

Effects of the tulobuterol patch on the treatment of acute asthma exacerbations in young children

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ABSTRACT

The tulobuterol patch (TP) is a β_2 -adrenergic agonist with a favorable pharmacokinetic profile used for asthma management in Japan. Because it contains tulobuterol in a molecular, crystallized form that is gradually absorbed percutaneously, TP exerts a prolonged bronchodilator effect exceeding 24 hours. Although it is a well-established treatment for asthma and wheezing, few studies have investigated whether it can reduce or prevent the symptoms associated with upper respiratory tract infections (URTIs) in young children. This study evaluated the effect of TP on the long-term management of asthma in young children. In this 1-year, randomized, multicenter, double-blind, placebo-controlled study, children aged 0.5–3 years old with mild-to-moderate persistent asthma were treated with either TP or placebo patch. The parents/guardians applied the TP or placebo patch to their children after URTI symptoms appeared. Respiratory symptoms were recorded daily during the 1-year observation period. Overall, 86 patients were enrolled and 80 were treated and analyzed in this study. All patients had been treated with anti-inflammatory drugs before enrollment. The time to symptom resolution was significantly shorter ($p = 0.001$) and the total respiratory symptom score ($p = 0.0457$) was significantly lower in the TP group than in the placebo group. In young children with mild-to-moderate asthma who had been treated with anti-inflammatory drugs, using the TP soon after the appearance of URTI symptoms led to quicker resolution of respiratory symptoms and lower respiratory symptom scores.

(Allergy Asthma Proc 33:e28–e34, 2012; doi: 10.2500/aap.2012.33.3542)

The onset of childhood asthma generally occurs during the first 3 years of life.¹ Asthma control in children <3 years old is significantly worse than that in

school children and adolescents.² Airway inflammation is known to underlie the pathology of asthma even in young children. Many studies have already assessed the effects of inhaled corticosteroids (ICSs)³ and leukotriene (LT) receptor antagonists⁴ in asthma patients and reported their long-term beneficial effects. In addition, exacerbation of asthma symptoms in young children is mainly related to viral infections, predominantly upper respiratory tract infection (URTI) with rhinovirus.⁵ Therefore, management of URTI symptoms in young children with asthma is an important clinical approach in asthma.

The tulobuterol patch (TP; Abbott Japan Co., Ltd., Tokyo, Japan) is a transdermal β_2 -adrenergic agonist with a favorable pharmacokinetic profile⁶ and is associated with good adherence⁷ for the management of asthma or wheezing. TP exerts a prolonged bronchodilator effect because it contains tulobuterol in a molecular and crystallized form (Fig. 1). After the patch is applied to the skin, molecular tulobuterol is gradually absorbed percutaneously. As the number of tulobuterol molecules in the patch decreases, these mol-

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Funded by Japan Allergy Foundation

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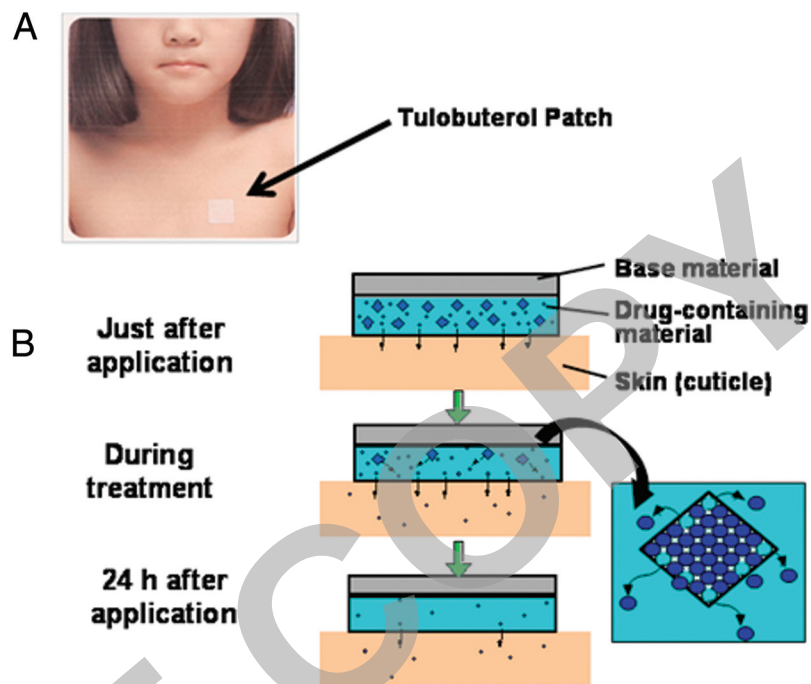


