

**Current Issues In  
Airway Pharmacology  
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**Beta-agonists**

- ▲ **Short-acting**
  - ▶ racemic albuterol
  - ▶ levalbuterol (Xopenex)
- ▲ **Long-acting**
  - ▶ salmeterol (Serevent)
  - ▶ formoterol (Foradil)
  - ▶ arformoterol (Brovana)

**Learning Objectives:**

- ▲ Explain the actions, effects, indications and contraindications for the following types of respiratory medications:
  - ▶ bronchodilators
  - ▶ corticosteroids
  - ▶ anti-inflammatory agents
  - ▶ mucokinetic agents
  - ▶ selected miscellaneous agents
- ▲ Given the necessary clinical information, recommend appropriate respiratory medications and dosages.

**Beta-agonists**

- ◆ **Ultra long acting**
  - ▶ indacaterol (Arcapta Neohaler)
  - ▶ olodaterol (Stiverdi Respimat)
  - ▶ vilanterol

**Bronchodilating Agents**

**Adrenergic autonomic control**

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

## Beta-agonist bronchodilators

▲ Action- stimulate intracellular adenylyl cyclase to increase levels of 3,5 cAMP

▲ Actions, vs. effects

- ▶ Actions - how the drug works
- ▶ Effects - what the drug does

## Short-acting beta-agonists

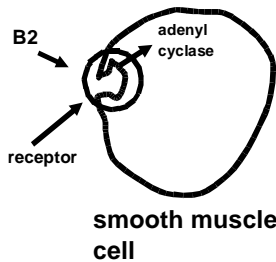
▲ Therapeutic effects:

- ▶ Bronchodilation
- ▶ Stabilize mast cells
- ▶ Increase mucous secretion
- ▶ Increase ciliary activity
- ▶ Inhibits bronchial edema
- ▶ Decrease airway hyper-responsiveness
  
- ▶ Relax uterine muscle - inhibits labor

## Activation of Beta2 receptors

▲ Beta2 adrenergic binds to receptor

▲ G protein in cell membrane activates adenylyl cyclase



## Short-acting beta-agonists

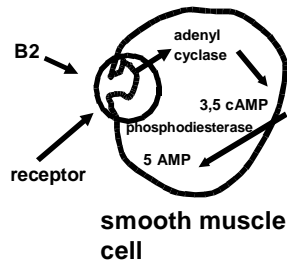
▲ Therapeutic effects:

- ▶ moderated by genetic differences in beta receptors (polymorphism)
- ▶ explains variability in response to beta agonists and beta blockers

## Activation of Beta2 receptors

▲ Adenylyl cyclase catalyzes formation of 3,5 cyclic AMP (cAMP) ==> relaxation

▲ cAMP inactivated by phosphodiesterase



## 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

- ▶ pre-exercise to prevent exercise-induced bronchospasm
- ▶ inhalational injury; e.g., smoke inhalation
- ▶ anaphylaxis
- ▶ severe hyperkalemia - moves K<sup>+</sup> into cells (dosage = 10 mg)

## Short-acting beta-agonists

### ^ Agents

- ▶ terbutaline - still in use??
- ▶ albuterol (racemic)
- ▶ levalbuterol (Xopenex)- R isomer of albuterol

### ^ Dosages

- ▶ albuterol - 2.5 mg or 2 pf Q 4-6 H
- ▶ levalbuterol - 0.63 or 1.25 mg TID

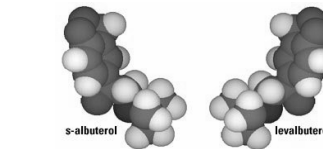
## Short-acting beta-agonists

### ^ Adverse effects:

- ▶ Skeletal muscle tremor- most common
- ▶ Tachyphylaxis (tolerance)
- ▶ Tachycardia, palpitation- B1 effects
- ▶ Hypokalemia - source of tachycardia??
- ▶ Hyperglycemia- precaution for diabetics

## Short-acting beta-agonists

### ◆ levalbuterol



Bad  
Guy

## Short-acting beta-agonists

### ^ Adverse effects:

- ▶ Sudden death - all B2 agonists have potential
  - ◆ Overusage ==> tachyphylaxis
  - ◆ Propellant??
  - ◆ Hypoxemia, due to dilation of pulmonary vasculature increasing perfusion of non-ventilated alveoli
  - ◆ Genetic factors?

