ARE LONG ACTING BETA AGONISTS SAFE?

JA Gogtay, SB Chhowala, Mumbai

INTRODUCTION

Asthma is a common chronic condition affecting people across age groups. It is estimated that globally 300 million people suffer from asthma. Guidelines for asthma, which have been available for nearly two decades, recommend inhaled corticosteroids (ICS) as first line maintenance treatment. However, for those patients not controlled on ICS alone the guidelines recommend the addition of inhaled long-acting beta-agonists (LABA’s) as a preferred option to increasing the dose of ICS or adding a leukotriene antagonist such as montelukast.

The two LABA’s; salmeterol and formoterol have been available since the early 1990’s. Though both these drugs belong to the same class of bronchodilators, they differ in their properties resulting in different rates of bronchodilation and duration of bronchodilator effect. The availability of the LABA’s was considered to be a major advance in asthma management. When given with ICS, LABA’s have shown to improve symptoms and lung function; reduce hospitalization and enhance the quality of life thereby reducing the morbidity caused due to asthma.

However, in spite of a successful and optimistic introduction LABA’s were soon mired with controversy. Going back into history, in the 1960’s and 70’s the more potent short acting β2-agonists isoproterenol and fenoterol were associated with increased asthma related deaths which led to their withdrawal from the market. With this background, there was always a concern that the use of LABA’s regularly may mask the underlying inflammatory process and symptoms, which might produce adverse asthma outcomes.

THE ISSUES WITH LABAS

The SNS and SMART studies

The SNS study (Serevent Nationwide Surveillance Study) was the first randomized, 16 week study performed in 1993 by Castle et al, to compare the safety of salmeterol and salbutamol (the most widely used short-acting β2-agonist) in asthma. 25,180 asthma patients requiring regular treatment with bronchodilators were recruited by their general practitioners in a 2:1 salmeterol: salbutamol ratio. The salmeterol group had 16,787 patients and salbutamol had 8393 patients.

There were 12 asthma related deaths in the salmeterol group and two in the salbutamol group, a three-fold higher risk of asthma related death in the salmeterol arm; however this finding was not statistically significant. Only 70% of patients received ICS and there were a higher proportion of withdrawals in the salbutamol group. The authors concluded that “Treatment over 16 weeks with either salmeterol or salbutamol was not associated with an incidence of deaths related to asthma in excess of that predicted... Serious adverse events occurred in patients most at risk on entry and were probably due to the disease rather than the treatment.” However, letters to the British Medical Journal questioned whether the mortality difference, though not statistically significant, may have been clinically significant.

The findings of the SNS study promoted the US-Food Drug Administration (FDA) to ask for further studies on the safety of salmeterol from the manufacturers. The SMART Study (Salmeterol Multicentre
Are Long Acting Beta Agonists Safe?

Asthma Research Trial) by Nelson et al was therefore designed under the mandate of the US-FDA.

This was a multicentre, randomized, double-blind, placebo-controlled, observational study designed to evaluate the effects of salmeterol on respiratory and asthma related deaths or life-threatening events (Figure 1). The study enrolled 26,355 subjects (> 12 years) to compare salmeterol (50 mcg, twice daily, administered by a metered dose inhaler) versus placebo when added to usual medications for asthma over a 28 week period. Recruitment to the trial was by large scale advertising through print, radio and television and later through study investigators.

An interim analysis of 26,355 patients resulted in an early termination of the study in 2003. The reasons cited for termination were increased asthma-related deaths in African-American subjects and difficulties in enrollment. The estimated sample size for the trial was 60,000 patients, but only approximately 26,000 could be enrolled. Based on the findings of this study in November 2005, the US-FDA announced important safety information regarding inhalers containing the LABA-salmeterol (Table 1).

CRITICAL ANALYSIS OF THE SMART STUDY

Less than half of the patients in the study were receiving inhaled steroids and in the African American group only 38% were taking ICS. Although the SMART study was not performed to evaluate the efficacy of ICS, the role and importance of ICS in asthma management was reaffirmed. When ICS was used, the combined asthma-related death or life-threatening experience was 1.24 (RR; 95% CI 0.59, 2.58) compared to 2.39 (RR; 95% CI 1.09, 5.22); indicating a statistical significant difference. The baseline characteristics of the African-American population with that of the whites were different. The former had lower lung function, more nocturnal symptoms, frequent emergency department visits and lesser ICS usage at baseline.

