Effect of Long-Acting $\beta_2$ Agonists on Exacerbation Rates of Asthma in Children

Hans Bisgaard, MD, Dr DMSc*

Summary. The purpose of this analysis was to examine the effect of long-acting $\beta_2$-adrenoceptor agonists (LABAs) on the asthma exacerbation rate in pediatric patients. Randomized controlled trials (RCT) that included the use of LABAs to treat symptoms of pediatric asthma in children on inhaled corticosteroids, that reported asthma exacerbation rates, and that were published as full papers in peer-reviewed journals were retrieved from a search of the medical literature. Eight studies were identified that fulfilled these criteria. An exacerbation was defined as deterioration in a patient’s asthma requiring a change in prescribed medication or not defined but reported as an asthma exacerbation or an asthma-related hospitalization. Analysis of data from the eight studies revealed no apparent protection from an asthma exacerbation among children on a LABA compared to patients on comparator treatment. The relative risk of an asthma exacerbation for LABA compared to placebo or short-acting $\beta_2$-adrenoceptor agonist (SABA) ranged from 0.95–1.86. The relative risk of hospitalization for asthma in patients treated with LABAs with regular maintenance with ICS ranged from 3.3–21.6 in the three studies that reported asthma-related hospitalizations. The lack of evidence for the control of asthma exacerbations in children regularly using a LABA should bring into question its general use as add-on therapy. Studies should be designed to directly explore the implications of these observations in pediatric patients. Pediatr Pulmonol. 2003; 36:391–398. © 2003 Wiley-Liss, Inc.

Key words: exacerbations; long-acting $\beta_2$-agonists; salmeterol; formoterol; asthma; children.

INTRODUCTION

International evidence-based guidelines on the management of adult and pediatric asthma recommend the regular use of long-acting $\beta_2$-adrenoceptor agonists (LABAs) as add-on therapy to established steroid treatment when asthma is incompletely controlled on inhaled corticosteroids (ICS).1 It is likely that inclusion of LABAs in pediatric treatment guidelines was derived from studies performed in adolescent and adult asthmatics that suggested that the addition of salmeterol2,3 or formoterol4 to ICS therapy was more effective in controlling symptoms of asthma than doubling the dose of ICS. The recommendation of LABAs for pediatric patients was seemingly based on extrapolation from adult data.

Pediatric asthma differs from adult asthma in many respects. Pharmacokinetics are often different and the disease less progressed, possibly with less irreversible changes. Therefore, such an “inherited” paradigm in pediatric patients deserves further examination.

A recent critical qualitative review of the literature on pediatric randomized controlled trials (RCT) using LABAs noted poor evidence for a bronchodilator effect with LABAs as regular add-on therapy in children.5 In addition, this review highlighted data suggesting that asthma exacerbations were increased with regular LABA treatment in pediatric patients.5 Because of these issues, the present literature survey and analysis were undertaken to evaluate methodologically reliable pediatric clinical trials to determine if asthma exacerbation rates were affected by the use or addition of a LABA. The purpose of this study was to determine the relative risk of an asthma exacerbation in children on regular treatment with LABAs in combination with inhaled corticosteroids, compared with children on a placebo or short-acting $\beta_2$-adrenoceptor agonist (SABA) in combination with inhaled corticosteroids.

METHODS

Identification of Clinical Trials

The available published English-language literature on the effects of maintenance therapy with a LABA in Copenhagen Studies on Asthma in Childhood (COPSAC), Department of Pediatrics, Copenhagen University Hospital, Amtssygehuset i Gentofte, Copenhagen, Denmark.

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asthmatic children (including adolescents) was identified with a computerized citation search between 1985–2003 of Medline, EMBASE, and Current Contents. This was augmented by a nonsystematic review of the asthma literature up until 2003. Criteria for selection of RCTs for inclusion in the review were direct comparison of a LABA with SABA or placebo in children on inhaled corticosteroid, and information on asthma exacerbations or asthma-related hospitalizations in asthmatic children. Studies that solely included children using a LABA as monotherapy were not included in the analysis, as monotherapy with these agents is not recommended for pediatric patients.1

Asthma Exacerbations

The definition of an asthma exacerbation varied from study to study. An asthma exacerbation was defined as deterioration in a patient’s asthma requiring a change in prescribed medication,6–10 or reported as an exacerbation.11–13 Three studies reported both exacerbations and hospitalizations due to asthma.8,12,13 Hospitalizations were considered separately from exacerbations for this analysis.

