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REVIEW

Long-Acting Beta-Agonists in Adult Asthma: Evidence that these Drugs are Safe

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Summary If asthma is not controlled with low-dose inhaled corticosteroids (ICS), by far the best next step is the addition of a long-acting, inhaled beta-agonist (LABA). Questions regarding the safety of this class of drug have been raised. However, careful examination of the reports which have raised concern in this regard does not reveal any evidence of an increased risk associated with the appropriate use (i.e. in combination with an inhaled ICS) of LABAs in asthma. There is much to suggest that the adverse outcomes associated with LABA monotherapy have been due to "masking of inflammation" rather than a toxic effect of the drugs. In some instances, this has likely allowed worsening asthma to be overlooked — with dire consequences. Studies in subjects receiving combination therapy with LABAs plus ICSs suggest that, if anything, there is an enhanced anti-inflammatory action with the LABA/ICS combination superior to that achieved with ICS alone at the same dose.

Contents

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The controversy regarding LABA therapy

Concern regarding the safety of use of long-acting, inhaled beta-agonists (LABAs) has arisen from prospective studies [1–4] that found an increase (sometimes not statistically significant) in asthma deaths or serious asthma exacerbations, and from anecdotal reports which reported an increase in asthma deaths, in patients using these drugs [5]. On the other hand there are very reassuring reports, such as the Cochrane systematic review of 85 studies with over 15,000 patients, which found a reduction in asthma exacerbations with the use of LABAs [6], and the case-control study of 532 asthma deaths in Great Britain between 1994 and 1998 [7]. In this population, LABAs, mostly salmeterol, were commonly prescribed (38% of the controls). Yet, adjusted for severity, the odds risk for death associated with a prescription for a LABA 1-5 years before the index date was only 0.74, suggesting, if anything, an inverse association with mortality. With these markedly differing messages regarding the safety of LABAs, there is a need to look closely at the published literature to try to decide whether there is a problem with their use.

The safety of LABAs should be assessed in the correct setting — i.e. with proper use of the drugs. LABAs were initially studied as add-on treatments to the subject's current asthma therapy [8,9]. This resulted, in many patients, in their use as the sole controller therapy. Although monotherapy with a LABA improved overall asthma symptoms, it appeared to do so largely through its bronchodilating properties. Studies specifically looking for potential anti-inflammatory effects were largely negative [10], although some reduction in neutrophils in bronchial biopsies was observed [11]. As a result of this lack of anti-inflammatory activity, the US National Heart, Lung and Blood Institutes (NHLBI) Guidelines for the Diagnosis and Management of Asthma, revised in 1997, unequivocally stated, ''Long-acting inhaled $beta_2$-agonists should be used only in conjunction with anti-inflammatory medication'' [12].

Why not LABA monotherapy?

The role of LABA monotherapy was specifically addressed in a study called Salmeterol Off Corticosteroids or ''SOCS'' conducted by the NHLBI-sponsored Asthma Clinical Research Network [13]. Subjects were first treated with an inhaled corticosteroid, triamcinolone acetonide (TAA) 400 mcg twice daily for six weeks. Those whose asthma became well controlled, 164 in number, were then randomized for 16 weeks to continue on TAA, to receive instead salmeterol 42 mcg twice daily, or to receive placebo. While asthma control deteriorated in those placed on placebo, there was no difference between those continuing on inhaled corticosteroids and those receiving monotherapy with salmeterol, for conventional clinical outcomes such as morning and evening peak flows, symptom scores, rescue albuterol use, or quality of life. There was, however, a difference in markers of airway inflammation; these remained controlled in those patients on inhaled corticosteroids, whereas in those on salmeterol alone there was a deterioration in sputum eosinophils, eosinophil cationic protein, exhaled nitric oxide and methacholine sensitivity, similar to the changes seen in the placebo group. There was also a difference between those patients continuing on inhaled corticosteroids and those on salmeterol — who had an increased rate of treatment failures and asthma exacerbations, again similar to those subjects who had been switched to placebo. The fundamental message from this study was ''The findings indicate that salmeterol should not be used as monotherapy for treatment of persistent asthma'' [13].

