Safety and Efficacy of β Agonists

James F Donohue MD

Both short-acting and long-acting β agonists have been used for many years for the treatment of asthma. Short-acting β agonists are life-saving and their role as rescue agents is unquestioned, but regular use is not recommended because of safety concerns and the effectiveness of asthma-controller medications. Long-acting β agonists are effective controller medications but have safety issues, so their use should be restricted to patients who are not optimally controlled on first-line controllers such as inhaled corticosteroids. The effect of the β receptor genotype on β agonist response is unclear but could hold promise for proper patient management. *Key words: asthma, β agonists, inhaled corticosteroids, β receptor, genotype*. [Respir Care 2008;53(5):618–622. © 2008 Daedalus Enterprises]

Introduction

β_2 agonists are a group of sympathomimetic agents that stimulate β_2 receptors in airway cells and produce various effects (Table 1).[1] Chief among these are smooth-muscle relaxation and bronchodilation, caused by activation of adenyl cyclase to produce cyclic 3′5′ adenosine monophosphate. β_2 agonists are commonly grouped as either short-acting (3–6 h duration of action) (SABAs) or long-acting (>12 h duration of action) (LABAs). Figure 1 depicts the evolution of the most commonly used SABA, albuterol, from the less selective agents epinephrine, norepinephrine, and isoproterenol, and the structure of the 2 currently available LABAs: salmeterol and formoterol. New ultra-long-acting β agonists (24-h duration of action), such as indacaterol, stereoisomeric formulations such as arformoterol and levalbuterol, and new combinations, are likely to be introduced.

Short-Acting β Agonists

Safety and Efficacy

SABAs can be given orally, parenterally, or via inhalation. The inhalation route is generally preferred because it

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Table 1. Effects of β Adrenergic Agonists on Airways

Relaxes airway smooth-muscle (proximal and distal airways)
Inhibits mast-cell mediator release
Inhibits plasma exudation and airway edema
Increases mucociliary clearance
Increases mucus secretion
Decreases cholinergic neurotransmission
Decreases cough
No effect on chronic inflammation

(Adapted from Reference 1.)

has the highest therapeutic ratio (beneficial effects/adverse effects). SABAs have been a backbone of therapy in airway diseases and have consistently produced effective bronchodilation and improved lung function. Because of their short duration of action, however, they are not good long-term maintenance medications and are generally reserved for rescue use.

The safety profile of SABAs has generally been good, although for decades there have been concerns that some patients may experience serious adverse effects.[2] For example, SABAs were implicated in 2 epidemics of asthma deaths in the 1960s and 1970s in the United Kingdom and New Zealand.[3,4] The mechanism(s) of death were not clear, but might have included excessive β agonist use in very sick asthmatics, rebound hyperresponsiveness due to short duration of action, tachyphylaxis, or some other process.[5,6] The effect may have also been due to a particular β agonist: fenoterol. In one epidemic there was a correlation between asthma mortality and fenoterol prescriptions/market share. When high-dose fenoterol was withdrawn from

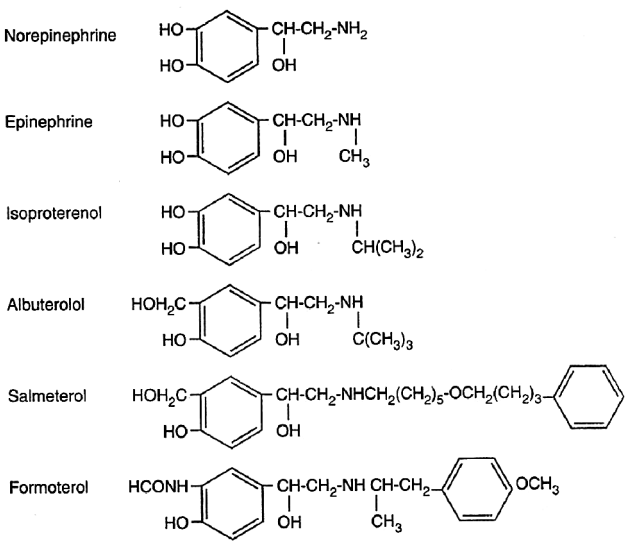

Fig. 1. Structures of adrenergic agonists. (From Reference 1, with permission.)

