Review: Safety of long-acting β2-agonists in the treatment of asthma

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Safety of long-acting $\beta_2$-agonists in the treatment of asthma

Mario Cazzola, Maria Gabriella Matera

Abstract: Several studies suggested an association between the regular use of $\beta_2$-agonists and asthma deaths. Whether this association represents adverse effects of $\beta_2$-agonist use or is entirely due to disease severity is a matter of ongoing debate. Previous literature indicates that confounding by poor asthma control may explain the apparent deleterious effects of inhaled $\beta_2$-agonists. Tolerance to nonbronchodilator effects of $\beta_2$-agonists may account for the increase in reactivity to indirect bronchoconstrictor challenges and explain why some studies have demonstrated enhanced bronchoconstriction in patients with asthma after regular $\beta_2$-agonist therapy. Nonetheless, the salmeterol multi-centre asthma research trial (SMART) found more asthma deaths (13 vs 3) and life-threatening asthma events (37 vs 22) in the salmeterol-treated asthmatic patients, although it was documented that among African-Americans, 5 times as many deaths and near-deaths from asthma occurred in those given salmeterol than in those given placebo, and among patients with asthma not using an inhaled corticosteroid (ICS) as a preventive (controller) medication, again more deaths and near-deaths from asthma occurred in those given salmeterol than in those given placebo. Only 38% of the African-Americans who participated in the study used an ICS. As a result of the findings from the SMART, FDA issued a public health advisory to highlight that long-acting $\beta_2$-agonists (LABAs) should not be the first medicine used to treat asthma. LABAs should be added to the asthma treatment plan only if other medicines, including the use of low-or-medium dose ICSs, do not control asthma. However, despite all of the concerns raised by the SMART, inhaled $\beta_2$-agonists remain the most effective bronchodilators available for the immediate relief of asthma symptoms and, as such, remain an important component of asthma management. Obviously, there are concerns about LABA treatment as monotherapy for asthma. Patients with asthma should be initiated and maintained on sufficiently high doses of ICSs and only patients whose asthma cannot be controlled should receive additional LABAs on a regular basis.

Keywords: Asthma, inhaled $\beta_2$-agonists, death from asthma, long-acting $\beta_2$-agonists, salmeterol.

Troubles with the regular use of short-acting $\beta_2$-agonists

Despite the significant contributions of inhaled synthetic sympathomimetic agonists to the therapeutic armamentarium of asthma, the benefit/risk ratio of these agents evoked controversy throughout the last half of the 20th century [Bernstein, 2002]. Actually, when short-acting $\beta$-agonists (SABAs) are taken regularly, the outcome usually differs little from that seen with placebo [Drazen et al. 1996; Dennis et al. 2000] or is even worse [Sears et al. 1990], although these agents provide rapid relief and protect against bronchoconstrictor stimuli. Moreover, the regular use of $\beta_2$-agonists has been blamed for the increases in mortality and morbidity of asthma that coincided with their introduction into the market [Barnes and Chung, 1992].

In effect, in the early 1960s, asthma mortality increased markedly in a number of countries, including New Zealand, Australia, and England. The weight of evidence suggested that the use of the isoprenaline forte inhaler was the major cause of the epidemics [Pearce et al. 2000], but, after that, several case-control studies in New Zealand showed that the potent and relatively non-$\beta_2$-selective agonist fenoterol doubled the risk of death from asthma [Crane et al. 1989]. In particular, the rise and fall in asthma...
mortality in New Zealand was attributed to the rise and fall in the prescription of fenoterol inhalers [Crane et al. 1989].

It must be highlighted that fenoterol was marketed in a high-dose preparation, dispensing 200 µg per puff compared with salbutamol at 100 µg per puff. Because fenoterol is about twice as potent as salbutamol, this meant that fenoterol was effectively a forte preparation at 4 times the strength of salbutamol [Beasley et al. 2006]. Moreover, fenoterol (like isoprenaline) is a full agonist at the β2-adrenoceptor, whereas salbutamol is a partial agonist. This would account for the observation that when used repeatedly, fenoterol had greater cardiac side effects than salbutamol, similar to those of isoprenaline [Beasley et al. 2006].