Statistical Analysis

The overall incidence of asthma exacerbations during treatment with a LABA was compared to the incidence during treatment with a comparator. Since only categorized data on number of patients with at least one exacerbation were available, data from each study were represented as a 2 × 2 contingency table. The relative risk of an asthma exacerbation and the associated 95% confidence interval (CI) was calculated for the LABA compared to the comparator for each of the individual studies. The relative risk of an asthma exacerbation and the associated 95% CI were calculated for the LABA compared to the comparator for each of the individual studies using SAS 8.12, which adds a value of 0.5 to each zero cell. If there were no exacerbations in both the LABA and the comparator group, the relative risk was undefined.14 Similar analyses of overall incidence and relative risk of hospitalization due to asthma were calculated for the three studies that reported asthma-related hospitalizations.

Because of differences in patient populations, comparator use, study design and duration, and definition of asthma exacerbation, the spectrum of calculated relative risks was reported, but no attempt was made to combine the individual estimates in an overall meta-analysis. The calculated weights for each study in Figure 1 represent the relative weight that would be given to the study estimate if a fixed-effects meta-analysis model for relative risk were used. Relative weights were calculated using Review Manager, version 4, software distributed and approved by the Cochrane collaboration (Cochrane Review Manager, Cochrane Collaboration, Oxford, UK, http://www.cc-ims.net/RevMan).

RESULTS

Studies

The search strategy yielded 71 citations. Trials that included children and adults were not evaluated, because pediatric patients were not analyzed separately. Eight trials met the inclusion criteria (Table 1).6–13 All eight studies were conducted between 1995–2002. The eight clinical trials were randomized, double-blind studies conducted according to good clinical practice and approved by local ethics committees. Five were placebo-controlled,6–8,11,12 seven were parallel-group design,7–13 and one was a cross-over design.6

Patients

The eight studies included a total of 2,401 mild to severe asthmatic patients ranging in age from 4–17 years (Table 1).

Asthma Exacerbations

None of the eight studies reported a statistically significant protective effect for asthma exacerbations among
### TABLE 1—Study Descriptions

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Mean age, years (range)</th>
<th>Asthma exacerbation definition</th>
<th>FEV₁ mean % predicted (range)</th>
<th>Duration of study</th>
<th>Treatment groups</th>
<th>Concomitant ICS (% of patients if known)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients on ICS maintenance therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bensch et al.⁸</td>
<td>518</td>
<td>9.2 (5–12)</td>
<td>Patients symptomatic despite maximum salbutamol</td>
<td>71 (60.1–81)</td>
<td>12 mo.</td>
<td>Formoterol 12 µg</td>
<td>Yes, percentage not specified</td>
</tr>
<tr>
<td>Von Berget et al.¹¹</td>
<td>426</td>
<td>10 (5–15)</td>
<td>Change in therapy</td>
<td>77.5 (62–92)</td>
<td>12 mo.</td>
<td>Formoterol 24 µg</td>
<td>Salmeterol Placebo 50 µg 52%</td>
</tr>
<tr>
<td>Lenney et al.⁹</td>
<td>847</td>
<td>10.1 (4–16)</td>
<td>Change in therapy other than β-agonists</td>
<td>79.3 (58–100)</td>
<td>3 mo. with 9 mo. ext</td>
<td>Salmeterol Placebo Salmeterol Salmeterol Placebo 25 µg 57% 50 µg 80%</td>
<td></td>
</tr>
<tr>
<td>Zarkovic et al.⁶</td>
<td>91</td>
<td>11 (6–15)</td>
<td>Change in therapy</td>
<td>1.89 (1)</td>
<td>6 mo. crossover</td>
<td>Salmeterol Placebo Salmeterol Placebo Salmeterol Placebo 200 µg 100 µg 50 µg 96%</td>
<td></td>
</tr>
<tr>
<td>Langton Hewer et al.¹²</td>
<td>24</td>
<td>14.5 (12–17)</td>
<td>Not defined</td>
<td>Not available</td>
<td>8 weeks</td>
<td>Salmeterol Placebo Salmeterol Placebo Placebo 100 µg 100%</td>
<td></td>
</tr>
<tr>
<td>Akpinarli et al.⁷</td>
<td>32</td>
<td>10.3 (6–14)</td>
<td>Systemic corticosteroids or increased bronchodilators</td>
<td>79.5 (60–116)</td>
<td>6 weeks</td>
<td>Placebo Formoterol Placebo 12 µg 100%</td>
<td></td>
</tr>
<tr>
<td>LABA adjunctive therapy with ICS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tal et al.¹³</td>
<td>286</td>
<td>11 (4–17)</td>
<td>Described under adverse events (serious and nonserious)</td>
<td>75.0 (40–114)</td>
<td>12 mo.</td>
<td>Budesonide/formoterol 80/4.5 µg Budesonide 100 µg Budesonide 200 µg 100%</td>
<td></td>
</tr>
<tr>
<td>Verberne et al.¹⁰</td>
<td>177</td>
<td>11.1 (6–16)</td>
<td>Systemic corticosteroids</td>
<td>88.8 (75.1–102.6)</td>
<td>12 mo.</td>
<td>Salmeterol + beclomethasone Beclomethasone Beclomethasone + placebo 50 µg 200 µg 400 µg 200 µg 100%</td>
<td></td>
</tr>
</tbody>
</table>