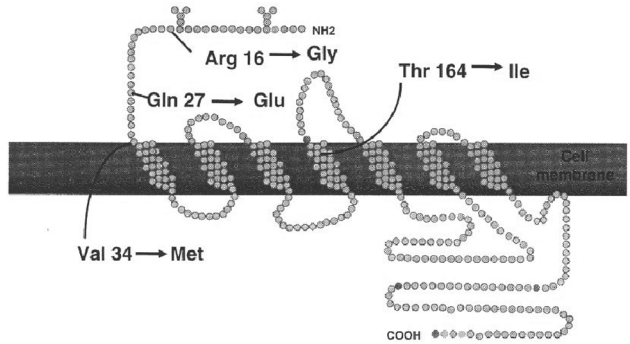

Fig. 2. β adrenergic receptor polymorphisms. (From Reference 10, with permission.)

the market, the asthma mortality plummeted back to baseline.[7]

More focused studies in the early 1990s also suggested that regular use of SABAs may produce serious adverse effects. Taylor et al, in a study of 64 patients, 50 of whom were on inhaled corticosteroids, analyzed the number of subjects without exacerbations versus the number of days of treatment.[8] When β agonists were used "as needed," as opposed to "regular use," there was a corresponding marked reduction in the frequency of exacerbations. The possibility was raised that with regular use of β agonists there were more exacerbations, occurring earlier and with greater severity, with greater decline in forced expiratory volume in the first second (FEV_1), more diurnal variation in peak expiratory flow (PEF), and greater sensitivity to methacholine.

In the United States the National Institutes of Health's Asthma Clinical Research Network also noted some conflicting signals with regular use of SABAs. The β Agonist in Mild Asthma Trial was designed to compare regular versus as-needed albuterol in 255 patients with mild asthma.[9] After a 6-week run-in period, patients were randomized to the therapy for 16 weeks, followed by an additional 4-week run-out period. PEF was higher with as-needed albuterol than with regular albuterol. However, there were no differences in the primary outcomes of PEF variability, FEV_1, number of puffs of albuterol, or symptoms. The conclusion was that as-needed SABA therapy is preferable to regular SABA use.

Genetic Variation in the β_2 Receptor and SABA Response

Over the last decade there has been a growing interest in genetic variations (polymorphisms) at several locations in the β_2 receptor (Figure 2), and whether these variations might explain different β agonist responses.[10] Taylor noted differences at position B16 between Arg/Arg and Gly/Gly that may be important in the response to β agonists.[11] This

led to a retrospective genetic analysis of the β-Agonist in Mild Asthma Trial data.[12] There was no effect with variations at the B27 locus, and no effect with B16 heterozygotes (Arg/Gly). However, when B16 Arg/Arg patients (1/6 of the population) were compared to B16 Gly/Gly patients, a difference was found in the primary outcome variable, a lower PEF, which was particularly noticeable during the 4-week run-out period. Taylor et al studied the influence of β-adrenergic receptor polymorphisms on asthma exacerbations.[13] Those with Arg/Arg at position B16 who received regular albuterol had more exacerbations than those on placebo and those on salmeterol. Individuals with Gly/Arg or Gly/Gly showed no such difference.

The β Adrenergic Response by GenotypE (BARGE) prospective analysis studied regular scheduled albuterol versus as-needed albuterol.[14] Patients were screened and genotyped. They had a 6-week run-in, all on placebo, then 16 weeks of treatment on active drug or placebo, then an 8-week run-out. Then there was a crossover 16 weeks of placebo or active treatment and a second 8-week run-out. Those on regular albuterol with B16 Arg/Arg had a much lower PEF than those on placebo or regular albuterol with B16 Gly/Gly. The PEF, FEV_1, symptoms, and rescue inhaler use improved significantly in B16 Arg/Arg patients with asthma when regular β agonists were withdrawn and ipratropium was substituted. The pattern was reversed in B16 Gly/Gly patients with asthma. These findings suggested that B16 Arg/Arg patients (1/6 of asthmatics) may benefit from minimizing short-acting β agonist use.

