



LONG ACTING BETA AGONISTS, IS LONGER BETTER?

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For many of us, long acting beta agonists are still new, compared to short acting agents. For example, salmeterol was approved in 1994 and formoterol did not make it to market until after the start of the 21st century in 2001. This article will review long acting adrenergic bronchodilator agents available and their indication for use. I will also discuss the black box warning now found on long acting beta agonists and combination products.

Long-acting agents, such as salmeterol, formoterol, and arformoterol are indicated for maintenance bronchodilation and control of bronchospasm, and for control of nocturnal symptoms in asthma or other obstructive diseases. National Asthma Education

and Prevention Program Expert Panel Report 3, 2007, (NAEPP EPR 3) guidelines, and The Global Initiative for Asthma (GINA) consider salmeterol, and formoterol a "controller" agent; its slow time to peak effect makes it a poor rescue drug. In asthma, a long-acting bronchodilator is usually combined

Long acting beta agonists appear to do more good than harm

with antiinflammatory medication for control of airway inflammation and bronchospasm. Even though formoterol has a rapid onset of action, similar to that of albuterol, its slower peak effect and prolonged activity make it a better maintenance drug than an acute reliever or rescue agent. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends long acting beta agonists be added to the treatment of patients in stage II.

Long-acting bronchodilators are contrasted with short-acting agents. Short-acting agents include albuterol, levalbuterol, and pirbuterol, although these agents at one time were considered longer acting in comparison with the ultrashort-acting catecholamines such as isoetharine.

The action of salmeterol in providing sustained protection from bronchoconstriction differs to a degree from that of the previously described adrenergic bronchodilators. The difference in salmeterol's pharmacodynamics is reflected in its pharmacokinetics with a slower onset and time to peak effect and a longer duration of action compared with previous adrenergic agents. The drug is a modification of the saligenin albuterol, with a long nonpolar (i.e., lipophilic) N-substituted side chain. Salmeterol thus consists of a polar, or hydrophilic, phenyl ethanolamine "head," with a

large lipophilic "tail" or side chain. As a result of this structure, salmeterol is lipophilic, unlike most b agonists, which are hydrophilic and approach the b receptor directly from the aqueous extracellular space. In contrast, salmeterol, as a lipophilic molecule, diffuses into the cell membrane phospholipid bilayer and approaches the b receptor laterally. The lipophilic nonpolar side chain then binds to an area of the b receptor referred to as the exosite, a hydrophobic region. With the side chain (tail) anchored in the exosite, the active saligenin head binds to and activates the b receptor at the same location as albuterol.

The binding properties of salmeterol, formoterol, and arformoterol differ from those of albuterol and other b agonists. Because the side chain of salmeterol is anchored at the exosite, the active head portion continually attaches to and detaches from the receptor site. This provides ongoing stimulation of the b receptor and is the basis for the persistent duration of action of salmeterol. This model of activity is supported by studies of the effect of b antagonists on the b-agonist action of salmeterol, as well as molecular binding studies. If albuterol is attached to the b receptor, the smooth muscle relaxation can be fully reversed by a b-blocking agent such as propranolol or sotalol, indicating a competitive blockade. When the b-blocking agent is removed, there is no further relaxation of smooth muscle. The albuterol has been displaced and the action of the drug is terminated. If salmeterol stimulates a receptor, a b antagonist such as propranolol will also reverse the effect of relaxation. However, when the propranolol is removed from the tissue, the relaxant effect of salmeterol is reestablished. This indicates that the salmeterol remains anchored in the receptor and is available to continually stimulate the b receptor once the blocking agent is removed.

The prolonged activity of formoterol is also thought to be due to its lipophilicity, although formoterol is less lipophilic than salmeterol. Formoterol and arformoterol, which is moderately lipophilic, enters the bilipid cell membrane, where it is retained, with the lipid layer acting as a depot and giving a long-acting effect. At the same time, formoterol and arformoterol can approach the b receptor from the aqueous phase, giving it a rapid onset of action.

Currently, salmeterol (Serevent) is only available in a dry powder inhalation formula, at 50 micrograms per inhalation. Salmeterol is also found in the combination product Advair,

which combines salmeterol and fluticasone. Advair is available as a dry powder inhaler and an HFA metered dose inhaler. Formoterol (Foradil) is available as a dry powder inhaler, at 12 micrograms per inhalation (Aerolizer) or 8.5 micrograms per inhalation (Certihaler). The newest formulation of formoterol is known as Performist, a wet nebulization ampoule containing 0.02 milligrams / 2 ml. Formoterol is also found in the combination product Symbicort, which combines formoterol and budesonide as a HFA metered dose inhaler. Arformoterol is the latest b2-selective agonist with a long-acting bronchodilatory effect of up to 12 hours in duration. Arformoterol is the single, (R,R)-isomer form of racemic formoterol, which is approved by the FDA as Brovana for maintenance treatment of COPD. The current recommend adult dose is 15 micrograms, twice daily. Brovana is available in 2 mL unit-dose vials and is for nebulization only.

Both the short-acting and long-acting b agonists show anti-inflammatory effects in vitro. Salmeterol, formoterol, and arformoterol inhibit human mast cell activation and degranulation in vitro, prevent an increase in vascular permeability with inflammatory mediators, and generally diminish the attraction and accumulation of airway inflammatory cells. Despite these in vitro anti-inflammatory effects, salmeterol, formoterol, and arformoterol have not been shown to inhibit accumulation of inflammatory cells in the airway or the rise in inflammatory markers in vivo. These drugs are not considered to have a sufficient effect on airway inflammation in patients with asthma to replace anti-inflammatory drugs such as corticosteroids.

Speaking of corticosteroids and combination products you may have noticed a large black box warning on the labels of long acting bronchodilators and combination products that include long acting bronchodilator agents. This warning was required after data from the SMART (Salmeterol multicenter asthma research trial) was reported to the FDA. Included in SMART were two known studies by Salpeter, etal and Nelson, etal. It is important to note that Salpeter and associates, in a meta-analysis, reported that long-acting b2 agonists increased the risk of asthma hospitalizations and deaths compared with placebo. In addition, Nelson and others also described an increase in death rate among patients using salmeterol; their findings reported the highest rate of death among African Americans. Please note that neither of these studies took into account the severity of asthma, or whether the participants used other medications. This means that some participants' asthma may have been worse than others. Concerning cotreatments, the studies could not account for other medications participants may have been taking, or with what regularity they were taking them. The latter could have serious consequences if, for example, a participant stopped using inhaled corticosteroids that were prescribed to treat their asthma. Any of these variables—asthma severity, presence of cotreatments, and patient adherence—could affect data interpretation. Nevertheless, the labeling of these agents has been changed to warn that death can occur.

Although this is new and important information to gleam, long acting beta agonists should be used. Both the NAEPP EPR 3 and GOLD guidelines recommend their use with the knowledge of the black box warning. Long acting beta agonists appear to do more good than harm.

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