Figure 1. (A) The tulobuterol patch in situ and (B) the mechanism responsible for its prolonged pharmacokinetic profile.

ecules are replenished by dissociation of the tulobuterol crystals into a molecular, absorbable form. Hence, although tulobuterol is a short-acting β -agonist (SABA), each TP has a duration of effect exceeding 24 hours in adults⁶ and in children,^{8,9} thus providing long-acting β -agonist activity.

Although its efficacy for the management of asthma and wheezing in young children has been established, there is little evidence for an effect of TP on exacerbations of asthmatic symptoms caused by URTIs in young children. Considering that patch preparations are a useful drug delivery system in clinical practice, we performed the present randomized, placebo-controlled study to determine whether TP suppresses the exacerbation of asthma and respiratory symptoms caused by URTIs.

METHODS

Patients

Children with asthma who satisfied the following criteria were included in this study: (1) aged 0.5–3 years and fulfilling the diagnostic criteria for infantile asthma established by the Japanese Pediatric Guideline for the Treatment and Management of Bronchial Asthma (JPGL)¹⁰; (2) had mild-to-moderate persistent asthma according to the JPGL classification of asthma severity, and (3) had a history of controller medication use (e.g., LT receptor antagonists, ICS, and disodium cromoglycate) for the long-term management of asthma. Asthma in children is defined by the JPGL as three or more independent episodes of wheezing/dyspnea, with intermittent long asymptomatic periods.¹⁰

Before diagnosing asthma, it is necessary to exclude other diseases associated with wheezing/dyspnea, such as airway foreign bodies and congenital airway obstructive disorders. Mild persistent asthma was defined by the JPGL¹⁰ as symptoms occurring at a frequency of less than once a week, with the patient having a normal daily life. Moderate persistent asthma was defined as symptoms occurring more than once a week, and sometimes with moderate or severe attacks.

The study protocol was first approved by the Ethics Committee of Jikei University on behalf of the study group (17-122 4343) and was then approved by the ethics committees of each participating facility before commencement of the study. The study design was explained to and informed consent was obtained from the parents/guardians of each patient before beginning the study.

Study Design

The objective of this study was to determine whether the TP is effective in suppressing the exacerbation of asthma and respiratory symptoms caused by URTIs. We chose a 1-year treatment period for the following reasons. First, had we chosen a short study period, such as 1–2 months, it is unlikely that we would observe a sufficient number of URTI-induced asthmatic symptoms or respiratory symptoms, and hence test the efficacy of early application of TP in this setting. Therefore, a longer observation time was needed to accumulate a sufficient number of events. Second, in Japan, exacerbation of asthma most often occurs in autumn. Therefore, to ensure that all patients experienced one

autumn on treatment, a 1-year treatment period was necessary. The expiration period of TP and placebo patches was therefore established as the study period for individual patients.

The primary end point was the difference in total symptom score at 1 year (sum of scores for all symptoms during the study). At the time of planning the study (2004), we could find no relevant data from which to calculate the sample size. Furthermore, considering the planned study duration (1 year), a pilot study was not deemed feasible; therefore, the study was started with the intent of including as many patients as possible across the participating institutions.

Treatments

Each parent/guardian was randomly provided with either 28 TPs (Abbott Japan Co., Ltd.) or 28 placebo patches, which were indistinguishable from the TPs in terms of external appearance and texture. The randomization sequence was based on a random number table generated in advance of the study by the Secretariat of the Japanese Society of Pediatric Allergy and Clinical Immunology.

