Inhaled Beta Agonists

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Summary

The $\beta_2$ adrenoreceptor is a large molecule of some 413 amino acids. The duration of stimulation of this receptor depends on where and for how long a $\beta_2$ adrenergic drug attaches itself to the $\beta_2$ adrenoreceptor. $\beta_2$ adrenergic drugs have been used for over 5,000 years, but only recently have we had the advantage of adrenergic drugs specific to the $\beta_2$ adrenoreceptor. The short-acting $\beta_2$ adrenergic drugs most frequently used include albuterol, pirbuterol, and levalbuterol. Levalbuterol, the R enantiomer of albuterol, has been described by some as a more effective bronchodilator than racemic albuterol, because it contains none of the S enantiomer. Some contend that the S isomer has pro-inflammatory properties. The 2 long-acting $\beta_2$ adrenergic drugs are salmeterol and formoterol. These drugs have a duration of 12 h and reportedly improve forced expiratory volume in the first second, quality of life, and symptoms. Some recent reports indicate that these drugs are associated with higher mortality, but several authors have registered the opinion that it is not the bronchodilator that should be questioned, but instead that the fault lies in the patient recruitment in those studies. Regardless, if these long-acting drugs are effective for a given patient, it would seem inadvisable to withdraw them, given the current state of evidence. Arformoterol tartrate, the R enantiomer of formoterol, was approved by the U.S. Food and Drug Administration in October 2006; it is available as a nebulizer solution, to be administered every 12 h. Several other long-acting R isomers and RR isomers are in the approval pipeline. Key words: inhaled agonist, adrenoreceptor, albuterol, pirbuterol, levalbuterol, bronchodilator, salmeterol, formoterol [Respir Care 2007;52(7):820–832. © 2007 Daedalus Enterprises]
Introduction

It is difficult to imagine trying to treat patients with obstructive lung disease or bronchospasm without β adrenergic bronchodilators. These drugs have been in use for several thousand years and have recently undergone refinement to become the β2-specific drugs we now use. In this paper I review the various β2 bronchodilators we use in everyday practice. Long-acting β2 adrenergic bronchodilators have been developed to act as controller drugs in both asthma and chronic obstructive pulmonary disease (COPD). Though most patients have a favorable response to these agents, some patients have a paradoxical response, for several possible reasons, including polymorphism of the β2 adrenoreceptor, and there is considerable controversy, depending on which literature one reads. The makers of the long-acting β2 bronchodilators now place a “black-box” warning on their products. Nevertheless, these drugs continue to be a mainstay in the treatment of bronchospasm. There are several new long-acting β2 bronchodilators in development, the most recent of which is arformoterol tartrate, which was approved by the U.S. Food and Drug Administration (FDA) in October 2006.

The β2 Adrenoreceptor

The β2 adrenoreceptor is a large molecule of some 413 amino acids (Fig. 1). Most of the molecule is in the muscle cell wall, but it also has a tail outside the cell, and several loops within the cytoplasm. Adrenoreceptors are classified as β1, β2, or β3, identified in cardiac, airway smooth muscle, and adipose tissue, respectively. β2 receptors are found in increasing density with increasing airway generations to the alveoli.1 β2 agonists (bronchodilators) interact with the β2 adrenoreceptor and relax airway smooth muscle (bronchodilation). The precise mechanism of short-acting β adrenergic bronchodilators (SABAs) and long-acting β adrenergic bronchodilators will be discussed individually.

History of β Adrenergic Bronchodilators

The herb ma huang contains ephedra and pseudoephedrine, which had been used in traditional Chinese medicine since 3000 BC for bronchodilation. It was not until the turn of the 20th century that epinephrine was extracted from the adrenal gland. This extract was used to treat asthma patients in 1900, and the first use of epinephrine as an aerosol was in 1910. A thorough review is found elsewhere.2 Isoproteranol and isoetharine were used until the 1970s, but had substantial β1 (cardiovascular) effects, namely tachycardia, increased blood pressure, smooth muscle relaxation, skeletal muscle tremor, and central nervous system stimulation, and those drugs were replaced by the more specific β2 agent metaproteranol. Epinephrine, isoproteranol, and isoetharine are all catecholamines, which consist of a benzene ring, 2 hydroxyl groups, and an amine side chain. The only difference among these three is the structure of the side chain. Catecholamines are rapidly inactivated by catechol-o-methyltransferase, which limits the effects of catecholamines to 1.5–3 h at most. Recently developed β adrenergic bronchodilators have a much longer duration of action, which is another reason why catecholamines are rarely used in aerosol therapy.

