Adrenergic Bronchodilators (Sympathomimetics)
Part 1

History & Development
• Adrenergic bronchodilators are all analogues of epinephrine
  – use of epinephrine by aerosol dates to 1910
  – 1926 ephedrine introduced
  – 1940 isoproterenol introduced
  – 1951 isoetharine introduced
  – 1973 metaproterenol released in U.S.
  – 1980’s terbutaline, albuterol, bitolterol & pirbuterol released
  – 1994 salmeterol introduced
  – 1999 levalbuterol introduced

Progression
• short-acting, non-specific agents (epinephrine, isoproterenol)
• intermediate-acting β2 specific (albuterol)
• long-acting (salmeterol)
• pure isomers (levalbuterol)
Clinical Indications

- General indication is relaxation of bronchial smooth muscle in the presence of reversible airflow obstruction associated with acute and chronic asthma, bronchitis, emphysema and bronchiectasis
- Usually categorized as short-acting and long-acting
- Short-acting agents
  - indicated for relief of acute episodes - termed "rescue drugs" in the National Asthma Education and Prevention Program Expert Panel II (NAEPP EPR II) guidelines
    - ultra-short-acting (<3 hours duration): epinephrine, isoproterenol, isoetharine
    - short-acting (4-6 hours duration): metaproterenol, terbutaline, albuterol, bitolterol, pirbuterol, levalbuterol

Clinical Indications

- Long-acting agents
  - are indicated primarily for maintenance bronchodilation, control of bronchospasm and control of nocturnal symptoms; usually combined with an anti-inflammatory drug
  - long-acting (12 hours duration): salmeterol, formoterol

Structure & Action

- Adrenergic bronchodilators can exist in 2 spatial arrangements, producing isomers, as shown here in the structure of epinephrine
Structure & Action

- The R-isomer (rectus or right), or levoisomer, is active on airway β receptors producing bronchodilation; the S-isomer (sinister or left), or dextroisomer, is not active on adrenergic receptors.
- Natural epinephrine (adrenaline) from the adrenal glands occurs only in the R-isomer.
- Epinephrine, albuterol and salmeterol have been synthetically produced as racemic mixtures, 50:50 mixtures of the R- and S-isomers.
- Levalbuterol, released in 1999, is the first synthetic inhaled solution available as the single R-isomer of racemic albuterol.

Classification of Sympathomimetics

- Catecholamine agents:
  - A group of similar compounds having a sympathomimetic action, mimicking the action of natural epinephrine.
  - The basic catecholamine chemical structure is that of a benzene ring with hydroxyl groups at the third and fourth carbon sites and an amine side chain attached at the first carbon position.

- Catecholamine agents:
  - All sympathomimetic bronchodilators are either catecholamines or derivatives of catecholamines.
  - Three drugs are in the catecholamine class:
    - Epinephrine
    - Isoproterenol
    - Isetharine
Classification of Sympathomimetics

- Catecholamine agents
  - epinephrine (Adrenaline, Primatene Mist) is a potent catecholamine that stimulates both \( \alpha \) and \( \beta \) receptors
    - does not have \( \beta_2 \) selectivity and the incidence of side effects is high, including tachycardia, increased BP, tremor, headache, and insomnia
    - has a rapid onset but a short duration of action
    - used by inhalation and subcutaneously to treat asthma and is also used IV as a cardiac stimulant and IM to control systemic hypersensitivity reactions
    - either a 1:100 solution of natural epinephrine for injection or a 2.25% solution of racemic epinephrine (S\(_2\)) is used for inhalation

Classification of Sympathomimetics

- Catecholamine agents
  - isoproterenol (Isuprel, Isuprel Mistometer) is a potent catecholamine bronchodilator that stimulates both \( \beta_1 \) and \( \beta_2 \) receptors
    - used widely at one time for nebulization
    - main disadvantages were its short duration and strong cardiac stimulation
    - it is metabolized to the weak \( \beta \) blocker, 3-methoxyisoproterenol, which may cause resistance to its bronchodilating effects

Classification of Sympathomimetics

- Catecholamine agents
  - isoetharine (Isoetharine HCl) was one of the first \( \beta_2 \) specific adrenergic bronchodilators in the U.S.
    - it is now considered obsolete as an inhaled bronchodilator
Classification of Sympathomimetics

- Keyhole theory of $\beta_2$ specificity
  - the larger the amine side chain attachment to the catechol base, the greater the $\beta_2$ specificity
  - if the catecholamine structure is seen as a key like shape, the larger the "key" (side chain) the more $\beta_2$ specific is the drug

