

RSPT 2217
Adrenergic Bronchodilators (Sympathomimetics)

Gardenhire
Chapter 6

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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

History & Development

- Progression
 - short-acting, non-specific agents (epinephrine, isoproterenol)
 - intermediate-acting β_2 specific (albuterol)
 - long-acting (salmeterol)
 - pure isomers (levalbuterol)

Clinical Indications

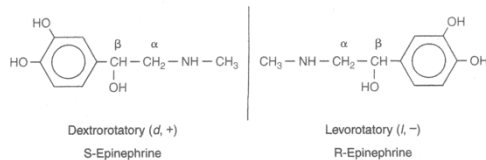
- General indication is relaxation of bronchial smooth muscle in the presence of reversible airflow obstruction associated with acute and chronic asthma, bronchitis, emphysema and bronchiectasis
- Usually categorized as short-acting and long-acting
- Short-acting agents
 - indicated for relief of acute 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): albuterol, levalbuterol, metaproterenol, terbutaline, bitolterol, pirbuterol,

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 and arformoterol

Structure & Action

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

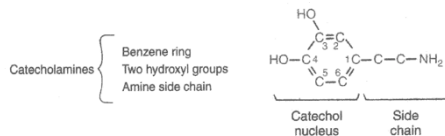


Structure & Action

- 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

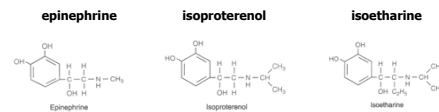
Classification of Sympathomimetics

- 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



Classification of Sympathomimetics

- Catecholamine agents
 - all sympathomimetic bronchodilators are either catecholamines or derivatives of catecholamines
 - three drugs are in the catecholamine class



Classification of Sympathomimetics

- Catecholamine agents
 - epinephrine (Adrenaline, Primatene Mist) is a potent catecholamine that stimulates both α and β receptors
 - does not have β_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

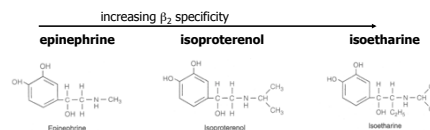
- Catecholamine agents
 - isoproterenol (Isuprel, Isuprel Mistometer) is a potent catecholamine bronchodilator that stimulates both β_1 and β_2 receptors
 - used widely at one time for nebulization
 - main disadvantages are its short duration and strong cardiac stimulation
 - it is metabolized to the weak β blocker, 3-methoxyisoproterenol, which may cause resistance to its bronchodilating effects

Classification of Sympathomimetics

- Catecholamine agents
 - isoetharine (Arm-A-Med Isoetharine, Isoetharine HCl) was one of the first β_2 specific adrenergic bronchodilators in the U.S.
 - it has a short duration of action, but a rapid onset
 - cardiac stimulation is minimal compared to isoproterenol

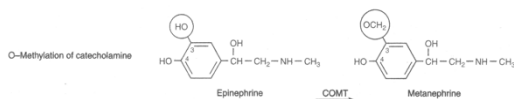
Classification of Sympathomimetics

- Keyhole theory of β_2 specificity
 - the larger the amine side chain attachment to the catechol base, the greater the β_2 specificity
 - if the catecholamine structure is seen as a key like shape, the larger the "key" (side chain) the more β_2 specific is the drug



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

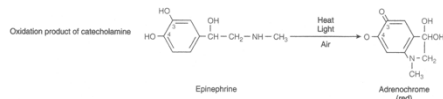


Classification of Sympathomimetics

- Metabolism of catecholamine agents
 - this new compound, metanephrine, is inactive on the adrenergic receptors, however, it may compete with β_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

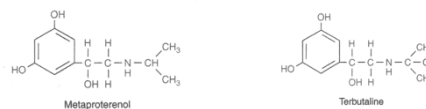
- Metabolism of catecholamine agents
 - catecholamines are also readily inactivated to inert adrenochromes by heat, light and air and should be stored in light-resistant amber bottles



- 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)

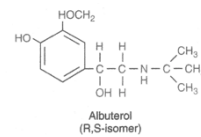


Classification of Sympathomimetics

- Resorcinol agents
 - 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 β_2 specific and causes fewer β_1 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

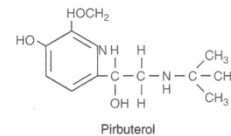


Classification of Sympathomimetics

- Saligenin agents
 - albuterol
 - availability
 - oral – tablets, extended-release tablets, syrup
 - inhalation – nebulizer solution, unit dose vials, MDI
 - β_2 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