¹ICS, inhaled corticosteroids; mo., months; ext, extension.
the LABA treatment groups when compared to placebo, SABA, or SABA + ICS. The relative risk for an asthma exacerbation among LABA-treated patients ranged from a high of 1.86 to a low of 0.97 in a variety of study designs with a variety of patients and comparators (Table 2, Fig. 1).

The use of LABA consisted of salmeterol in 5 studies, and formoterol in 3 studies. Six studies compared a LABA to placebo in groups of patients, the majority of whom were using regular maintenance ICS treatment. These studies are listed in increasing order of ICS use (Table 1). The report by Bensch et al. did not state the percentage of patients using ICS, so this study is arbitrarily listed first in the subgrouping. Two studies evaluated the use of formoterol compared to placebo in patients taking regular maintenance ICS throughout the study period. The study by Akpinarli et al. found no asthma exacerbations in either group over 6 weeks of treatment. In a larger 12-month study, Bensch et al. evaluated two doses of formoterol compared to placebo and found similar rates of exacerbations in each group (Table 2); however, the two formoterol study groups had a significantly greater number of hospitalizations related to asthma (Table 3). The study of Von Berg et al. of 426 asthmatic children reported asthma exacerbation rates of 62% and 53% for salmeterol and placebo treatments, respectively, over 12 months of treatment (Table 2). In this study, patients on salmeterol had a significantly higher risk of asthma exacerbation during the 12 months, with a relative risk of 1.18 (Table 2). In this study, patients on salmeterol and placebo treatments, respectively, over 12 months of treatment (Table 2). In this study, patients on salmeterol and placebo treatments, respectively, over 12 months of treatment (Table 2).

The number of patients experiencing at least one exacerbation was 53% with salmeterol, and 46% with placebo (Table 2).

Langton Hewer et al. recruited 24 severely asthmatic children with poorly controlled asthma and compared the use of a high dose of salmeterol to placebo for 8 weeks of active treatment. The number of children experiencing exacerbations was higher in the salmeterol group compared with placebo (6 vs. 4 children).

Two studies evaluated a LABA added to a regime of regular ICS maintenance treatment (Table 1). Tal et al. evaluated a budesonide/formoterol combination compared to an equivalent dose of budesonide for 12 weeks. The percentage of patients with an asthma exacerbation was 5.4% in the budesonide/formoterol group, and 2.9% in the budesonide-alone group (Table 2). Verberne

<table>
<thead>
<tr>
<th>Reference</th>
<th>LABA</th>
<th>Comparator</th>
<th>N/N total (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bensch et al.</td>
<td>F12</td>
<td>P</td>
<td>67/171 (39%)</td>
<td>0.97 (0.75, 1.26)</td>
</tr>
<tr>
<td></td>
<td>F24</td>
<td></td>
<td>68/171 (40%)</td>
<td>0.99 (0.76, 1.28)</td>
</tr>
<tr>
<td>Von Berg et al.</td>
<td>S</td>
<td>P</td>
<td>137/220 (62%)</td>
<td>1.18 (1.00, 1.40)</td>
</tr>
<tr>
<td></td>
<td>S25</td>
<td>Sa</td>
<td>75/279 (27%)</td>
<td>0.91 (0.70, 1.19)</td>
</tr>
<tr>
<td></td>
<td>S50</td>
<td></td>
<td>89/290 (31%)</td>
<td>1.04 (0.81, 1.34)</td>
</tr>
<tr>
<td>Zarkovic et al.</td>
<td>S</td>
<td>P</td>
<td>43/81 (53%)</td>
<td>1.15 (0.84, 1.51)</td>
</tr>
<tr>
<td>Langton Hewer et al.</td>
<td>S</td>
<td>P</td>
<td>6/11 (54%)</td>
<td>1.64 (0.62, 4.30)</td>
</tr>
<tr>
<td>Akpinarli et al.</td>
<td>F</td>
<td></td>
<td>0/16 (0%)</td>
<td>Undefined</td>
</tr>
<tr>
<td>Tal et al.</td>
<td>Bu/F</td>
<td></td>
<td>8/148 (5.4%)</td>
<td>1.86 (0.57, 6.05)</td>
</tr>
<tr>
<td>Verberne et al.</td>
<td>S + B200</td>
<td></td>
<td>10/60 (16.6%)</td>
<td>1.43 (0.58, 3.50)</td>
</tr>
</tbody>
</table>