<table>
<thead>
<tr>
<th>Increasing $\beta_2$ specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>epinephrine</td>
</tr>
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</table>

Classification of Sympathomimetics

- Metabolism of catecholamine agents
  - catecholamines are rapidly inactivated by the cytoplasmic enzyme catechol-O-methyltransferase (COMT) found primarily in the liver and kidneys but throughout the body as well
  - COMT transfers a methyl group to the carbon-3 position on the catechol nucleus, producing metanephrine

Classification of Sympathomimetics

- Metabolism of catecholamine agents
  - this new compound, metanephrine, is inactive on the adrenergic receptors, however, it may compete with $\beta_2$ adrenergic agents, producing drug tolerance or tachyphylaxis
  - catecholamines are ineffective given orally because of another enzyme, sulfatase, found in the bowel and liver; therefore administration is limited to inhalation or injection routes
  - a third enzyme monoamine oxidase (MAO), found in the GI tract, is also capable of degrading catecholamines; it helps convert catecholamines to 3-methoxy-4-hydroxymandelic acid, which is excreted in urine
Classification of Sympathomimetics

- Metabolism of catecholamine agents
  - catecholamines are also readily inactivated to inert adrenochromes by heat, light and air and should be stored in light-resistant amber bottles

  ![Oxidation product of catecholamine](image)

  - as a result of this oxidation, residue left in the nebulizer or rain-out in tubing may appear pinkish and a patient’s sputum may even appear pinkish following aerosol treatment with catecholamines

Classification of Sympathomimetics

- Resorcinol agents
  - the next step in the evolution of sympathomimetics was a modification of the catechol nucleus in an attempt to improve the short duration of action of catecholamines
  - the hydroxyl group at the carbon-4 site was moved to the carbon-5 site, resulting in the new resorcinol agents, metaproterenol (Alupent) and terbutaline (Brethaire)

  ![Metaproterenol and Terbutaline](image)

  - since these agents are not inactivated by sulfatase or COMT, both can be taken orally and have a much longer duration of action, 4-6 hours, compared to the catecholamines — however, both are slower to reach peak effect (30-60 min.)
  - because of its side chain, terbutaline is more β₂ specific and causes fewer β₁ side effects
  - for these reasons, the resorcinol group is well-suited for maintenance therapy
Classification of Sympathomimetics

- Saligenin agents
  - Further modification of the catechol nucleus at the carbon-3 site resulted in the new saligenin agent albuterol, (Ventolin, Proventil, Proventil HFA) known as salbutamol in Europe.

Classification of Sympathomimetics

- Saligenin agents
  - albuterol
    - availability
      - oral – tablets, extended-release tablets, syrup
      - inhalation – nebulizer solution, MDI, DPI
    - β₂ preferential effect
    - may be taken orally
    - duration of action is up to 6 hours
    - peak effect is in 30-60 min.

Classification of Sympathomimetics

- Pirbuterol
  - available as pirbuterol acetate (Maxair)
  - structurally similar to albuterol except for a pyridine ring in place of the benzene ring
Classification of Sympathomimetics

- **Pirbuterol**
  - availability
    - inhalation - breath-actuated MDI
      - onset of action is 5-8 min.
      - peak effect is in 30 min.
      - duration of action is approximately 5 hours
    - oral
      - onset of action is 1 hour
      - peak effect is in 2 hours
      - duration of action is 5-6 hours
  - side effects are similar to other β₂ agonists

Classified of Sympathomimetics

- **Bitolterol**
  - bitolterol (Tornalate) consists of two toluate ester groups on the aromatic ring at the carbon-3 and carbon-4 sites

- **Bitolterol**
  - bitolterol must be converted in the body to its active catecholamine form, colterol
Classification of Sympathomimetics

- **Bitolterol**
  - because of this necessary conversion, bitolterol is referred to as a prodrug
  - bitolterol is protected from COMT by the two ester groups and the structure of the side chain prevents oxidation by MAO
  - colterol is a catecholamine and is subject to COMT, however, conversion to colterol is a gradual process resulting in a prolonged duration of action of up to 8 hours while onset of action is similar to metaproterenol
  - its bulky side chain gives colterol a preferential \( \beta_2 \) effect
  - bitolterol is available as an MDI and nebulizer solution, however, it has not been widely accepted for clinical use

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Classification of Sympathomimetics