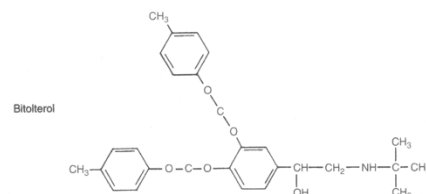


Classification of Sympathomimetics

- 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 β_2 agonists

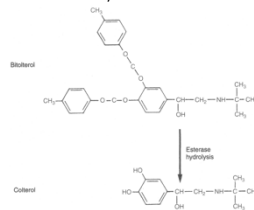
Classification of Sympathomimetics

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



Classification of Sympathomimetics

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

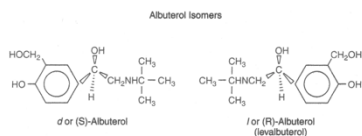


Classification of Sympathomimetics

- 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 β_2 effect
 - bitolterol is available as an MDI and nebulizer solution, however, it has not been widely accepted for clinical use

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

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 FEV₁ with an 8 hour duration compared to racemic albuterol, but the side effects were equivalent to the racemic dose

Classification of Sympathomimetics

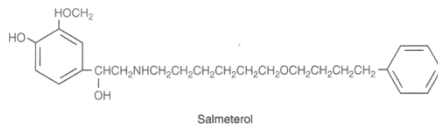
- Long-acting β adrenergic agents
 - the development of bronchodilating agents has been moving away from non-specific, short-acting agents to those with more β_2 specificity and a longer duration of action
 - the need is for agents that can control nocturnal symptoms and that require fewer doses/day
 - included in this grouping are sustained-release albuterol (Proventil Repetabs, Volmax), salmeterol (Serevent), formoterol (Foradil) and arformoterol (Brovana)

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

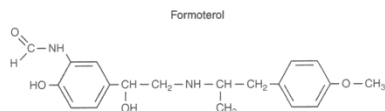


Classification of Sympathomimetics

- 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 β_2 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 mcg formoterol produced the same increase in airway conductance at 1 minute as did 200 mcg albuterol and twice the increase in airway conductance at 1 minute as did 50 mcg salmeterol

Classification of Sympathomimetics

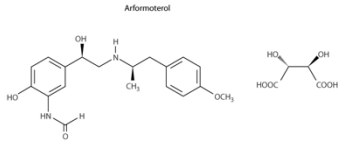
- Long-acting β adrenergic agents
 - the efficacy of formoterol in relaxing bronchial smooth muscle is higher than albuterol which is higher than salmeterol, however, salmeterol remains a better choice for patients with cardiovascular disease
 - a single isomer form (RR-formoterol) is currently under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

- Long-acting β adrenergic agents
 - arformoterol is the latest β_2 selective agent with a long-acting bronchodilatory effect of up to 12 hours
 - arformoterol is the single, (*R,R*)-isomer form of racemic formoterol
 - approved by the FDA for maintenance treatment of COPD
 - Available in 2 ml unit dose vials for nebulization only
 - Recommended adult dose is 15 mcg BID



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

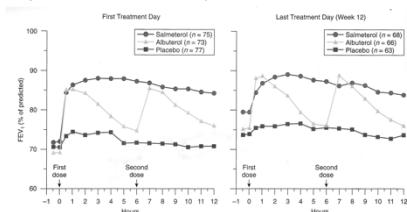
- Clinical use of long-acting β agonists
 - points to consider
 - long-acting β agonists are not recommended for rescue bronchodilation because with their longer duration and increased lipophilic properties, accumulation and toxicity is a risk
 - a shorter-acting β agonist should be prescribed and available 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

Classification of Sympathomimetics

- 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

- Clinical use of long-acting β agonists
 - 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 Schedule

Drug	Brand Name	Receptor Preference	Adult Dosage	Time Course (Onset, Peak, Duration)
Ultra Short-Acting Adrenergic Bronchodilator Agents				
Epinephrine	Adrenalin Cl, Epinephrine Mist, Primatene Mist	α_1, β	SVN: 1% solution (1:100), 0.25-0.5 ml (2.5-5.0 mg) qid MDI: 0.22 mg/puff, puffs as ordered or needed	Onset: 3-5 min Peak: 5-20 min Duration: 1-3 hr
Racemic epinephrine	microNefrin, Nephron, S2	α_1, β	SVN: 2.25% solution, 0.25-0.5 ml (5.63-11.25 mg) qid	Onset: 3-5 min Peak: 5-20 min Duration: 0.5-2 hr
Isoetharine	Isoetharine HCl	β_2	SVN: 1% solution, 0.5 ml (5.0 mg) q4h	Onset: 1-4 min Peak: 15-60 min Duration: 1-3 hr
Short-Acting Adrenergic Bronchodilator Agents				
Metaproterenol	Alupent	β_2	SVN: 0.4%, 0.6%, 5% solution, 0.3 ml (15 mg) tid, qid MDI: 650 µg/puff, 2 or 3 puffs tid, qid Tab: 10 mg and 20 mg, tid, qid Syrup: 10 mg per 5 ml	Onset: 1-5 min Peak: 60 min Duration: 2-6 hr
Albuterol	Proventil, Proventil HFA, Ventolin, Ventolin HFA, ProAir, AccuNeb	β_2	SVN: 0.5% solution, 0.5 ml (2.5 mg), 0.63 mg, 1.25 mg and 2.5 mg unit dose, tid, qid MDI: 90 µg/puff, 2 puffs tid, qid Tab: 2 mg, 4 mg, and 8 mg, bid, tid, qid Syrup: 2 mg/5 ml, 1-2 tsp tid, qid	Onset: 15 min Peak: 30-60 min Duration: 5-8 hr