The patch was to be applied to the child when the guardian considered that the asthma symptoms were likely to be exacerbated, such as if the child developed a fever or had symptoms consistent with a URTI, including cough and nasal discharge. The duration of patch application was decided by each guardian. During the 1-year observation period, the guardians recorded their child's respiratory symptoms in a daily diary. Each guardian brought his/her child to the hospital every 4–8 weeks for patch refills, for assessment of vital signs and relevant clinical parameters, and for review of the patient's diary. Compliance was assessed at each visit by confirmation of the number of patches the patient had used and the necessity of delivery of new boxes.

The TP and placebo patches were applied once daily to the chest, back, or arm of the child at a dose of 0.5 mg (one 0.5-mg patch) for children aged 0.5–2 years and 1 mg (two 0.5-mg patches) for children aged 3–4 years. For subjects who turned 3 years old during the study, the dose was increased to 1 mg (two 0.5-mg patches).

During the study period, the use of other β_2 -adrenergic agonists was to be avoided. However, if the child's condition did not improve within several hours of applying the patch, the guardian administered a SABA to the child (either by inhalation or orally), which is normally done in general clinical practice in Japan. Rescue systemic corticosteroid was not administered to treat children with acute exacerbations. When the response to SABA administration was poor, children visited the emergency room (ER).

Data Analysis

The primary end point was the change in respiratory symptom scores during the 1-year study period, which were assessed on a 4-point scale that has been used for many years in clinical practice in Japan.^{11–13} 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. Only data sets with <15% missing data were included in the analysis.

The duration of hospitalization and frequency of ER visits for acute asthma, number of days with activity limitations, and frequency of SABA inhalation were collected from medical records and patient diaries and compared between the TP and placebo groups.

Differences in demographic (sex and age) and clinical characteristics (severity, duration of illness, presence/absence of complications, disease history, *etc.*) were compared between the two study groups using the χ^2 -test, Fisher's exact test, Wilcoxon's two-sample test, or Student's two-sample test, as appropriate. Wilcoxon's rank-sum test and repeated-measures analysis of variance were used to compare treatment efficacy outcomes between the two groups of patients.

RESULTS

Patient Disposition and Characteristics

Overall, 86 patients were included in this study and randomized to one of the two treatment groups. Of these, 6 patients did not return to the hospital after randomization and were excluded from the study. Therefore, 80 patients (TP group = 39; placebo group = 41) were included in the final analysis. As summarized in Table 1, there were no significant between-group differences in the male-to-female ratio, age, height, body weight, or asthma severity. All of the patients received controller medication(s) for asthma before enrollment, with most receiving LT receptor antagonists (TP group versus placebo group: 71.8% versus 80.5%), followed by ICS (48.7% versus 65.9%), disodium cromoglycate (15.4% versus 29.3%), and theophylline (17.9% versus 9.8%). Although the use of these drugs tended to be higher in the placebo group, these differences were not statistically significant.

Clinical Outcomes

The outcomes at 1 year after the start of the study are summarized in Table 2. The median number of times

Table 1 Patient characteristics

	TP	Placebo Patch	<i>p</i> Value
<i>n</i>	39	41	
Sex (male/female)			0.3280*
Male	30 (76.9)	27 (65.9)	
Female	9 (23.1)	14 (34.1)	
Age (yr)	2.1 ± 0.8	1.9 ± 0.9	0.2976#
Height (cm)	90.0 ± 7.4	88.5 ± 8.8	0.4130#
Body weight (kg)	13.2 ± 2.5	12.7 ± 2.5	0.3740#
Severity			0.6416§
Mild	22 (56.4)	21 (51.2)	
Moderate	17 (43.6)	20 (48.8)	
Concomitant drugs			
Any anti-inflammatory drug	100	100	—
LT receptor antagonist	28 (71.8)	33 (80.5)	0.4352*
ICS	19 (48.7)	27 (65.9)	0.1745*
Theophylline	7 (17.9)	4 (9.8)	0.3431*
DSCG	6 (15.4)	12 (29.3)	0.1829*

*Fisher's exact test.

#*t*-test.

§Wilcoxon's rank-sum test.

ICS = inhaled corticosteroid; LT = leukotriene; DSCG = disodium cromoglycate; TP = tulobuterol patch.

