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ORIGINAL ARTICLE

Effects of Transdermal Tulobuterol in Pediatric Asthma Patients on Long-Term Leukotriene Receptor Antagonist Therapy: Results of a Randomized, Open-Label, Multicenter Clinical Trial in Japanese Children Aged 4-12 Years

Toshio Katsunuma[1], Takao Fujisawa[2], Mizuho Nagao[2], Akira Akasawa[3], Ichiro Nomura[4], Akiko Yamaoka[5], Hisashi Kondo[6], Kei Masuda[7], Koichi Yamaguchi[8], Akihiko Terada[9], Masanori Ikeda[10], Kenji Nishioka[11], Yuichi Adachi[12] and Kazuyuki Kurihara[13]

ABSTRACT

Background: Few studies have examined the efficacy or safety of a transdermal β_2 agonist as add-on medication to long-term leukotriene receptor antagonist (LTRA) therapy in pediatric asthma patients.

Methods: In this randomized, open-label, multicenter clinical trial, children aged 4-12 years on long-term LTRA therapy were treated with tulobuterol patches (1-2 mg daily) or oral sustained-release theophylline (usual dose, 4-5 mg/kg daily) for 4 weeks. LTRAs were continued throughout the trial. Outcomes included volume of peak expiratory flow (% PEF), fractional exhaled nitric oxide (FeNO), clinical symptoms and adverse events.

Results: Thirty-three and 31 patients were treated with tulobuterol patches and theophylline, respectively. % PEF measured in the morning and before bedtime was significantly higher at all times in the treatment period compared with baseline in the tulobuterol patch group ($p < 0.001$), and was significantly higher in the tulobuterol patch group compared with the theophylline group. FeNO was similar and unchanged from baseline in both groups. There were no drug-related adverse events in either group.

Conclusions: These results suggest that short-term use of a transdermal β_2 agonist is an effective therapy for pediatric asthma without inducing airway inflammation in children on long-term LTRA therapy.

KEY WORDS

asthma, child, preschool, theophylline, transdermal patch, tulobuterol

[1]Department of Pediatrics, Jikei Daisan Hospital, [3]National Center for Child Health and Development, [7]International University of Health and Welfare, Mita Hospital, [8]The Fraternity Memorial Hospital, Tokyo, [2]National Hospital Organization Mie Hospital, [6]Kondo Children's Hospital, Mie, [4]National Hospital Organization Kanagawa Hospital, [11]Nishioka Clinic, [13]Kanagawa Children's Medical Center, Kanagawa, [5]Saitama Medical University, Saitama, [9]Daido Hospital, Aichi, [10]Department of Pediatrics, Fukuyama Medical Center, Hiroshima and [12]Department of Pediatrics, University of Toyama, Toyama, Japan.

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Correspondence: Toshio Katsunuma, Department of Pediatrics, Jikei Daisan Hospital, The Jikei University, 4–11–1 Izumi-Honcho, Komae, Tokyo 201–8601, Japan.
Email: tkatsunuma@jikei.ac.jp

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INTRODUCTION

Low-dose inhaled corticosteroids (ICS) or leukotriene receptor antagonists (LTRAs) are widely used for long-term management of pediatric asthma.[1] ICS are generally recommended as the initial controller medication, although LTRAs are increasingly being considered instead of ICS.[2-4] Indeed, LTRAs are particularly useful in patients who need to avoid steroids, and in patients with allergic rhinitis.[5-7] They may also be useful in infants, as they can provide effective long-term asthma control, similar to that achieved with low-dose ICS.[8] The most common add-on medications in mild pediatric asthma are β_2 stimulants, although the Japanese Pediatric Guidelines for the Treatment and Management of Bronchial Asthma also recommend theophylline as an add-on medication for mild asthma.[9]

The tulobuterol patch (Abbott Japan Co., Ltd., Tokyo, Japan) is a transdermal β_2-adrenergic agonist that was approved in Japan in 1998, and is widely accepted by patients for management of asthma or wheezing. The tulobuterol patch has a favorable pharmacokinetic profile,[10] and is associated with good adherence[11] for the management of asthma or wheezing. The tulobuterol patch provides a prolonged bronchodilator effect because it contains molecular and crystallized forms of tulobuterol. Upon application to the skin, the molecular tulobuterol is gradually absorbed percutaneously. The depleted tulobuterol molecules in the patch are then replenished by dissociation of crystallized tulobuterol into absorbable tulobuterol molecules. Therefore, although tulobuterol is a short-acting β_2 agonist, each patch provides effects lasting over 24 hours in adults[10] and children,[12,13] thus providing long-acting β_2 agonist activity.