- **Levalbuterol**
  - levalbuterol \((Xopenex)\) is the pure R-isomer of racemic albuterol
  - although the S-isomer is inactive on adrenergic receptors, it is not completely inactive and the S-isomer effects may antagonize the bronchodilating effects of the R-isomer

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Classification of Sympathomimetics

- **Levalbuterol**
  - available in a nebulizer solution in 3 strengths: a 0.31 mg unit dose, a 0.63 mg unit dose and a 1.25 mg unit dose
  - in one study, the 0.63 mg dose was shown to be comparable to the 2.5 mg racemic albuterol dose in onset and duration (keep in mind that the 2.5 mg racemic dose contains 1.25 mg R-isomer and 1.25 mg S-isomer) and the side effects of tremor and heart rate changes were less with this dose
  - the 1.25 mg dose showed a higher peak effect on FEV\(_1\) with an 8 hour duration compared to racemic albuterol, but the side effects were equivalent to the racemic dose
Classification of Sympathomimetics

- Long-acting β adrenergic agents
  - the development of bronchodilating agents has been moving away from non-specific, short-acting agents to those with more β₂ specificity and a longer duration of action
  - the need is for agents that can control nocturnal symptoms and that require fewer doses/day
  - three such agents are sustained-release albuterol (Proventil Repetabs, Volmax), salmeterol (Serevent) and formoterol (Foradil)

Classification of Sympathomimetics

- Long-acting β adrenergic agents
  - Sustained-release albuterol
    - available as 4 or 8 mg tablets with sustained activity up to 12 hours
    - Repetabs achieve this with a formulation that contains 2 mg of drug in the coating and 2 mg in the tablet core for release after several hours
    - Volmax uses an osmotic gradient to draw water into the tablet to dissolve the albuterol and release the drug through a pin hole in the tablet, resulting in a duration of action of 8-12 hours or the equivalent of taking 2 doses of racemic albuterol

Classification of Sympathomimetics

- Long-acting β adrenergic agents
  - salmeterol represents a new generation of long-acting bronchodilators
  - it is a modification of albuterol with a long lipophilic nonpolar N-substituted side chain
Classification of Sympathomimetics

- Long-acting β adrenergic agents
  - the increased duration of action of salmeterol is due to its increased lipophilicity conferred by the long side chain
  - the "tail" of the molecule anchors at an exosite in the cell membrane allowing for continuous activation of the β receptor
  - this action is achieved because the active head portion of the side chain continually attaches and detaches from the active receptor site providing ongoing stimulation of the β receptor and is the basis for the persistent duration of action
  - salmeterol has a slower onset of action and time to peak effect, but also a longer duration of action (12 hours) as compared to other adrenergic agents

Classification of Sympathomimetics

- Long-acting β adrenergic agents
  - formoterol is another long-acting β₂ selective agent
  - as with salmeterol, formoterol has a long side chain making it more lipophilic and therefore longer acting (through a similar mechanism as salmeterol) than earlier generation β adrenergic agents

Classification of Sympathomimetics

- Long-acting β adrenergic agents
  - formoterol is available as a racemic mixture of RR, SS-formoterol using the Aerolizer inhaler
  - it is recommended for maintenance treatment of asthma in children and adults over age 5 and for acute prevention of exercised-induced bronchospasm in children and adults 12 years and older
  - in one study, 24 µg formoterol produced the same increase in airway conductance at 1 minute as did 200 µg albuterol and twice the increase in airway conductance at 1 minute as did 50 µg salmeterol
Classification of Sympathomimetics

- Long-acting β adrenergic agents
  - the efficacy of formoterol in relaxing bronchial smooth muscle is higher than albuterol which is higher than salmeterol, however, salmeterol remains a better choice for patients with cardiovascular disease
  - a single isomer form (RR-formoterol) is currently under development by Sepracor (Xopenex, Allegra, Clarinex)

Classification of Sympathomimetics

- Anti-inflammatory actions
  - both short-acting and long-acting β agonists show anti-inflammatory actions in vitro
    - salmeterol and formoterol inhibit human mast cell activation and degranulation
  - neither drug is considered to have an effect on airway inflammation sufficient to replace corticosteroids