Conclusions About Short-Acting β Agonists

SABAs are essential as rescue medications to relieve symptoms, prevent exercise-induced asthma, and treat exacerbations. Usually in these acute settings, high doses can be given at short intervals. In contrast, there appears to be no benefit from regular use of SABAs in the maintenance therapy of asthma. Additional research should clarify the role of β receptor polymorphisms.

Long-Acting β Agonists

Safety and Efficacy

The LABAs have been developed as maintenance therapy for obstructive airway disease. As with SABAs, the inhalation route provides the highest therapeutic ratio. A recent Cochrane review of 67 studies, which involved over 42,000 patients, concluded that LABAs indeed were effective in the control of chronic asthma and that their use (both with and without inhaled corticosteroids) was associated with better pulmonary function, fewer symptoms, less rescue medication, and higher quality-of-life scores.[15]

As with SABAs, there are safety concerns about LABAs. The first pertinent large study was the Serevent Nationwide Surveillance Study, by Castle et al,[16] in which there was no run-in and there was a requirement for regular use of bronchodilators. Of those who participated, 69% were on concurrent inhaled steroids. 16,787 patients received salmeterol, and 8,393 received albuterol. There were no significant differences in overall serious events, withdrawals, or asthma-related hospitalizations, but there was a slight difference in asthma-related deaths: there were 12 deaths in the salmeterol group and 2 in the albuterol group. The relative risk was 3.0, but the difference was not statistically significant ($p = 0.105$). Asthma-related withdrawals were much greater in the albuterol group, and that difference was statistically significant ($p < 0.001$).

More recently, the Salmeterol Multicenter Asthma Research Trial (SMART) was performed in the United States, following the approval of salmeterol for asthma maintenance.[17] This large study included 13,176 patients who were randomized to salmeterol, and a similar number who received placebo plus usual care, for a 28-week period. Patients were followed with phone contacts every 4 weeks, and case reports of serious adverse events were collected. The primary outcomes were respiratory deaths and life-threatening experiences (intubations). The secondary outcomes were respiratory deaths, asthma death or life-threatening experience, or asthma death. A morbidity and mortality review committee reviewed all the events and rated the likelihood that the deaths were respiratory and/or asthma-related, with a scale of (A) unrelated, (B) unlikely related, (C) possibly related, or (D) almost certainly related. The data safety monitoring board performed a study oversight interim analysis and made recommendations to the sponsoring company. The SMART did not reach predetermined stop criteria at the interim analysis, and the data safety monitoring board initially recommended timely completion within 2 years, or if that was not possible, that the study be discontinued. SMART was then discontinued because of difficulties with enrollment and findings in African American patients.

The results of SMART have been controversial. There were differences in baseline asthma characteristics between whites and African Americans. The African Americans had a lower baseline PEF, more nocturnal symptoms, more emergency department visits and hospitalizations, and more intubations in their lifetimes. Also, in the previous 12 months the African Americans had more hospitalizations and more emergency department visits. There were also baseline differences in use of inhaled corticosteroids (whites 49%, African Americans 38%). In SMART, 13 died in the salmeterol arm, versus 3 in the placebo arm (relative risk 4.37, 95% confidence interval 1.25–15.34). On the primary outcome of respiratory death or life-threatening experience there was no significant difference overall (rela-

tive risk 1.40, 95% confidence interval 0.91–2.14), but in the African American patients there were important differences between salmeterol and placebo (relative risk 4.1, 95% confidence interval 1.54–10.90). SMART was not designed to assess the effects of inhaled corticosteroids, but they did appear to provide a protective effect.