Subsequent studies suggested that increased asthma deaths and near deaths could be a class effect of β-agonists rather than being due to the toxicity of fenoterol alone [Spitzer et al. 1992]. This opinion has been strengthened by the results of a study of regular versus as-needed salbutamol in people with mild asthma that showed a consistent trend toward more symptoms, reduced lung function and increased airway responsiveness in the group treated regularly 4 times a day with salbutamol [Cockcroft et al. 1993], although for all outcomes except airway responsiveness, the differences were not statistically significant. More detailed mechanistic studies showed that regular use of salbutamol may enhance early and late asthmatic reactions to allergen [Drazen et al. 1996; Cockcroft et al. 1995] and the degree of bronchial constriction resulting from standardized exercise challenge [Inman and O’Byrne, 1996].

Numerous reports have confirmed that the regular use of SABAs increases airway responsiveness to histamine or methacholine [Anonymous, 1999] although a further analysis of the Saskatchewan data indicated that the risk of death was much greater among those patients who had only fenoterol prescribed than among those who had only salbutamol prescribed [Pearce and Hensley, 1998].

Causes of the increase in severity of asthma and regular use of β2-agonists

In an attempt to explain the phenomenon, also termed β-agonist paradox, it was hypothesized that, by treating symptoms of asthma with drugs such as β2-agonists able to inhibit mast cell degranulation, increased inflammation is allowed to occur, which may lead to the chronic appearance of excess repair tissue and the acceleration of the disease process [Page et al. 1993]. However, causes of the increase in severity of asthma are multifactorial. Frequent use of SABAs may reduce lung function, increasing airway responsiveness, and impair control of asthma, despite use of inhaled corticosteroids (ICSs). It is noteworthy that regular administration of β2-agonists leads to down-regulation of β2-adrenoceptors (β2-ARs), but this does not seem to affect bronchodilator responses because of the large reserve of β2-ARs on airway smooth muscle cells. However, tolerance to nonbronchodilator effects of β2-agonists has been demonstrated in vitro in inflammatory cells, such as mast cells, neutrophils, and monocytes, which is consistent with the relatively low density expressed by these cells [Chong et al. 1995; Barnes, 1999]. Other mechanisms for these effects may include increased responsiveness to allergen, interaction with corticosteroid receptors, altered mucociliary function, differential effects of enantiomers, and masking of symptoms by β2-agonist use [Barnes, 1999].

It must be highlighted that, although several case-control studies support the possible relationship between inhaled β-agonists and deaths in asthma, often it is not possible to separate the acute effects of SABAs from strong confounding by poor asthma control. This is the reason why many researchers believe that the clinical problem is probably not overtreatment with inhaled β-agonists, but undertreatment with ICSs and other efficacious strategies [Suissa et al. 2000; Eisner, 2001].

Inhaled long-acting β2-agonists in asthma

Long-acting β2-agonists (LABAs), available for the past decade, were designed specifically for regular use, as their duration of action is at least 12 h. Their intended use is prospective, to prevent symptoms, whether spontaneous or due to some environmental or activity-related airway challenge. The regular use of LABAs is now established in asthma guidelines as the preferred option for second-line controller therapy in addition to ICSs [Global Initiative for Asthma, 2006]. This has been driven by data showing beneficial effects of LABAs on exacerbation rates, in turn suggesting a
Impact of long-acting \( \beta_2 \)-agonists on morbidity and mortality