## Short-acting beta-agonists

### ^ levalbuterol

- ▶ R isomer is therapeutically active ==> levalbuterol is more potent
- ▶ S isomer likely to produce adverse effects ==> levalbuterol has reduced adverse effects, such as tolerance
- ▶ levalbuterol is more expensive
- ▶ may be cost-effective if ordered appropriately

### Short-acting beta-agonists

- ▲ levalbuterol
  - ▶ indications
    - ◆ replace albuterol in event of adverse effects
    - ◆ emergency care for asthma
    - ◆ may be a cost-effective substitute

### Long-acting beta-agonists

- ▲ Controversy- may increase risk of death from asthma
  - ▶ desensitization of beta2 receptors
  - ▶ decreased effective numbers of beta2 receptors
  - ▶ bronchiolar hyperreactivity

### Short-acting beta-agonists

- ▲ cost per dose (SVN)
  - ▶ racemic albuterol (generic)- .24/unit
  - ▶ levalbuterol- .80/unit
- ▲ cost per dose (MDI)
  - ▶ racemic albuterol (generic)- .09/puff
  - ▶ levalbuterol- .29/puff

### Long-acting beta-agonists

- ▲ Agents
  - ▶ salmeterol (Serevent)
  - ▶ formoterol (Foradil)
    - ▶ shorter onset than salmeterol
    - ▶ more cost-effective
  - ▶ arformoterol (Brovana)
- ▲ Dosages
  - ▶ salmeterol - 50 mcg Q12 H
  - ▶ formoterol - 12 mcg Q12 H
  - ▶ arformoterol- 15 mcg Q12H

### 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
  - ▶ prevention of EIB

### Long-acting beta-agonists

- ▲ Agents
  - ▶ Arfomoterol (Brovana)
    - ▶ approved for COPD
    - ▶ R isomer (like Xopenex)
    - ▶ shorter onset
    - ▶ nebulizer solution
    - ▶ may not mix with other medications
  - ▶ Dosage - 15 mcg BID

### Long-acting beta-agonists

- ▲ Agent
  - ▶ Indacaterol (Arcapta Neohaler) - 24 H duration
  - ▶ May replace BID tiotropium for stable COPD
  - ▶ Dosage - 75 mcg daily
- ▲ Agent on the horizon
  - ▶ ULABA under development
  - ▶ Carmoterol- 30 H duration

### ▶ Alpha agonists

- ▲ levo-epineprine (Levophed) - vasopressor for shock
- ▲ racemic epinephrine (racinephrine)
  - ▶ weak alpha, beta1, beta2
  - ▶ current indications???

### Long-acting beta-agonists

- ▲ Agent
  - ▶ vilanterol- 24H duration only in combination inhaled DPI
    - ▶ Breo- vilanterol & fluticasone
    - ▶ Trelegy Ellipta- fluticasone, umeclidinium, and vilanterol
    - ▶ Anoro Ellipta- umeclidinium, vilanterol

### Anticholinergics

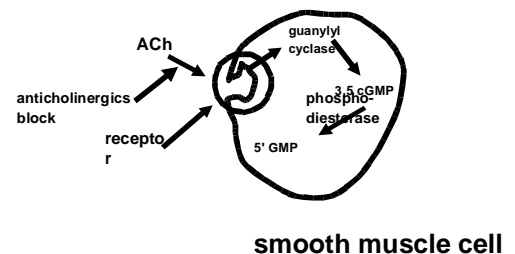
- ▲ Actions
  - ▶ Block acetylcholine receptor sites
  - ▶ Inhibit guanylate cyclase, so reduce intracellular 3,5 cyclic GMP
- ▲ Therapeutic effect - relax bronchial muscle in large airways- effective for COPD
- ▲ Prototype - atropine

### Alpha agonists

- ▲ d-epinephrine - alpha, beta1 and beta2 agonist
  - ▶ severe asthma
  - ▶ anaphylaxis
  - ▶ shock
  - ▶ croup, bronchiolitis