Dosing Schedule

Firbuterol	Maxair Autohaler	β_2	MDI: 200 µg/puff, 2 puffs q4-6h	Onset: 5 min Peak: 30 min Duration: 5 hr
Levalbuterol	Xopenex, Xopenex HFA	β_2	SVN: 0.31 mg/3 ml tid, 0.63 mg/3 ml tid, or 1.25 mg/3 ml tid; Concentrate 1.25 mg/0.5 ml, tid MDI: 45 µg/puff, 2 puffs q4-6h	Onset: 15 min Peak: 30-60 min Duration: 5-8 hr
Long-Acting Adrenergic Bronchodilator Agents				
Salmeterol	Serevent	β_2	DPI: 50 µg/blister bid	Onset: 20 min Peak: 3-5 hr Duration: 12 hr
Formoterol	Foradil	β_2	DPI: 12 µg/inhalation bid	Onset: 15 min Peak: 30-60 hr Duration: 12 hr
Arformoterol	Brovana	β_2	SVN: 15 µg/2 ml unit dose, bid	Onset: 15 min Peak: 30-60 hr Duration: 12 hr

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
 - inhalation is painless and safe
 - 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

Routes of Administration

- 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 β_2 agonists such as terbutaline and albuterol should be used to reduce side effects

Routes of Administration

- 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

Routes of Administration

- 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 do 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 mcg/kg/min
 - adult dosages - 0.03-0.2 mcg/kg/min
 - both until bronchial relaxation or side effects occur

Routes of Administration

- Parenteral administration
 - isoproterenol
 - however, the combination of myocardial stimulation and hypoxia can lead to serious dysrhythmias, so isoproterenol by this route should be avoided in acute asthma
 - albuterol
 - IV as a bolus, 100-500 mcg or by infusion, 4-25 mcg/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	nausea
palpitations & tachycardia	tolerance to drug effects
headache	loss of bronchoprotection
insomnia	worsening of V/Q ratio
increased BP	hypokalemia
nervousness	bronchoconstrictor reaction
dizziness	

Adverse Side Effects

- Adverse side effects seen with β agonists
 - tremor
 - due to stimulation of β_2 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 β_2 receptors in the heart

Adverse Side Effects

- Adverse side effects seen with β agonists
 - cardiac effects
 - β_2 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

Adverse Side Effects

- Adverse side effects seen with β agonists
 - 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 not 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 A_2 (PLA₂) may destabilize membrane support of the β receptor
 - cytokines, such as interleukin 1 β can cause desensitization of β receptors

Adverse Side Effects

- Adverse side effects seen with β agonists
 - altered β receptor function can also be caused 2° to inflammation
 - corticosteroids can reverse the desensitization of β receptors and are said to potentiate the response to β agonists - and β 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 and is measured with doses of histamine, methacholine or cold air - this protection appears to decline at a faster rate than does the bronchodilating effect

Adverse Side Effects

- Adverse side effects seen with β agonists
 - 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 β agonists
 - drops in P_{aO_2} rarely exceed 10 mmHg and are statistically significant but may be physiologically negligible

Adverse Side Effects

- Adverse side effects seen with β agonists
 - metabolic disturbances
 - β 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 hyper-responsiveness
 - 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

The β Agonist Controversy

- Asthma morbidity and mortality
 - causes that **may** lead to worsening asthma severity include
 - 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 (20%)
- Assess patient's subjective reaction to treatment
- Assess ABGs or SpO_2 as prn for acute stages of asthma or COPD to monitor changes in ventilation and oxygenation

RC Assessment of β Agonist Therapy

- Note effect of β 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 β agonists do not treat inflammation
- Instruct patients on proper use and cleaning of aerosol delivery devices

RC Assessment of β Agonist Therapy

For long-acting β agonists

- Assess ongoing lung function, including pre-dose FEV_1
- Assess amount of rescue β 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

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