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Review Article

Long-acting β_2-adrenergic receptor agonist in pediatric asthma

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Abstract

Long-acting β_2-adrenergic receptor agonists (LABA), a class of agents for the long-term management of childhood bronchial asthma, are recommended for use in combination with steroid inhalation for the treatment of the morning dip in severe childhood asthma. In the present review, salmeterol (SM), a LABA inhalant with a long-acting bronchodilator effect, was compared with the recently introduced tulobuterol patch (TBP) in terms of safety and efficacy, based on their respective clinical effects on childhood asthma. From a clinical perspective, both drugs had a preventive effect by suppressing the morning dip and exercise-induced asthma when used concomitantly with an inhaled corticosteroid, and both agents were associated with a lower incidence of adverse effects on the cardiovascular system than oral β_2-adrenergic receptor agonists. Based on these findings, both SM and TBP are concluded to be highly efficacious and safe bronchodilator agents that are appropriate for the long-term management of childhood asthma.

Key words: bronchodilator, long-acting β_2-adrenergic receptor agonist, pediatric asthma, salmeterol, short-actingβ_2-adrenergic receptor agonist, tulobuterol patch.

Introduction

Bronchial asthma is defined as a reversible bronchial occlusive disease and agents with potent bronchodilator effects, such as β_2-adrenergic receptor agonists, have long been used as first-choice agents for asthma attacks. In recent years, the pathology of bronchial asthma has come to be recognized as eosinophil-mediated chronic inflammation of the airways and the clinical value of various anti-inflammatory agents, such as inhaled corticosteroids, has been emphasized,[1] even in children. Therefore, the place of β_2-adrenergic receptor agonists as therapeutic agents has been reviewed and short-acting β_2-adrenergic receptor agonists (SABA) are preferred as relievers, whereas long-acting β_2-adrenergic receptor agonists (LABA) are recommended as controllers (Fig. 1). Salmeterol (SM) is an LABA and the tulobuterol patch (TBP), a recently developed β_2-adrenergic receptor agonist transdermal absorption system, is a drug delivery system (DDS) that provides long-acting and effective bronchodilation. In the present paper, we review the role of these agents as controllers in the treatment of childhood asthma.

Long-acting β_2-adrenergic receptor agonists

Of the many formulations of β_2-adrenergic receptor agonists available, oral preparations, inhalants, quantitative inhalation-type aerosols (aerosol, metered dose inhalers) and patch compounds are currently used. β_2-Adrenergic receptor agonists are classified according to their β_2-adrenergic receptor selectivity, duration of effectiveness and formulation (Table 1). The SABA have been used to treat acute attacks (relievers) and the oral drugs procaterol, clenbuterol and formoterol have recently been classified as controllers. In recent years LABA, such as salmeterol or TBP, have been shown to have high efficacy in the treatment of severe asthma when combined with anti-inflammatory agents, such as inhaled corticosteroids (Fig. 1).

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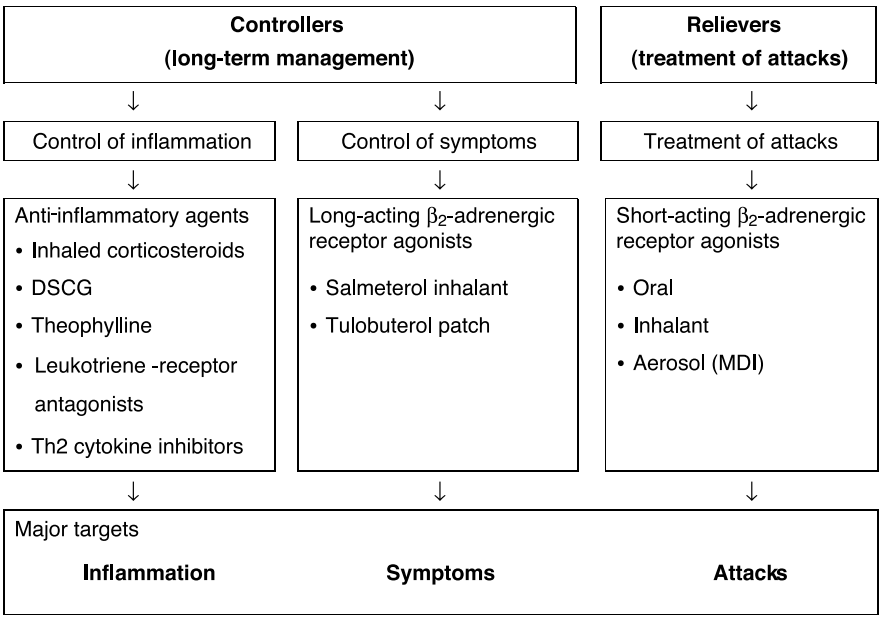

Fig. 1 Rank of long-acting β_2-adrenergic receptor agonists as agents for the treatment of pediatric bronchial asthma. DSCG, disodium cromoglycate; MDI, metered dose inhaler.