Therefore, the possibility of increased number of deaths in the African-American population could be due to the more severe disease or may be due to genetic predisposition such as increased prevalence of the Arg-Arg polymorphism at position 16 of the β2-receptor. Moreover, compliance to treatment was also poor in this subgroup of patients.

FDA joint advisory committee report (December 2008) found that an asthma composite endpoint (asthma-related death, intubation or hospitalization) showed a statistically significant risk difference estimate for LABA without assigned ICS v/s. non-LABA treatment of 3.63 (95% CI 1.51, 5.75) per 1000 subjects. There was a statistically non significant risk difference estimate for LABA with assigned ICS v/s assigned ICS treatment of 0.25 (95% CI – 1.69, 2.18) per 1000 subjects. The risk was similar or slightly higher in children.

The lead author of the SMART study published a paper a year later clarifying some of these issues and the manner in which patients were recruited. The conclusion was that there was no increased risk.

PLAUSIBLE MECHANISMS FOR THESE FINDINGS

Subsensitivity

Regular use of LABA's may lead to the loss of their bronchoprotective effects. This may happen as a result of down-regulation, receptor internalization and the uncoupling of the G-protein-adenyl cyclase unit with subsequent development of tachyphylaxis of the response to the effects upon smooth muscle and inflammatory cells. However, this
phenomenon does not generally apply to the bronchodilator effects. Subsensitivity of the $\beta_2$-receptor may also occur when using ICS.

$\beta_2$-agonist Polymorphisms

It has been suggested that asthmatics who are homozygous for arginine (Arg-16) have an impaired therapeutic response to salmeterol regardless of their concomitant ICS use. Such polymorphisms may be more common in patients of different ethnic backgrounds.

Masking of Inflammation

Due to the immediate bronchodilation offered by LABA's patients sometimes tend to use LABA's more regularly but adhere less stringently to the prescribed ICS. This may lead to masking of the underlying inflammation and make the patient more susceptible to exacerbations in response to triggers and over the years may be airway remodeling. There are conflicting reports on the anti-inflammatory properties of LABA's.

Reliever Effect in Acute Asthma

Regular use of LABA's as mentioned earlier may lead to the subsensitivity of the $\beta_2$-receptor. This may cause a blunting in the reliever response to salbutamol during an exacerbation.

Results from Other Meta-Analysis indicate no increased risk or indicate benefit

Several meta-analyses based on the randomized controlled trials assessing the use of LABA's and the risk of asthma related deaths have since been published. A summary of some key results are presented in Table 2. Overall, all these meta-analysis results suggest that increased risk of asthma death seems to occur only when studies that have used LABA without ICS are included. The Cochrane analysis of LABA's by Cates et al in 2009, showed no difference in asthma-related deaths due to salmeterol when added to ICS. Malcolm Sears et al have indicated that patient outcomes are optimal when LABAs are used in sufficient doses of ICS needed to control inflammation.

RECOMMENDATIONS FOR LABAS IN ASTHMA

All the studies reviewed have shown that LABA's which added to ICS have actually reduced the risk of exacerbation and improved asthma control. Use of LABAs reduces the need for higher doses of ICS and therefore the potential risks of high doses while maintaining asthma control. Use of LABAs without ICS may lead to worsening of the disease.

Hence to conclude:

1. LABAs should not be used alone
2. LABAs should be added to the treatment only when asthma is uncontrolled despite the use of appropriate doses of ICS
3. Combination inhalers containing ICS with LABAs should be used rather than individual inhalers since this will ensure that both drugs are taken
4. Physician education on the inflammatory nature of asthma and that ICS constitute the first line maintenance treatment should be widely implemented

Table 2 : A Selection of meta-analysis and systematic reviews of LABA adverse outcomes in asthma