Combination therapy

The SOCS study clearly confirms the use of an inhaled corticosteroid (ICS) rather than a long-acting, inhaled beta-agonist for treatment of mild persistent asthma (Step 2 therapy [12]). What is the appropriate therapy when low-dose inhaled corticosteroids fail to provide adequate control of asthma? The available options are: to increase the dose of inhaled corticosteroids; to add an inhaled LABA; to add sustained-release theophylline; or to add a leukotriene pathway modifying agent. From the standpoint of control of the typical parameters used to assess asthma control, the LABA-ICS combination is clearly the most effective. Meta-analyses have confirmed that adding a LABA to a dose of ICS which is failing to control asthma adequately produces a superior reduction of symptoms and use of rescue medication, and superior improvement in pulmonary function, when compared with doubling (or more than doubling) the dose of ICS [14]. A meta-analysis of nine randomized, controlled studies of salmeterol vs. theophylline, in which the majority were using inhaled corticosteroids, similarly showed salmeterol to be superior in terms

of both symptoms and pulmonary function [15]. At least three studies have compared, in patients whose asthma was not adequately controlled by low dose inhaled corticosteroids, the addition of salmeterol or a leukotriene receptor antagonist [16–18]. For each study, all measures of symptom control, rescue albuterol use and pulmonary function improvement, favored the addition of the LABA over the addition of the leukotriene receptor antagonist.

If the results of adding a LABA to an incompletely-effective dose of ICS is so clearly the most effective choice at Step 3 of asthma therapy, why is there any question regarding their use in this situation? The only answer is the concerns with safety. The addition of a higher dose of inhaled corticosteroid, of theophylline, or of a leukotriene pathway modifier, are all perceived as steps which add additional anti-inflammatory activity, whilst the addition of a LABA is perceived as a step adding only a bronchodilator. Is this correct?

Evidence suggesting an anti-inflammatory action of LABAs when added to ICS

The first suggestion that LABAs might be more than just a bronchodilator when they are added to an ICS came with the FACET study [19]. Eight-hundred and fifty-two patients with asthma were first treated for four weeks with 800 mcg of budesonide twice daily. They were then randomized to either budesonide 100 mcg or 400 mcg twice daily, and half in each group received additional formoterol 12 mcg twice daily. As might be anticipated, all the conventional measures of asthma control, pulmonary function, symptoms and rescue albuterol use were improved by the addition of formoterol to either dose of budesonide. What was not anticipated was that the addition of formoterol to either dose of budesonide reduced the occurrence of asthma exacerbations — both minor exacerbations and those requiring prednisone treatment. A meta-analysis examining the addition of salmeterol to low dose inhaled corticosteroids as compared to at least doubling the dose of ICS confirmed the findings of FACET [14] — namely, that the addition of the LABA produced a greater reduction in exacerbations than the higher dose of ICS. Furthermore, two studies comparing the addition of salmeterol or the leukotriene antagonist montelukast to an inhaled corticosteroid found that there were significantly fewer exacerbations of asthma with the LABA plus ICS compared to the LTRA plus ICS [16,18].

Exacerbations of asthma are considered to be a reflection of ongoing airway inflammation and hence a reduction in exacerbations is considered evidence of anti-inflammatory activity. Direct evidence for some anti-inflammatory activity of LABAs when added to ICS has also been sought (see Table 1). In each study there was a significant anti-inflammatory effect seen with the combination of an inhaled steroid and salmeterol, which was not seen with the same dose of inhaled steroid alone — or in two cases with a considerably higher dose of inhaled steroid alone [20–22].

A re-examination of the SMART study

In view of the great difference in the effect of LABAs on underlying airway inflammation when combined with an ICS as opposed to being given as monotherapy, it is appropriate to examine the use of ICSs in those studies reporting deleterious

Table 1 Anti-inflammatory effects of LABAs added to ICSs

Li [20]	Participants	Duration	ICS + Placebo	ICS + salmeterol	ICS + Fluticasone
	45 on ICS	12 weeks	N.C.	↓Eosinophils in lamina propria $p < .01$	↓Activated lymphocytes
Wallin [21]			FP 200 μg bid	FP 200 μg + salmeterol 50 μg bid	FP 500 μg bid
	56 previously on ICS	12 months	N.C.	↓ Mast cells	N.C.
Koopsmans [22]				FP + salmeterol	FP
	26 cross-over	Bronchial challenge		↓Serum IL-5 at 1 and 6 hours; ↓peripheral eosinophils at 6 and 24 hours	

N.C. = No change.