To date, however, no studies have investigated the efficacy of the tulobuterol patch as an add-on medication to LTRA for the management of mild pediatric asthma. The Japanese Pediatric Guidelines recommend that studies should include theophylline as the first-line add-on medication. Therefore, the aim of this study was to compare the effects of short-term continuous use of the tulobuterol patch with that of sustained-release theophylline as add-on medications for children aged 4-12 years with mild-to-moderate asthma on long-term treatment with a LTRA.

METHODS

PATIENTS

Children aged 4-12 years with bronchial asthma under treatment for mild persistent asthma diagnosed according to the Japanese pediatric guidelines for the treatment and management of bronchial asthma,[9] or continued wheezing, dyspnea or diurnal variation in peak expiratory flow (PEF) ≥20% despite treatment with LTRAs, or stable PEF, were eligible for this study. Children meeting any of the following criteria were excluded: treatment with a long-acting β_2 agonist or regular treatment with an oral β_2 agonist; history of hypersensitivity to the tulobuterol patch or skin diseases such as atopic dermatitis, for whom the tulobuterol patch was considered inappropriate; diseases considered unsuitable for treatment with β_2 agonists (e.g., hyperthyroidism, hypertension, heart disease or diabetes mellitus) or theophylline (e.g., epilepsy, hyperthyroidism, acute nephritis, congestive heart failure, liver disease); history of serious adverse reactions to tulobuterol or theophylline; history of severe neurological disorders (e.g., epilepsy, convulsions or abnormal electroencephalogram); or fever ≥37.5℃. Patients who were deemed inappropriate to participate in the study by their attending physician were also excluded from the study.

Diurnal variation in PEF was calculated as [(daily maximum PEF) - (daily minimum PEF)] / {[(daily maximum PEF) + (daily minimum PEF)] / 2} × 100.

Reliable PEF was defined as the difference between the second highest and the highest PEF value being <15% of the highest PEF measurement of three consecutively measured values.

The nature of the study was explained to all patients and their parents/guardian, and written informed consent was obtained from the parents/guardians. Informed consent was also obtained from older children when considered appropriate. The study was carried out in accordance with the principles of the Declaration of Helsinki, 1995, and revised in Seoul, 2008. The clinical trial registration number is UMIN 000002921.

Patients were withdrawn from the study in the event of any of the following: a child or parent/guardian requesting discontinuation of the study medication; continuation of the study being deemed difficult because of adverse reactions, worsening of complications (including where ICS were considered necessary) or worsening of symptoms; the child not attending the follow-up visits; or any other situation in which continuing the study was deemed inappropriate by the attending physician.

STUDY DESIGN AND TREATMENTS

This was a randomized, open-label, parallel-group, multicenter (15 centers) clinical study performed in Japan between January 2007 and June 2009. Japanese children meeting the eligibility criteria entered a 1-2-week run-in phase and were treated with a LTRA (pranlukast or montelukast) alone. LTRAs were used in accordance with their approved dose regimens. At the end of the run-in phase, patients received either the tulobuterol patch (Abbott Japan Co., Ltd.) or sustained-release theophylline (AstraZeneca, London, UK) for 4 weeks.

Randomization was performed using the sealed envelope method using a randomization table generated

by Kumiko Ohta at the Clinical Research Division of National Mie Hospital.

The tulobuterol patch was applied once-daily at bedtime to the chest, back or upper arm, at a dose of 1 mg for children aged 3-<9 years, or 2 mg for children aged ≥9 years. Sustained-release theophylline (4-5 mg/kg per dose; twice-daily in the morning and at bedtime) was administered in accordance with the Japanese Pediatric Guidelines for the Treatment and Management of Bronchial Asthma.[9] Inhaled or oral steroids were prohibited from 1 month before study commencement. Other β_2 agonists were prohibited, except for the use of oral/inhaled β_2 agonists at the onset of an asthma exacerbation. Anti-allergic drugs, inhaled anticholinergic, antihistamine, antitussives/expectorants and traditional Chinese medicines initiated before the study were allowed, providing their dose and regimen remained unchanged throughout the study. Patients requiring ICS therapy during the treatment period to treat deteriorating symptoms were excluded from the evaluation.