Classification of Sympathomimetics

- Clinical use of long-acting β agonists
  - long-acting β agonists are indicated for maintenance therapy of asthma which is not controlled by regular low-dose inhaled corticosteroids and for chronic obstructed lung disease needing daily inhaled bronchodilator therapy for reversible airway obstruction
  - national guidelines recommend introduction of salmeterol in Step 3 asthma (asthma not controlled by lower doses of anti-inflammatory medications)
  - use of long-acting β agonists may prevent the need to increase inhaled doses of corticosteroids
Classification of Sympathomimetics

- Clinical use of long-acting β agonists
  - points to consider
    - long-acting β agonists are not recommended for rescue bronchodilation because with their longer duration and increased lipophilic properties, accumulation and toxicity is a risk
    - a shorter-acting β agonist should be prescribed and available for asthmatics if additional bronchodilator therapy is needed between scheduled doses of their long-acting β agonist; patients must be well educated in the uses and differences between long-acting and short-acting β agonists

- Clinical use of long-acting β agonists
  - points to consider
    - although they may have anti-inflammatory effects, short-acting or long-acting β agonists are not substitutes for inhaled corticosteroids in asthma maintenance
    - with the difference in rate of onset it might be useful to classify β agonists as fast and slow as well as short- and long-acting, with salmeterol being a slow and long-acting bronchodilator and formoterol being a fast and long-acting bronchodilator
    - the addition of a long-acting β agonist to inhaled corticosteroids can lead to improved lung function and decreased symptoms
    - a combination of salmeterol and fluticasone (Advair Diskus) demonstrates superior asthma control and better lung function than either drug taken alone

- Classification of Sympathomimetics
  - because of their prolonged duration, long-acting β agonists taken twice daily have a greater area under the curve (AUC) when measuring changes in FEV$_1$ than do short-acting β agonists taken 4 times daily
Classification of Sympathomimetics

- Clinical use of long-acting β agonists
  - Unlike albuterol, which tends to return to baseline in 4-6 hours, salmeterol provides a more sustained level of bronchodilation, giving a higher baseline of lung function
  - The same effect has been found in comparing b.i.d. salmeterol with q.i.d. inhaled ipratropium bromide (Atrovent), a shorter acting anticholinergic bronchodilator

Dosing Schedules

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Dosage</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>Oral solution</td>
<td>0.125-0.25 mg/kg bid</td>
<td>3-5 min</td>
<td>5-10 min</td>
<td>3-4 hr</td>
</tr>
<tr>
<td></td>
<td>Inhalation solution</td>
<td>0.025 mg/mL</td>
<td>1 min</td>
<td>5 min</td>
<td>15 min</td>
</tr>
<tr>
<td></td>
<td>Nasal spray</td>
<td>0.05 mg/mL</td>
<td>5 min</td>
<td>15 min</td>
<td>1 hr</td>
</tr>
<tr>
<td>Ipratropium</td>
<td>Oral solution</td>
<td>0.5 mg/mL bid</td>
<td>5 min</td>
<td>15 min</td>
<td>4 hr</td>
</tr>
<tr>
<td></td>
<td>Inhalation solution</td>
<td>0.5 mg/mL bid</td>
<td>5 min</td>
<td>15 min</td>
<td>2 hr</td>
</tr>
<tr>
<td></td>
<td>Nasal spray</td>
<td>0.5 mg/mL</td>
<td>10 min</td>
<td>30 min</td>
<td>6 hr</td>
</tr>
</tbody>
</table>

Dosing Schedules

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</tr>
</thead>
<tbody>
<tr>
<td>Albuterol</td>
<td>Oral solution</td>
<td>0.5 mg/mL bid</td>
<td>3 min</td>
<td>10 min</td>
<td>4 hr</td>
</tr>
<tr>
<td></td>
<td>Nasal spray</td>
<td>0.2 mg/mL bid</td>
<td>5 min</td>
<td>15 min</td>
<td>6 hr</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>Oral solution</td>
<td>0.25 mg/mL bid</td>
<td>5 min</td>
<td>15 min</td>
<td>4 hr</td>
</tr>
<tr>
<td></td>
<td>Nasal spray</td>
<td>0.25 mg/mL bid</td>
<td>5 min</td>
<td>15 min</td>
<td>6 hr</td>
</tr>
<tr>
<td>Formoterol</td>
<td>Oral solution</td>
<td>0.5 mg/mL bid</td>
<td>5 min</td>
<td>15 min</td>
<td>6 hr</td>
</tr>
<tr>
<td></td>
<td>Nasal spray</td>
<td>0.5 mg/mL bid</td>
<td>10 min</td>
<td>20 min</td>
<td>12 hr</td>
</tr>
</tbody>
</table>