Another feature of the β2 bronchodilators is that they exist as stereoisomers. Stereoisomers are nonsuperimposable mirror-image forms of the same drug, called enantiomers or isomers (Fig. 2). The R (levorotary) isomer is the active drug. The S (dextrorotary) isomer, is the inactive form, although controversy on this exists, which will be discussed below. Stereoisomers often exist in 50/50 ratios in solution.3

Indications for SABAs

SABAs are often used for asthma flares, as needed for rescue bronchodilation, following exposure to an allergen or irritant, or in preparation for exercise in the presence of exercise-induced bronchospasm.4 SABAs are used in mild COPD as needed, preferably in combination with an anticholinergic bronchodilator, and in moderate-to-severe COPD (regular use).5 SABAs are used for wheezing of bronchospastic origin, and for relief of acute reversible airway obstruction.

SABA Mechanism of Action

The β2 receptor exists in an active form and an inactive form, in equilibrium. The receptor is in the activated form when associated with the α unit of the G protein. The β2 agonist attaches to the β receptor at several sites, labeled III through VI, in the muscle cell membrane (Fig. 3). This activates stimulatory G protein, bound to the intracellular side of the cell membrane. Adenyl cyclase is activated by G protein, which increases the synthesis of 3’-5’ cyclic adenosine monophosphate from adenosine triphosphate.
Cyclic adenosine monophosphate causes smooth-muscle relaxation by inactivating myosin light chain kinase, which is an enzyme that causes smooth-muscle contraction. Increased cyclic adenosine monophosphate also inhibits intracellular calcium release, leading to relaxation of airway smooth muscle and decreasing the sensitivity of contractile proteins.

A β agonist interacts with the β receptor by binding at several sites. The albuterol molecule (which is hydrophilic) accesses the receptor from the extracellular compartment and has a rapid onset of action. The nitrogen of the β agonist binds to an aspartate residue while 2 serine residues bind with the hydroxyl groups on the benzene ring of the β agonist; however, its time at the active site is limited, resulting in a relatively short duration of action (4–6 h). The lipophilic agonists have a longer duration of action because they burrow into the cell membrane, which will be discussed in more detail below. The R enantiomer is more active because of an optimal interaction between the “down” orientation of the β-OH group and the serine residue on the receptor. For albuterol, the R enantiomer is at least 100 times more potent as a β2 agonist than is the S enantiomer. Some agonists, such as fenoterol, formoterol, and procaterol, have 2 asymmetric centers, and there are 4 enantiomers: RR, RS, SR, and SS. The difference in activity between the RR and SS forms of formoterol is 1,000-fold.

β agonist potency is a function of its affinity to the receptor and its efficacy. Isoproteranol has a very high affinity to the receptor, whereas albuterol has a relatively low affinity. Salmeterol and formoterol (long-acting β adrenergics) have high affinities. A full agonist has a high efficacy. Most of the β agonists have an intermediate efficacy. Formoterol has a high efficacy, whereas most saligenins (such as albuterol) have a moderate efficacy. Despite this, their clinical effectiveness as bronchodilators is not compromised.

Examples of Short-Acting β2 Agonists

This review does not discuss the older β adrenergics, as they are rarely used, have considerable cardiovascular adverse effects, and are quite short-acting. Rather, it starts with metaproteranol.

Metaproteranol (Fig. 4) is a resorcinol. Placement of the hydroxyl at the carbon 5 position creates the resorcinol nucleus, to resist degradation by the enzyme catechol-o-methyltransferase and thus increase the duration of action. Metaproteranol is racemic, and the R and S enantiomers are in equal proportions in all its preparations. It has an onset of 1–5 min and a duration of action of 2–6 h. As of December 2006, the proprietary metered-dose inhaler (MDI) preparation, Alupent, is $53 for 200 puffs.

Albuterol (see Fig. 2) is a saligenin, because there is a methyl group at position 3 and a hydroxyl at position 4,
which increases its duration of action to 5–8 h. Its onset of action is 15 min. A generic MDI preparation of albuterol is approximately $20 for 200 puffs; however, the new hydrofluoroalkane propellant preparation (Pro-Air) is approximately $36. All chlorofluorocarbon propellant MDIs will be off the market by January 2008. Albuterol is also racemic, and whether the S isomer is actually inert is discussed below.

Albuterol can also be nebulized continuously, at 7.5–15 mg/h, with a larger-volume nebulizer than is used for a one-time treatment. An increasing number of emergency departments are administering continuous albuterol to patients with asthma, because it saves time and money compared with administering several small-volume nebulizer treatments. Stein and Levitt reported no differences in peak flow improvement or duration of stay with a 15-mg/h dose versus a 7.5-mg/h dose of albuterol. They reported that the upper limit of acceptable dose is about 0.4 mg/kg/h, beyond which there is a significant drop in serum potassium and a significant increase in heart rate.

Intravenous administration of \( \beta_2 \) adrenergics has also been reported in patients with severe bronchospasm unresponsive to inhaled bronchodilators. Roberts et al reported that intravenous aminophylline, but not inhaled albuterol, significantly reduced duration of hospital stay in a group of 40 children with severe asthma. Sellers and Messahel reported on the administration of intravenous salmeterol in 7 patients with severe asthma who were unresponsive to inhaled albuterol. They administered 5-\( \mu \)g/kg boluses of albuterol to children and 250-\( \mu \)g boluses of albuterol to young adults. Signs of improvement included decreased wheezing, decreased coughing, and decreased use of accessory muscles, ability to talk, and increased arterial oxygen saturation. They concluded that immediate care of acute severe asthma should include the use of intravenous albuterol to achieve a predictable delivery of \( \beta_2 \) agonist to bronchial smooth muscle, given that in severe asthma, the airways are narrowed such that aerosolized particles may not reach the small airways.

