Learning Objective:
◆ Explain 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

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

Short-acting beta-agonists
- Indications
  - asthma- as a rescue medication
  - COPD - reduces hyperinflation
  - cystic fibrosis- regardless of PFT responsiveness
  - pulmonary edema??- may reduce edema by clearing lung water
  - ARDS/ALI??- no benefits
Short-acting beta-agonists

**Indications**
- severe hyperkalemia - moves K+ into cells (dosage = 10 mg)
- inhalational injury; e.g., smoke inhalation
- anaphylaxis

FYI - Link to abstract on albuterol and hyperkalemia (free registration required)

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

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

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

**Agents**
- terbutaline
- albuterol (racemic)
- levalbuterol (Xopenex) - R isomer of albuterol

Bad Guy
Short-acting beta-agonists
◆ levalbuterol
  ➤ R isomer is therapeutically active
  ➤ S isomer likely to produce adverse effects
  ==> levalbuterol is more potent as it has reduced adverse effects, such as tolerance
  ➤ levalbuterol is more expensive
  ➤ cost-effective if ordered appropriately

Short-acting beta-agonists
◆ levalbuterol
  ➤ indications
  ➤ replace albuterol in event of adverse effects
  ➤ emergency care for asthma

Short-acting beta-agonists
◆ 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
◆ 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

Long-acting beta-agonists
◆ Controversy: may increase risk of death from asthma
  ➤ desensitization of beta2 receptors
  ➤ decreased effective numbers of beta2 receptors
  ➤ bronchiolar hyperreactivity

Long-acting beta-agonists
◆ Agents
  ➤ Salmeterol (Serevent)
  ➤ effective for asthma, COPD
  ➤ Formoterol (Foradil)
  ➤ shorter onset than salmeterol
  ➤ more cost-effective
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

- **Agents**
  - Indacaterol (Arcapta Neohaler) - 24 H duration
  - FDA approval July 2011
  - Better outcomes than tiotropium for COPD?
  - Agent on the horizon
  - Carmoterol- 30 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

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

Activation of M3 receptors

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

Anticholinergics

- **Adverse effects**
  - cardiovascular events - greater than six months on drug
    - myocardial infarction
    - stroke
    - cardiovascular death

Anticholinergics
◆ Indications
  ► COPD - maintenance and exacerbations
  ► asthma
  ► exacerbations
  ► requires multiple doses

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

Anticholinergics
◆ tiotropium bromide (Spiriva)
  ► 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, Duvoent

Bronchodilators and Mechanical Ventilation
◆ Administration to patients without obstructive disease:
  ► longer duration of ventilation (+5D)
  ► no difference in mortality, pneumonia
  ► greater cost ($450/patient)


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 (FENO) measurement

- marker for airway inflammation
- used to adjust dosage of corticosteroids
- currently considered not medically necessary, so no payment

FYI - Link to article on FENO and asthma
http://content.nejm.org/cgi/reprint/352/21/2163.pdf

Agents

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

- beclomethasone (Vanceril, Beclovent)
- flunisolide (Aerobid)
- fluticasone (Flovent)
- triamcinolone (Azmacort)
- budesonide (Pulmicort)
- mometasone (Asmanex)

Combination agents

- fluticasone and salmeterol (Advair)
- formoterol and budesonide (Symbicort)
- formoterol and mometasone (Dulera)
- 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

Leukotriene Modifiers
◆ Effects
  ► prevent inflammation & airway remodeling
  ► permit elimination or reduction in systemic steroids
  ► decreases exacerbations when used with inhaled steroids

Leukotriene Modifiers
◆ Agents- all administered orally
  ► montelukast (Singulair)
  ► zafirlukast (Accolate)
  ► zileuton (Zyflo)- may cause liver failure

Mucokinetist 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 n-acetylcysteine for mucokinesis
◆ acetylcysteine aerosol may damage lung epithelia
◆ for patients with chronic bronchitis or COPD, oral mucolytics reduce:
  ► exacerbations
  ► days of illness
  ► days of antibiotic use

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

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

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

FYI - click to see article on MgSO4 and asthma
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

FYI - click to see article on nebulized lidocaine and asthma
http://download.journals.elsevierhealth.com/pdfs/journals/0091-6749/PIIS0091674904010711.pdf

Lidocaine
◆ 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

FYI - Click to download article on furosemide for dyspnea
FYI - click for website about history of inhalation devices, with pictures
http://inhalatorium.com/page2.html

Review & Summary
◆ Short-acting beta agonists
  ◆ actions - stimulate 3,5 cAMP
  ◆ therapeutic effects
  ◆ adverse effects
  ◆ indications
  ◆ specific agents

Review & Summary
◆ Long-acting beta agonists
  ◆ indications
  ◆ controversy - sudden death in asthma
  ◆ specific agents

Review & Summary
◆ Anticholinergics
  ◆ action - inhibit acetylcholine
  ◆ effects - dilate larger airways
  ◆ adverse effects
  ◆ indications
  ◆ agents
Review & Summary

- Bronchodilators and ventilation
  - use in patients without obstruction - costly
  - administration by nebulizer - should avoid

- Corticosteroids
  - actions
  - effects - potentiate beta agonists and reduce inflammation
  - adverse effects - many systemic effects
  - indications - asthma, COPD
  - specific agents

- Leukotriene modifiers
  - actions
  - effects - prevent inflammation
  - indication - asthma
  - agents - oral administration

- Mucokinetic agents
  - Pulmozyme for CF is only aerosolized mucolytic with any evidence of effectiveness
  - Oral n-acetylcysteine improves COPD

- Magnesium sulfate
  - indication - status asthmaticus
  - administered by aerosol or IV

- Lidocaine
  - antitussive
  - administer by aerosol or IV

- Furosemide (Lasix)
  - reduces dyspnea
  - opioids do not work

References

- Ghee-Chee P. Inhaled corticosteroids in obstructive airway disease. Respir Care 2007;52(7):852-858.
- Rubin BK. Mucolytics, expectorants and mucokinetic preparations. Respir Care 2007;52(7):859-865.
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Duarte AG. Inhaled bronchodilator administration during mechanical ventilation. Respir Care 2004;49(6):6323-634.