Following SMART, a meta-analysis of 19 studies that involved LABA use, in over 33,000 patients, concluded that LABA use was associated with more exacerbations and asthma deaths.[18] However, these conclusions were heavily influenced by the SMART results, and the authors of the meta-analysis noted that asthma deaths were very rare in all studies. Earlier meta-analyses did not find a mortality effect from LABA use,[19,20] and the most recent Cochrane review[15] did not find evidence of more exacerbations or hospitalizations with LABA use, but did acknowledge the mortality effects observed in SMART. With that backdrop, the United States Food and Drug Administration issued a "black box" warning for all LABAs.[21]

Importantly, the finding of more deaths with salmeterol in SMART contrasts with national statistical data on United States asthma deaths and prescriptions for salmeterol and salmeterol/inhaled corticosteroid combinations. Whereas the number of asthma deaths peaked above 5,000/y in the mid-1990s, in the United States the death rate declined to below 4,000/y in the present decade, as the prescriptions for salmeterol and salmeterol/inhaled corticosteroid combinations increased. Extrapolation of the mortality data from SMART suggests that in 2004 there would have been 2–3-fold more asthma deaths than were reported in the national statistics. It is reassuring to note that this did not occur.

Safety concerns about the other available LABA, formoterol, focus less on asthma deaths than on serious asthma exacerbations.[22] In the 3 pivotal studies, plus the post-marketing 16-week, phase-4 study, there seemed to be a signal that with formoterol serious asthma exacerbations were more common, especially with higher doses and in the pediatric study.[23–25] However, in the large post-marketing study, serious asthma-related adverse events that required hospitalization were rare in all groups. In the phase-3 studies, serious asthma exacerbations occurred more frequently with formoterol 24 μg twice a day than with formoterol 12 μg twice a day. The 24 μg twice-a-day dose is not approved in the United States.

Genetic Variability and Long-Acting β Agonists

As with SABAs, a key question is whether the β_2 receptor genotype impacts LABA response. Taylor et al compared the PEF response to albuterol or salmeterol in patients with different B16 genotypes.[13] The patients who received regular albuterol for 26 weeks and who had the B16 Arg/Arg genotype had lower PEF than those who had the Arg/Gly or Gly/Gly genotypes. In contrast, there was no such PEF reduction when salmeterol was given regularly. There was no unusual drop-off in PEF during the run-out period. This contrasts with the Asthma Clinical Research Network's 2 studies of salmeterol: one of salmeterol monotherapy after discontinuing inhaled corticosteroids, and the second combined with inhaled corticosteroids. Compared to Gly/Gly individuals, Arg/Arg homozygous patients (retrospectively studied) did not benefit from salmeterol, and had lower PEF, greater PEF variability, and higher exhaled nitric oxide. The difference in PEF and PEF variability was accentuated in the run-out period.[26]

Recent large pharmaceutical studies found no effect of β receptor genotype on the response to LABAs when combined with inhaled corticosteroids.[27,28] In one study, 2,250 asthmatics were randomized to a fixed combination of budesonide/formoterol, fixed-dose fluticasone/salmeterol, or budesonide plus formoterol maintenance and as rescue. B16 polymorphism had no effect on exacerbations, lung function, or use of rescue medication. In a second trial of 405 asthmatics, an open-label extension for 7 months also did not show any pharmacogenetic effects from variation at site B16.

Conclusions About Long-Acting β Agonists

LABAs are highly effective maintenance agents in asthma, but the Canadian[29] and United States[30] asthma guidelines advise that LABAs should be used only in combination with inhaled corticosteroids—not as asthma monotherapy—in patients with asthma severity of step 3 or higher.[29,30] Several large studies of LABAs and B16 polymorphisms are underway.

Summary

As noted by O'Byrne and Adelroth in an editorial, asthma continues to be poorly controlled in many patients, as reflected in surveys and baseline characteristics of most patient populations in insurance databases and clinical trials.[31] Less than half of the patients in most trials report inhaled corticosteroid use at baseline. In most studies patient adherence to inhaled corticosteroid therapy has not been well documented, but it appears from pharmacy databases that the refill rate is less than 50% of prescribed medications. The SMART study did not assess whether combination therapy of a LABA plus inhaled corticosteroid carries the same risk as LABA monotherapy. At baseline, African Americans had more severe asthma than the overall population. It is unclear whether LABA monotherapy or other factors explain the higher risk of asthma death in African Americans. It is also unclear whether the results of SMART apply to all LABAs. Practitioners should

follow the current asthma guidelines.[29,30] Neither LABAs nor LABA/inhaled corticosteroid combinations are indicated in patients with step 1 or step 2 asthma that is controlled by inhaled corticosteroids alone or other recommended agents. For patients with asthma severity of step 3 or higher, the LABA/inhaled corticosteroid combinations appear to be safe and effective.