The British Thoracic Society stated that the role of intravenous \( \beta_2 \) agonists in addition to nebulized treatment remains unclear. They state that continuous intravenous infusion should be considered when there is uncertainty about reliable inhalation or for severe refractory asthma. They recommend a 15-\( \mu \)g/kg bolus of intravenous albuterol early in treatment as an adjunct in severe cases.

The recent Global Initiative for Asthma guidelines include the use of intravenous \( \beta_2 \) agonists in patients with poor response (peak expiratory flow < 30% of predicted, severe symptoms, hypercapnia and hypoxemia), and to admit the patient to the intensive care unit.

Pirbuterol (Maxair) has a pyridine ring instead of a benzene ring (Fig. 5). The adverse effects of pirbuterol are similar to those of other \( \beta_2 \) adrenergics. It has a 5-min onset of action and duration of 5 h. It comes in a breath-actuated MDI. The patient retracts the lever on the device, places the mouthpiece in the mouth, and inhales the medication. Pirbuterol is $100 for a 400-puff MDI.

Bitolterol (Tornalate, Fig. 6), is a prodrug; it is converted to the active agent colterol by esterase hydrolysis, which eliminates the 2 toluate ester groups and replaces them with 2 hydroxyl groups. The onset of action is 3–4 min, with a duration of 5–8 h. Bitolterol is not available in the United States.

Tulobuterol (Fig. 7) is a drug discussed in the Japanese literature. It has a chloride at position 6 on the benzene ring. It is delivered dermally, via patch, similar to the nicotine patch used for smoking cessation. It has a peak serum concentration in 8–12 h and a 24-h duration. It is reported to improve morning peak expiratory flow and quality of life. It may be a useful controller medication.
Levalbuterol (also known as R albuterol or Xopenex) is the single R isomer of racemic albuterol (Fig. 8). Levalbuterol causes less tremor and heart-rate change with a 0.63-mg dose than does albuterol. Rau states that levalbuterol has a higher peak effect on forced expiratory volume in the first second (FEV₁) in asthma than does racemic albuterol, but another study, with COPD patients, found no significant difference in FEV₁ between single-dose and as-need treatment. The onset is 15 min and the duration of action is 5–8 h. A 200-puff MDI of hydrofluoropropylene-propelled Xopenex is $57. The 1.25 mg/3 mL saline dose is $85 for 25 doses ($3.40/dose). Table 1 summarizes the names, dosages, durations, delivery methods, and prices of the β₂ adrenergic drugs.

**Evidence for Using Single-Isomer β Agonists**

For 35 years, racemic albuterol has been used in the treatment of bronchospasm. However, since 1973 there have been reports of unexpected bronchospasm and airway hyperresponsiveness, sometimes termed “β agonist paradox.” It is theorized that the S isomer, once thought to be inert, actually increases bronchospasm and is pro-inflammatory in a susceptible group of patients. This may be due to polymorphisms of the β receptor. There are 9 polymorphisms of the β₂ receptor. One is the arginine/arginine (arg/arg) polymorphism at the 16th amino acid position of the receptor, which is found in one sixth of the asthmatic population in the United States and 25% of African-Americans. The presence of the arg/arg polymorphism (and perhaps others) is associated with impaired bronchodilator response to racemic albuterol and a rapid deterioration of morning peak flow. Studies of levalbuterol (R albuterol) cited by Ameredes and Calhoun concluded that levalbuterol use is safe, efficacious, and provides equivalent increase in FEV₁. Other studies have shown modest to moderate improvement in FEV₁ (5–20%), as compared with racemic albuterol. These effects have occurred without paradoxical bronchospasm. Other findings about levalbuterol from Ameredes and Calhoun’s editorial included: (1) a > 35% increase in FEV₁, or 120–300 mL increase in FEV₁, when using levalbuterol versus racemic albuterol; (2) two thirds fewer admissions when using levalbuterol (and, thus, cost savings); and (3) less frequent dosing (every 6–8 h vs every 4 h).

For years it was believed that S albuterol was inert, but this well-referenced editorial revealed several facts that suggest that S albuterol is not inert and can be antagonistic to the desired β₂ response. According to Ameredes and Calhoun, the S isomer: may influence the activation of R albuterol, acting as an antagonist or inverse agonist; can promote release of factors that favor inflammation and smooth-muscle contraction; may increase pro-inflammatory cytokine release; may promote intracellular calcium release and release of agents that favor smooth-muscle contraction; and can counteract the effects of steroids.