Table 2 Adverse Outcomes in the SMART study in relation to ICS use at Randomization [2]

	Salmeterol	Placebo	Relative Risk
Incidence of asthma deaths and life-threatening experiences			
Baseline ICS use	16	13	1.2404 N.S.
No baseline ICS use	21	9	2.3920 (1.0964,5.2188
Incidence of asthma deaths			
Baseline ICS use	4	3	1.3522 N.S.
No baseline ICS use	9	0	Not calculable

outcomes with LABAs. The Serevent Multicenter Asthma research Trial (SMART) was initiated in the U.S. in 1996 [2]. Subjects with asthma, 12 years of age or over, who had not previously used a LABA, were enrolled. They were seen once in one of 6,163 clinical research centres at which time they were given a seven-month supply of salmeterol or placebo. The only subsequent contact was by a monthly telephone call. A total of 26,357 subjects were enrolled. The outcome of interest was an asthma attack resulting in death or intubation. This occurred in 37 subjects who had randomized to salmeterol and 22 on placebo, a difference that was statistically significant (95% confidence intervals 1.0075, 2.8912). What of the use of inhaled corticosteroids? Forty-eight percent of the subjects reported using inhaled corticosteroids when they were seen at randomization. There was no attempt to determine degree of adherence with inhaled corticosteroids at randomization or persistence in their use during the course of the study. Despite these limitations, the excess of all life-threatening events and of asthma deaths was largely in those denying ICS at randomization (Table 2). The excess of life-threatening and fatal attacks in African-Americans in the SMART study has been well publicized. A possible explanation for this excess is that the African-Americans were less often using ICS and had less well-controlled asthma as judged by pulmonary function, symptoms, or emergency room or hospital visits in the previous year. However, if the SMART study is analyzed by the two phases of recruitment, a different picture of risk emerges. During the first phase, subjects were recruited by media advertising and, on responding to a telephone number, were assigned to investigators based on geographical proximity. In the second phase, subjects were recruited by the investigators. Even though only 58% of subjects were recruited in the first phase and there was a higher percentage of African-Americans in the second phase, almost all the excess intubations and deaths occurred in subjects recruited in the first phase (Table 3). This suggests that a small group of subjects with asthma, not on inhaled corticosteroids, and likely to be without ready access to medical care, received symptomatic relief with salmeterol, which masked worsening asthma until it became so severe that it resulted in a fatal or near-fatal attack.

Are the untoward outcomes in the SMART study due to β_2-adrenergic receptor polymorphism? Patients having the Arg: Arg 16 genotype of the β_2-adrenergic receptor have been reported as not doing well with salmeterol [23] or as doing well [24]. Either way, the Arg: Arg 16 genotype is not an apt explanation of the findings in the SMART study. Twelve percent of Caucasians and 22% of African-Americans have been reported to have that genotype. Therefore, there were more Caucasians than African-Americans with Arg; Arg 16 in the SMART study, yet all the excess adverse events were in the African-American subjects.

Is there synergy between LABAs and ICSs?

The reduction in asthma exacerbations is difficult to explain on the basis of the addition of a

Table 3 Adverse Outcomes in the SMART study in relation to phase of recruitment [2]

	Phase 1 $N = 15,342$, A-A 17%		Phase 2 $N = 11,013$, A-A 19%	
	Salmeterol	Placebo	Salmeterol	Placebo
Asthma Death & intubation	31	17	6	5
Asthma Death	10	3	3	0

A-A = African-American.

bronchodilator to an anti-inflammatory ICS. This raises the issue of possible synergy between the two classes of drugs. Arguments for synergy relate to three observations. The first, already discussed, is the reduction of exacerbations — and therefore presumably in airway inflammation — with the addition of a LABA to an ICS. However, one analysis of nearly a thousand subjects who received either fluticasone proprionate (FP) 88 mcg plus salmeterol 42 mcg, or FP 220 mcg twice daily, found that there were not only fewer exacerbations with the combination (8.8 percent vs. 13.8 percent) but also that the response to prednisone treatment of the exacerbation was about two days sooner with the combination therapy [25]. Another study suggesting some synergy between LABAs and ICSs is a meta-analysis that compared four studies in which the same doses of salmeterol and of fluticasone were administered either in separate or the same canisters [26]. There was a significantly greater improvement in morning peak flow if the two drugs were delivered from the same canister. The most reasonable explanation for this finding is that the effect of the two drugs is enhanced if they are delivered to the same cell — in other words, synergy.

