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Continued overleaf

Long acting beta₂ agonists: are they safe?

These agents are very effective add-on therapies for asthma patients who fail to respond to low-medium doses of inhaled corticosteroids, but their safety remains uncertain

The story of modern bronchodilator therapy began with the use of adrenal extract to treat asthma in 1900. Ephedrine was introduced in 1924. α and β receptors were defined by Ahlquist in 1948, and this led to the development of the first drug (isoprenaline) with specific β actions. Lands and his colleagues showed that the β receptors had 2 subgroups with β_1 being responsible for inotropic and chronotropic effects on the heart, and β_2 mediating bronchodilation. This led to development of agents with relative selectivity, having a much greater effect on β_2 receptors than on β_1 receptors.

Much controversy has surrounded the use of short-acting β -agonists in patients with asthma since their introduction over 50 years ago [1]. Asthma mortality rates increased worldwide in the 1960s, when inhaled β -agonists were introduced to the market [2]. Similar increases in mortality were seen in New Zealand when the strong inhaled β -agonist fenoterol was introduced; mortality decreased rapidly when use of the drug was severely curtailed, and widespread use of inhaled corticosteroids (ICS) was instituted [3].

Until the early 1990s, the only effective inhaled bronchodilators available were short-acting β_2 agonists such as salbutamol. Since they have a duration of action of only 4 to 6 hours, patients whose asthma symptoms were not controlled by inhaled corticosteroids needed to use them several times a day to obtain continuous relief. To overcome this problem, inhaled β_2 -agonists with a duration of action of 10 to 16 hours were developed. These long-acting beta-agonists (LABA), such as salmeterol and formoterol, are effective in improving symptom control and lung function for 12 hours or more when added to inhaled corticosteroid therapy. A striking observation is that this clinical benefit of adding β_2 agonists applies for LABA, but not for short-acting β_2 agonists [4]. Slow release β_2 agonists tablets also improve lung function and symptoms, but side-effects occur more frequently.

The long-acting β_2 -agonists have been widely prescribed for the management of asthma for some years, but their use too has been controversial for much of that time. The safety of LABA has been and continues to be a matter of great concern. As monotherapy with LABA is considered to have little or no anti-inflammatory effect in asthma, despite offering significant symptomatic relief, and adding LABA to an unchanged dose of ICS would insufficiently control the underlying inflammation, or might even mask its progression, resulting in the loss of long term asthma control. Although several studies [5, 6] and a Cochrane database review [7] have supported the efficacy and safety of LABA for treating asthma, others [8, 9] have reported worrisome rates of serious asthma morbidity and death with their use.

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Wijerama House
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After the United States Food and Drug Administration (US-FDA) received post-marketing reports of several asthma-related deaths associated with the long-acting β_2 -agonist salmeterol, the salmeterol multi-centre asthma research trial (SMART) [9] was performed. Inexplicably, SMART was not designed to test the hypothesis that salmeterol was safe to use as an adjunct to inhaled corticosteroids: patients underwent randomization without consideration of their current corticosteroid therapy, and no records of such therapy were kept during the trial. This study followed more than 26 000 participants for 6 months, and found a 4-fold increased risk for asthma-related deaths. The trial data were not initially published, but were submitted to the US-FDA. In July 2005, an advisory panel to the FDA concluded that strong warnings of increased risk should be placed on the labeling of all LABA, with recommendations that they be used only after other asthma drugs have failed [10, 11]. The results of SMART were subsequently published [9].

Recently, a new participant entered the debate on the safety of LABA. That is the meta-analysis by Salpeter and colleagues [12]. Pooled results from 19 trials with 33 826 participants, of whom 26 000 came from the SMART study, followed for 16 848 patient-years showed that, LABA use increases the risk for hospitalizations due to asthma, life-threatening asthma exacerbations, and asthma-related deaths. Similar risks were found with salmeterol and formoterol in both children and adults. Concomitant inhaled corticosteroids did not adequately protect against these adverse effects. The use of LABA could be associated with a clinically significant number of unnecessary hospitalizations, intensive care unit admissions, and deaths each year.

However, the assertion that concomitant use of ICS does not adequately protect against rare adverse events associated with LABA use is not valid as this meta-analysis included only studies for which patients were randomized to LABA or placebo, and nearly 50% of patients were not receiving concomitant ICS. There are numerous studies in patients receiving ICS and LABA. In fact, a meta-analysis of 18 studies concluded that asthma exacerbations were infrequent and similar in ICS plus LABA group compared to ICS alone [7].

Both the SMART study and the meta-analysis by Salpeter and colleagues have failed to give clear answers to the questions on the safety issues of LABA when used as an adjunct to ICS. Further studies are needed to re-evaluate whether concomitant use of inhaled corticosteroids can completely protect against the adverse effects of LABA and whether the benefits of LABA are worth the risks. Until the manufacturers of these drugs undertake such studies to clear the air, the safety of long-acting beta-agonists will remain uncertain.

Considering all the available data, what recommendations can we make to the clinicians now?