1CI, confidence interval; LABA, long-acting beta2 agonist; Sa, salbutamol; S, salmeterol; S25, 25 μg salmeterol; S50, 50 μg salmeterol; F, formoterol; F12, 12 μg formoterol; F24, 24 μg formoterol; Bu, budesonide; B, beclomethasone; B200, 200 μg beclomethasone; B400, 400 μg beclomethasone; P, placebo.

2Included in graph.
et al. compared a combination of salmeterol plus beclomethasone to two doses of beclomethasone in 177 asthmatic children. Over the year of treatment, the higher dose of beclomethasone had the lowest number of exacerbations, while beclomethasone plus salmeterol or placebo showed similar incidences of exacerbations (Table 2).

Hospitalizations

Hospitalizations due to asthma were reported only in the studies by Bensch et al., Langton Hewer et al., and Tal et al., and are summarized in Table 3. All of these trials had a large percentage of patients on concomitant ICS during the course of the study. The percentage of patients hospitalized due to asthma was 3–9% in the LABA group, with no hospitalizations in any of the comparator treatment groups for the three studies. The relative risk of hospitalization for asthma in patients treated with LABAs was elevated in each of the three studies, ranging from 3.3–21.6, and was greatest in the two 12-month studies.

DISCUSSION

The studies reviewed in this analysis indicated no protection from asthma exacerbations in pediatric asthmatic patients treated with salmeterol or formoterol, as compared with children on corticosteroids, short-acting beta agonists, or placebo. The relative risk of asthma exacerbations was generally increased from regular treatment with LABA. Asthma-related hospitalization was significantly increased from LABA, with relative risk estimates ranging from 3.3–21.6.
The asthma exacerbation rate was not the primary endpoint in any of the reported pediatric studies; however, the asthma exacerbation rate is an essential measure of asthma control, and may be regarded as a marker of underlying airway inflammation, a key feature of the pathology associated with asthma. Hospitalizations due to asthma were included in this analysis because they represent the most serious of exacerbations, i.e., those that are potentially life-threatening. Therefore, an examination of exacerbation rates and asthma-related hospitalizations is central to evaluating the effectiveness of asthma therapy in pediatric patients.

There are limitations to any conclusions drawn from the data provided by these studies. These clinical trials differed in design, population, drug therapy, and length. Definitions of an asthma exacerbation varied with individual studies. An asthma exacerbation was uniformly defined in only 5 of the 8 studies as an increase in symptoms requiring a change in medication. Two studies reported asthma exacerbations related to medication use. For example, Von Berg et al. did not define an asthma exacerbation; however, exacerbations were reported as related to a change in study medication. Langton Hewer et al. determined asthma exacerbations from diary cards, presumably related to symptoms and use of relief medication. An asthma exacerbation leading to hospitalization was reported separately in two studies.

Two of the 8 studies had less than 50 patients enrolled in the trials, and were arguably too small and of too short a duration (8 weeks or less) to produce significant data on exacerbation rates. These were included because it is important to consider all the available evidence, and even studies with small numbers of patients can be informative. Langton Hewer et al. recruited only 24 children and the dose of salmeterol was higher than in the other studies, possibly due to the severity of the asthma in these children. However, this study merits inclusion as these subjects represent a very important group of children whose asthma was severe, with persistent symptoms that impinged upon their lives to such an extent that they were residential pupils at the United Kingdom’s National School for Asthma and Eczema (Pilgrim’s School). Additionally, in this live-in setting, the patients’ asthma was carefully monitored on a day-to-day basis, adding to the reliability of the results.