Even though they presented thorough evidence of the potential hazards of the S isomer, they concluded that more comprehensive studies of R and S albuterol are needed to fully resolve this issue. However, they also concluded that “the notion that S albuterol is ‘inert’ under all conditions is no longer tenable, and it is highly relevant that the FDA no longer allows synthesis of new therapeutic compounds in a racemic form unless it can be demonstrated that the distomer has no deleterious effects.” On the other hand, there is evidence against using single-isomer β agonists, presented in a companion editorial. Barnes noted that (1) the association between asthma mortality and greater use of rescue β₂ agonists appears to reflect greater severity of asthma and under-use of inhaled corticosteroids, as opposed to the residual effect of S albuterol; (2) studies that have found increased inflammation in vitro in the presence of S albuterol have not been replicated in vivo, and are difficult to interpret; (3) decreased protection against inhaled methacholine challenge was not confirmed in carefully controlled studies (protective effects were similar for S albuterol and RS albuterol); (4) bronchodilator effects and adverse effects in response to single doses of R and RS albuterol were identical, with no effect of S albuterol; (5) there was no negative effect of racemic albuterol in adenosine monophosphate challenge studies; (6) there was no long-term bronchodilator advantage of R albuterol alone; (7) there was no difference in duration of hospitalization of asthmatics between R albuterol and racemic albuterol; (8) there were no differences in
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Table 1. Summary of $\beta_2$ Adrenergic Bronchodilators

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Names</th>
<th>Dosages</th>
<th>Duration (h)</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metaproteranol</td>
<td>Metaprel</td>
<td>SVN: 15 mg every 4–6 h</td>
<td>2–6</td>
<td>Unit dose: $30/25 doses (generic)</td>
</tr>
<tr>
<td></td>
<td>Alupent</td>
<td>MDI: 650 $\mu$g/puff 2–3 puffs, every 4–6 h</td>
<td></td>
<td>MDI: $56/200$ puffs (Alupent)</td>
</tr>
<tr>
<td>Albuterol</td>
<td>Ventolin</td>
<td>SVN: 2.5 mg every 4–6 h</td>
<td>5–8</td>
<td>Unit dose: $45/60$ doses (generic)</td>
</tr>
<tr>
<td></td>
<td>Proventil</td>
<td>MDI: 90 $\mu$g/puff 2–3 puffs every 4–6 h</td>
<td></td>
<td>MDI: $17/200$ puffs (generic)</td>
</tr>
<tr>
<td></td>
<td>ProAir HFA</td>
<td>MDI: 200 $\mu$g/puff 2 puffs every 4–6 h</td>
<td>5</td>
<td>$36 (ProAir)</td>
</tr>
<tr>
<td></td>
<td>Maxair</td>
<td></td>
<td></td>
<td>$100/400$ puffs</td>
</tr>
<tr>
<td>Levalbuterol</td>
<td>Xopenex</td>
<td>SVN: 0.63 mg or 1.25 mg every 6 h</td>
<td>5–8</td>
<td>Unit dose: $85/24$ doses</td>
</tr>
<tr>
<td></td>
<td>Xopenex HFA</td>
<td>MDI: 2 puffs every 6 h</td>
<td></td>
<td>$57/200$ puffs</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Serevent</td>
<td>DPI: 50 $\mu$g every 12 h</td>
<td>12</td>
<td>$142/60$ puffs</td>
</tr>
<tr>
<td>Formoterol</td>
<td>Foradil</td>
<td>DPI: 12 $\mu$g every 12 h</td>
<td>12</td>
<td>$128/60$ puffs</td>
</tr>
</tbody>
</table>

SVN = small-volume nebulizer
MDI = metered-dose inhaler
DPI = dry powder inhaler
HFA = hydrofluoroalkane

adverse effects between R albuterol and racemic albuterol; and (9) R albuterol is more expensive.

Barnes concluded that:

The activity of normally used racemic albuterol resides in the R-enantiomer, whereas the (S)-enantiomer is inactive. Some in vitro studies have demonstrated that the S-enantiomer may increase contractility of airway smooth muscle or mediator release, but this has not been confirmed in recent animal studies in vivo. More important, in patients with asthma, no consistent differences have been found with (R)-albuterol compared with (R,S)-albuterol in bronchodilation, bronchoprotection, or side effects, whereas S albuterol is inactive with no documented adverse effects.

In his editorial, Barnes did not address administration of racemic albuterol specifically to patients who may have a $\beta$-adrenoreceptor polymorphism. That issue remains unresolved in the case of albuterol.

To summarize, it appears that levalbuterol is as good as (or better than) racemic albuterol for bronchodilation. This better bronchodilation is more evident in patients with asthma than in those with COPD. It also appears that levalbuterol is cost-effective, if fewer doses can be administered and if it actually is used to decrease duration of stay. Its use as a substitute for racemic albuterol on a treatment-for-treatment basis is not cost-effective.

