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Editorial

LABAs and Asthma: From the SMART Study to the SMART Approach

Inhaled beta-2-agonists have been used for almost half a century in the treatment of asthma. Yet the use of the long-acting beta-agonists (LABAs) formulations remains mired in controversy, and the verdict on their benefit-to-risk ratio repeatedly questioned. The LABAs, when used with or without inhaled corticosteroids (ICS) confer beneficial effects to patients with asthma. A Cochrane review[1] that analysed 85 randomised controlled trials using LABAs found statistically significant improvements in morning peak expiratory flow rates, asthma symptoms, quality of life, and the need for rescue medications when compared to placebo. When used in combination with ICS, there was a significant reduction in asthma exacerbations as well. Global Initiative for Asthma guidelines[2] recommend their use in Step 3 or 4 in the management of asthma, *i.e.* stages associated with a poor level of control despite low-dose ICS.

The controversy regarding the use of LABAs began in the 1960's when an epidemic of asthma deaths was observed in atleast six countries, including England and New Zealand. This epidemic coincided with the use of an aerosolised formulation of a high-dose β_2-agonist isoprenaline, called "Isoprenaline Forte", and was reported only in countries where this high-dose formulation, containing almost five times the standard dose was used.[3] In the 1970's a second epidemic of asthma-related deaths took place in New Zealand, and this temporally coincided with and was attributed to the use of a new short-acting β_2-agonist fenoterol.[4] The termination of the epidemic also coincided with the withdrawal of the drug from the market.

Salmeterol and formoterol were developed by Glaxo-SmithKline (GSK) and Novartis, respectively, in the 1990s. Both drugs had a duration of action of more than 12 hours, the major difference being the rapid onset of action with formoterol.[5,6] With the apprehension created by the earlier epidemics of asthma mortality associated with β_2-agonists, the Serevent Nationwide Surveillance (SNS) trial was commissioned in the United Kingdom to analyse the safety of salmeterol. Twenty-five thousand and one hundred eighty-nine asthma patients were randomised in a 2:1 ratio to receive either salmeterol 50µg twice a day or albuterol 200µg four times a day, in addition to their existing asthma therapy for 16 weeks. The relative risk of death in the salmeterol group was three times that in the albuterol group, although this was not found to be statistically significant.[7]

The largest and the most cited evidence against the use of LABAs comes from the Salmeterol Multicenter Asthma Research Trial (SMART),[8] a study that was conducted as a consequence of the fears raised by the SNS trial. The study was launched in 1996, with the aim of recruiting 60,000 patients. The patients were randomised to receive either salmeterol 42µg twice a day or placebo in addition to their regular asthma therapy for 28 weeks. In 2003, the study was prematurely terminated because of difficulty in enrolling the targeted number of patients, and because of an interim analysis that revealed significantly higher rates of secondary outcomes (respiratory-related deaths, asthma-related deaths, combined asthma-related life-threatening experiences). Among the 26,355 subjects studied, adverse outcomes were mainly seen in African Americans, and in this cohort, those patients who were not taking ICS prior to randomisation were found to be at greatest risk. However, the authors admitted that since SMART was not designed to evaluate the influence of ICS on study outcomes, no valid conclusion could be drawn from the study regarding the use of ICS.

Several hypotheses have been postulated to explain increased mortality due to LABAs. A postulated mechanism is the direct cardiotoxicity due to overdosing coupled with concurrent hypoxia. Overdosing with LABAs has been postulated to be a consequence of poorly controlled asthma with worsening symptoms. Tolerance to LABAs resulting from a combination of reduced receptor numbers secondary to receptor internalisation and reduced production along with uncoupling of receptors to downstream signalling pathways following repeated activation is also a possible reason why patients overdose on the drugs.[9] Higher doses of LABAs, coupled with hypoxia has been shown in experimental models to be cardiotoxic, causing fatal cardiac depression and asystole.[10] The reduction of peripheral vascular resistance leading to decreased diastolic blood pressure has also been hypothesised as being a contributory factor to death.[11] Hypokalemia caused by these drugs can cause ventricular tachyarrhythmias as well.[12]

Genetic factors have also been postulated to be responsible for the adverse effects of LABAs. Genetic polymorphisms of amino-acid 16 (arginine or glycine) of the β_2 adrenergic receptor play an important role in the clinical response to β-agonists.[13]African-Americans more commonly have the Arg/Arg 16 genotype, a genotype that confers an individual with an increased risk of adverse events with the use of LABAs.[14] Prolonged QTc interval, an adverse effect of β_2-agonists, has also been postulated to be seen more frequently in certain races.[15]