### Activation of M3 receptors

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



### Anticholinergics

- ^ Indications - ipratropium
  - COPD- maintenance and exacerbations
  - asthma
    - exacerbations
    - requires multiple doses
    - discontinue when under control

### Anticholinergics

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

### Anticholinergics

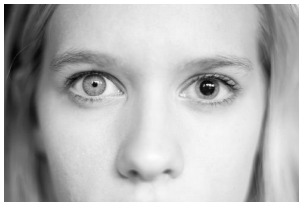
- ^ Dosages - ipratropium
  - adults
    - MDI 2 inhalations (36 mcg) QID
    - CFC free inhalation aerosol: 2 inhalations (34 mcg) QID
    - Nebulizer solution: 500 mcg QID
  - neonates - nebulized solution: 25 mcg/kg TID.
  - infants and children - nebulized solution: 125 to 250 mcg TID

### Anticholinergics

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

### Anticholinergics

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



### Anticholinergics

- ^ tiotropium bromide (Spiriva)
  - dry powder inhaler
  - 18 mcg per dose
  - duration 24-36 H
  - effective for COPD
    - increased FEV1
    - slower decline in FEV1
    - increased exercise capacity
    - reduced exacerbations

### Anticholinergics

- ▲ Umeclidinium (Incruse Ellipta)
  - ▶ dry powder inhaler
  - ▶ 18 mcg per dose
  - ▶ duration 24-36 H
  - ▶ effective for COPD

### Bronchodilators

- ▲ PDE4 inhibitors
  - ◆ roflumilast (Daliresp)
  - ◆ apremilast (Otesla)
    - ▶ included in Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for severe COPD
    - ▶ daily tablet
    - ▶ bronchodilator
    - ▶ decreases inflammation
    - ▶ decreases exacerbations

### Combination bronchodilators

- ▲ Combination of albuterol and ipratropium indicated for:
  - ▶ COPD
  - ▶ ER management of asthma
- ▲ Available as Combivent, Duoneb, Respimat
- ▲ Dosage - 2 puffs, QID up to 12 times daily. Each puff releases
  - ▶ 21 mcg ipratropium
  - ▶ 120 mcg albuterol

### Bronchodilators and CMV

- ▲ Administration to patients without obstructive disease:
  - ▶ longer duration of ventilation (+5D)
  - ▶ no difference in mortality, pneumonia
  - ▶ greater cost (\$450./patient)

### Bronchodilators

- ▲ Nonspecific phosphodiesterase (PDE) inhibitors; e.g., theophylline
  - ▶ high risk/benefit ratio - adverse effects
  - ▶ low cost
  - ▶ reserved for patients who cannot use aerosols

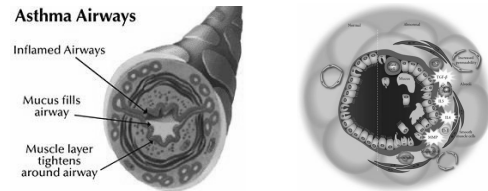
### Bronchodilators and Mechanical Ventilation

- ▲ Administration via nebulizer, vs. MDI
- ▲ Nebulizer disadvantages
  - ▶ bacterial contamination
  - ▶ greater cost (\$300,000/year)
  - ▶ altered ventilatory parameters
  - ▶ less efficiency

# Anti-inflammatory Agents

## Corticosteroids

- ▲ Therapeutic effects for asthma
  - ▶ potentiate beta-agonists
  - ▶ reduce edema
  - ▶ prevent inflammation and resultant irreversible airway remodeling

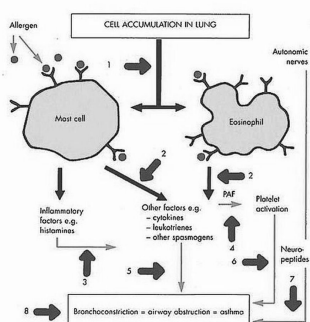


## Corticosteroids

- ▲ Actions
  - ▶ Increase number & responsiveness of beta- adrenergic receptors
  - ▶ Stabilize mast cell lysosomes
  - ▶ Decrease:
    - IGE synthesis
    - histamine synthesis
    - eicosanoid synthesis