Table 1 Types and special features of β_2-adrenergic receptor agonists

Generic name	Selectivity	Duration of (adrenergic receptors)	Formulation action (h)
First generation			
Epinephrine	α_1, β_1, β_2	< 1	Injection, inhalant
Isoproterenol	α_1, $\beta_1 = \beta_2$	< 1	Injection, inhalant
Second generation			
Salbutamol	$\beta_1 < \beta_2$	4–5	Tablet, syrup, dry syrup, inhalant, MDI
Terbutaline	$\beta_1 < \beta_2$	4–6	Tablet, syrup, granule
Third generation			
Fenoterol	$\beta_1 << \beta_2$	8	Tablet, syrup, dry syrup, MDI
Procaterol	$\beta_1 << \beta_2$	8–10	Tablet, minitablet, syrup, inhalant, MDI
Tulobuterol	$\beta_1 << \beta_2$	8	Tablet, dry syrup, patch*
Formoterol	$\beta_1 << \beta_2$	10	Tablet, dry syrup, inhalant
Clenbuterol	$\beta_1 << \beta_2$	10–12	Tablet
Salmeterol	$\beta_1 << \beta_2$	12	Inhalant

*Only for Hokunalin®.

MDI, metered dose inhaler.

Salmeterol

Special features of salmeterol

The selectivity of salmeterol for the β_2-adrenergic receptors of airway smooth muscle is approximately 85 000-fold its selectivity for the β_1-adrenergic receptors of the heart, indicating very high β_2-adrenergic receptor selectivity of the drug.[2] Salmeterol manifests efficacy within 15–17 min after inhalation. Although it is slightly slower acting than salbutamol, its duration of action is more than 12 h, implying that two doses a day are sufficient.

Suppressive effect of salmeterol on the morning dip

In a randomized double-blind trial of 207 asthmatic patients ranging in age from 4 to 11 years, changes in forced expiratory volume in 1 s ($FEV_{1.0}$) were compared during 12 weeks of treatment with salmeterol (50 μg) and a placebo inhalant. The $FEV_{1.0}$ increased significantly with improvement in lung function for 12 h on day 1 in the group treated with salmeterol compared with controls and a similar tendency was observed even after the 12 week regimen.[3]

Combined effect of salmeterol and an inhaled corticosteroid in childhood asthma

The effect of salmeterol combined with an inhaled corticosteroid was examined in a total of 206 moderate to severe cases.[4] Patients currently being treated with beclomethasone propionate (BDP) or budesonide at a mean dose of 750 μg/day were divided into two groups, one treated with salmeterol inhalant (50 μg) in combination twice a day for 12 weeks and the other treated without the salmeterol inhalant. The time-related changes (%) in morning peak expiratory flow (PEF) were monitored in the two groups. The results showed marked improvement in morning PEF measured at 4 week intervals (during 1–4 weeks, 5–8 weeks and 9–12 weeks) in the combined-treatment group compared with the monotherapy group, suggesting that the morning dip in the former group was markedly suppressed.[4] A meta-analysis of the results in patients over 12 years of age showed highly convincing efficacy in patients treated with combination therapy.[5,6] Interestingly, methacholine-induced airway hypersensitivity was no more severe in patients treated with salmeterol alone for 4 months than in patients treated with salbutamol alone.[7] However, controversial findings, such as absence of improvement of airway hypersensitivity in patients treated with salmeterol alone but improvement in those treated with BDP alone, have been reported in patients treated with salmeterol or BDP alone for 1 year.[8] Therefore, the results cited above do not support treatment with salmeterol alone on a long-term basis[8,9] and, instead, support therapy with a combination of an LABA and inhaled corticosteroid. One reason for this is that β_2-adrenergic receptor agonists prevent the decrease in steroid receptor sensitivity caused by repeated exposure to inhaled corticosteroids and, because steroids reverse the down-regulation and reduction in number of β_2-adrenergic receptors induced by repeated dosing with β_2-adrenergic receptor agonist,[10] corticosteroids and β_2-adrenergic receptor agonists compensate for the shortcomings of each other.