There is strong support for the occurrence of synergy between the LABAs and the ICSs. In vitro studies have shown that activation of the β-adrenergic receptor by LABAs primes the glucocorticoid receptor (GR) so that the corticosteroid is more readily translocated into the nucleus where it exerts its anti-inflammatory activity [27]. This LABA-induced GR-primed enhanced translocation has been demonstrated in cells obtained from sputum induced from subjects inhaling the combination of an ICS and a LABA compared to those inhaling either an ICS or a LABA alone [27,28]. The combination of FP 100 mcg and salmeterol 50mcg enhanced GR nuclear translocation to a degree comparable to that seen with 500mcg of FP alone [27]. The enhanced nuclear translocation in subjects inhaling the combination, as compared to those on either drug alone, was also associated with greater evidence of steroid-mediated effects in the nucleus such as suppression of cytokine secretion from sputum cells, and granulocyte macrophage-colony stimulating factor (GM-CSF), released on activation of normal T cells expressed and activated (RANTES), and interleukin-8 [28]. Thus, there is evidence supporting the occurrence of a beneficial interaction between LABAs and corticosteroids *in vitro* in a number of airway cells relevant to asthma. This interaction may explain the enhanced favorable effect on exacerbations repeatedly observed with the combination of a LABA and an ICS.

Additional benefits from combining LABA with ICS

Despite the convincing evidence of the effectiveness of ICS in most patients with asthma, it is well known that patients' adherence to treatment with these drugs is often poor [29]. Reasons are many and include: fear of steroids; not understanding what the role is of ICS in asthma treatment; cost; and lack of any sense of immediate benefit from their use. The combination of a LABA with an ICS overcomes the last of these causes. A 24-month analysis was conducted of patient adherence to prescribed medication using administrative claims data from a large managed care organization [30]. Prescription refill rates in 3503 patients were compared for salmeterol, fluticasone, the salmeterol-fluticasone combination, and montelukast. The refill rate for the salmeterol-fluticasone combination (3.98) was significantly higher than for fluticasone alone (2.29), or the fluticasone component of the combination when dispensed in separate devices (2.36), or with montelukast (2.15). Those who are concerned with the potential side effects of inhaled corticosteroids are reassured by using the lowest possible dose. The combination of a LABA with the ICS again helps accomplish this [31]. Seven hundred and sixty subjects with asthma entered a study to demonstrate this steroid-sparing effect of salmeterol. Subjects were required to be well controlled on 250 mcg twice-daily of FP, but to show deterioration in asthma control when the ICS dose was reduced to 100 mcg twice daily. They were then stabilized again on the 250 mcg twice-daily dose before randomization to either continue receiving the 250 mcg twice-daily dose or to receive salmeterol-fluticasone combination 50/100 mcg twice-daily. Five hundred and fifty-eight subjects met the final randomization criteria and entered the study, which lasted for 12 weeks for half the subjects and 24 weeks for the other half. Although the study was designed to show that the combination was not inferior to the higher dose of ICS alone, most of the outcomes were significantly better with the lower dose of ICS plus LABA, including pulmonary function, percent of symptoms free days, use of rescue albuterol and percent of rescue free days, while the withdrawal rate for worsening asthma over the first 12 weeks was 5% in the combination group and 7% in the high dose ICS group.

Conclusions

The combination of a long-acting inhaled beta-agonist (LABA) with a low-dose of inhaled corticosteroid (ICS) is the treatment of choice when the low dose inhaled steroid is not sufficient.

The combination of a LABA and an ICS is more effective than a higher dose of ICS or combination of a low dose of ICS with any of the other alternatives — theophylline, or a leukotriene pathway modifying agent. This superiority extends to all the components of asthma control including pulmonary function, symptoms, rescue inhaler use, and exacerbations.

There is evidence both *in vitro* and *in vivo to* suggest that there is a favorable interaction between LABAs and ICSs at the receptor level, leading to enhanced steroid effect.

The addition of a LABA to an ICS also increases patient adherence to ICS therapy, both by providing a feeling of immediate symptom improvement and by allowing the use of a lower dose of ICS.

Balanced against all these advantages of LABA use is the question of safety. Careful examination of the reports which have caused concern in this regard does not reveal any evidence of an increased risk associated with the appropriate use of LABAs in asthma — i.e. in combination with an ICS. There is much to suggest that the adverse outcomes with LABA monotherapy have been due to 'masking of inflammation' rather than a toxic effect of the drugs. This has likely allowed, in some instances, worsening asthma to be overlooked, with dire consequences. Studies in subjects receiving combination therapy with LABA plus ICS suggest, if anything, an enhanced anti-inflammatory action with the combination, superior to that achieved with the ICS alone at the same dose.

Perhaps the final proof of the safety of the LABAs comes from asthma mortality data in the U.S. Deaths from asthma peaked in 1996 at 5667. This was two years after the introduction of salmeterol in the US. Subsequently, use of salmeterol, largely in combination with fluticasone, has increased 5-fold while deaths from asthma in the U.S. have steadily fallen to 3780 in 2004, the last year with official data [32,33].

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