Not all of the patients in Bensch et al., Von Berg et al., Lenney et al., Zarkovic et al., and Langton Hewer et al. were on maintenance ICS therapy during the clinical trial, and it is possible that all of the exacerbations in the LABA arm occurred only in patients not on ICS. It is more reasonable to assume that at least some of the patients not on ICS controller medication were mild asthmatics whose symptoms were controlled with short-acting β-agonists, and that the proportion of patients on ICS was similar in the LABA arm compared to the comparator group. LABAs did not provide protection from asthma exacerbations in any of the studies; nor did they provide protection from hospitalizations. Hospitalizations for asthma occurred in trials in which the majority of patients were on concomitant ICS.

Asthma exacerbation was the primary outcome in one large RCT in adults that found a protective effect from adding formoterol to a maintenance dose of ICS. This study examined the exacerbation rate in adults taking formoterol and budesonide, and showed that higher doses of budesonide reduced asthma exacerbations compared to formoterol added to a low dose of budesonide. Exacerbations were reduced with formoterol only when LABA was added to the higher dose of budesonide. This suggests that patients must be well-controlled on corticosteroid before any additional benefit of LABA can be demonstrated. A meta-analysis on nine RCT comparing the addition of formoterol to ICS vs. increasing the dose of corticosteroid supported the protective effect of regular LABA on exacerbation rates in adults. However, the meta-analysis revealed only a modest protective effect by the addition of LABA to ICS (a difference of 2.7% for exacerbation, and of 2.4% for moderate or severe exacerbation), and none of the nine studies included in this meta-analysis showed a protective effect on exacerbation rates individually. Additional studies in adults also showed relatively moderate protective effects of LABA added to ICS therapy. Other studies showed deteriorations of asthma and increased asthma events and death in some patients taking the drug. Recently, a large clinical trial of salmeterol in adults (SMART) was halted prematurely due to the suggestion of an increase in the incidence of life-threatening or asthma-related deaths in patients taking the medication.

Results from this analysis of eight pediatric studies failed to demonstrate a protective effect of LABA, even when studies reported an improvement in lung function measurements. The lack of improvement in asthma control (as assessed by exacerbation rates and/or hospitalizations) may be explained by a failure to address the underlying inflammation that is not recognized symptomatically (i.e., “masking” of asthmatic inflammation). However, this rationale does not explain an increased risk of exacerbations among patients treated with LABA + ICS alone. Thus, it is possible that chronic exposure to β-agonists may result in direct adverse effects within the airway, independent of concomitant anti-inflammatory therapy. Alternatively, both adults and children may develop tolerance to the bronchoprotective effects of LABAs. Pediatric patients treated with salmeterol demonstrated reduced bronchoprotection against exercise-induced asthma over time, despite concomitant use of ICS. Studies examining exercise-induced asthma and adenosine monophosphate challenge in
The use of LABA monotherapy without concomitant controller medication was studied by Verberne et al., who showed a marked increase in asthma exacerbations compared to ICS in pediatric patients treated for a year. Deterioration of asthma was also seen in large clinical trials of adults treated with a LABA and not taking concomitant ICS, or when corticosteroids were withdrawn. LABAs must be used with caution in adults not treated with controller medication, and are not recommended for children as sole controller therapy. However, the results for clinical trials where ICS was permitted or was included as part of the maintenance therapy did not demonstrate any added protection by the addition of LABA. Additionally, hospitalizations due to asthma occurred in the studies of patients taking LABA and regular ICS therapy.

The differences between the adult studies and the pediatric studies reviewed here may be due to differing populations, study designs, or stages of disease pathology. Further differences between treatment effects in pediatric and adult populations may be speculated to be due to different stages of a chronic disease, with pediatric asthma having fewer chronic changes. The latter may respond more readily to treatment with ICS, while the former may be less responsive, leaving residual bronchoconstriction for the LABA to act upon. Such a hypothesis would suggest that the different responses to regular LABA are the differences between early asthma and late phase of the disease. However, this is purely speculative, and more research is needed to explain whether such differences exist between LABA response in adults and pediatric patients.

Clearly there is no evidence in the pediatric literature to suggest that a LABA protects against asthma exacerbations. Additionally, asthma exacerbations may be increased in some patients taking a LABA, even when used as an add-on to ICS. Future studies must address this important issue. Taken together with the ambiguous evidence for clinically significant bronchodilation from regular treatment, the present findings suggest that it is prudent to reconsider the standard recommendation that LABAs be used routinely as regular add-on treatment in children with asthma. Subgroups of asthmatic children may benefit from regular LABA use, but there is at present little evidence for the general recommendation of LABA as standard add-on treatment in pediatric asthma management.

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