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Discussion

Colice: Jim, I know of at least 4 studies that showed no increased evidence of deterioration of asthma with albuterol: Ken Chapman et al[1] did a study; Jeff Drazen et al[2] did a 16-week study, Sarah Dennis et al[3] did a year-long study, and we published a study[4] of regular albuterol use 4 times a day. If there is a concern—and of course these patients were not genotyped—if there is a concern about the Arg/Arg genotype, which could occur in 15–20% of patients, is there another genotype that is actually protective or beneficial with the use of albuterol?

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Donohue: It's probably true that there are multiple polymorphisms that enter into deterioration during regular therapy, but still it's a good starting point.[1–3] You're absolutely right, Gene, that the preponderance of the literature is from the National Institutes of Health, and those are very well done studies. That's why I like the Asthma Clinical Research Network studies, even though they're small in number. The Pharma studies are always much bigger and show no association with Arg/Arg and deterioration.

The jury is still out on this; we don't have enough information. I wouldn't use short-acting β agonists regularly in asthma or chronic obstructive pulmonary disease, because there's a lot of loss of bronchial protection. But certainly the combinations with inhaled corticosteroids are okay.

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Diette: I really appreciate the balance you built into your talk, because I think it's tough to wield all that data at once. I've studied the mortality curves, and I think that in terms of what the ecology is in the background of the United States, they are very hard to interpret. When inhaled corticosteroids came on the market in 1989—and they were already starting to zoom upwards in the market even before salmeterol was on the market—if you look at the curves, there's a point at which about half of asthmatics were starting to use inhaled steroids; that's the point where the mortality curve starts to bend favorably.

I think it's still possible for salmeterol to have a negative effect and inhaled steroids to have a positive effect, and if the inhaled steroids have a more protective effect than the long-acting β agonists do a negative effect, you'll still see the same curves that we actually observe. The long-acting β agonists would have to outstrip the benefits of inhaled corticosteroids to see that epidemic type curve that you're talking about.

Donohue: That is an excellent point, because it's not really comparable to the fenoterol and isoprenaline data, where they were really the only drugs used. But I just pulled down the data from 2005 that was just released, and there were only 40 additional deaths in the national asthma statistics, so it's still pretty low: in the 3,000 range. But your points are well taken; it's just an association, and I wouldn't want to make any statement about causality. But to me it is reassuring that the death rate isn't really going up, which would be a concern when a drug is widely used, particularly the ser-event-plus-fluticasone combination.

Enright: Are you worried about the abuse potential of formoterol, given it's rapid onset of action? People in the real world may think that it's much like their rescue inhaler and take formoterol much more often than prescribed, or much more often than used in clinical trials.

Colice: ProAir HFA [hydrofluoroalkane, the propellent] has a red plastic actuator and Symbicort has a red plastic actuator.

Donohue: Yes, that could lead to some confusion. Formoterol is different than salmeterol, because there's a dose response. Salmeterol is in a 50-μg dose in the Diskus, but a 100-μg dose is approved in the United Kingdom. You really start paying the price in adverse effects as you up the dose. Salmeterol is slow in onset; you can see some effects at 15 minutes and 30 minutes, but it really takes an hour before you see the 15% increase in FEV_1.

In contrast to salmeterol, which approaches the receptor through the lipid biophase, formoterol probably binds to the receptor through the aqueous and through the lipid, and it's on the receptor within 3 minutes, where you can measure a biologic effect. Formoterol is a bomb. It is a really big drug, and the reason it's in the dose it's in is that it's really hard to formulate it. And it's really an effective drug, I have worked a great deal with it. The dose that is chosen is really a function of formulation.