## 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 (short list)
  - ▶ Hypokalemic alkalemia
  - ▶ Diabetes mellitus
  - ▶ Cushingoid fat distribution; e.g., moon face, buffalo hump
  - ▶ Amenorrhea
  - ▶ Growth failure
  - ▶ Osteoporosis
  - ▶ Hirsutism (hairiness)

### Inhaled corticosteroids (ICS)

- ▲ **Adverse effects for aerosol route**
  - ▶ oral thrush - reduced by spacer and mouth rinsing
  - ▶ decreased bone density (dose related)
  - ▶ increased risk of fractures (boys)
  - ▶ skin bruising
  - ▶ risk for serious pneumonia in COPD
    - ▶ greatest with fluticasone
    - ▶ least with budesonide

### Inhaled corticosteroids (ICS)

- ▲ **Agents**
  - ▶ beclomethasone (Beclovent) - 40 or 80 mcg BID
  - ▶ fluticasone (Flovent) - 44, 110, or 220 mcg BID
  - ▶ triamcinolone (Azmacort) 150 or 300 mcg BID
  - ▶ budesonide (Pulmicort) 200 or 400 mcg BID
  - ▶ mometasone (Asmanex) 220 mcg daily or BID
  - ▶ ciclesonide (Alvesco) - 80 or 160 mcg BID

### Corticosteroids

- ▲ **Exhaled nitric oxide (F<sub>E</sub>NO) measurement**
  - ▶ marker for airway inflammation
  - ▶ used to adjust dosage of corticosteroids
  - ▶ covered by SOME insurance providers for diagnosis of eosinophilic asthma and guidance of steroid therapy

### Corticosteroids

- ▲ **Combination agents**
  - ▶ fluticasone (100, 250 or 500 mcg) & salmeterol (50 mcg) (Advair) -
  - ▶ formoterol 4.5 mcg and budesonide (160 mcg) BID (Symbicort)
  - ▶ formoterol (5 mcg) and mometasone (100 or 200 mcg BID) (Dulera)
  - ▶ no differences in effectiveness or tolerability for asthmatic patients

### Corticosteroids

- ▲ **Agents - oral or parenteral routes**
  - ▶ prednisone- oral, systemic- indicated for acute, severe asthma
  - ▶ dexamethasone (Decadron)
  - ▶ methylprednisolone (Solu Medrol)
  - ▶ hydrocortisone

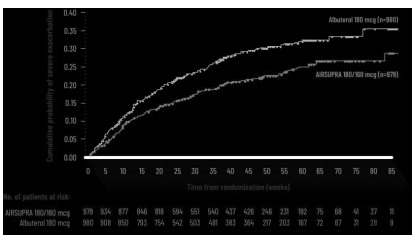
### Corticosteroids

- ▲ **Combination agents**
  - ◆ **albuterol and budesonide (airsupra)**
    - ▶ Recent FDA approval for exacerbations
    - ▶ Compared to albuterol, 28% decrease in episodes becoming hazardous
    - ▶ Patients greater than 4YO, 90/80 mcg 2 MDI inhalations daily PRN
    - ▶ No more than 12 inhalations in a 24-hour period

## Corticosteroids

### ▲ Combination agents

- ◆ albuterol and budesonide (airsupra)
- ◆ hazardous episodes, upper limb albuterol



## Leukotriene Modifiers

### ▲ Therapeutic effects

- ▶ prevent inflammation & airway remodeling
- ▶ permit elimination or reduction in systemic steroids
- ▶ decrease exacerbations when used with inhaled steroids

### ▲ Adverse effects

- ▲ neuropsychiatric events - agitation, etc.
- ▲ flu-like symptoms

## Leukotriene modifiers

### ▲ Actions

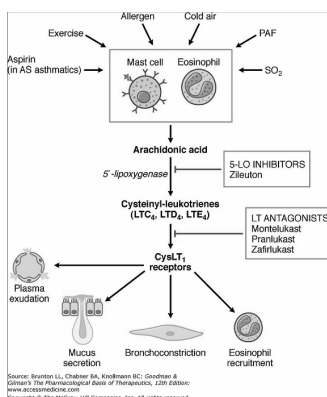
- ▶ inhibit leukotriene (formerly SRS-a) production OR
- ▶ prevent binding of leukotrienes to receptor sites