ENDPOINTS

The primary endpoint was the volume of peak expiratory flow (% PEF) measured in the morning and before bedtime. Secondary endpoints included asthma symptoms, airway inflammation levels, use of as-needed β_2 agonists, and adverse drug reactions. Patients were asked to perform PEF tests three times in the morning and before bedtime every day, and the maximum value at each time was recorded in a diary. The diary was also used to record clinical symptoms, including symptoms of exacerbations, frequency of exacerbations, coughing, sputum, activities of daily living, nocturnal sleep, and frequency of using as-needed β_2 agonists. Airway inflammation was assessed by measuring fractional exhaled nitric oxide (FeNO) using a NIOX MINO (Aerocrine, Solna, Sweden) during the run-in period, and after 2 and 4 weeks of treatment. Symptoms and laboratory anomalies that newly occurred or deteriorated during the study were recorded. For all events, the date of onset and resolution, severity, treatment required, outcome and causal relationship with the study drug were recorded.

STATISTICAL ANALYSIS

Considering the results of prior studies in pediatric patients[14,15] the change in PEF from baseline was assumed to be 5.0 L/min in patients receiving theophylline and 18.0 L/min in those receiving treatment with the tulobuterol patch, with a common standard deviation of 26.0 L/min. Therefore, with a two-sided significance level of 5% and 80% power, the sample size was calculated to be 64 patients per group. Allowing for a 10% dropout rate, the target sample size was 70 patients per group. The secondary endpoint of asthma symptoms was assessed on a 4-point scale that has been used for many years in clinical practice in Japan.[16] A score of 1 was given to patients with a cough. A score of 3 was given to patients with a cough, mild wheezing, no retractive breathing, or mild retractive breathing. A score of 6 was given to patients who had a cough, apparent wheezing, apparent retractive breathing, and dyspnea. A score of 9 was given to patients who had a cough, marked wheezing, markedly retractive breathing, and marked dyspnea. Scores of 2, 4, 5, 7, and 8 do not exist. The scoring system uses scores of 1, 3, 6, and 9 instead of 1, 2, 3, and 4 to provide a weighting for the degree of exacerbation. For comparisons of demographic data and baseline characteristics between the two groups, χ^2 test, Fisher's exact probability test, Wilcoxon's two-sample test and Student's two-sample test were used as appropriate. Student's one-sample and two-sample tests were used for within-group and between-group comparisons of efficacy outcomes. For all analysis, values of $P < 0.05$ were considered statistically significant. All statistical analyses were done using SAS ver. 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

PATIENT CHARACTERISTICS

Overall, 80 patients were screened and considered eligible for the study. Of these, 14 withdrew consent before treatment allocation. Thirty-four patients were treated with tulobuterol patches and 32 patients with theophylline. Two patients were withdrawn from the study: one patient allocated to the theophylline group used a generic tulobuterol patch during the study and one patient in the tulobuterol patch group had a compliance of ≤10%. Therefore, 33 patients treated with tulobuterol patches and 31 with theophylline were analyzed. The characteristics of patients in both groups are summarized in Table 1; these characteristics were not significantly different between the two groups.

% PEF

Figure 1 shows the changes in % PEF from baseline (run-in period) to week 4 of treatment. % PEF measured in the morning (Fig. 1A) and before bedtime (Fig. 1B) improved significantly in the tulobuterol group within 1 week of starting treatment, and continued to increase thereafter.

Although % PEF measured in the morning and before bedtime in the theophylline group also increased significantly at week 1, the magnitude of the increase was much smaller than that seen in the tulobuterol group, and % PEF remained significantly lower than those in the tulobuterol patch group. Interestingly, the improvement in % PEF measured before bedtime at week 1 in the theophylline group was lost by week 2, as % PEF measured before bedtime at weeks 2, 3 and 4 was not significantly different to that at baseline in this group.