It's the same problem they had in the development of tioproprium, which was getting a formulation you could consistently give to patients. In fact, indacaterol is a derivative; it's been toned down a little. After you get a 24-hour effect you don't get the peak adverse effect.

Formoterol is very interesting in the toxicity and the serum level; you can measure it during the first 4 hours of a 12-hour drug, so it doesn't seem to have much systemic effect after the first couple of hours. The systemic effects are related to a peak; the dose response you could go up probably safely in someone without heart disease easily 6- or 8-fold and still get some effect, but you're going to start seeing changes in the [electrocardiogram] QT.

Certainly if it's the first dose you can probably knock the potassium down and the glucose up a little bit. Tolerance to those adverse effects occurs right away, and they're not usually important. With a patient with heart disease you really don't want to go up on that dose escalator. The FDA is concerned about the 24-mg versus 12-mg.

So I'm not sure I buy into the variable-dosing scheme, particularly if it gets very high. I'd put a lid on that somewhere around 24-mg: maybe double the dose. I really am concerned about carte blanche use of this agent. Do you have some insight into that, Paul?

Enright: Only that I've been involved in the Cardiovascular Health Study,[1,2] which included a big population-based sample of older adults, and some 35% of them had subclinical coronary cardiovascular disease that they didn't know about until tests were done to find it. So when you start using a drug like that in people who haven't got the diagnosis, it might not be safe. Of course these are sudden deaths.

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Donohue: The complete agonists are probably a tad more effective than a partial agonist, but aren't quite so safe. Down-regulation, though it is a little more likely with a partial agonist such as salmeterol, might make the patient less able to respond to albuterol in an acute emergency. I agree. I really don't want high doses of these drugs being given. That explains the racemic formoterol (Dey Laboratories) solution being a really modest dose, as is the approved single isomer aformoterol (Sepracor). So a modest dose is chosen. These are important points. One can't really give high doses except maybe in the intensive care or hospital setting, where it's a life-or-death situation.

Rubin:* These meetings are great for doing an in-depth evidence-based look at each of these aspects of care. You're the kick-off clinician on this. In real life what I see in my pediatric practice is that the kids who come in treated by family doctors and pediatricians in the community who are still afraid of steroids are often treated with several-times-a-day albuterol or levalbuterol via nebulization plus or minus oral montelukast. These proceedings are going to be published in RESPIRATORY CARE, and the respiratory therapists who read this are the primary educators who are going to go in there. What message would you tell them as they go to treat their patients?

Donohue: I particularly want to tell Dr Stoloff how much I admire the latest iteration of the NAEPP [National Asthma Education and Prevention Program] asthma guidelines.[1] If we really stick to that excellent document, we'll all treat our patients very well. It is really helpful with the things that Dr Sorkness said about asthma monitoring. Use the drugs you're supposed to. If you use long-acting β agonists with a patient who has asthma stage 3 or higher, use them with steroids, and use the guidelines to help you. That's my take-home message. You can't go wrong if you do that.

1. Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda MD: National Institutes of Health, National Asthma Education and Prevention Program; 2007. NIH Publication No. 08-4051. Available from http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. *Accessed February 12, 2008.*

Stoloff: The reason we gave equal preference in the adult population, and we also alluded to that in children ages 5–12, was because in the adult papers, in all the data we saw, if you looked at impairment—not risk or exacerbation, but impairment—the patients did better with combination therapy than they did with medium doses of inhaled corticosteroids. However, there was much less difference in all the studies in the frequency of exacerbation in those on combination therapy versus monotherapy of a higher dose of inhaled corticosteroids, not double the dose.

Given the FDA's position of a black-box warning, looking at risk/benefit ratio, we thought it was most equitable to offer the clinician an opportunity to make a decision based on their perception and how they saw the ability to gain control for the population they were treating and the individual patient. That's why we did what we did, and the discussions concerning that were the most vociferous that I have ever heard in our discussions over 13 years.

Donohue: Thank you for the clarification.

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