Because of the concern that regular use of SABAs may be associated with increased morbidity and mortality from the loss of control of asthma, careful pre- and post-marketing studies on the LABAs salmeterol and formoterol have been undertaken to determine whether such risks occur with these agents. One post-marketing surveillance study of salmeterol [Castle et al. 1993] showed a three-fold increase in deaths in the salmeterol group compared with the placebo group, but the difference was not significant as the rate of “events” was low and not different from what was expected. Another prescription-event monitoring study [Mann et al. 1996] provided no evidence that the use of salmeterol is associated with excess mortality. Moreover, a large well-controlled study with formoterol [Pauwels et al. 1997], with exacerbation as primary outcome, provided reassuring information that addition of formoterol to either low-dose or higher-dose ICS did not increase the frequency of mild or severe exacerbations of disease and was associated with improved control of symptoms and lung function, although three small clinical studies raised concerns about a possible link between the use of higher doses of this agent (24 \( \mu \)g bid) and an increase in serious asthma exacerbations [Mann et al. 2003]. Because of the safety concerns raised by these studies, the FDA asked the manufacturer to conduct a phase IV postmarketing clinical trial to investigate further the relative safety of the 2 different doses of formoterol. This phase IV trial, which enrolled 2,085 patients with stable persistent asthma of whom 1,347 received regular concomitant antiinflammatory therapy during the study, documented that treatment with formoterol 24 \( \mu \)g bid was not associated with an increase in serious asthma exacerbations compared with the lower formoterol doses or placebo [Wolfe et al. 2006] (Table 1). Moreover, there were no deaths in this study. It is not surprising, therefore, that a latest review, which has examined the evidence presented in Cochrane systematic reviews for the effectiveness and safety of LABAs, has provided evidence that LABAs are safe and beneficial in control of asthma and has also suggested that there is a group of mild relatively stable patients, not using ICS, who may be better off using LABA than repeat dosing with SABA [Walters et al. 2005] (Figure 1).

Nevertheless, in 1996, due to reports of paradoxical bronchospasm and, moreover, the documented non significant increased risk of asthma-related death [Castle et al. 1993] associated with the use of salmeterol and previous epidemics of asthma-related deaths in patients taking other \( \beta_2 \)-agonists [Spitzer et al. 1992], the Salmeterol Multicenter Asthma Research Trial (SMART) was designed in order to further evaluate the effects of salmeterol on respiratory- and asthma-related deaths or life-threatening episodes. A total of 26,353 patients completed the study, of which 13,174 had received salmeterol and 13,179 placebo. There was no significant difference in combined number of respiratory related deaths or life-threatening experiences (intubation and ventilation), which was the primary outcome (salmeterol=48; placebo=42) or in time to onset of the primary event. No significant differences were seen between salmeterol and placebo in the incidence of any secondary endpoint (asthma-related deaths and combined asthma-related deaths or life-threatening experiences), with the exception of asthma-related death which occurred rarely and was significantly higher in salmeterol vs placebo (13 vs 3).

### Table 1. Serious asthma exacerbations in asthmatic subjects receiving formoterol [from Wolfe et al. (2006)].

<table>
<thead>
<tr>
<th>Serious asthma exacerbations</th>
<th>Formoterol, 12 ( \mu )g twice daily ((n = 527))</th>
<th>Formoterol, 24 ( \mu )g twice daily ((n = 527))</th>
<th>Formoterol, 12 ( \mu )g twice daily plus as needed ((n = 517))</th>
<th>Placebo ((n = 514))</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Subjects receiving inhaled corticosteroids</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Exacerbations treated with prednisone</td>
<td>31 (5.9%)</td>
<td>33 (6.3%)</td>
<td>23 (4.4%)</td>
<td>45 (8.8%)</td>
</tr>
</tbody>
</table>
Figure 1. Effect size and pooled results for morning PEF in studies comparing LABAs with placebo in asthma (from Walters et al. [2005]). This article was published in Respiratory Medicine, Volume 99, Walters JA, Wood-Baker R, Walters EH. Long-acting β2-agonists in asthma: an overview of Cochrane systematic reviews pp. 384–95. Copyright Elsevier 2005.