Table 1 Patient characteristics

	Tulobuterol patch	Theophylline	*p*
n	33	31	
Sex (M/F)	17/16	21/10	0.212*
Age (years)	7.5 ± 2.0	8.5 ± 2.0	0.056
Height (cm)	124.5 ± 13.0	128.3 ± 13.1	0.250
Weight (kg)	26.7 ± 9.1	27.6 ± 9.4	0.713
Concomitant use of antihistamines (Yes/No)	8/25	9/22	0.779*
% PEF in the morning	84.6 ± 13.7	89.8 ± 13.6	0.055
% PEF before bedtime	90.7 ± 11.4	93.6 ± 12.1	0.248
FeNO (ppb)	35.7 ± 22.2	36.6 ± 23.6	0.881

P-values were determined using t-tests, except *Fischer's exact test. PEF, peak expiratory flow; FeNO, fractional exhaled nitric oxide.

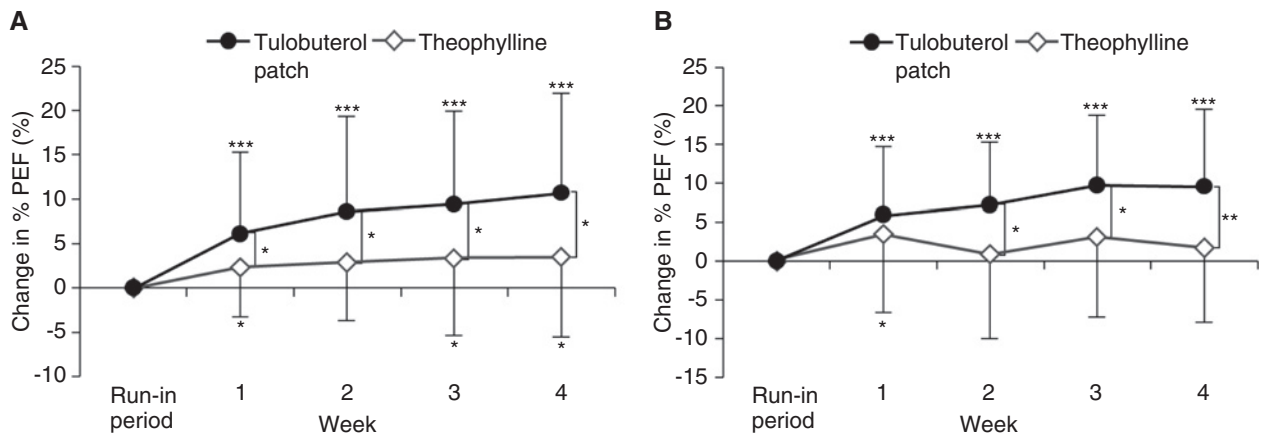

Fig. 1 Changes in % peak expiratory flow (PEF) in the morning (**A**) and before bedtime (**B**). *$P < 0.05$, **$P < 0.001$, and ***$P < 0.001$ vs run-in (Student's one-sample test) or theophylline (Student's two-sample test).

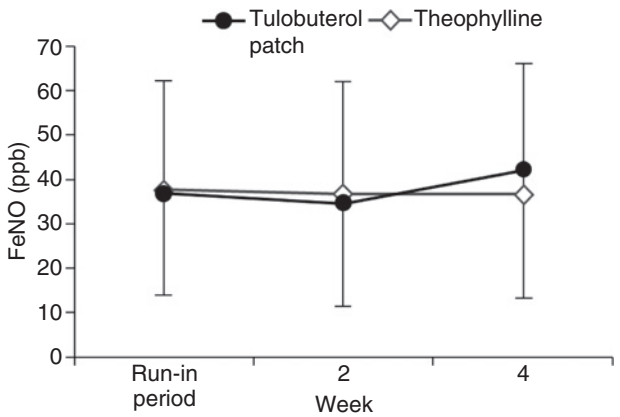

Fig. 2 Changes in fractional exhaled nitric oxide (FeNO). There were no significant differences in FeNO at weeks 2 or 4 vs run-in (Student's one-sample test) or vs theophylline (Student's two-sample test).

FeNO

FeNO, a marker of eosinophilic asthma inflammation, was determined at baseline and at the end of weeks 2 and 4 on treatment. As shown in Figure 2, there were no marked changes in FeNO during the study in either group. This indicates that neither the tulobuterol patch nor theophylline affected airway inflammation.