Table 2 Clinical outcomes

	TP	Placebo Patch	<i>p</i> Value
<i>n</i>	39	41	
Frequency of patch use (days; median [range])	3 (1–38)	3 (1–36)	
Fever (days)	12.7 ± 8.9	12.5 ± 11.5	0.670
URTI symptoms			
Sneezing (days)	12.6 ± 17.2	10.6 ± 12.8	0.902
Nasal discharge (days)	59.4 ± 41.4	82.1 ± 60.6	0.184
Nasal congestion (days)	18.4 ± 30.7	23.6 ± 40.6	0.755
Restricted activity (days)	7.0 ± 12.7	9.1 ± 25.5	0.913
Concomitant drug treatment score	1968.9 ± 1143.6	2305.1 ± 1262.0	0.808
Frequency of β_2 -adrenergic agonist use	12.0 ± 36.2	33.9 ± 70.4	0.107
Length of hospital stay (days)	0.5 ± 1.7	0.9 ± 3.1	0.918
Frequency of ER visits for asthma exacerbation	1.1 ± 1.3	1.3 ± 1.9	0.775

Concomitant drug treatment score was determined as described in Yamamura, 1983.¹³

TP = tulobuterol patch; URTI = upper respiratory tract infection; ER = emergency room.

the patches were used was 3 days in the TP group (range, 1–38 days) and 3 days in the placebo group (range, 1–36 days).

As shown in Fig. 2 A, the total respiratory symptom score over the 1-year study period was significantly lower in the TP group than in the placebo group ($p = 0.045$). Figure 2 B shows the changes in respiratory symptom scores after each URTI episode. In both groups, the symptoms decreased gradually over time and were almost completely resolved within 13 days after the 1st day of patch application. During the symp-

tomatic period, the rate of symptom alleviation was significantly quicker in the TP group than in the placebo group ($p = 0.001$). In terms of etiology, fever was recorded on ~12 days in both groups (TP group versus placebo group, 12.7 versus 12.5 days). Although the number of days the children experienced URTI symptoms (*i.e.*, nasal discharge, sneezing, and nasal congestion) tended to be greater in the placebo group than in the TP group, these differences were not significant. The number of days in which the child experienced restricted activity and the frequency of ER visits for