It is essential to follow current guidelines [13, 14] that emphasize the use of inhaled corticosteroids as the first line of treatment for patients with mild to moderate persistent asthma symptoms, as it has been clearly shown that the ICS are better and safer than LABA (and leukotriene modifiers or theophyllines) as initial therapy. Exact threshold for introduction of steroid inhalers has never been firmly established. A British guideline [13] recommends starting ICS if there have been exacerbations of asthma in the last 2 years, there has been a need to use inhaled β_2 agonists more than 3 times per week, symptomatic more than 3 times per week or waking more than 1 night per week. An American guideline [14] recommends initiating ICS, if symptomatic more than 2 times per week but less than 1 time per day, or more than 2 nights per month. For patients who do not achieve at least good control (minimal daily or nocturnal symptoms and infrequent exacerbations requiring systemic corticosteroids or emergency department visits) with ICS, several options are available.

Strong evidence from clinical trials consistently indicates that the use of LABA added to low-to-medium doses of ICS, leads to improvements in lung function and symptoms, and reduces the need for quick relief with short-acting β_2 agonists. However, 40 to 50 percent of all patients with uncontrolled asthma achieve good control with moderate doses of ICS (fluticasone 500 μ g per day) alone, with only 10 to 15 percent more achieving the same control with the addition of LABA [6]. Adding a leukotriene modifier or theophylline to ICS or doubling the dose of ICS also improves outcomes, but the evidence is not as substantial. The role of long term anticholinergics, such as tiotropium bromide, has yet to be established in patients with persistent asthma, as no randomized controlled trials support this therapy [15]. Adjunctive therapy combinations have not been studied in children younger than 5 years of age. For this age group, there are two preferred options for treating moderate asthma: either the addition of LABA to a low dose of ICS, or medium-dose ICS as monotherapy.

In conclusion, ICS in sufficient amounts (ie. beclomethasone dipropionate 400-800 μ g a day for adults and 200-400 μ g a day for children) should be used as initial therapy to control symptoms in patients with mild to moderate persistent asthma symptoms. LABA should not be used as monotherapy for such patients, but these agents are one of the most effective add-on therapies for patients who fail to respond to low-medium doses of ICS, though safety of LABA remains uncertain. Such patients may also benefit from the addition of leukotriene-receptor antagonists, low-dose theophylline therapy or doubling the dose of steroids. At present, it is not possible to recommend one over the others, although the FDA recommends the use of LABA only after the other drugs have failed. Patients should be advised not to use LABA as "rescue" medication, and to also have a short-acting bronchodilator to use as needed for acute asthma symptoms. LABA should not be initiated in patients with acutely deteriorating asthma, and should never be used as a replacement for ICS. Patients should be taking optimal doses of ICS before starting LABA therapy and only the lowest effective dose should be prescribed.

References

1. Taylor DR, Sears MR, Cockcroft DW. The beta-agonist controversy. *Medical Clinics of North America* 1996; **80**: 719-48.
2. Hussey PS, Anderson GF, Osborn R, Feek C, McLaughlin V, Millar J, et al. How does the quality of care compare in five countries? *Health Affairs* 2004; **23**: 89-99.
3. Beasley R, Pearce N, Crane J, Burgess C. Withdrawal of fenoterol and the end of the New Zealand asthma mortality epidemic. *International Archives of Allergy and Immunology* 1995; **107**: 325-7.
4. Taylor DR, Town GI, Herbison GP, Boothman-Burrell D, Flannery EM, Hancox B, et al. Asthma control during long-term treatment with regular inhaled salbutamol and salmeterol. *Thorax* 1998; **53**: 744-52.
5. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *American Journal of Respiratory and Critical Care Medicine* 2005; **171**: 129-36.
6. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *American Journal of Respiratory and Critical Care Medicine* 2004; **170**: 836-44.
7. Ni Chroinin M, Greenstone IR, Ducharme FM. Addition of inhaled long-acting beta₂-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naïve adults. [Systematic Review] *Cochrane Airways Group Cochrane Database of Systematic Reviews*. August 2005.
8. Martin RM, Shakir S. Age- and gender-specific asthma death rates in patients taking long-acting beta₂-agonists: prescription event monitoring pharmacosurveillance studies. *Drug Safety* 2001; **24**: 475-81.
9. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006; **129**: 15-26.
10. U.S. Food and Drug Administration. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Pulmonary and Allergy Drugs Advisory Committee. Transcript of 13 July 2005 meeting. Accessed at <http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4148T1.pdf>
11. U.S. Food and Drug Administration. FDA Public Health Advisory. Serevent, Advair, Foradil. 2005. Accessed at <http://www.fda.gov/cder/drug/advisory/LABA.htm>
12. Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-analysis: effect of long-acting β -agonists on severe asthma exacerbations and asthma-related deaths. *Annals of Internal Medicine* 2006; **144**: 904-12.
13. British guideline on management of asthma. A national clinical guideline, British Thoracic Society and Scottish Intercollegiate Guidelines Network, November 2005.
14. National Asthma Education and Prevention Program. NAEPP Expert Panel Report, Guidelines for the Diagnosis and Management of Asthma – Update on Selected Topics 2002, NIH Publication No. 02-5075.
15. Westby M, Benson M, Gibson P. Anticholinergic agents for chronic asthma in adults, *Cochrane Airways Group Cochrane Database of Systematic Reviews* 2004.

Bandula Wijesiriwardena, Physician, Colombo South Teaching Hospital, Kalubowila, Sri Lanka.
e-mail: <bandulawije@lycos.com>. (Competing interests: none)