ASTHMA EXACERBATION SCORES AND SYMPTOMS

Exacerbation scores, which were determined based on the symptoms and frequency of exacerbations, were determined during the run-in period, during weeks 1-2, and weeks 3-4 of treatment. Scores improved in both groups, from 14.2 ± 20.9 in the run-in period to 8.2 ± 22.2 during weeks 3-4 in the tulobuterol patch ($p = 0.41$), and from 10.5 ± 14.6 to 7.6 ± 15.8 in the theophylline group ($p = 0.43$), although these improvements were not statistically significant (Table 2).

Asthma symptoms in terms of the number of exercise-induced exacerbations and the number of days with good sleep were also recorded over 2 weeks in the run-in period and at weeks 3-4. As shown in Table 2, the number of exercise-induced ex-

Table 2 Asthma symptoms and frequency of β_2 agonist administration

		Tulobuterol patch	Theophylline
Exacerbation scores	During the run-in period	14.2 ± 20.9	10.5 ± 14.6
	At weeks 1-2 of treatment	13.3 ± 24.6	7.6 ± 15.7
	At weeks 3-4 of treatment	8.2 ± 22.2	7.6 ± 15.8
Number of exercise-induced exacerbations	During the run-in period	0.9 ± 2.5	0.4 ± 1.1
	At weeks 3-4 of treatment	0.2 ± 0.7	0.1 ± 0.2
Number of days with good sleep (%)	During the run-in period	10.2 ± 5.8 (72.9)	10.9 ± 6.6 (77.9)
	At weeks 3-4 of treatment	13.0 ± 5.0 (92.9)	12.3 ± 4.7 (87.9)
Frequency of oral β_2 agonist administration (*n*)	During the run-in period	1.7 ± 5.2	0.1 ± 0.4
	At weeks 1-2 of treatment	0.5 ± 1.7	0.5 ± 1.2
	At weeks 3-4 of treatment	0.1 ± 0.4	1.1 ± 5.6
Frequency of inhaled β_2 agonist administration (*n*)	During the run-in period	0.5 ± 1.8	0
	At weeks 1-2 of treatment	0.3 ± 0.8	0.1 ± 0.2
	At weeks 3-4 of treatment	0.4 ± 1.2	0.5 ± 3.1

acerbations decreased in both groups, while the number and proportion of days with good sleep increased in both groups. However, these changes did not reach statistical significance. The frequency of oral and inhaled β_2 agonist administration tended to decrease between the observation period and week 3-4 of treatment in the tulobuterol patch group, but increased in the theophylline group (Table 2).

SAFETY

Adverse events were rare. Acute upper respiratory inflammation was reported in one patient treated with theophylline, but was not considered related to the investigational drug. No drug-related adverse effects occurred during the study.

DISCUSSION

In this study, we compared the effects of short-term continuous use of a transdermal β_2 agonist (tulobuterol patch) with those of sustained-release theophylline as add-on medications in combination with a LTRA in 4-12-year-old children with mild persistent asthma or moderate pediatric asthma. We found that the tulobuterol patch significantly increased % PEF in the morning and before bedtime at all times in the treatment period compared with baseline values. Although theophylline elicited significant increases in morning % PEF at weeks 1, 3 and 4, and in % PEF measured before bedtime at week 1, the magnitude of the increase at all times (except % PEF measured before bedtime at week 1) during the treatment period was significantly smaller than that achieved with the tulobuterol patch. The frequency of as-needed β_2 agonist administration tended to decline over time in the tulobuterol patch group, although increased slightly in the theophylline group. These results indicate that add-on tulobuterol patch is superior to theophylline in terms of improving % PEF in children with mild-to-moderate asthma on long-term treatment with a LTRA.

Among adults, patients with moderate to severe asthma experienced significant improvements in health-related quality of life and morning % PEF following 4 weeks of treatment with the tulobuterol patch. Morning % PEF was significantly lower in patients treated with the tulobuterol patch than in those treated with salmeterol, although health-related quality of life scores were similar in both groups.[17]

Of note, we observed no tachyphylaxis during continuous use of the tulobuterol patch for 4 weeks. Tachyphylaxis is a phenomenon characterized by decreased responsiveness of a receptor following continuous exposure to an agonist; in this setting tachyphylaxis results in a reduced bronchodilator effect of the β_2 agonist,[18] as has already been reported for albuterol.[19] It is also important to consider that tachyphylaxis is particularly common in patients with airway inflammation.[20] However, in our study, the improvements in respiratory function (i.e., % PEF) in the tulobuterol group seemed to increase gradually, without signs of decreasing over time, although we cannot rule out the possibility of a plateauing or reduction in % PEF with longer-term usage. Salmeterol, a long-acting β_2 agonist, was also found to not induce tachyphylaxis,[21] suggesting that the tulobuterol patch may elicit similar effects to salmeterol.