The salmeterol multicenter asthma research trial (SMART)
The SMART was designed to randomise 60,000 asthma patients to either salmeterol 50 µg twice daily or placebo [Nelson et al. 2006]. The study duration was 28 weeks. Following visit 1, subjects were not required to return for clinic visits but instead were to be contacted every 4 weeks by telephone for evaluations and data collection related to respiratory-related life-threatening events, serious adverse events, concomitant medication use,
A public health advisory because of the results of the SMART

As a result of the findings from the SMART, FDA issued a public health advisory to highlight recommendations about use of a LABA medicine for asthma [FDA Public Health Advisory, 2007]. In particular, it was stressed that LABAs should not be the first medicine used to treat asthma.
**Table 2.** Primary cause of death as recorded on the death certificate for all asthma-related deaths in the SMART study (from Nelson *et al.* (2006)).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Race</th>
<th>Age, Yr</th>
<th>Sex</th>
<th>Comorbidities</th>
<th>Reported Baseline Asthma Medications</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol</td>
<td>Caucasian</td>
<td>67</td>
<td>Female</td>
<td></td>
<td>Zafirlukast, albuterol, prednisone, albuterol</td>
<td>Not listed</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Caucasian</td>
<td>46</td>
<td>Female</td>
<td>Allergic rhinitis, depressive disorder</td>
<td>Not available</td>
<td></td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Caucasian</td>
<td>56</td>
<td>Male</td>
<td>Allergic rhinitis, arthritis</td>
<td>Ipratropium bromide, albuterol, theophylline</td>
<td>Bronchial asthma</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Caucasian</td>
<td>62</td>
<td>Male</td>
<td>Other</td>
<td>Cromoly, ipratropium bromide/albuterol, albuterol, theophylline, prednisone</td>
<td>Emphysema</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Caucasian</td>
<td>46</td>
<td>Male</td>
<td></td>
<td>Albuterol, theophylline</td>
<td>Chronic bronchial and bronchial asthma with acute asthmatic bronchitis</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>African American</td>
<td>37</td>
<td>Female</td>
<td></td>
<td>Metaproterenol, albuterol, triamcinolone acetate, prednisone</td>
<td>Not available</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>African American</td>
<td>47</td>
<td>Male</td>
<td>Allergic rhinitis, chronic sinusitis</td>
<td>Ipratropium bromide, albuterol, theophylline</td>
<td>Acute exacerbation of asthma</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>African American</td>
<td>41</td>
<td>Female</td>
<td>Allergic rhinitis, hypertension</td>
<td>Albuterol, theophylline</td>
<td>Asthma</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>African American</td>
<td>47</td>
<td>Female</td>
<td>Allergic rhinitis, bronchitis, chronic hypertension, headache, arthritis, depressive disorder</td>
<td>Albuterol, terbutaline, triamcinolone acetate</td>
<td>Hypertensive cardiovascular disease</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>African American</td>
<td>56</td>
<td>Male</td>
<td>Diabetes</td>
<td>Ipratropium bromide, albuterol, flumisolide, theophylline</td>
<td>Atherosclerotic heart disease*</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>African American</td>
<td>14</td>
<td>Male</td>
<td>Bronchitis, chronic sinusitis, chronic hypertension, ulcers</td>
<td>Albuterol, theophylline Montelukast, prednisone</td>
<td>Bronchial asthma</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>African American</td>
<td>51</td>
<td>Male</td>
<td></td>
<td></td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Placebo</td>
<td>Caucasian</td>
<td>34</td>
<td>Female</td>
<td>Allergic rhinitis, bronchitis, chronic depressive disorder</td>
<td>Zafirlukast, albuterol, beclomethasone dipropionate, prednisone</td>
<td>Coronary atherosclerosis</td>
</tr>
<tr>
<td>Placebo</td>
<td>Not provided</td>
<td>61</td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Coroner’s report rather than death certificate.*
LABAs should be added to the asthma treatment plan only if other medicines, including the use of low- or medium-dose corticosteroids, do not control asthma.

This advice is correct, but it seems to be redundant. In effect, we have known for a long time that LABAs are highly effective therapeutic agents for asthmatics who experience excessive symptoms or physiologic impairment despite the regular administration of low doses of ICSs (equivalent to 12 puffs of beclomethasone daily, 50 µg per puff, total 600 µg) [Moore et al. 1998]. This is the reason why international guidelines recommend regular use of LABAs for any patient on low-dose ICSs still experiencing daytime symptoms once [Global Initiative for Asthma, 2006]. In any case, a large Cochrane systematic review for the effectiveness and safety of LABAs [Walters et al. 2003a] has provided evidence that LABAs are safe and beneficial in control of asthma; intriguingly, subgroup analyses indicate that this is true when ICSs are used and in their absence. Two other Cochrane systematic reviews have found that LABAs are more effective than regular SABAs [Walters et al. 2003b], and are as effective as theophylline with fewer side-effects [Shah et al. 2003]. These reviews support guidelines in the use of LABAs as additional therapy when asthma is inadequately controlled by ICSs at moderate dose.

