Adrenergic Bronchodilators (Sympathomimetics) Part 2

**Routes of Administration**

- Inhalation route
  - preferred route because
    - onset is rapid
    - smaller doses are needed compared to the oral route
    - side effects e.g. tremor and tachycardia are reduced
    - drug is delivered directly to the target organ
  - continuous nebulization
    - continuous administration of inhaled adrenergic agents has been used to avoid respiratory failure, intubation and mechanical ventilation
    - NAEPP EPR II guidelines recommend 2.5-5 mg of albuterol by nebulizer every 20 min. x 3 doses, as well as 10-15 mg/hr by continuous nebulization

- continuous nebulization
  - the choice of continuous versus intermittent administration is not clear due to mixed results from studies that show varying levels of patient improvement with both methods; the results overall seem to support continuous nebulization for patients with severe airflow obstruction
  - delivery methods include
    - measured refilling of an SVN
    - volumetric infusion pump with an SVN
    - use of a large reservoir nebulizer e.g. the HEART or HOPE
  - toxicity and monitoring
    - continuous nebulization is not standard therapy and the patients for which it is prescribed have serious airflow obstruction problems
Routes of Administration

- continuous nebulization
  - potential complications include cardiac dysrhythmias, hypokalemia, hyperglycemia and significant tremor
  - close monitoring of patients receiving continuous nebulization is always indicated
  - selective β2 agonists such as terbutaline and albuterol should be used to reduce side effects

- Oral route
  - advantages are
    - ease and simplicity of administration
    - short time of administration
    - exact reproducibility and control of delivered dose
  - not the preferred route because
    - onset of action is about 1.5 hours, compared to 5 min. by inhalation route
    - peak effect is about 2 hours, compared to 30 min-1 hour by inhalation route
    - larger doses are required compared to inhalation route
    - frequency and degree of side effects are greater compared to inhalation route

- Parenteral administration
  - β adrenergic bronchodilators can also be given subcutaneously and intravenously - usually in the emergency management of acute asthma
  - subcutaneous administration
    - epinephrine - 0.3 mg q 15-20 min, up to 1 mg in 2 hrs
    - terbutaline - 0.25 mg repeated in 15-30 min, up to 0.5 in 4 hr
  - it has been suggested that both inhalation and subcutaneous administration of β adrenergic bronchodilators be used to manage acute obstruction
  - intravenous administration
Routes of Administration

- **Parenteral administration**
  - **intravenous administration**
    - has been used most often with isoproterenol and albuterol
    - may be of benefit since by this route the drug is available to all areas of the lung and not just the ventilated areas; although recent studies indicate that aerosols to have an impact on obstructed areas
    - isoproterenol - not clearly advantageous for bronchodilation by this route; dose is limited by tachycardia; administration requires an infusion pump, cardiac monitor and close observation
      - children’s dosages - 0.1-0.8 µg/kg/min
      - adult dosages - 0.03-0.2 µg/kg/min
      - both until bronchial relaxation or side effects occur

- **albuterol**
  - IV as a bolus, 100-500 µg or by infusion, 4-25 µg/min
  - although more β-specific, the clinical usefulness of IV albuterol has not been clearly established

Adverse Side Effects

- **Adverse side effects seen with β agonists include**
  - tremor
  - palpitations & tachycardia
  - headache
  - insomnia
  - increased BP
  - nervousness
  - dizziness
  - nausea
  - tolerance to drug effects
  - loss of bronchoprotection
  - worsening of V/Q ratio
  - hypokalemia
  - bronchoconstrictor reaction
Adverse Side Effects

- Adverse side effects seen with β agonists
  - tremor
    - due to stimulation of β2 receptors in skeletal muscle
    - dose related
    - more common with oral administration
    - tolerance to tremors usually develops in a period of days or weeks
  - cardiac effects
    - dose-limiting effect is tachycardia
    - increases cardiac output and oxygen consumption
    - newer agents have limited cardiac effects, however effects can still occur, probably due to β2 receptors in the heart

- cardiac effects
  - β2 agonists also cause vasodilation, which can cause a reflex tachycardia
  - agents like albuterol and terbutaline can actually improve cardiac performance - they cause peripheral vasodilation and increase myocardial contractility without increasing oxygen demand by the heart; the net effect is a reduction in afterload and improvement in cardiac output with no oxygen cost, so these agents can be attractive for use in patients with congestive heart failure
  - tolerance to drug effect
    - tolerance is a concern because using the drug is actually reducing its effectiveness

