



ADRENERGIC BRONCHODILATORS AND SIDE EFFECTS: WHAT DO YOU LOOK FOR? *By Doug Gardenhire EdD, MS, RRT-NPS*

In the last two issues I had discussed the use of short and long acting adrenergic bronchodilators. I have not discussed in any detail however, a little something known as side effects. Overall, bronchodilators are safe, but only when professionals understand how they work and can correctly notice side effects.

In general, the term side effect indicates any effect other than the intended therapeutic effect. The most common clinically observed side effects of adrenergic bronchodilators are tremor, tachycardia, tolerance to bronchodilator effect, loss of bronchoprotection, nervousness, worsening ventilation to perfusion ratio, hypokalemia, and sensitivity to additives and propellants. It must be emphasized that the number and severity of these side effects vary from patient to patient; not every side effect is seen with each patient. It must be remembered that the later adrenergic

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agents (albuterol, bitolterol, pirbuterol, levalbuterol, salmeterol, formoterol, and arformoterol) are much more beta 2 specific than previous agents such as epinephrine and isoetherine. Because of this, there is a greater likelihood of cardiac stimulation causing

tachycardia and blood pressure increases with the last three agents than with the newer drugs. The more recent agents are safe, and the side effects listed are more of a nuisance than a danger and are easily monitored by the respiratory therapist.

Tremor

The annoying effect of muscle tremor with beta agonists is due to stimulation of beta 2 receptors in skeletal muscle. It is dose related, and is the dose-limiting side effect of the beta 2 specific agents, especially with oral administration. This side effect is much more noticeable with oral delivery, which provides a rationale for aerosol administration of these agents.

Cardiac Effects

The older adrenergic agents with strong beta 1 and alpha stimulating effects were considered dangerous in the presence of congestive heart failure. The dose-limiting side effect with these agents is tachycardia. They increase cardiac output and oxygen consumption by stimulating beta 1 receptors, leading to a decrease in cardiac efficiency, which is the work relative to oxygen consumption. Newer agents have a preferential beta 2 effect to minimize cardiac stimulation. However, tachycardia may also follow use of the newer agents, and there is evidence that this is due to the pres-

ence of beta 2 receptors even in the heart. Beta 2 agonists cause vasodilation, and this can also cause a reflex tachycardia. Despite this effect, agents such as terbutaline or albuterol can actually improve cardiac performance. Albuterol and terbutaline can cause peripheral vasodilation and increase myocardial contractility without increasing oxygen demand by the heart. The net effect is to reduce afterload and improve cardiac output with no oxygen cost. Although there are no written standards, most healthcare practitioners accept no more than a 20% change in pretreatment pulse after bronchodilator therapy has been initiated. This is why it is important to check the pulse rate before, during, and after bronchodilator therapy to evaluate cardiac response. If the pulse rate has increased more than 20% relative to the pretreatment pulse, stopping treatment with referral to the prescribing healthcare practitioner may be warranted to prevent unwanted cardiac effects.

Tolerance to Bronchodilator Effect

Adaptation to a drug with repeated use is a concern because use of the drug is actually reducing its effectiveness. With beta agonists, there is evidence of an acute desensitization of the beta receptor within minutes of exposure to a beta agonist, as well as longer term desensitization. This decrease in bronchodilator response has been observed with both short-acting and long-acting beta agonists.

Although use of an inhaled beta agonist does cause a reduction in peak effect, the bronchodilator response is still significant and stabilizes within several weeks with continued use. Such tolerance is not generally considered clinically important and does not contraindicate the use of these agents. The same phenomenon of tolerance is also responsible for diminished side effects, such as muscle tremor, among patients regularly using inhaled beta agonist bronchodilators. Corticosteroids can reverse the desensitization of beta receptors and are said to be able to potentiate the response to beta agonists.

Loss of Bronchoprotection

The bronchodilating effect of a beta agonist can be measured on the basis of airflow change, as indicated by, for example, a change in FEV1 or peak expiratory flow rate (PEFR). The bronchoprotective effect refers to the reaction of the airways to challenge by provocative stimuli such as allergens or irritants and is measured with doses of histamine, methacholine, or cold air.

Central Nervous System Effects

Commonly reported side effects of the adrenergic bronchodilators include headache, nervousness, irritability, anxiety,

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and insomnia, which are caused by central nervous system stimulation. Feelings of nervousness or anxiety may be due to the muscle tremor seen with these drugs, rather than to direct central nervous system stimulation.

Fall in Arterial Oxygen Pressure

A fall in arterial oxygen pressure (PaO₂) has been noted with isoproterenol administration during asthmatic bronchospasm, as ventilation improves and the exacerbation is relieved. The same effect has subsequently been noted with newer beta agonists such as albuterol and salmeterol. The mechanism for this seems to be an increase in perfusion of poorly ventilated portions of the lung. It is known that regional alveolar hypoxia produces regional pulmonary vasoconstriction in an effort to shunt perfusion to lung areas of higher oxygen tension. Administration of inhaled beta agonists may reverse hypoxic pulmonary vasoconstriction by beta 2 stimulation, increasing perfusion to underventilated lung regions. Preferential delivery of the inhaled aerosol to better ventilated lung regions increases the ventilation-perfusion mismatch. Oxygen tension falls most in subjects with the highest initial PaO₂. Decreases in PaO₂ rarely exceed 10 mmHg, and the PaO₂ values tend to be on the flat portion of the oxyhemoglobin curve, so that drops in arterial oxygen saturation (SaO₂) are minimized. Oxygen tensions usually return to baseline within 30 minutes.

Metabolic Disturbances

Adrenergic bronchodilators can increase blood glucose and insulin levels, as well as decrease serum potassium levels. This is a normal effect of sympathomimetics. In diabetic patients, clinicians should be aware of a possible effect on glucose and insulin levels. Hypokalemia has also been reported after parenteral administration of albuterol and epinephrine. The mechanism of the effect on potassium is probably activation of the sodium-potassium pump by the

beta receptor, with enhanced transport of potassium from the extracellular to the intracellular compartment.

Propellant Toxicity

The use of chlorofluorocarbon (CFC; e.g., Freon) powered MDIs can cause bronchospasm of hyperreactive airways. It appears there is no noticeable difference in adverse reactions among patients using a CFC MDI and those using a hydrofluoroalkane (HFA) MDI. A dry powder formulation is an ideal alternative formulation to an MDI if sensitivity to propellants exists, assuming drug availability and adequate inspiratory flow rate. Use of a nebulizer instead of an MDI may also be considered if bronchospasm occurs in a patient. Finally, the oral route offers an alternative to the inhalation route of administration.

Sensitivity to Additives

An increasingly publicized problem for those with hyperreactive airways is sensitivity to sulfite preservatives, with resulting bronchospasm. Sulfating agents are used as preservatives for food and are also used as antioxidants for bronchodilator solutions to prevent degradation and inactivation. There have been reports of coughing and wheezing, as well as pruritus, after use of sulfite-containing bronchodilators. Other additives and preservatives that can potentially have an effect on airway smooth muscle include benzalkonium chloride (BAC), ethylenediamine tetraacetic acid (EDTA), and hydrochloric or sulfuric acid to adjust pH of the solution. Clinicians should check aerosol formulations for BAC or EDTA, and if symptoms of bronchoconstriction occur, consider these as a possible cause.

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