Even so, Hasford and Virchow (2006) believe that in view of the results of the SMART, the existence of salmeterol-related excess mortality has to be assumed with certainty and, consequently, only patients whose asthma cannot be controlled by sufficiently high doses of ICSs should receive additional LABAs on a regular basis and, in any case, LABAs should be withdrawn from patients who do not profit from their use. Moreover, when considering the results of the SMART, Martinez has proposed to start treating asthmatic patients with ICS alone, adding leukotriene antagonists like montelukast or even theophylline (which is almost never used anymore) and reserving LABA for those still requiring salbutamol (a SABA) twice or more daily [Martinez, 2009]. He has also suggested that the manufacturers of LABAs should fund additional studies to confirm or refute the hypothesis that use of LABAs in addition to ICS increases severe asthma exacerbations.

### Table 3. Combined asthma-related death or life threatening experiences in the SMART study by use of inhaled corticosteroids at baseline (from Nelson et al. [2006]).

<table>
<thead>
<tr>
<th>Category</th>
<th>Salmeterol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline ICS use</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>African American ICS use</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>No baseline ICS</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td>African American no ICS use</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

ICS: Inhaled corticosteroid.

This recommendation does not seem to be useful for asthmatic patients. In fact, a body of evidence is documenting that the addition of a LABA to ICS therapy not only can improve asthma symptoms and reduce exacerbations, but is also safe [Gibson et al. 2005].

### A re-examination of the SMART

A critical assessment of the results of the SMART clearly shows that, in contrast to recommendations of current asthma management guidelines (Global Initiative for Asthma, 2006), there was a low level of ICS use (47%) in the entire population in the SMART. Only 50% of Caucasian patients were receiving treatment with an ICS, and in African-American patients, who had more severe asthma at entry, only 38% were using ICS therapy at baseline. Although there was no attempt to determine degree of adherence with ICSs at randomization or persistence in their use during the course of the study, no significant differences were seen for primary events and asthma-related events, including deaths in the total population of patients receiving ICSs at baseline. However, in the total population of patients not receiving ICSs at baseline, there was a statistically significant greater number of asthma-related deaths in all patients taking salmeterol compared with those taking placebo (Table 3).

Another crucial point is the documentation that in Caucasian patients (71% of the study population) there were no significant differences between treatment groups for primary events and asthma-related events. In African-American participants (17% of the study population), the study showed a statistically significant greater number of primary events and asthma-related events, including deaths, in patients compared with those taking placebo, although it is important to note that less than 1% of all African-Americans...
enrolled in the study experienced such events during the 28-week trial.

It is likely that the lower level of ICS use may have contributed to the higher rate of asthma-related events among African-Americans. Inadequate pharmacotherapy of African-Americans compared with Caucasians have been shown to exist in other studies and may contribute to racial disparities in asthma-related health outcomes [Pawar and Smith, 2006]. Over the past 25 years, African-Americans have experienced higher rates of emergency department visits, hospitalizations, and death due to asthma compared with other ethnic groups in the US [Boudreaux et al. 2003]. African-Americans of lower socioeconomic groups are particularly vulnerable to asthma morbidity and mortality, although certain behavioural or cultural factors may be possibly related to this observation.

In any case, it must be highlighted that the study was not sufficiently powered a priori to evaluate properly post hoc subgroup analysis for the effects of ICS use or ethnic origin, but indicated that the risks were greater in African Americans who were using ICS less frequently [Lipworth, 2007].