Long-Acting $\beta_2$ Agonists

Long-acting $\beta_2$ agonists (LABAs) are designed to have effect for 12 h or more. Presently, salmeterol (Serevent), formoterol (Foradil), and arformoterol (Brovana) are available. Several additional LABAs are in development.

Indications for LABAs

The indications for a LABA are: moderate-to-severe persistent asthma (twice-a-day for 12-h formulations), although this may change with the new guidelines due out in fall 2007; moderate-to-severe COPD (twice-a-day for 12-h formulations); maintenance bronchodilation; control of bronchospasm; and control of nocturnal symptoms in asthma and other obstructive diseases.

LABA Mechanism of Action

As a result of their structure, salmeterol and other LABAs are lipophilic and diffuse into the cell membrane (Fig. 9). The “tail” binds into the $\beta$ receptor at an exosite. When the tail is in association with the exosite, the molecule is prevented from dissociating from the receptor. The “head” binds to and activates the $\beta_2$ receptor at the same place where albuterol binds. The head continually attaches and detaches from the receptor site, by the Charni`ere (hinge) principle; the flexion is about the oxygen atom on the tail. This repeating attachment process prolongs the drug’s action.

Examples of LABAs

Salmeterol (Serevent) is a racemic LABA (Fig. 10). It has an onset of 20 min and duration of 12 h. It costs approximately $132 for 60 50-$\mu$g doses, which is a
1-month supply. Salmeterol comes in powder form, in an inhaler called a Diskus. The patient rotates the Diskus to the open position, presses the trigger fully, which releases the powder into the chamber, then places the lips on the mouthpiece, inhales fully and rapidly, and does a breath-hold. When finished, the patient rotates the inhaler shut. Salmeterol is only for long-term control of symptoms, so it is used only twice a day, never for acute symptoms.

Formoterol (Foradil) is also a racemic LABA (Fig. 11). It has an onset of 15 min and duration of 12 h. It costs approximately $117 for 60 12-μg doses, which is a 1-month supply. Formoterol comes in capsule form that is used with a single-dose powder inhaler called an Aerolizer. The patient opens the Aerolizer and places the capsule in it, closes the Aerolizer, pushes the opposing buttons to puncture the capsule, puts the mouthpiece to the lips, inhales rapidly and fully, and does a breath-hold. Then the patient opens the Aerolizer and disposes of the capsule.

**LABA Controversy**

In a 1993 study of patients with asthma, Castle et al reported that 12 of 16,787 patients who were using salmeterol died. This represented an insignificant incidence of death related to salmeterol. These deaths were attributed to the severity of the patients’ illness at study entry rather than to some adverse effect of salmeterol.31 There have been other drugs implicated in higher asthma mortality, and when these drugs (isoprenaline and fenoterol) were withdrawn, the death rate decreased.32

There was suspicion that part of that mortality was due to the use of LABAs, so the Salmeterol Multi-center Asthma study Research Trial (SMART) was initiated.33 With a population of 26,355 subjects, the SMART study was conducted at 6,163 sites in the United States to compare respiratory-related and asthma-related outcomes in subjects receiving usual asthma pharmacotherapy alone versus usual asthma therapy plus salmeterol. The major finding was that there were slightly but statistically significantly more respiratory-related and asthma-related deaths or life-threatening experiences in the salmeterol group, compared with the placebo group. There were also significantly more respiratory-related deaths or life-threatening experiences in the African-American patients who used salmeterol, which was one of the reasons the study was stopped at the interim analysis. At screening, the African-American patients had a lower peak expiratory flow, had more nocturnal symptoms, reported less inhaled corticosteroid use, and had a higher percentage of hospitalizations and emergency department visits than did whites. It was unknown if in the African-American population there was a genetic predisposition to paradoxical bronchospasm, or a patient behavior, such as delay in seeking care (poor compliance with study treatments or asthma medications), that would account for the higher death rate. It may be that the African-Americans who participated in the study were more acutely ill than the white participants, but the study did not evaluate these differences. For both whites and African-Americans, there was a higher incidence of asthma-related death and life-threatening experiences among patients who reported no baseline inhaled corticosteroid use and who used salmeterol. As was mentioned earlier, there is a higher incidence of β2 adrenoreceptor polymorphism among African-Americans. Additional studies are needed to determine if paradoxical bronchospasm due to adrenoreceptor polymorphism was the cause of death in those patients.

A recent meta-analysis of LABAs and asthma exacerbations reviewed 19 trials that enrolled 33,826 participants.34 The authors concluded that, compared to placebo, LABAs increased the risk for hospitalization for an asthma exacerbation, life-threatening asthma attack, and asthma-related death. Hospitalizations were more frequent among both adults and children, and with salmeterol and formoterol.

LABA-related deaths might be explained by several phenomena. First is worsened asthma control, caused by desensitization of the adrenoreceptor. Desensitization is a protective mechanism to prevent overstimulation of the receptor in the context of excessive β2 agonist exposure. Desensitization has 3 mechanisms: uncoupling of the receptors from adenylate cyclase; internalization of uncoupled receptors; and phosphorylation of internalized re-
receptors, which is prominent. Phosphorylation results in
uncoupling of stimulatory G protein and blocking of the
connection between G protein and adenyl cyclase by an-
other protein, arrestin. With continued stimulation of the
receptor, an internalization of receptors occurs, which re-
sults in a loss of cell surface receptors: the fewer the
number of cell surface receptors, the less effective the
bronchodilator.