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison ICS use</th>
<th>Asthma-related hospitalizations</th>
<th>Life-breathing asthma</th>
<th>Asthma-related mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events/subject or % (total)</td>
<td>Odds ratio (95% CI)</td>
<td>Events/subject or % (total)</td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>Salpeter et al RCT &gt; 3 mo</td>
<td>LABA vs. Variable</td>
<td>53/3083</td>
<td>2.6 (1.6, 4.3)</td>
<td>50/15443</td>
</tr>
<tr>
<td>All ages</td>
<td>PL</td>
<td>12/2008</td>
<td>25/4.538</td>
<td></td>
</tr>
<tr>
<td>Jaeschke et al RCT &gt; 3 mo</td>
<td>LABA + ICS vs.</td>
<td>66/12060</td>
<td>0.74 (0.53, 1.03)</td>
<td>2/29401</td>
</tr>
<tr>
<td>Excluded children &lt; 12 years</td>
<td>ICS</td>
<td>77/10336</td>
<td>0.29401</td>
<td></td>
</tr>
<tr>
<td>Rodrigo et al RCT &gt; 1 mo</td>
<td>LABA vs. Variable</td>
<td>2.6 (6049)</td>
<td>1.01 (0.75, 1.36)</td>
<td>58/15831</td>
</tr>
<tr>
<td>All ages</td>
<td>PL</td>
<td>3 (6049)</td>
<td>36/14797</td>
<td></td>
</tr>
<tr>
<td>Rodrigo et al RCT &gt; 1 mo</td>
<td>LABA + ICS vs.</td>
<td>116/9331</td>
<td>0.85 (0.74, 0.97)</td>
<td>0/42466</td>
</tr>
<tr>
<td>All ages</td>
<td>LABA + ICS</td>
<td>619/58983</td>
<td>0.85 (0.74, 0.97)</td>
<td>0/42466</td>
</tr>
<tr>
<td>Hirst et al Adult cohort &amp; case control studies published (n = 3)</td>
<td>LABA + ICS vs. Variable (same device)</td>
<td>619/58983</td>
<td>0.85 (0.74, 0.97)</td>
<td>0/42466</td>
</tr>
<tr>
<td>unpublished (n = 4)</td>
<td>LABA + ICS</td>
<td>308/24013</td>
<td>1/15804</td>
<td></td>
</tr>
</tbody>
</table>

a Ratio (LABA vs. placebo or LABA + ICS vs. ICS) = Peto odds ratio, odds ratio, relative risk, odds, ratio CI = confidence interval, ICS = inhaled corticosteroid, NA = not available, PL = placebo, RCT = randomized controlled trial
5. Education patients on the nature of the disease and the importance of taking their treatment regularly even when asymptomatic needs to be reaffirmed.

6. In COPD beta agonists have demonstrated benefit and recommended.

**STATUS OF LABA’S IN COPD**

It would be very naïve to assume that the issue of safety of the use of LABAs in asthma may not influence its use in COPD. A meta-analysis performed by Aaron et al in 2007 of β₂-receptor in COPD suggests that they improve lung function, reduce the breathlessness and exacerbations and improve quality of life. Also, in the TORCH study, in which one arm of the patients received salmeterol alone for 3 years, there were no increased adverse events and as compared to salmeterol-fluticasone combination arm. The risk of death in the salmeterol arm did not differ significantly from that in the placebo arm. Another meta-analysis by Rodrigo et al suggested the beneficial effects of the use of LABA’s in patients with moderate-to-severe COPD and a 21% decrease in severe exacerbations when compared to placebo.

Pooled safety results of indacaterol (recently introduced LABA for the maintenance treatment of COPD) have not indicated any increased risk of acute respiratory serious events, COPD exacerbations were significantly reduced. The number of deaths adjusted per patient-year was lower with indacaterol than with placebo. (RR 0.21 [95% CI 0.07 – 0.660]; p = 0.008).

**CONCLUSIONS**

LABA’s are undoubtedly effective in improving lung function and relieving symptoms of asthma and COPD. Data has shown that serious safety concerns in asthma have been raised only when used as monotherapy whereas when used in combination with ICS the same drugs have been associated with decreased risk of asthma related events. This makes a case for more widespread usage of combination therapy of ICS with LABAs in patients with moderate to severe asthma, in both adults and pediatrics.

**REFERENCES**

10. Sears MR. The addition of long acting beta agonists to inhaled steroids in asthma. *Curr Opin Palm Med* 2011;17:23-28