



A review on the use of long-acting beta-2 agonist (LABA) in children with asthma

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Introduction

In 2010, the spotlight on asthma treatment in children was put back on the use of long-acting beta-2 agonist (LABA). The U.S. Food and Drug Administration (FDA) announced new safety controls for the use of LABA in asthma.¹ It is suggested that LABA should never be used alone in the treatment of asthma in adults and children due to an increased risk of severe worsening of asthma symptoms, leading to hospitalisation in both children and adults and death in some patients with asthma. The agency also required the drug companies to issue new drug labels with additional information to patients and health care professionals with regards to the safe use of LABA recently in June 2010.² Incidentally, a few meta-analyses concerning the use of LABA in children with asthma were published recently. In Hong Kong, salmeterol is prepared either alone or in combination with fluticasone. Formoterol also exists either alone or in combination with budesonide.³ The current paper aims to provide an update on LABA in asthmatic children.

Pharmacodynamics of LABA

What makes salmeterol/formoterol longer acting (with a duration of action 12 hours vs. 4 hours in salbutamol)? The answer lies in their lipophilicity. Salmeterol and formoterol are more lipophilic than salbutamol so that a proportion of the drug will be sequestered into cell membranes of lung tissues after administration.⁴ It has been postulated that high concentrations of both drugs deposited in the lipid cell

membranes of the bronchial smooth muscle remain in the vicinity of the beta2-receptors for prolonged periods (depot hypothesis) resulting in their sustained duration of effect.

Clinical guidelines review

Based on various guidelines on asthma management in children, LABA is mainly recommended to be used as add-on therapy for patients whose asthma is not controlled on low to high doses of inhaled glucocorticosteroids. However, there is no consensus in the first choice of stepping up treatment among various guidelines yet (i.e. addition of LABA vs. stepping up Inhaled Corticosteroids (ICS)).

According to the latest GINA guideline,⁵ LABA's are primarily "used as add-on therapy in children older than 5 years whose asthma is insufficiently controlled by medium doses of inhaled glucocorticosteroids or as single-dose therapy before vigorous exercise". There are limited studies investigating the effect of LABA in children 5 years or younger with asthma.

According to the British Thoracic Society (BTS) guideline,⁶ the first choice as add-on therapy to inhaled steroids in adults and children (5-12 years) is an inhaled long-acting beta-2 agonist, which should be considered before going above a dose of 400 mcg beclomethasone (BDP) or equivalent per day.

However, according to asthma guideline by the National Heart, Lung, and Blood Institute,⁷ for patients ≥ 5 years of age who have moderate persistent asthma or asthma inadequately controlled on low-dose ICS, the option to increase the ICS dose should be given equal weight to the option of adding LABA and this choice of LABA addition should be weighted against the risk of inducing severe exacerbations. For patients ≥ 5 years of age who have severe persistent asthma, the combination of LABA and ICS is the preferred therapy.

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Meta-analyses review

In the literature, there is a large variety of study investigating the use of LABA in children with asthma. In general, they could be classified according to the investigating drug (e.g. LABA alone vs. LABA + ICS in combination) or severity of asthma (e.g. persistent asthma). We summarised the beneficial and adverse effects of LABA in different situations as follows:

Efficacy

(i) Addition of LABA & ICS to children with persistent asthma:

Sorkness et al.⁸ published one of the landmark studies investigating the use of LABA & ICS for children with persistent asthma. This Paediatric Asthma Controller Trial (PACT) trial was a multi-centre randomised study recruited 285 children with mild-moderate persistent asthma who were not on controller medications at least 2 weeks before randomisation. It compared the addition of salmeterol 50 mcg BD + fluticasone 100 mcg daily (PACT combination) vs. fluticasone 100 mcg BD vs. montelukast 5 mg nocte in the management of asthma primarily in terms of asthma control days. The results showed that fluticasone monotherapy and PACT combination were comparable in many patient-measured outcomes, including percent of asthma control days compared with montelukast. Fluticasone monotherapy was superior for clinic-measured FEV1/forced vital capacity, maximum bronchodilator response, exhaled nitric oxide. Growth over 48 weeks was not statistically different among three groups. However, Tal et al.⁹ showed different results in a multi-centre European study. The trial involved 286 children with moderate persistent asthma controlled by at least 400 mcg budesonide. It compared budesonide/formoterol 80/45 mcg BD with budesonide 200 mcg BD on peak expiratory flow (PEF). The results showed that the combination of budesonide/formoterol provided rapid improvements in PEF and FEV1 compared to inhaled budesonide alone.