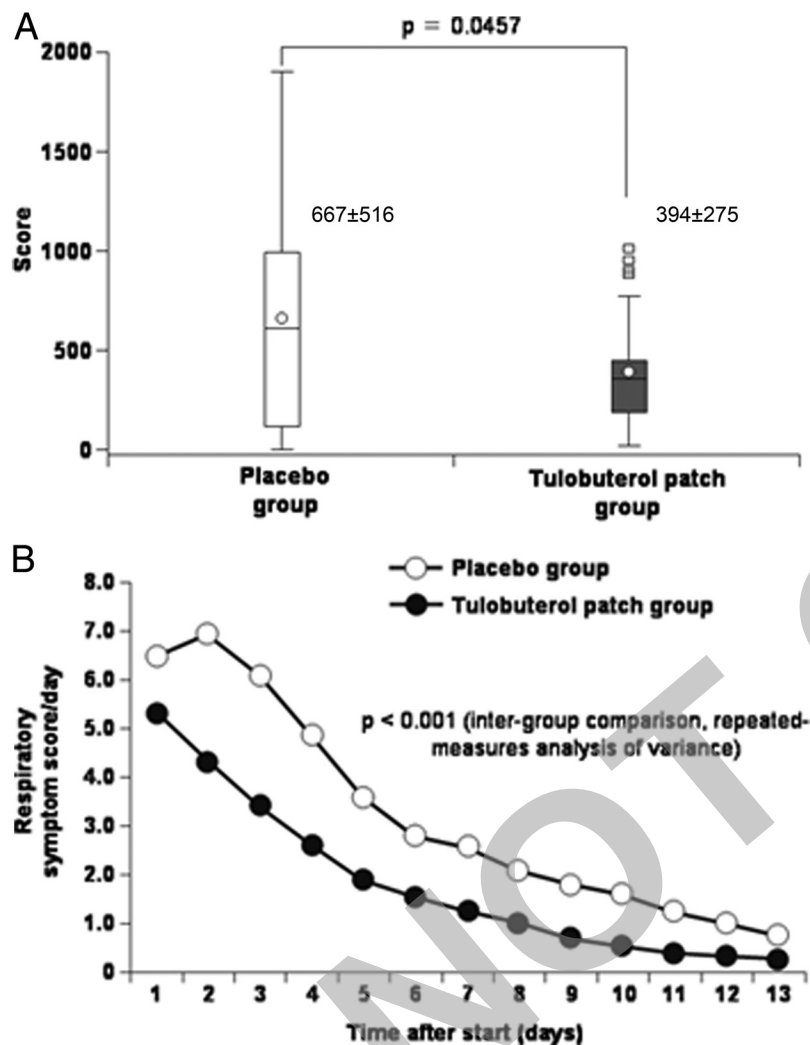


Figure 2. (A) Comparison of total symptom scores during the 1-year observation period and (B) time course of changes in respiratory symptom scores for each upper respiratory tract infection (URTI) episode.

asthma exacerbation were fewer, although not significantly, in the TP group than in the placebo group. Furthermore, the frequency of β_2 -adrenergic agonist use was lower and the duration of hospital stay was shorter in the TP group than in the placebo group, although these differences did not reach statistical significance.

Safety

Overall, there were 3 adverse events in 2 patients treated with TP and 10 events in 6 patients treated with placebo. Events in the TP group included acute gastroenteritis and allergic rhinitis in one patient, and acute pneumonia in another patient. Events in the placebo group included bloody stool, gastroenteritis, and varicella (one patient each); acute gastroenteritis and herpangina in one patient; pneumonia and respiratory syncytial virus infection in one patient; and infectious mastitis, acute gastroenteritis, and hemolytic streptococcal infection in one patient. All of the adverse events were minor and were considered unrelated to the treatments.

DISCUSSION

In this randomized, placebo-controlled study of children aged ≤ 3 years with mild-to-moderate asthma being treated with anti-inflammatory drugs, respiratory symptoms (*i.e.*, cough and wheezing) resolved more quickly after the onset of URTI symptoms with TP than with placebo. Furthermore, the total symptom score was significantly lower with TP than with placebo over the 1-year study period. Notably, the total number of days in which the patients experienced fever was similar in both groups (~ 12 days). These results suggest that the frequency of URTI was similar in both groups, and that TP was more effective in suppressing URTI-related symptoms.

In children, the $C_{\max}$, $T_{\max}$, and area under the curve for the TP were 1.33 ± 0.21 ng/mL, 14.0 ± 2.0 hours, and 27.1 ± 4.2 ng $\cdot$ mL $^{-1}$ per hour, respectively, after the application of a 1-mg TP for children weighing < 30 kg or a 2-mg TP for children weighing ≥ 30 kg,⁹ similar to those reported in adults.⁶ A study on 180 children

with asthma revealed that the use of the TP for 1 week did not significantly affect pulse rate or blood pressure and had no serious adverse reactions with regard to subjective symptoms, although headache, palpitation, and erythema/itchy skin were noted in 1, 1, and 21 patients, respectively.⁸ When URTI-related symptoms or wheezing occur, the TP can be easily applied without waking the child. In Japan, this preparation is now well accepted by both asthmatic patients and their parents/guardians. To date, however, few studies have attempted to document the long-term effects of TP on the exacerbation of asthma and respiratory symptoms caused by URTIs. In this study, we found that TP suppressed the progression of respiratory symptoms (cough, wheezing, and dyspnea) when applied soon after their appearance in young children with asthma, with quicker resolution of symptoms and lower total symptom scores.

The mechanisms underlying the beneficial effects of TP on the exacerbation of asthma and respiratory symptoms caused by URTIs could not be ascertained in the present study. However, possible explanations include the antiasthmatic properties of tulobuterol and suppression of cough, wheezing, and dyspnea. It is also possible that, like other β_2 -adrenergic agonists,^{14–16} tulobuterol may exert anti-inflammatory effects that act synergistically or influence those of anti-inflammatory drugs. Additional studies are clearly needed to examine whether TP directly suppresses cough or other symptoms, the role of concomitant anti-inflammatory drugs, and the impact of sustained blood tulobuterol levels to fully understand the effects of TP in the management of URTI symptoms.