Another factor in worsening asthma control is down-
regulation of receptors after several hours of agonist
exposure. This is defined as a net loss of cellular re-
ceptors. Systemic corticosteroids reverse β2 adrenorecep-
tor down-regulation in patients with asthma, but this effect
does not extend to inhaled corticosteroids.

Other factors that may worsen asthma control are in-
creased bronchial hyperreactivity with regular use of β
adrenergics, and a reduced response to rescue inhaler.
Salpeter et al estimated that the risks of severe exacer-
bation and asthma-related death were 2–4-fold higher; there
was an absolute increase in asthma-related death of 0.06–
0.07% over 6 months. This indicates that LABAs cause
approximately 1 death per 1,000 patient-years of use. Since
salmeterol is one of the most widely prescribed medica-
tions in the world (3.5 million adults treated in the United
States in 2004), salmeterol may be responsible for 4,000 of
the 5,000 asthma-related deaths in the United States each
year. This is quite a remarkable statement for the refereed
literature! Salpeter et al acknowledged the limitations of
their review, including the uncertainty of odds ratios and
risk differences when the number of events is small. They
also stated that there have been no true placebo-controlled
trials of LABAs in asthma. As a result of that study and the
SMART data, GlaxoSmithKline placed a black-box warn-
ing on Seretide Diskus and Advair Diskus, which states,
in part: “Long-acting β2 adrenergic agonists, such as sal-
meterol, the active ingredient in Seretide Diskus, may
increase the risk of asthma-related death. Therefore, when
treating patients with asthma, [salmeterol] should only be
used as additional therapy for patients not adequately con-
trolled on other asthma-controller medications (eg, low-
to-medium-dose inhaled corticosteroids) or whose disease
severity clearly warrants initiation of treatment with 2 main-
tenance therapies. . . .” That FDA document provides
the drug label and patient medication guides for all the
LABAs presently in use (salmeterol, formoterol, RR for-
meroterol, and the compound drugs that contain these LA-
BAs, Advair Diskus and Symbicort). The precaution in the
black-box warning and in that report emphasizes the im-
portance of inhaled corticosteroid use in the treatment of
asthma: steroids actually treat the disease, whereas LABA
preparations treat only the symptoms. Improvement in
symptoms may give the patient and clinician a false sense
of security, since the patient may feel better. Appropriate
steroid use should generally be instituted and shown to be
inadequate in the control of asthma before the addition of
a LABA.

LABAs in Asthma

Since the above-mentioned studies, several others have
looked at β2 receptor polymorphism and the safety of
salmeterol, especially in combination with fluticasone. In
a study of 183 patients with moderate persistent asthma
and who had the arg/arg, glycine/glycine (gly/gly), or arg/
gly genotypes, salmeterol was administered with flutica-
sone, Bleecker et al reported significant improvement in
morning peak flow, with no variation among these geno-
types. There was no salmeterol-only group. The impor-
tant point here is that when salmeterol and an inhaled
steroid are given together in this patient cohort, there is
improvement. This therapeutic approach is consistent with
current asthma guidelines, such as those of the National
Asthma Education and Prevention Program and the Global
Inhaled Beta Agonists

Initiative for Asthma. In contrast, Wechsler et al reviewed the morning peak flow of asthma patients in 2 randomized controlled studies by the Asthma Clinical Research Network: the salmeterol or corticosteroids trial and the salmeterol with and without inhaled corticosteroids trial. In the salmeterol or corticosteroids trial, patients were randomized to receive placebo, triamcinolone, or salmeterol. In the salmeterol with and without inhaled corticosteroids trial, patients were randomized to receive salmeterol and triamcinolone and salmeterol, or salmeterol and placebo. Patients from both groups who were arg/arg homozygous had a lower morning peak flow than patients who were gly/gly homozygous. Even with concurrent inhaled corticosteroids, these patients had more severe symptoms. These differences may be due to differences in receptor down-regulation between the various receptor polymorphisms or to genotype-specific differences in loss of bronchoprotection, among others.

Though the receptor polymorphisms are a concern, Lang, in his review of the evidence of LABA safety, noted a decrease in asthma deaths since the introduction of salmeterol and salmeterol/fluticasone combinations. Data he obtained from the Centers for Disease Control and Prevention show a decrease in asthma mortality in 2000–2002. He quoted numerous studies that demonstrated the effectiveness of combinations of inhaled corticosteroids and long-acting $\beta$ adrennergics. His explanation of the SMART finding of higher mortality with salmeterol was: (1) acknowledgment of the effect of genetic arg/arg polymorphism on the response to salmeterol (decreased morning peak expiratory flow, more exacerbations); (2) higher risk among African-Americans who are homozygous for the arg/arg polymorphism, but because this polymorphism is distributed as suggested, there should have been more fatalities in whites than in African-Americans because of the make-up of the racial groups in SMART; (3) African-Americans were less likely to receive continuous, ongoing medical care essential for asthma care, they made less use of inhaled corticosteroids, they had worse lung function at initiation of the study, and they had a greater likelihood of receiving asthma care in the emergency department; and (4) salmeterol monotherapy masks inflammation because it treats the symptoms but not the underlying inflammation.