Clinical benefits of salmeterol in exercise-induced asthma

To assess the effectiveness of salmeterol in suppressing exercise-induced asthma (EIA), salmeterol inhalant (50 μg/day) was administered prophylactically once to 13 asthmatic patients aged 8–15 years who had an exercise load-induced $FEV_{1.0}$ reduction of > 15%. Exercise loading was performed 1.5 and 9 h after administration and $FEV_{1.0}$ was measured 30 min after loading-indicated reductions. The salmeterol inhalant had a prophylactic effect on EIA.[11] No differences in EIA were observed when two salmeterol powder-delivery devices were used[12] and salmeterol inhalation had a longer-acting prophylactic effect on EIA than the SABA albuterol.[13]

Safety of salmeterol

The safety margin of salmeterol and salbutamol have already been established in a double-blind study on childhood asthma comparing the two drugs.[14] The incidence of adverse reactions in children in Japan is 2.8% and one case of palpitations (0.31%) and two cases of tremors (0.62%) have been documented (Table 2). The incidence of adverse effects in the cardiovascular and nervous systems was significantly lower than with oral β_2-adrenergic receptor agonists.

Ranking of salmeterol according to pediatric asthma treatment guidelines

Salmeterol inhalant is a useful agent with sufficient efficacy for the long-term management or control of childhood asthma in ordinary family life. The Global Initiative for Asthma (GINA) 2002 Guidelines (Fig. 2) recommend combined use with an anti-inflammatory agent, such as inhaled corticosteroid, from step 3 onward.[1] In addition, salmeterol has again been recommended for combined therapy with anti-inflammatory agents, such as inhaled corticosteroids, for 6–15-year-old asthma patients in Japan according to the 2002 Japanese Pediatric Allergy Guidelines on Childhood Asthma Management and Treatment.[15]

Table 2 Comparison of the adverse effects of salmeterol and the tulobuterol patch giving the incidence of adverse effects in children after official approval for use in Japan

Item	TBP	Salmeterol
No. subjects evaluated	401	322
No. with adverse effects	41	9
Incidence adverse effects (%)	10.22	2.80
No. with palpitations (%)	1 (0.25)	1 (0.31)
No. with tremor (%)	0 (0)	2 (0.62%)
No. with throat discomfort (%)	–	1 (0.31)
No. with redness at patchsite (%)	21 (5.24)	–

TBP, tulobuterol patch.

Recommended medications by level of severity: Children		
All steps: In addition to daily controller therapy, a rapid-acting inhaled β_2-adrenergic receptor agonist should be taken as needed to relieve symptoms, but should not be taken more than three to four times a day.		
Level of severity	Daily controller medications	Other treatment options
Step 1: Intermittent asthma	• None necessary	
Step 2: Mild persistent asthma	• Inhaled glucocorticosteroid (100–400 µg budesonide or equivalent)	• Sustained-release theophylline, *or* • Cromone, *or* • Leukotriene modifier
Step 3: Moderate persistent asthma	• Inhaled glucocorticosteroid (400–800 µg budesonide or equivalent)	• Inhaled glucocorticosteroid (<800 µg budesonide or equivalent) *plus* sustained-release theophylline, *or* • Inhaled glucocorticosteroid (<800 µg budesonide or equivalent) *plus* long-acting inhaled β_2-adrenergic receptor agonist, *or* • Inhaled glucocorticosteroid at higher doses (>800 µg budesonide or equivalent), *or* • Inhaled glucocorticosteroid (<800 µg budesonide or equivalent) *plus* leukotriene modifier
Step 4: Severe persistent asthma	• Inhaled glucocorticosteroid (>800 µg budesonide or equivalent) *plus* one or more of the following, if needed: • Sustained-release theophylline • Long-acting inhaled β_2-adrenergic receptor agonist • Leukotriene modifier • Oral glucocorticosteroid	
All steps: Once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the maintenance therapy should be tried in order to identify the minimum therapy required to maintain control.		

Fig. 2 Drug regimens for the long-term management of pediatric bronchial asthma (Global Initiative for Asthma[1]).

Further studies on salmeterol

Airway vascular remodeling in adults is unaffected by 3 month combination therapy consisting of salmeterol inhalant and an inhaled corticosteroid.[16] However, airway remodeling is induced by the salmeterol inhalant combined with steroid inhalation in rats.[17] Thus, an investigation of the effect of salmeterol inhalant on airway remodeling in childhood asthma is needed.

Tulobuterol patch

Special features of TBP

The TBP (Hokunalin-Tape®; Abbott and Maruho pharmaceutical, Osaka, Japan) exploits the transdermal absorption model formula to deliver the quantity of drug required for the time required to attenuate systemic adverse effects and suppress the morning dip. In short, systemic adverse effects can be attenuated by preventing excessive increases in drug concentration coupled with suppression of the morning dip by administration before bedtime, because attainment of the peak blood concentrations requires an interval of approximately 10 h.[18,19] A single administration of TBP each day is sufficient to provide the daily effects required.