In view of the conflicting results available in the literature, Ni Chroinin et al. tried to address this question in a Cochrane Review¹⁰ for steroid-naïve patients with asthma (no inhaled steroids used in the preceding 28 days prior to enrollment). The authors studied the effect on the addition of LABA to ICS compared with ICS alone (same and higher doses) in steroid-naïve patients with persistent asthma. The study included 27 trials (22 adult; 5 paediatric).

It showed that the combination of ICS and LABA was not associated with a significantly lower risk of patients with exacerbations requiring oral corticosteroids (RR 1.04; 95% confidence interval (CI) 0.73 to 1.47) or requiring hospital admissions (RR 0.38; 95% CI 0.09 to 1.65) compared to a similar dose of ICS alone. However, the combination of LABA and ICS led to a significantly greater improvement from baseline in FEV1 (0.12 L/sec; 95% CI 0.07 to 0.17), in symptoms (SMD -0.26; 95% CI -0.37 to -0.14) and in rescue β_2 -agonist use (-0.41 puffs/day; 95% CI -0.73 to -0.09) compared with a similar dose of ICS alone. When compared with a higher dose of ICS alone, the combination of LABA and ICS was associated with a higher risk of patients requiring oral corticosteroids (RR 1.24; 95% CI 1 to 1.53) and study withdrawal (RR 1.31; 95% CI 1.07 to 1.59). However, it was commented that children appeared to respond similarly to adults though no firm conclusions can be drawn regarding combination therapy in steroid-naïve children because of the small number of children contributing data.

Ni Chroinin et al.¹¹ also reviewed the benefit of adding LABA to ICS (same and doubled doses) in children with uncontrolled persistent asthma (inadequately controlled on a baseline dose equivalent to 400 mcg/day of beclomethasone or less). The authors studied 25 trials involving 5572 children. Their results showed that when compared to ICS (same dose) alone, the addition of LABA to ICS was not associated with a significant reduction in exacerbations requiring oral steroids (RR 0.92; 95% CI 0.60 to 1.40). However, there was a significantly greater improvement in FEV1 with the addition of LABA (0.08 Litres, 95% CI 0.06 to 0.11). When compared to ICS (doubled dose), the addition of LABA demonstrated no significant difference in the risk of an exacerbation requiring oral steroids (RR 1.5, 95% CI 0.65 to 3.48). Again, there was a significantly greater improvement in morning PEF (MD 7.55 L/min; 95% CI: 3.57 to 11.53) and evening PEF (MD 5.5 L/min; 95% CI 1.21 to 9.79).

(ii) LABA versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma

Ducharme et al.¹² has reviewed the use of LABA vs. anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. The study included 11 trials including 6030 patients. However, all of them were adult patients. It showed that exacerbations requiring systemic corticosteroids was significantly lower with the addition of LABA compared with anti-



leukotrienes (RR=0.83; 95% CI: 0.71, 0.97). Moreover, the morning PEF (16 L/min; 95% CI: 13 to 18), evening PEF (12 L/min; 95% CI: 9 to 15), FEV1 (80 ml; 95% CI: 60 to 100), rescue-free days (9%; 95% CI: 5% to 13%), symptom-free days (6%; 95% CI: 2 to 11), rescue use of β_2 -agonists (-0.5 puffs/day; 95% CI: -0.2 to -1), quality of life (0.1; 95% CI: 0.05 to 0.2), symptom score (Standard Mean Difference -0.2; 95% CI: -0.1 to -0.3), night awakenings (-0.1/week; 95% CI: -0.06 to -0.2) and patient satisfaction (RR 1.12; 95% CI: 1.07 to 1.16) were all significantly improved in the LABA group compared with anti-leukotrienes. Therefore, the authors concluded that in asthmatic adults inadequately controlled on low doses of inhaled steroids, the addition of LABA is better than anti-leukotrienes for preventing exacerbations requiring systemic steroids.