Lang suggested a format for notifying patients about the potential for harm from long-acting $\beta$ adrennergics, which includes the risks and benefits, the FDA’s black-box warning, the differences in opinion about LABAs, the alternative treatments, and the importance of follow-up. Additional studies are needed to answer the questions raised by the SMART, but meanwhile the benefits of combined LABA and inhaled corticosteroids outweigh the risks. The SMART data should not discourage prescribing LABAs to patients with moderate or severe persistent asthma, or from continuing LABAs in patients who are doing well.

It is evident that adding a LABA to inhaled corticosteroid in moderate-to-severe persistent asthma is safe. In a Cochrane review by Ni Chronin et al, LABA plus inhaled corticosteroid resulted in: no lower risk of exacerbation (versus inhaled corticosteroids alone); a significant increase in FEV$1$ and symptom-free days with the addition of a LABA; and no difference in the use of rescue SABAs. Importantly, there was no significant group difference in adverse events, treatment withdrawals, or withdrawals due to poor asthma control. Ni Chronin et al concluded that there is insufficient evidence at present to recommend combination therapy, rather than inhaled corticosteroids alone, as a first-line treatment in steroid-naïve adults. This reinforces the guidelines from the National Asthma Education and Prevention Program and the Global Initiative for Asthma.

In the most recent review to date, Walters and colleagues provide the latest word on this issue in asthma. This Cochrane review included 68 studies, which included 42,333 adults and children, over 4–52 weeks. The objective was to compare the effects of regular inhaled LABA versus placebo in chronic asthma. Regular LABA treatment resulted in: increased morning and evening peak expiratory flow; significantly increased FEV$1$; significantly fewer symptoms, day and night; significantly less use of rescue medications; and a large reduction in the odds of experiencing at least one major exacerbation. Regarding asthma-related death, in those who were not using inhaled corticosteroids at baseline, the number of participants who suffered asthma-related death was higher in the LABA groups than in the placebo groups. For those who were taking inhaled corticosteroids at baseline, the relative risk was 1.34 (95% confidence interval 0.30–5.97). For those who were not taking inhaled corticosteroids at baseline, the relative risk was 18.98 (95% confidence interval 1.1–326). Walters et al commented on the observed mortality in the SMART, in which there was no significant difference in asthma-related death between African-Americans and whites. All the excess in death occurred in the first 3-year phase of recruitment, in particular in 1998, when recruitment was by community advertisement, rather than through the subsequent method of recruitment thorough doctors’ clinics. The excess of deaths was also predominantly in those not on inhaled corticosteroids, and it may be that excess mortality relates to patients with poorly controlled asthma, who are not on inhaled corticosteroids. Though genetic polymorphism may play a role in the mortality, it seems more likely that danger arises if a LABA.
is prescribed without inhaled corticosteroids in a patient with poorly controlled asthma, who should definitely be on inhaled corticosteroids according to standard guideline definitions. I believe these data reinforce that patients with persistent asthma must receive inhaled corticosteroids first, and then should be evaluated and receive LABA if necessary, consistent with current guidelines.

LABAs in COPD

LABAs are a recommended part of care in patients with moderate-to-very-severe COPD, according to the Global Initiative for Chronic Obstructive Lung Disease. Since the heart has $\beta_2$ receptors, $\beta$ agonists can increase contractility, decrease peripheral vascular resistance, increase pulse pressure, increase cardiac output, and change serum potassium and magnesium. However, large surveys have documented the safety of LABAs in COPD, when administered at therapeutic doses. In patients with cardiovascular disease, LABAs should be used cautiously, as they may exacerbate underlying cardiac disease.

Despite these potential cardiovascular complications, LABAs remain a mainstay of therapy for moderate-to-very-severe COPD. A recent meta-analysis of 9 randomized clinical trials, with $> 3,500$ patients, found that when salmeterol was used instead of placebo or usual therapy, patients were less likely to withdraw early, they were less likely to suffer a moderate/severe exacerbation, had a better health status, and had a greater increase in FEV$_1$. That analysis reviewed studies that lasted for over a year. There was no tachyphylaxis or death reported, in contrast to the previously discussed analysis by Salpeter et al. Stockley et al. noted that the Salpeter’s analysis was influenced by a single study of formoterol, its erratum, and accompanying unpublished data.