Suppressive effect of TBP on the morning dip

Changes in morning and night-time PEF values have been measured before and after the administration of

tulobuterol dry syrup and TBP.[20] After 1 week of administration, both preparations elicited a significant increase in the morning and night-time PEF values compared with pretreatment values, but there were similar degrees of improvement in PEF and no significant differences between the dosage forms. Based on this finding, the improvement in pulmonary function in childhood asthma by TBP administered once daily before bedtime is equivalent to the effect achieved by two daily oral doses of dry syrup. Furthermore, a suppressive effect on morning dip was implied and a concentration-dependent improvement effect of tulobuterol on PEF was also shown.[21]

Combined effects of TBP and inhaled corticosteroid in childhood asthma

Changes in the asthma attack scores in seven cases of severe asthma (mean age 9 years) treated with a combination of inhaled corticosteroid and TBP for 6 months showed significant attenuation for the first month, followed by significant decreases until 6 months of administration compared with the value 1 month before the start of therapy; PEF values also increased significantly.[21] These findings suggest that good efficacy can be achieved for at least 6 months by combination therapy consisting of an inhaled corticosteroid and TBP and that no adverse effects were encountered. The combined therapy with TBP was effective against the morning dip in severe childhood asthma, despite the repeated corticosteroid inhalation regimen.[22] The results strongly suggest that long-term use of TBP is required for the persistent suppression of the morning dip.

Clinical benefits of TBP in EIA

Five patients with severe asthma (mean age 8 years) who were subject to EIA were treated with combination therapy, consisting of an inhaled steroid plus TBP. The preventive effects on EIA were monitored with a peak flowmeter before and after combined therapy and the PEF values were compared. Decreased postexercise PEF values were reversed and a significantl improvement in PEF values was observed even at 6 h after exercise loading. These findings suggest that TBP not only suppresses the morning dip in severe asthma, but is also useful as a prophylactic agent for EIA.[22]

Safety of TBP

Based on the adverse effects encountered in children (Table 2), the induction of tremors and palpitations by TBP was noted at the time of drug approval in Japan, but the incidence of these side-effects was a significantly lower than with other oral β_2-adrenergic receptor agonists. No tremors have been reported in children and only one case of palpitations (0.25%) has been documented.[22] However, trivial skin problems, such as itching, rashes and irritation at patch sites, have been encountered in 5.2% of cases tested.[22]

Ranking of TBP according to the pediatric asthma treatment guidelines

The TBP is a useful agent for the long-term management and control of childhood asthma in daily family life. The TBP has a long-acting bronchodilator effect equivalent to that of LABA and the 2002 Guidelines for the Treatment and Management of Childhood Asthma in Japan[15] recommend TBP for use in combined therapy with anti-inflammatory agents, especially inhaled corticosteroid, in patients of all ages from infancy to adolescence.

Further study on TBP

Studies on drug tolerance and adverse effects, as well as the effects of TBP on airway hypersensitivity and airway remodeling over a 1 year period of continuous use, are

Table 3 Comparison of the special features of salmeterol and the tulobuterol patch

Item	TBP	Salmeterol
Duration of action (h)	24	12
Suppression of morning dip	+	+
Effectiveness of ICS in combination with	+	+
Suppressive effect on EIA	+	+
Appropriate age range (years)	0.5–15	6–15
Drug compliance	+ (visually apparent)	+
Education	+ (simple)	± (complicated procedure)

TBP, tulobuterol patch; ICS, inhaled corticosteroid; EIA, exercise-induced asthma.

warranted in children. Multicenter studies have recently confirmed the absence of adverse effects of a continuous 2 week regimen of TBP and inhaled-steroid combined therapy on airway hypersensitivity[23] and TBP can be used as a reliever for short periods in actual clinical practice to prevent night-time–morning acute asthma attacks. When used in this way, the parents must use TBP to prevent transient attacks based on an individual assessment. In doing so, the use of TBP may result in the apparent control of asthma, whereas in reality airway inflammation may persist, progress or be exacerbated. In other words, the use of TBP may lead to undertreatment by anti-inflammatory agents. Parents of asthmatic children should be given proper guidance with thorough complementary explanations on the correct use of TBP.

CONCLUSIONS

The special features (Table 3) and adverse effects (Table 2) of salmeterol and TBP, both of which are agents with a long-acting bronchodilator action, were compared. The duration of action, appropriate age range, drug compliance and education differ little from those of combined therapy with inhaled corticosteroids in terms of suppressing the morning dip, preventing EIA and the low incidence of adverse effects on the cardiovascular system. Thus, salmeterol and TBP have high efficacy and an excellent safety margin as bronchodilators for the long-term management of childhood asthma. Furthermore, the special features of the drug design of these two agents facilitate age-related administration routes: salmeterol is appropriate for children more than 6 years of age, whereas TBP is appropriate for infants more than 6 months of age.

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