Literature in this aspect for children is very limited. Miraglia del Giudice et al.¹³ published a double-blind randomised crossover trial involving 48 steroid naïve children (7-11 years) with asthma. The primary outcomes were FeNO and FEV1. The participants were randomised to four groups for two consecutive one-month periods, (Group 1): first month: budesonide 200 mcg twice daily; second month: budesonide 400 mcg twice daily; (Group 2): first month: budesonide 200 mcg twice daily+formoterol 9 mcg twice daily; second month: budesonide 200 mcg twice daily+montelukast 5 mg once daily; (Group 3): first month: budesonide 200 mcg twice daily+montelukast 5 mg once daily; second month budesonide 200 mg+formoterol 9 mcg twice daily; (Group 4): first and second month: budesonide 400 mg twice daily. The results showed that all treatment groups resulted in a significant increase in lung function and a decrease in FeNO compared with values at baseline. Budesonide+montelukast in combination was the most effective treatment for reducing FeNO levels with mean FeNO decreased from 24.8 ± 0.9 ppb to 18.2 ± 1.1 ppb ($P < 0.01$) at the end of Month 2 and from 38.7 ± 1.3 ppb at baseline to 19.0 ± 1.1 ppb ($P < 0.01$) at the end of Month 1 in group (2) and (3) respectively. Significant better improvement in FEV-1 was seen in the groups treated with ICS + formoterol or montelukast than the groups with ICS alone. The authors concluded that add-on therapy with monteleukast plus low-dose budesonide is more effective than the addition of LABA or doubling the dose of budesonide for controlling FeNO in asthmatic children. However, the results from this study may be affected by carry-over effect in the study design and

the number of children involved (each arm=12) was too small. The conclusion should be interpreted with caution.

(iii) Long-acting beta-2 agonists as an inhaled corticosteroid-sparing agent for chronic asthma in adults and children

In a previous Cochrane Review, Gibson et al.¹⁴ tried to address the question on whether LABA could be used as a sparing agent for inhaled corticosteroid for chronic asthma. They reviewed and included 10 published randomised controlled trials in their study. Three out of 10 studies had enrolled adolescents (>12 years) as participants. The study included participants who have stable asthma maintained on regular moderate to high dose ICS (>400 mcg/day BDP equivalent in adults, >200 mcg/day BDP equivalent in children) for a minimum of one month prior to study entry, and not using LABA. It compared reduced dose (mean 60% reduction) ICS+LABA combination to a fixed moderate/high dose ICS. It was shown that there was no significant difference in severe exacerbations requiring oral corticosteroids (RR 1.0, 95%CI 0.76 to 1.32), withdrawal due to worsening asthma (RR 0.82, 95%CI 0.5 to 1.35) or airway inflammation. However, there were significant improvements in FEV1 (change from baseline WMD 0.10, 95%CI 0.07 to 0.12), morning & evening PEF and percent rescue free days with LABA. Since there were no studies carried out in children, the results may not be applied to children. The authors concluded that in adult patients with asthma using moderate to high maintenance doses of ICS, the addition of LABA has an ICS-sparing effect.

(iv) Addition of LABA alone as regular treatment:

Lenney et al.¹⁵ published a study involving 847 asthmatic children. They compared the regular use of salmeterol (25 mcg & 50 mcg BD) with salbutamol (200 mcg BD) on PEF's (morning, evening) and asthma exacerbations in a 12-month period. In this study, they showed that the PEF (morning and evening), asthma symptoms score and exacerbations requiring rescue use of salbutamol were significantly better in the group receiving regular use of salmeterol compared with salbutamol while having similar adverse event rates. The recommendation for regular use of LABA in asthma control has actually been controversial. Walters et al. addressed this issue in a recent Cochrane Review.¹⁶ They reviewed the literature and selected 31 studies (3/31 recruiting children <12 years, 28/31 recruiting adolescent to