- tolerance to drug effect
  - acute desensitization of β receptors can occur within minutes of β agonist administration with long-term desensitization to follow - removal of the β agonist apparently allows the receptors to return to a fully active state
  - such tolerance is no considered clinically important and does not contraindicate the use of β agonists
  - altered β receptor function can also be caused 2° to inflammation
    - increased levels of phospholipase A2 (PLA2) may destabilize membrane support of the β receptors
    - cytokines, such as interleukin 1β can cause desensitization of β receptors
Adverse Side Effects

- Adverse side effects seen with \( \beta \) agonists
  - altered \( \beta \) receptor function can also be caused 2\(^*\) to inflammation
    - corticosteroids can reverse the desensitization of \( \beta \) receptors
      and are said to potentiate the response to \( \beta \) agonists - and \( \beta \)
      agonists may in turn have a positive effect on corticosteroid
      function
    - loss of bronchoprotection
      - bronchoprotection, as opposed to bronchodilation, refers to the
        reaction of the airways to provocative stimuli - this protection
        appears to decline at a faster rate than does the bronchodilating
        effect
  - CNS effects
    - side effects such as headache, nervousness, irritability, anxiety,
      and insomnia are caused by CNS stimulation
    - the feeling of nervousness may be more the result of muscle
      tremor rather than direct CNS stimulation
    - these types of CNS effects should be noted by the clinician and
      may warrant changes in medication dosage
  - decrease in \( P_{aO_2} \)
    - noted with albuterol and salmeterol and are probably due to an
      increase in perfusion to poorly ventilated lung regions by the
      reversal of hypoxic pulmonary vasoconstriction by \( \beta \) agonists
    - drops in \( P_{aO_2} \), rarely exceed 10 mmHg and are statistically significant
      but may be physiologically negligible
  - metabolic disturbances
    - \( \beta \) agonists can increase blood glucose and insulin levels and
      decrease serum K\(^+\) levels - these are normal effects of
      sympathomimetics
    - clinicians should be aware of possible glucose/insulin changes in
      the diabetic patient
    - hypokalemia is a short-lived effect
    - all of these metabolic disturbances are minimized with aerosol
      administration because serum levels remain low
    - propellant toxicity and paradoxical bronchospasm
      - 4-7% of users of MDI may experience this phenomenon
      - switch to DPI, SVN or oral administration
### The β Agonist Controversy

- **Asthma morbidity and mortality**
  - on the rise, despite advances in the understanding of asthma and the availability of improved asthma drugs
  - most of the studies implicating the use of β agonists as the cause have not been conclusive
  - causes that may lead to worsening asthma severity include
    - use of β agonists allows individuals to expose themselves to asthma triggers with no immediate response as a warning, but with development of progressive airway inflammation and increasing bronchial hyperresponsiveness
    - repeated self-administration of β agonists provides temporary relief of symptoms, causing an underestimation of severity and leading to a delay in seeking medical attention
    - β agonists do not block progressive inflammation which can lead to death from lethal airway obstruction and hypoxia

- **Insufficient use of anti-inflammatory agents with the use of β agonists to control the inflammatory nature of asthma and target the symptoms of wheezing and airway resistance**
- **Accumulation of the S-isomer with racemic β agonists could exert a detrimental effect on asthma control**
- **There is increased airway irritation with environmental pollution and lifestyle changes**
- **NAEPP guidelines stress that asthma is a disease of chronic airway inflammation and treatment with β agonists alone does not address the inflammation - concurrent β agonist/anti-inflammatory therapy should be evaluated along with controlling environmental factors**

### RC Assessment of β Agonist Therapy

- **Assess effectiveness of therapy based on the clinical indications for the aerosol agent**
- **Monitor flow rates to assess reversibility of airflow obstruction**
- **Perform respiratory assessment pre- and post-treatment**
- **Assess pulse before, during and after treatment**
- **Assess patient's subjective reaction to treatment**
- **Assess ABGs or SpO₂ as prn for acute stages of asthma or COPD to monitor changes in ventilation and oxygenation**
RC Assessment of \( \beta \) Agonist Therapy

- Note effect of \( \beta \) agonist therapy on blood glucose and \( K^+ \) levels if back-to-back or continuous therapy is ordered
- Over the long term, monitor changes in PF studies
- Instruct patients in use of peak flow devices and on interpretation of values - make sure patients have an action plan
- Emphasize to patients that \( \beta \) agonists do not treat inflammation
- Instruct patients on proper use and cleaning of aerosol delivery devices

RC Assessment of \( \beta \) Agonist Therapy

For long-acting \( \beta \) agonists

- Assess ongoing lung function
- Assess amount of rescue \( \beta \) agonist use and nocturnal symptoms
- Assess number of exacerbations, unscheduled physician visits and hospitalizations
- Assess days of absence because of symptoms
- Assess ability to reduce the dose of concomitant inhaled corticosteroids