

**Current Issues In  
Airway Pharmacology**  
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<http://www.geocities.com/jonesapjr/index.html>

**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
  - f* racemic albuterol
  - f* levalbuterol
- ◆ Long-acting
  - f* salmeterol
  - f* formoterol
  - f* arformoterol (Brovana)

**Beta-agonist bronchodilators**

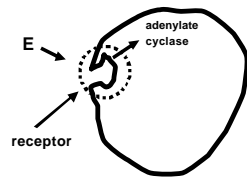
- ◆ Action- stimulate intracellular adenylate cyclase to increase levels of 3,5 cAMP

**Adrenergic autonomic control**

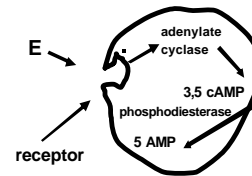
- f* Adrenergic receptors
  - ◆ alpha, in vascular walls- vasoconstriction
  - ◆ Beta1, in myocardium- cardiotoxic effects
  - ◆ Beta2, in vascular and bronchiolar smooth muscle- dilation

**Activation of Beta2 receptors**

- f* Catecholamine binds to receptor
- f* G protein in cell membrane activates adenylate cyclase

**Activation of Beta2 receptors**

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

**Short-acting beta-agonists**

- ◆ Therapeutic effects:
  - f* Bronchodilation
  - f* Vasodilation
  - f* Stabilizes mast cells
  - f* Increase mucous secretion
  - f* Increase ciliary activity
  - f* Inhibits bronchial edema

**Short-acting beta-agonists**

- ◆ Therapeutic effects:
  - f* Bronchodilation
  - f* Vasodilation
  - f* Stabilize mast cells
  - f* Increase mucous secretion
  - f* Inhibits bronchial edema
  - f* Decrease airway hyper-responsiveness
  - f* Relax uterine muscle

**Short-acting beta-agonists**

- ◆ Therapeutic effects:
  - f* moderated by genetic differences in beta receptors (polymorphism)
  - f* 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  
<http://www.medscape.com/medline/abstract/2919849?prt=true>

**Short-acting beta-agonists**

◆ **Adverse effects:**

- f Skeletal muscle tremor- most common
- f Tachyphylaxis (tolerance)
- f Tachycardia, palpitation- B1 effects

**Short-acting beta-agonists**

◆ **Adverse effects:**

- f Sudden death
- f Overusage ==> tachyphylaxis?
- f Propellant??
- f Hypoxemia, due to dilation of pulmonary vasculature increasing V/Q mismatch

**Short-acting beta-agonists**

◆ **Adverse effects:**

- f Hypokalemia- sometimes given to correct hyperkalemia for renal patients
- f Hyperglycemia

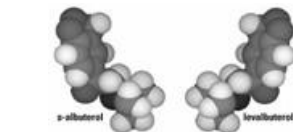
**Short-acting beta-agonists**

◆ **Agents**

- f terbutaline
- f albuterol (racemic)
- f levalbuterol (Xopenex)- R isomer of albuterol

**Short-acting beta-agonists**

◆ **levalbuterol**



↗  
**Bad Guy**

**Short-acting beta-agonists**◆ **levalbuterol**

*f* R isomer is therapeutically active  
 ==> levalbuterol is more potent

*f* S isomer likely to produce  
 adverse effects ==> levalbuterol  
 has reduced adverse effects, such  
 as tolerance

*f* levalbuterol is more expensive

*f* cost-effective if ordered  
 appropriately

**Short-acting beta-agonists**◆ **levalbuterol**

*f* indications

*f* replace albuterol in event of  
 adverse effects

*f* emergency care for asthma

**Short-acting beta-agonists**◆ **cost per dose (SVN)**

*f* racemic albuterol (generic)-  
 .75/dose

*f* levalbuterol- 3.50/dose

◆ **cost per dose (MDI)**

*f* racemic albuterol (generic)-  
 .09/puff

*f* levalbuterol- .29/puff

**Long-acting beta-agonists**

◆ **Action-** same as short-acting;  
 but, binds with B2 receptor  
 repeatedly

◆ **Indications-** maintenance therapy  
 for:

*f* moderate-to-severe persistent  
 asthma

*f* moderate-to-severe persistent  
 COPD

**Long-acting beta-agonists**

◆ **Controversy-** may increase risk of  
 death from asthma

*f* desensitization of beta2 receptors

*f* decreased effective numbers of  
 beta2 receptors

*f* bronchiolar hyperreactivity

**Long-acting beta-agonists**◆ **Agents**

*f* Salmeterol (Serevent)

*f* effective for asthma, COPD

*f* Formoterol (Foradil)

*f* shorter onset than salmeterol

*f* more cost-effective

**Long-acting beta-agonists**

- ◆ Agents
  - f Arfomoterol (Brovana)
  - f recently approved and released for COPD
  - f R isomer (like Xopenex)
  - f shorter onset
  - f nebulizer solution
  - f may not mix with other medications

**Long-acting beta-agonists**

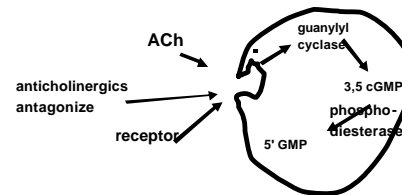
- ◆ Agents on the horizon
  - f Carmoterol- 30 H duration
  - f Indacaterol- 24 H duration

**Anticholinergics**

- ◆ Actions
  - f Block acetylcholine receptor sites
  - f Inhibit guanylate cyclase, so reduce intracellular 3,5 cyclic GMP
- ◆ Therapeutic effects
  - f Relax bronchial muscle in large airways- effective for COPD

**Activation of M3 receptors**

f Guanylyl cyclase catalyzes formation of 3,5 cyclic GMP (cGMP) ==> contraction



**Anticholinergics**

- ▲ Adverse effects
  - ◆ drying of mouth, pulmonary secretions- atropine
  - ◆ tachycardia- atropine
  - ◆ anisocoria- severe eye damage
  - ◆ allergy to MDI

Link to picture of anisocoria  
<http://i28.servimg.com/u/f28/11/84/45/20/pictur10.jpg>

**Anticholinergics**

- ▲ Adverse effects
  - ◆ cardiovascular events - greater than six months on drug
    - f myocardial infarction
    - f stroke
    - f cardiovascular death

\*Singh S, Loke Y, Furberg Curt. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease. JAMA 2008;300:1439-1449

**Anticholinergics**◆ **Indications**

- f* COPD- maintenance and exacerbations
- f* asthma
- f* exacerbations
- f* requires multiple doses

**Anticholinergics**

- ◆ ipratropium bromide (Atrovent)
- ◆ oxitropium bromide (Oxivent)
  - f* not available in US
  - f* duration 8-12 H- has been questioned

**Anticholinergics**◆ **tiotropium bromide (Spiriva)**

- f* dry powder inhaler
- f* duration 24-36 H
- f* effective for COPD
  - f* increased FEV1
  - f* slower decline in FEV1
  - f* increased exercise capacity
  - f* reduced exacerbations

**Combination Bronchodilators**

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

**Bronchodilators and Mechanical Ventilation**◆ **Administration to patients without obstructive disease:**

- f* longer duration of ventilation (+5D)
- f* no difference in mortality, pneumonia
- f* greater cost (\$450./patient)

Chang L, Shyoko H, Haithcock, JA, et al. Utilization of bronchodilators in ventilated patients without obstructive disease. Respir Care 2007;52(2):154-158.

**Bronchodilators and Mechanical Ventilation**

- ◆ **Administration via nebulizer, vs. MDI**
  - f* bacterial contamination
  - f* greater cost (\$300,000/year)
  - f* altered ventilatory parameters
  - f* less efficiency

Duarte AG. Inhaled bronchodilator administration during mechanical ventilation. Respir Care 2004;49(6):6323-634.

## Anti-inflammatory Agents

### Corticosteroids

#### ◆ Actions

- f* Increase number & responsiveness of beta-adrenergic receptors
- f* Stabilize mast cell lysosomes
- f* Decrease:
  - f* IGE synthesis
  - f* histamine synthesis
  - f* eicosanoid synthesis

### Corticosteroids

#### ◆ Therapeutic effects for asthma

- f* potentiate beta-agonists
- f* reduce edema
- f* prevent inflammation and resultant irreversible airway remodeling

### Corticosteroids

#### ◆ Effects for COPD

- f* fewer exacerbations
- f* early use improves lung function and quality of life
- f* withdrawal leads to lung function deterioration
- f* continued smoking may impair therapy