adults) to be eligible in investigating the different effect with regular use of LABA vs. short-acting beta-2 agonist (SABA) in the control of stable asthma. The results showed that LABA was significantly better than SABA for a variety of lung function measurements including morning highest forced expiratory flow measured with a peak flow meter (PEF) (Weighted Mean Difference (WMD) 33 L/min 95%CI 25 to 42) or evening PEF (WMD 26 L/min 95% CI 18 to 33); and had significantly lower scores for day and night time asthma symptom scores and percentage of days and nights without symptoms. It was also associated with a significantly lower use of rescue medication both during the day and night. The authors also commented that the risk of exacerbations was not different between the two types of agent, but most studies were of short duration which limits the power to test for such differences.

Adverse events

Is the use of LABA in asthma safe? This question has been controversial in the literature over the past 20 years. Back in 1993, Castle et al. demonstrated a possible risk in the use of LABA for asthma in their severe nationwide surveillance (SNS) study.¹⁷ It was a double-blind trial involving 25,180 patients with asthma lasting for 16 weeks. The participants were randomly assigned to receive the addition of LABA (Salmeterol) or SABA (Albuterol) to determine the impact of beta-agonists on asthma and respiratory-related mortality. Although the results did not meet statistical significance, it showed a tendency of increased deaths (respiratory and related to asthma) among patients receiving LABA (12 vs. 2 deaths; 0.07% vs. 0.02%; Relative risk= 3.0, $p=0.105$). Later, other larger trials with longer study periods were performed to address the same issue. From the Salmeterol Multicenter Asthma Research Trial (SMART),¹⁸ it was found that LABA therapy was associated with increased asthma-related death (RR: 4.37, CI: 1.2-15.37), respiratory-related death (RR: 2.2, CI: 1.1-4.4) and combined asthma-related death (RR: 1.7, CI: 1.0-2.9) in this 28-week-long, double-blind study involving 26,355 patients with asthma who were randomly assigned to receive salmeterol or placebo. Subgroup analysis was also performed and found that mortality was significantly higher among black men enrolled in the trial. The study was therefore discontinued early as a result of these findings.

Because of these alarming concerns, the FDA performed a multiple analysis¹⁹ of 110 studies

evaluating the use of LABA's in patients with asthma ($n=60,954$). It showed that there was an increased risk for severe exacerbation of asthma symptoms in patients using LABA's. Specifically, there were more asthma-related deaths, intubations, and hospitalisations in those receiving LABA's compared with those receiving therapy that did not include LABA's, with the largest risk observed in children age 4 to 11 years. Therefore, the FDA concluded that there is an increased risk for severe exacerbation of asthma symptoms, leading to hospitalisations in paediatric and adult patients as well as death in some patients using LABA's for the treatment of asthma. One of the recent Cochrane Reviews focusing on the safety of LABA in asthma echoed the results. Cates et al.²⁰ reviewed 22 studies (8032 participants) involving the use of regular formoterol compared with placebo or SABA for chronic asthma. The results showed that there were 3 deaths occurred on regular formoterol and none on placebo, but the difference was not statistically significant. It was not possible to assess disease specific mortality in view of the small number of deaths. But non-fatal serious adverse events were significantly increased in those with formoterol (Peto OR 1.57; 95% CI 1.06 to 2.31) and this increase was larger in children than in adults, but the impact of age was not statistically significant.

The results were different when LABA was given with an ICS. Cates et al. also reviewed the adverse effects associated with the use of salmeterol/formoterol plus ICS compared with same dose of ICS in the use for chronic asthma in two recent Cochrane Reviews.^{21,22} The results mainly showed that both deaths and non-fatal serious adverse events were similar between groups. The authors also commented that numbers of patients suffering adverse events were too small and the results could be imprecise to confidently rule out a relative increase in all-cause mortality or non-fatal adverse events.

Summary

In summary, LABA in combination with ICS remains a useful combination for treatment of asthmatic children with no evidence of increased severe adverse event compared with other treatment regime. It is important to note that regular review of asthma control with clinical assessment and spirometry for children on this combination is essential for optimal asthma management.



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