LABAs have also been blamed for masking inflammation. In the Salmeterol or Corticosteroids (SOCS) study,[16] comparing the use of triamcinolone 400µg twice a day with salmeterol 42µg twice a day and with placebo in patients with mild persistent asthma, it was found that although spirometric parameters and symptoms were similar in the salmeterol and triamcinolone groups, there was a statistically significant increase in sputum eosinophils in the salmeterol group compared to the triamcinolone group, suggesting that the improvement in symptoms among asthmatic patients on LABAs might mask the underlying inflammation, and this unchecked and possibly worsening inflammation predisposes these individuals to serious, life-threatening asthma exacerbations.

A recent meta-analysis that included 215 studies with 106,575 subjects,[17] concluded that the odds-ratio (OR) for risk of asthma mortality with the use of LABAs was 2.7 (95% confidence interval [CI] 1.4 to 5.3). However, in the subset of patients not prescribed ICS, the OR was 7.3 (95% CI 1.8 to 29.4). In 63 other studies where subjects were randomised to receive the combination of salemeterol/ fluticasone or ICS, no mortality was reported among 22600 patients. Recent Cochrane reviews[18,19] analysing the same question have come to similar conclusions. The US Food and Drug Administration reviewed the risks and benefits of inhaled LABAs for asthma and concluded that for adults the benefits of combination inhalers outweighed the risks.[20] While some analyses have reported a greater mortality in combined inhalers that use formoterol as the LABA component,[17] other reviews have refuted this claim.[21]

The OPTIMA trial[22] had an arm that included 698 patients with mild persistent asthma randomised to receive placebo, low-dose ICS monotherapy (budesonide 100µg twice a day) or the combination of budesonide 100µg twice a day and formoterol 4.5µg twice a day. While both treatment groups had superior rates of exacerbation over a year when compared to placebo, there was no difference between the treatment arms. Given the adverse effect apprehensions of LABAs, it would seem prudent to use low-dose ICS monotherapy in patients with mild persistent asthma.

An adequately powered, randomised controlled study[23] that compares mortality and clinical parameters between patients using varying doses of ICS with patients using ICS/LABA combined inhalers would settle the controversy over the increased mortality attributable solely to LABA use. However, such a study designed to rule out a 20% increase in mortality would require approximately 700,000 subjects per group,[23] and is therefore, unlikely to be conducted. In the absence of such a study, and given the benefits of use of LABAs, it would be reasonable to conclude from the above meta-analyses that LABAs, when used for the treatment of asthma, should be used in combination with ICS.

An unpublished questionnaire-based study of disease control among asthmatic patients in South Asia was conducted in 2002. The study was commissioned by a pharmaceutical company and conducted by A.C. Nelson, a market research firm. The study, titled "Asthma insights and reality in South Asia (AIRSA)", in its Indian arm identified 403 current asthmatic patients by surveying 8000 households in nine cities in the country. A gross paradox was noticed in the results: despite the fact that more than 85% of the subjects interviewed were found to be poorly controlled with their current medication, only 2% of respondents used ICS in the control of their asthma, highlighting a reality that non-ICS mono- and poly-therapy is widely abused in India, and data on the adverse consequences of such an approach are lacking.

While a ban on the sale of LABAs as single-drug inhalers may seem like a simple solution for India, the clinical overlap between patients with asthma and chronic obstructive pulmonary disease (COPD), and the established role of LABAs in COPD coupled with a controversial role of ICS in COPD make a ban unfeasible.

The Symbicort SMART[24] inhaler solution that suggests the use of a single inhaler (budesonide and formoterol in combination) for maintainence and reliever therapy in the treatment of asthma is a step in the right direction, as it prevents LABA monotherapy. However, the strategy does have the potential of exposing the patient to high doses of LABAs, *albeit* with concomitant ICS therapy, and vigilance is warranted in the use of this novel and promising solution to better asthma control. The maximum approved dosage per day with this approach (36µg/day formoterol in adults and 18µg/ day in children below 12 years of age)[25] needs to be emphasised and made clear to the patients when their asthma control strategy includes this single inhaler approach.

In conclusion, the proven benefits of LABAs in the improvement of subjective and objective parameters of asthma control in patients with moderate to severe asthma, and their role in decreasing the need for higher doses of ICS make them valuable drugs in the management of the disease. However, caution needs to be exercised in prescribing them without adequately controlling the inflammation that is the hallmark of the disease. When used along with ICS, they have been found to be safe and effective and can be recommended for use.

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