Most recently, a Cochrane review$^{55}$ of LABAs in poorly reversible COPD found (1) a significantly better FEV$_1$ increase with salmeterol than with placebo; (2) a significant increase in morning peak expiratory flow; (3) no significant difference in walk distance between salmeterol and placebo; (4) significant improvement in the total, activity, and impact domain scores on the St George’s Respiratory Questionnaire with $100 \mu g$ of salmeterol daily; (5) significantly less dyspnea with salmeterol; (6) lower odds of exacerbation with salmeterol; (7) less use of rescue SABA; and (8) no deaths reported.

Several reports detail the use of inhaled corticosteroids in the care of patients with COPD. Inhaled corticosteroids are added to the regimen in the event of frequent exacerbations, according to the Global Initiative for Chronic Obstructive Lung Disease. Most frequently, $250 \mu g$ of fluticasone is added to $50 \mu g$ of salmeterol, twice daily, in a combination product. Soon a combination of budesonide and formoterol will be available.

Kiri et al. reported a $38\%$ risk reduction among patients with severe COPD given an inhaled corticosteroid with a LABA, compared to those given an inhaled corticosteroid with a SABA. The patients who received both LABA and inhaled corticosteroid had a lower risk of rehospitalization and lower incidence of death within 12 months of discharge. Likewise, Gudmundsson et al. reported lower mortality when inhaled corticosteroids were combined with LABA, compared with no LABA or inhaled corticosteroids, only LABA, or only inhaled corticosteroids. The most recent study to date is the Toward a Revolution in COPD Health study, which reported data from 6,112 patients with severe COPD (mean post-bronchodilator FEV$_1$ $44\%$ of predicted), in 4 groups: salmeterol $50 \mu g$ plus fluticasone $500 \mu g$ twice a day; salmeterol $50 \mu g$ twice a day; fluticasone $500 \mu g$ twice a day; and placebo twice a day. The results were: (1) no difference in risk of death in the salmeterol and placebo groups; (2) exacerbation rate $25\%$ lower in the salmeterol-plus-fluticasone group, and significantly lower in the salmeterol-only and fluticasone-only groups than in the placebo group; (3) significant improvement from baseline in the Saint George’s Respiratory Questionnaire score, with the greatest change in the salmeterol-plus-fluticasone group; and (4) FEV$_1$ increased the most in the salmeterol-plus-fluticasone group. Mortality in the salmeterol-plus-fluticasone group was lower, but not statistically significantly lower than in the placebo group; however, Kiri et al speculated that that lack of significant difference was only because the study was underpowered to detect that effect.

I believe it is clear that LABA therapy in moderate-to-very-severe COPD is justified and that the hazards are minimal, given the clear outcomes differences of using LABA over placebo or SABA alone. Clinicians need to monitor the effects of LABAs in their patients and be prepared to use an alternative (such as a long-acting anticholinergic drug) in the event of an adverse effect (eg, decreasing pulmonary function or increased bronchospasm).

Fig. 12. Chemical structure of RR formoterol. Color code: gray = carbon; blue = nitrogen; red = oxygen white = hydrogen.
New LABAs

Several new LABAs are under development. In October 2006, the FDA approved arformoterol tartrate (RR formoterol, brand name Brovana), an enantiomer of formoterol. It is expected to be marketed starting by the second quarter of 2007, as an inhalation solution (15-μg dose) for long-term, twice-daily (morning and evening) maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema (Fig. 12). Arformoterol significantly improves FEV₁ immediately after dosing, and has a duration of ≤ 24 h. Studies published before the decision to dose every 12 h showed FEV₁ improvements of > 15% after 24 h. Adverse effects include increased pulse, blood glucose, and tremor, but at a rate no more than placebo. Arformoterol also reduces interleukin-8 production from dust mite and ragweed allergen-stimulated small airway epithelial cells.⁴⁹

Carmoterol (Fig. 13) firmly binds to the β₂ receptor. It is an RR enantiomer with a rapid onset and long duration. It improves FEV₁ for > 30 h in mild asthma and restores FEV₁ within 20 min of inhalation. It is being developed in both MDI and powder preparations.

Indacaterol (Fig. 14) is being developed in a once-daily formulation. It has a quick onset, > 24-h control, and strong efficacy in both asthma and COPD. The goal in developing indacaterol is once-daily therapy of LABA and inhaled corticosteroids.⁴⁹

Summary

Several SABAs are available, and their adverse effects are well known. LABAs anchor in the receptor, which gives them long duration of action. When used in the absence of inhaled corticosteroids, LABAs increase mortality in poorly controlled asthma. However, their advantages (improved airflow and decreased symptoms and exacerbations) outweigh the mortality risk, when used properly. Some believe consideration should be given to withdrawing LABAs from the market. Though single-isomer SABAs and LABAs are available, their use to the exclusion of racemates is unproven. Several LABAs are under development that may offer once-a-day dosing, with or without tiotropium and inhaled corticosteroids.

Acknowledgments

I greatly appreciate the assistance of Bryan Op’t Holt PhD, for creating the molecular model illustrations for this article.

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