## Leukotriene Modifiers

### ▲ Agents- all administered orally

- ▶ montelukast (Singulair)
- ▶ zafirlukast (Accolate)
- ▶ zileuton (Zyflo)- may cause liver failure

## Leukotriene modifiers



## Omalizumab (Xolair)

### ▲ Action - binds to circulating IgE, inhibiting its interaction with mast cell receptors and decreasing the number of receptors on basophils

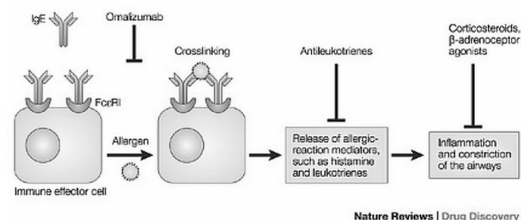
### ▲ Effects

- ▶ decreases allergic reactions
- ▶ improves pulmonary function (FEV1)
- ▶ increases dosage of allergen required to produce bronchoconstriction
- ▶ reduces need for steroids
- ▶ improves quality of life

### Omalizumab (Xolair)

- ▲ Adverse effects
  - ▶ anaphylaxis
  - ▶ local injection site reactions
  - ▶ occasional urticaria-like eruptions
  - ▶ viral infections
- ▲ Administration - subcutaneous injection  
0.5 mg/kg BW Q 2 or 4 wks.
- ▲ Serum level monitoring required
- ▲ Very expensive!!!

### Actions of drugs for asthma



### Benralizumab (Fasenra)

- ▲ Inhibits or eliminates eosinophils
- ▲ Indication - eosinophilic asthma (50% of asthmatics)
- ▲ 30mg subcutaneous injection
- ▲ Cost - \$5197/ml
- ▲ Free, if payment is denied by insurer

## Mucokinetic Agents

### Dupilumab (Dupixent)

- ▲ Interleukin 4 and 13 inhibitor
- ▲ Moderate to severe asthma
- ▲ Subcutaneous injection

### dornase alfa (Pulmozyme)

- ▲ Action - enzymatically breaks down DNA in CF mucus
- ▲ Effects:
  - ▶ decreases mucus viscosity
  - ▶ slows rate of lung deterioration
  - ▶ improves survival

### dornase alfa (Pulmozyme)

- ^ Indication - cystic fibrosis
- ^ Adverse effects:
  - hypersensitivity reactions
  - chest pain
  - pharyngitis
  - rash
  - voice alteration

### Hypertonic saline

- ^ Indications:
  - cystic fibrosis - effective as Pulmozyme for some patients
  - bronchiectasis
  - viral bronchiolitis
  - sputum induction
- ^ Administration - nebulize 10 mL 3% NaCl

### dornase alfa (Pulmozyme)

- ^ Administration - 2.5 mg once or twice daily
- ^ Very expensive - weak evidence for cost-effectiveness

### n-acetylcysteine (Mucomyst, NAC)

- ^ Action - a direct reactive oxygen species scavenger (antioxidant)
- ^ Effects:
  - may influence mucin expression by acting on oxidative stress and inflammation
  - mucolysis?
  - may improve pulmonary function
  - may reduce risk of hospitalization

### Hypertonic saline

- ^ Action - increased osmolarity increases secretion of water to airway lumen.
- ^ Therapeutic effects:
  - increased mucociliary clearance
  - anti-infective?
  - anti-inflammatory?
- ^ Adverse effect - rare bronchospasm

### n-acetylcysteine (Mucomyst)

- ^ Adverse effects
  - nausea, vomiting
  - constipation, diarrhea
  - rash
  - mucosal irritation (inhaled)
  - bronchospasm (inhaled)

### n-acetylcysteine (Mucomyst)

#### ^ Indications:

- ▶ acetaminophen overdose
- ▶ Stable COPD
- ▶ alcoholic liver pathology
- ▶ oxidative stress prevention

#### ^ Administration

- ▶ weak evidence to support nebulized NAC
- ▶ intended for oral administration

### Ethanol (Jim Beam)

#### ^ Action - alter surface tension of bubbles

#### ^ Alleged effect - reverse foaming in pulmonary edema fluid

#### ^ Adverse effects

- ▶ irritates mucosa severely
- ▶ alters protein in edema fluid, creating particles to obstruct airways