NO levels are correlated with the eosinophil count in sputum and methacholine airway hypersensitivity, a useful marker of airway inflammation in asthma.[22] It has been reported that long-term continuous use of β_2 agonists may enhance airway inflammation.[23-25] Therefore, we assessed FeNO as a surrogate marker for airway inflammation that can be easily assessed in the clinic. After 4 weeks of treatment, there were no insignificant increases in FeNO in either group, which suggests that these drugs in combination with

a LTRA do not worsen airway inflammation in pediatric asthma.

Considering that asthma is at least partly caused by eosinophilic inflammation and that β_2 agonists are generally suspected of aggravating inflammation, particularly when used as monotherapy,[26,27] the concomitant use of a β_2 agonist with an anti-inflammatory drug, such as an ICS, is often preferred.[28] However, in a study in adults, adding the tulobuterol patch to ICS significantly improved bronchial hyperresponsiveness and significantly decreased the sputum eosinophil count compared with ICS alone.[29] The results of that study and of our own should allay these fears, as the use of the tulobuterol patch in combination with a LTRA did not worsen FeNO in our study.

The present results suggest two important avenues for future research. First, it should be determined if there is an optimal duration of treatment with tulobuterol patch, if treatment should continue until complete normalization of airway function is achieved, or if we should discontinue treatment once the patient achieves a certain threshold of lung function (e.g., based on % PEF relative to individuals without pediatric asthma). Clearly, continuing long-acting β_2 agonist therapy in patients with good lung function and marked improvements in airway inflammation is unnecessary, as they could benefit more from as-needed short-acting treatments. Second, it seems likely that not all patients show clinically significant improvements in lung function/airway responsiveness, despite treatment with either drug. In this situation, the patient may benefit from switching to or adding ICS therapy but, the question remains, how long should we wait until we switch/intensify therapy? Studies focusing on these two avenues are now needed to provide the evidence needed to optimize the treatment algorithm for pediatric asthma.

The results of this study should be interpreted with care considering the limitations. First, this was an open-label study. Although this could have been avoided by providing the participants with placebo patches or tablets, we believe that a blinded study would have led to difficulties in adherence to the assigned treatments.

A second limitation is that the sample size was smaller than planned, which reduced the statistical power of the study. Because general practices were included among the institutes participating this study, the study plan that was followed was different from the original study plan and patient enrollment took longer than was foreseen, limiting the number of patients that could be enrolled within the time-frame of the study. Nevertheless, the difference in PEF between the two groups was statistically significant and the magnitude of the difference was larger than that originally hypothesized for the sample size calculation. Of course, additional studies would be useful to confirm the current findings.

Third, although the mean exacerbation scores showed large numerical differences between the run-in period and weeks 3-4 of treatment, the differences were not statistically significant. This is probably because of the large variation in values, and because our study was underpowered to detect significant differences in this parameter. This variation may be driven by outliers, or marked variation in responses among individual patients. Future studies aimed at examining improvements in exacerbation scores may need to include a larger number of patients to provide adequate power for this analysis.

The final limitation that should be discussed is that we used % PEF measured in the morning and before bedtime as the primary endpoint in children ranging in age from 4 to 12 years. Many clinicians may believe that % PEF is inaccurate in younger children because of the difficulty in obtaining reliable and consistent recordings. However, % PEF is often used as a primary endpoint in studies of pediatric asthma,[30,31] and reliable values can be achieved in children aged 4-5 years with appropriate instruction.[1] To ensure that PEF could be measured reliably, only patients with stable PEF, defined as the difference in three PEF values within 15%, were included in this study.

In conclusion, we found that the tulobuterol patch elicited significantly greater improvements in % PEF measured in the morning and before bedtime compared with sustained-release theophylline in children on long-term LTRA therapy. These effects of the tulobuterol patch were achieved without worsening FeNO, indicating that it does not exacerbate airway inflammation in children. These results suggest that short-term continuous use of a transdermal β_2 agonist is an effective therapy for pediatric asthma without inducing airway inflammation.

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