To date, several interventional studies have reported the effects of treatments for repeated episodes of wheezing in infants and young children. For example, Panickar *et al.* showed no clinical advantage of oral prednisolone therapy in children aged 10–60 months with wheezing triggered by viral infection and which required hospitalization.¹⁷ On the other hand, the Childhood Asthma Research and Education study showed that ICS and a LT receptor antagonist were effective against URTI-induced intermittent respiratory symptoms in children aged <6 years with moderate-to-severe intermittent wheezing.¹⁸ However, other studies have shown conflicting results for ICSs.^{19,20}

Nevertheless, no studies have investigated the efficacy of β_2 -adrenergic agonists against URTI-related symptoms in infants and young children with asthma. In the earlier studies, interventions were started after the symptoms of asthma became evident after the onset of URTI-related symptoms. In contrast, in our study, we began to use the TP at an earlier time point with the application of either the TP or the placebo

patch after the onset of URTI-related symptoms, but before the onset of asthma symptoms.

Several limitations of this study need to be discussed. First, we enrolled children with a history of using several classes of anti-inflammatory drugs, with LT receptor antagonists being the most common. We did not choose to limit the current study to a specific class of anti-inflammatory drug. It is possible that the use of some of these drugs may have influenced the current results, although the proportion of children using each class of drug was similar in both groups. We think that by enrolling children with a history of using different (and in some cases multiple) classes of drugs, our study better reflects actual clinical practice, where it is rare for children to use just one specific class of drugs. Second, the study was relatively small and we did not perform a power calculation to prospectively determine the required number of patients. Third, it is possible that adherence/use of the allocated study drug was less than expected, and that treatments other than oral/inhaled SABAs were used to treat exacerbations. Finally, the study was conducted in young children; therefore, the results may not be generalizable to older children, who may need different doses or durations of administration.

The major advantages of the TP are that it is simple to use and has a long duration of action. Although the mechanism underlying the effectiveness of this preparation in treating URTI symptoms remains unclear, the TP is a practical, convenient and effective means of treating asthma in infants and young children. We believe that the results of our study will help to improve the long-term management of asthma in young children.

ACKNOWLEDGMENT

The authors thank Kana Shinno, Keiko Kaneta, and Shiho Yamamoto for their secretarial assistance and Dr. Nicholas Smith for his editorial support. The PET Study Group includes the following investigators: Toshio Katsunuma (principal investigator; Department of Pediatrics, Jikei Daisan Hospital, Tokyo), Y. Ohya (Department of Allergy, National Center for Child Health and Development, Tokyo), T. Fujisawa (Institute for Clinical Research, Mie National Hospital, Mie), K. Akashi (Tsunan Hospital, Niigata), N. Imamura (Department of Pediatrics, Imamura Hospital, Kagoshima), M. Ebisawa (Department of Pediatric Allergy, National Hospital Organization Sagami National Hospital, Kanagawa), K. Daikoku (National Hospital Organization Hiroshima-Nishi Medical Center, Hiroshima), N. Kondo (Department of Pediatrics, Gifu University Graduate School of Medicine, Gifu), A. Terada (Department of Pediatrics and Allergy, Daido Hospital, Aichi), S. Doi (Department of Pediatrics, Osaka Prefecture Medical Center for Respiratory and Allergic Diseases, Osaka), T. Nishimuta (National Hospital Organization Shimoshizu National Hospital, Chiba), T. Noma (Department of Pediatrics, Kitasato University Hospital, Kanagawa), Y. Hamasaki (Department of Pediatrics, Saga Medical School Faculty of Medicine, Saga University, Saga), K. Kurihara (Department of Allergy, Kanagawa Children's Medical Center, Kanagawa), K. Masuda (Masuda Pediatric Clinic, Tokyo), T. Yamada (Yamada Pediatric Clinic, Na-

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