#### ^ Bottom line - Don't do it!!!

### NaHCO<sub>3</sub> (Arm & Hammer™)

#### ^ Action - alkalinizes secretions

#### ^ Therapeutic effects - decreases mucus viscosity?

#### ^ Indications

- ▶ no evidence for effectiveness in mucus mobilization
- ▶ metabolic acidemia (IV)
- ▶ stomach acidity
- ▶ baking

### Miscellaneous Agents

### NaHCO<sub>3</sub> (Arm & Hammer™)

#### ^ Adverse effects

- ▶ irritates mucosa
- ▶ increases gastrointestinal bacteria

### Magnesium Sulfate (MgSO<sub>4</sub>)

#### ^ Actions:

- ▶ inhibits acetylcholine release
- ▶ inhibits histamine release

#### ^ Effects (IV MgSO<sub>4</sub>):

- ▶ reduces the rate of hospital admissions
- ▶ improves pulmonary function in patients with severe acute asthma

### Magnesium Sulfate

- ▲ Not recommended for routine use.
- ▲ Dose
  - ▶ 25 mg/kg, up to 2.0 g by IV
  - ▶ 2.5 mg in 3.0 mL NaCl by nebulizer??
  - ▶ 151 mg/dose
- ▲ Weak evidence for aerosol administration

### Aerosols for Dyspnea

- ▲ Opioids (morphine)
  - ▶ Action - combine with CNS opioid receptors to suppress response to CO<sub>2</sub> and hypoxemia
  - ▶ Effects - alter perception of dyspnea in selected patients with COPD and terminal carcinoma
  - ▶ Severe dyspnea; e.g., hospice care
  - ▶ Administer orally- aerosol route requires more study

### Lidocaine

- ▲ Actions
  - ▶ inhibits nociceptor (cough, pain) response- component of acute asthma
  - ▶ inhibits eosinophil activation
- ▲ Therapeutic effects
  - ▶ decreased airway hyper- responsiveness
  - ▶ increased histamine threshold
  - ▶ antitussive

### Aerosols for Dyspnea

- ▲ Furosemide (Lasix)
  - ▶ Action - suppress C fibers in bronchial epithelium (theoretical)
  - ▶ Therapeutic effects:
    - ▶ reduces dyspnea in COPD and lung cancer
    - ▶ suppresses cough
    - ▶ suppresses bronchospasm
  - ▶ Dosage 20 mg Q4H
  - ▶ Weak evidence in favor

### Lidocaine

- ▲ Adverse effects
  - ▶ upper airway numbness - aspiration
  - ▶ lidocaine toxicity
  - ▶ methemoglobinemia (rare)
- ▲ Administration- 2.5 mL 2-4% by nebulizer

**END**

### Review & Summary

- ▲ **Short-acting beta agonists**
  - ▶ actions- stimulate 3,5 cAMP
  - ▶ therapeutic effects
  - ▶ adverse effects
  - ▶ indications
  - ▶ specific agents

### Review & Summary

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

### Review & Summary

- ▲ **Long-acting beta agonists**
  - ▶ indications
  - ▶ controversy- sudden death in asthma
  - ▶ specific agents

### Review & Summary

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

### Review & Summary

- ▲ **Anticholinergics**
  - ▶ action- inhibit acetylcholine
  - ▶ effects- dilate larger airways
  - ▶ adverse effects
  - ▶ indications
  - ▶ agents
- ▲ **Phosphodiesterase inhibitors**

### Review & Summary

- ▲ **Leukotriene modifiers**
  - ▶ actions
  - ▶ effects- prevent inflammation
  - ▶ indication- asthma
  - ▶ agents- oral administration
- ▲ **Omalizumab**
  - ▶ severe, allergic asthma
  - ▶ subcutaneous administration

## Review & Summary

### ▲ Mucokinetic agents

- ▶ Pulmozyme
- ▶ Hypertonic saline
- ▶ n-acetylcysteine - oral administration
- ▶ NaHCO<sub>3</sub> - bogus
- ▶ Ethanol

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## Review & Summary

- ▲ Magnesium sulfate - asthma
- ▲ Lidocaine - antitussive
- ▲ Opioids - dyspnea
- ▲ Furosemide - dyspnea

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