**Combination Bronchodilators**

**Combination of albuterol and ipratropium indicated for:**
- COPD
- ER management of asthma
- Available as Combivent, Duvent

Bronchodilators and Mechanical Ventilation

**Administration to patients without obstructive disease:**
- Longer duration of ventilation (+5D)
- No difference in mortality, pneumonia
- Greater cost ($450/patient)

**Administration via nebulizer, vs. MDI**
- Bacterial contamination
- Greater cost ($300,000/year)
- Altered ventilatory parameters
- Less efficiency


Duarte AG. Inhaled bronchodilator administration during mechanical ventilation. Respir Care 2004;49(6):632-634.
Anti-inflammatory Agents

Corticosteroids

- Actions
  - Increase number & responsiveness of beta-adrenergic receptors
  - Stabilize mast cell lysosomes
  - Decrease:
    - IgE synthesis
    - Histamine synthesis
    - Eicosanoid synthesis

Corticosteroids

- Therapeutic effects for asthma
  - Potentiate beta-agonists
  - Reduce edema
  - Prevent inflammation and resultant irreversible airway remodeling

Corticosteroids

- Effects for COPD
  - Fewer exacerbations
  - Early use improves lung function and quality of life
  - Withdrawal leads to lung function deterioration
  - Continued smoking may impair therapy

Corticosteroids

- Adverse systemic effects - reduced by aerosol route (short list)
  - Hypokalemic alkalemia
  - Diabetes mellitus
  - Cushingoid fat distribution
  - Moon face
  - Buffalo hump

Corticosteroids

- Adverse systemic effects - reduced by aerosol route (short list)
  - Hypokalemic alkalemia
  - Diabetes mellitus
  - Cushingoid fat distribution
  - Amenorrhea
  - Growth failure
  - Osteoporosis
  - Hirsutism (hairiness)
### Corticosteroids

#### Adverse effects for aerosol route
- Oral thrush
  - Reduced by spacer
  - Reduced by mouth rinsing
- Decreased bone density (dose related)
- Increased risk of fractures (boys)
- Skin bruising

#### Exhaled nitric oxide (F\textsubscript{E}NO) measurement
- Marker for airway inflammation
- Used to adjust dosage of corticosteroids
- Currently considered not medically necessary, so no payment

Link to article on F\textsubscript{E}NO and asthma
http://content.nejm.org/cgi/reprint/352/21/2163.pdf

### Corticosteroids

#### Agents
- Prednisone - oral, systemic - indicated for acute, severe asthma
- Dexamethasone (Decadron)
- Methylprednisolone (Solu Medrol)
- Hydrocortisone

#### Combination agents
- Fluticasone and salmeterol (Advair)
- Formoterol and budesonide (Symbicort)
- No differences in effectiveness or tolerability for asthmatic patients*

**Leukotriene Modifiers**

**Actions**
- Inhibit leukotriene (formerly SRS-a) production OR
- Prevent binding of leukotrienes to receptor sites

**Effects**
- Prevent inflammation & airway remodeling
- Permit elimination or reduction in systemic steroids
- Decreases exacerbations when used with inhaled steroids

**Agents** - all administered orally
- Montelukast (Singulair)
- Zafirlukast (Accolate)
- Zileuton (Zyflo) - may cause liver failure

**Mucokinetic Agents**

**Aerosolized Mucolytic Therapy**

- Research demonstrates improvement in CF with aerosolized combined DNA-ase (Pulmozyme)

**Mucolytic Therapy**
- Oral n-acetylcysteine (COPD): may improve pulmonary function
- May reduce risk of hospitalization
- Effects may be due to antioxidant activity
Oral Mucolytic Therapy
◆ there is no evidence to support nebulized n-acetylcysteine for mucokinesis
◆ acetylcysteine aerosol may damage lung epithelium


Oral Mucolytic Therapy
◆ there is no evidence to support nebulized NaHCO3 for mucokinesis
◆ NaHCO3 aerosol irritates bronchial epithelia

Miscellaneous Agents

Magnesium Sulfate (MgSO4)
◆ Actions:
  ✓ inhibits acetylcholine release
  ✓ inhibits histamine release
◆ Effects (IV MgSO4):
  ✓ reduces the rate of hospital admissions
  ✓ improves pulmonary function in patients with severe acute asthma

http://pedsccm.wustl.edu/All-Net/english/pulmpage/resptail/MGSO4.HTML
http://www.med.umich.edu/pediatrics/ebm/cats/magnesium.htm

Magnesium Sulfate
◆ Not recommended for routine use.
◆ Dose- 25 mg/kg, up to 2.0 g
Lidocaine

Actions
- inhibits nociceptor (cough, pain) response - component of acute asthma
- inhibits eosinophil activation

http://www.pulmonaryreviews.com/apr02/asthma.html

Effects
- reduces steroid requirement
- potentiates beta2 agonists
- antitussive

Administration - 2.5 mL 2-4% by nebulizer

Aerosols for Dyspnea

- aerosol opioids do not reduce dyspnea or improve exercise tolerance.
- aerosol furosemide may reduce dyspnea in COPD and lung cancer

References

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