### Corticosteroids

#### ◆ Adverse systemic effects- reduced by aerosol route (short list)

- f* Hypokalemic alkalemia
- f* Diabetes mellitus
- f* Cushingoid fat distribution
  - f* moon face
  - f* buffalo hump

### Corticosteroids

#### ◆ Adverse systemic effects- reduced by aerosol route (short list)

- f* Hypokalemic alkalemia
- f* Diabetes mellitus
- f* Cushingoid fat distribution
- f* Amenorrhea
- f* Growth failure
- f* Osteoporosis
- f* Hirsutism (hairiness)

**Corticosteroids****^ Adverse effects for aerosol route**

- ◆ oral thrush
  - f* reduced by spacer
  - f* reduced by mouth rinsing
- ◆ decreased bone density (dose related)
- ◆ increased risk of fractures (boys)
- ◆ skin bruising

**Corticosteroids**

- ◆ Exhaled nitric oxide ( $F_{E}NO$ ) measurement
  - f* marker for airway inflammation
  - f* used to adjust dosage of corticosteroids
  - f* currently considered not medically necessary, so no payment

Link to article on  $F_{E}NO$  and asthma  
<http://content.nejm.org/cgi/reprint/352/21/2163.pdf>

**Corticosteroids**

- ◆ Agents
  - f* prednisone- oral, systemic- indicated for acute, severe asthma
  - f* dexamethasone (Decadron)
  - f* methylprednisolone (Solu Medrol)
  - f* hydrocortisone

**Corticosteroids**

- ◆ Agents
  - f* beclomethasone (Vanceril, Beclovent)
  - f* flunisolide (Aerobid)
  - f* fluticasone (Flovent)
  - f* triamcinolone (Azmacort)
  - f* budesonide (Pulmicort)

**Corticosteroids**

- ◆ Agents
  - f* ciclesonide (Alvesco)
  - f* approved by FDA January, 2008
  - f* once daily MDI
  - f* additional research needed comparing effectiveness with other agents

**Corticosteroids**

- ◆ Combination agents
  - f* fluticasone and salmeterol (Advair)
  - f* formoterol and budesonide (Symbicort)
  - f* no differences in effectiveness or tolerability for asthmatic patients\*

\*Busse WW. Comparison of adjustable and fixed dose budesonide/formoterol pressurized metered-dose inhaler and fixed dose fluticasone propionate/salmeterol dry powder inhaler in asthma patients. J Allergy Clin Immunol 2008;121:1407-1414.

**Leukotriene Modifiers**◆ **Actions**

- f* inhibit leukotriene (formerly SRS-a) production OR
- f* prevent binding of leukotrienes to receptor sites

**Leukotriene Modifiers**◆ **Effects**

- f* prevent inflammation & airway remodeling
- f* permit elimination or reduction in systemic steroids
- f* decreases exacerbations when used with inhaled steroids

**Leukotriene Modifiers**◆ **Agents- all administered orally**

- f* montelukast (Singulair)
- f* zafirlukast (Accolate)
- f* 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 (NAC):**
  - f* may improve pulmonary function
  - f* may reduce risk of hospitalization
  - f* 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 n-acetylcysteine for mucokinesis
- ◆ acetylcysteine aerosol may damage lung epithelia
- ◆ for patients with chronic bronchitis or COPD, oral mucolytics reduce:
  - f* exacerbations
  - f* days of illness
  - f* days of antibiotic use

**Oral Mucolytic Therapy**

- ◆ there is no evidence to support nebulized NaHCO<sub>3</sub> for mucokinesis
- ◆ NaHCO<sub>3</sub> aerosol irritates bronchial epithelia

Rubin BK. Mucolytics, expectorants and mucokinetic preparations. Respir Care 2007;52(7):859-865.

**Miscellaneous Agents****Magnesium Sulfate (MgSO<sub>4</sub>)**

- ◆ Actions:
  - f* inhibits acetylcholine release
  - f* inhibits histamine release
- ◆ Effects (IV MgSO<sub>4</sub>):
  - f* reduces the rate of hospital admissions
  - f* improves pulmonary function in patients with severe acute asthma

<http://pedscm.wustl.edu/All-Net/english/pulmpage/respfail/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**

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

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

**Lidocaine**◆ **Effects**

- f* reduces steroid requirement
- f* potentiates beta2 agonists
- f* 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**

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