It is also possible that the untoward outcomes in the SMART might be due to β2-AR polymorphism. In fact, polymorphisms of the β2-AR can affect regulation of the receptor [Lipworth et al. 1999]. There is a growing body of evidence that β2-AR genotype (position 16) is a marker for adverse clinical outcomes with chronic β2-agonist exposure [Israel et al. 2004; Taylor et al. 2000]. In particular, there is documentation that the homozygous arginine (Arg) genotype at position 16 of the β2-AR may have an impaired therapeutic response to salmeterol in either the absence or presence of concurrent ICS use [Wechsler et al. 2006]. Approximately 15% of the population is homozygous for Arg 16, but it has been documented that African-Americans have an increased frequency of B16 Arg/Arg [Ellsworth et al. 2002]. This finding raises the question of whether a possible small increased rate of death and/or severe deteriorations in asthma symptoms mainly in African-Americans subjects receiving salmeterol, as documented in the SMART, is related to an ethnic-specific pharmacogenetic difference. Nonetheless, it has been documented that although the benefits of salmeterol appeared to be least in the Arg/Arg subgroup, in whom the rate of major exacerbations was nearly three times that of homozygous Gly-16 subjects, there was a similar pattern in the frequency of major exacerbations across genotypes during the placebo treatment period [Taylor et al. 2000]. This finding questions the role of β2-AR polymorphism, although β2-AR polymorphisms within genes are also associated with the long-QT syndrome and the heterogeneity of these genes in African-Americans has been postulated as cause of death in the SMART [Williams, 2006]. In effect, it has been documented that inhaled β-agonists significantly prolong the QTc interval in a dose-dependent and gene-dependent manner [Antzelevitch, 2002].

It must been emphasized that, in any case, Nelson (2006a) believes that the B16 Arg/Arg genotype is not a pertinent explanation of the findings in the SMART. B16 Arg/Arg occurs in one-sixth of Caucasians and up to one-fifth of African-Americans. Therefore, there were more Caucasians than African-Americans with B16 Arg/Arg in the SMART, yet all the excess adverse events were in the African-American subjects.

It is also interesting to note that the occurrence of serious respiratory and asthma-related events was different during the two separate phases of patient recruitment of this study. Patients recruited during the initial phase of the study had more serious respiratory-related events from salmeterol compared with placebo. Those recruited during the second phase of the study (i.e. from investigators’ study populations) showed no imbalances between treatment groups in the number of serious respiratory- and asthma-related events compared with phase 1 [Nelson, 2006b]. It is known that an established physician–patient relationship can have a positive impact on the quality of overall asthma care for individual subjects. Moreover, this finding suggests that a small group of subjects with asthma, not on ICSs, 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 [Nelson, 2006a].

How to overcome the risk of death for asthma with LABAs

Despite all of the concerns raised by the SMART and a recent meta-analysis of the effect of LABAs on severe asthma exacerbations and asthma-related deaths [Salpeter et al. 2006],
which documented that LABA use increases the risk for hospitalizations due to asthma, life-threatening asthma exacerbations, and asthma-related deaths with similar risks found with salmeterol and formoterol and in children and adults, inhaled $\beta_2$-agonists remain the most effective bronchodilators available for the immediate relief of asthma symptoms and, as such, remain an important component of asthma management [O’Byrne and Adelroth, 2006].

Obviously, there are concerns about LABA treatment as monotherapy for asthma, and Asthma Guideline recommendations [Global Initiative for Asthma, 2006] emphasize the need for adequate anti-inflammatory therapy before starting any add-on treatment, including LABAs. Patients with asthma should be initiated and maintained on sufficiently high doses of ICSs and only patients whose asthma cannot be controlled should receive additional LABAs on a regular basis. Currie (2006) has correctly highlighted that since guidelines [Global Initiative for Asthma, 2006] advocate the early use of ICSs in the treatment of asthma, it is incredulous to consider that the investigators involved in the SMART felt it reasonable to enrol a majority of individuals who were being inappropriately managed in the community. It is well known, in fact, that monotherapy with LABAs might cause worsening, and this supports the opinion of Salpeter and colleagues [Salpeter et al. 2006], but if used in patients with at least moderately severe asthma, in combination with appropriate doses of ICS, this has not been proven [Pauwels et al. 1997; O’Byrne et al. 2001; Bateman et al. 2004; Salpeter et al. 2005]. In the converse has been shown – that is, that there is an improvement in exacerbations and mortality in patients using combination therapy with ICS and LABAs [Pauwels et al. 1997; Greening et al. 1994]. It is important to highlight that the meta-analysis of Salpeter and colleagues [Salpeter et al. 2006] includes only studies in which patients were randomly assigned to LABAs or placebo and nearly 50% of patients were not receiving concomitant ICSs. The authors attempted to control for this limitation by examining studies that reported concomitant ICS use in more than 75% of patients, but adherence to unblinded ICS use in those studies is unknown. In addition, all patients reported using ICSs in addition to study medications in only 1 study; therefore, only that study could potentially assess whether concomitant ICS effects affected the outcomes [Nelson and Dorinsky, 2006]. These findings are important in limiting the value of this meta-analysis also considering that there is a large body of evidence documenting that ICSs and LABAs have a separate but complementary role in the management of asthma [Barnes, 2002] and, consequently, LABAs in combination with ICSs are the most effective asthma treatment currently available for the management of asthma.

This opinion fits with asthma mortality data in the US. These data document that deaths from asthma peaked in 1996, two years after the introduction of salmeterol in the US, at 5,667. Subsequently, use of salmeterol, largely in combination with fluticasone, has increased 5-fold while deaths from asthma in the US have steadily fallen to 3,780 in 2004 [American Lung Association Epidemiology & Statistics Unit Research And Scientific Affairs, 2007]. In any case, SMART has been designed as a real-world, observational study evaluating the addition of salmeterol or placebo to usual pharmacotherapy for asthma. In addition, SMART was initiated in 1996, which was prior to the 1997 revision of the National Institutes of Health asthma guidelines [National Asthma Education and Prevention Program, 1997]. Furthermore, the reported use of ICSs at baseline in SMART (47%) was much higher than the average ICS use (10 to 20%) as reported by a large US national survey in 1998 [Asthma in America, 2007]. Therefore, it is premature (and inappropriate) of Martinez (2005) and Salpeter et al. (2006) to suggest that withdrawal of LABAs should even be considered. LABAs have proven efficacy and safety if used in addition to ICS for patients with asthma. Even so, since in the setting of ICS withdrawal, B16Arg/Arg patients may experience adverse effects with salmeterol [Wechsler et al. 2006], these specific patients might benefit from alternate asthma treatment strategies.

An alternative possibility should be the use of enantiomers of $\beta$-agonists, considering that the adverse effects on asthma progression with regular use of $\beta_2$-agonists has raised the possibility that these may be due to undesirable effects of the accompanying (S)-enantiomer [Page and Morley, 1999]. Interestingly, it has been documented that the (S)-enantiomers of salbutamol and formoterol are able to reverse the (R)-enantiomer and dexamethasone effects and this suggests suppression of the anti-inflammatory effects, perhaps through an
antagonistic mechanism similar to propranolol [Ameredes and Calhoun, 2005]. Nonetheless, Barnes (2006) has recently highlighted that in patients with asthma, no consistent differences have been found with (R)-salbutamol compared with (R,S)-salbutamol in bronchodilatation, bronchoprotection, or side effects, whereas (S)-salbutamol is inactive with no documented adverse effects. (R)-salbutamol is only currently available as a nebulized form, but in view of its clinical equivalence and considerably higher costs compared with the normal (R,S)-salbutamol, this treatment cannot be recommended in any patient groups. Similar considerations appear to apply to other β2-agonists.

At present time, some new once-daily β2-agonists are under development for treating asthma [Cazzola et al. 2005]. Once-daily dosing would allow better compliance and management of patients if desensitization and accumulation do not occur. Obviously, the once-daily approach has been combined with the enantiomer issue in order to avoid what has been observed in the SMART. Nonetheless, these novel agents need to be assessed for this risk prior to approval for widespread use in patients with asthma. In particular, a specific study that will demonstrate that these agents are safe in B16Arg/Arg patients will be mandatory before they will be allowed to enter into the market.

References


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