Effect of Transdermal Tulobuterol Added to Inhaled Corticosteroids in Asthma Patients

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ABSTRACT

Background: Tulobuterol tape is the first long-acting transdermal preparation of a β_2-agonist designed to release tulobuterol in an optimal fashion over a 24-hour period. We investigated the additive effect of tulobuterol tape in adult asthma patients treated with inhaled corticosteroids.

Methods: A randomized, double-blind, double-dummy, parallel-group, multicenter trial was conducted. Male and female patients with a diagnosis of asthma requiring inhaled short-acting β_2-agonists despite treatment with inhaled corticosteroids took tulobuterol tape (1 mg or 2 mg) and corresponding placebo tapes for 4 weeks.

Results: Mean morning peak expiratory flows (PEF) in the 1 and 2 mg/day groups were significantly increased from the baseline value by 23.8 and 35.9 L/min at week 4, respectively. The increase in mean morning PEF in the 2 mg/day group was significantly higher than that in the 1 mg/day group. The mean evening PEF was significantly increased in both treatment groups compared with baseline values. Although the increase in mean evening PEF in the 2 mg/day group was greater than that in the 1 mg/day group, the difference between groups was statistically significant only at week 1. The safety profiles of the two treatments were similar.

Conclusions: In patients with persistent asthma who require inhaled short-acting β_2-agonists while receiving inhaled corticosteroids, transdermal tulobuterol significantly improved PEF in a dose-dependent manner, *i.e.*, greater effect with 2 mg than with 1 mg per day.

KEY WORDS

bronchial asthma, long-acting β_2-agonist, transdermal therapeutic system, tulobuterol tape

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INTRODUCTION

Chronic airway inflammation plays an essential role in the pathogenesis of bronchial asthma, and inhaled corticosteroids are recognized as first-line agents for the treatment of persistent asthma. [1-3] However, monotherapy with inhaled corticosteroids may not fully control the symptoms or prevent exacerbations of persistent asthma. International guidelines on asthma management, therefore, have recommended that the inhaled long-acting β_2-agonists salmeterol and formoterol should be used as "controllers" and the inhaled short-acting β_2-agonists as "relievers".[1-4]

Tulobuterol tape is the first long-acting transdermal preparation of a β_2-agonist designed to release tulobuterol in an optimal fashion over a 24-hour period. When it is applied once daily at bedtime, the blood concentration of tulobuterol does not increase abruptly, as often occurs with oral preparations, peaks early in the morning when respiratory function usually decreases to its lowest level, and is maintained at effective levels for 24 hours.[5] Tulobuterol tape has less frequent adverse events than conventional oral tulobuterol preparations, and when used at bedtime can prevent a marked drop in peak expiratory flow (PEF) early in the morning by exerting a bronchodilator effect for 24 hours.[6-10] Tulobuterol tape is now commonly used in Japan as a long-acting β_2-agonist, while in the United States and Europe the most frequently used long-acting β_2-agonists are in-

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Table 1 Demographic and Clinical Characteristics at Baseline

Variables	Treatment Groups			
	1 mg (*n* = 116)		2 mg (*n* = 123)	
Age, yr				
Mean (SE)	53.1	(1.5)	52.6	(1.3)
Range	20-78		19-77	
Gender, No. (%)				
Female	59	(51)	59	(48)
Male	57	(49)	64	(52)
Body height, cm				
Mean (SE)	159.6	(0.7)	160.0	(0.8)
Range	140-178		139-180	
Body weight, kg				
Mean (SE)	60.2	(1.0)	59.2	(1.0)
Range	38-90		36-99	
Mean (SE) morning PEF, L/min	328.4[a]	(9.0)	332.4[b]	(9.0)
Mean (SE) evening PEF, L/min	351.3[c]	(9.2)	355.7[b]	(9.4)
Mean (range) inhaled corticosteroid use, μg/day				
Budesonide	667	(400-800)	571	(200-1,600)
Fluticasone	520	(200-800)	495	(100-800)
Beclomethasone	627	(150-1,600)	504	(200-1,200)

[a]: *n* = 116, [b]: *n* = 119, [c]: *n* = 114.

haled salmeterol and formoterol, the efficacy of which is maintained through sustained binding to β_2 receptors.[11-13]

One of the important features of long-acting β_2-agonists is their additive effects when used with inhaled corticosteroids, which have been observed with both salmeterol and formoterol.[14-21] However, the effects of tulobuterol tape administered together with inhaled corticosteroids have not yet been investigated. In the present study, we administered tulobuterol tape at doses of 1 or 2 mg/day to patients with persistent asthma already using inhaled corticosteroids in order to evaluate its efficacy as a long-acting β_2-agonist and to compare its effects at two different doses.

METHODS

This was a multicenter, double-blind, parallel-group comparative study designed to examine the efficacy and safety of tulobuterol tape of 2 mg/day and 1 mg/day over a 4-week treatment period in patients with persistent asthma currently treated with inhaled corticosteroids. The study was conducted at 35 clinical centers in Japan. Blinding was ensured using a double-dummy technique in which patients received either tulobuterol tape 1 or 2 mg and the corresponding placebo.

PATIENT POPULATION

Male patients and nonpregnant or nonlactating female patients ≥16 years old were eligible if they had

had a diagnosis of asthma as defined by the American Thoracic Society[22] for at least 6 months and had used inhaled corticosteroids at a constant dosage for at least 4 weeks prior to screening with short-acting β_2-agonists as needed (more than 4 puffs a week). Written informed consent was obtained from each patient, and the study was approved by the Institutional Review Board at each center.

STUDY DESIGN

After an initial screening visit, during which study participants underwent a physical examination and a relevant medical history, eligible patients were asked to use a standard peak flowmeter (Mini Wright; Clement Clark International Ltd; Harlow, UK) to measure PEF daily in the morning and at bedtime, and to record the highest of three-time forced exhalation as well as symptoms and medications on daily diary cards during a 14-day run-in period. Patients were allocated at random to treatment with 1 mg/day or 2 mg/day of tulobuterol tape, when their PEF increased by ≥ 15% after inhalation of short-acting β_2-agonists at the usual dose during the run-in period and/or their mean PEF at bedtime was ≥ 15% higher than that in the morning during the week before randomization. Patients were allowed to use salbutamol as required for symptom control but no other sympathomimetic agents. No oral or injected corticosteroids were allowed throughout the study. When patients received xanthines, anticholinergics, antiallergics, Chinese herbal medicines or expectorants dur-
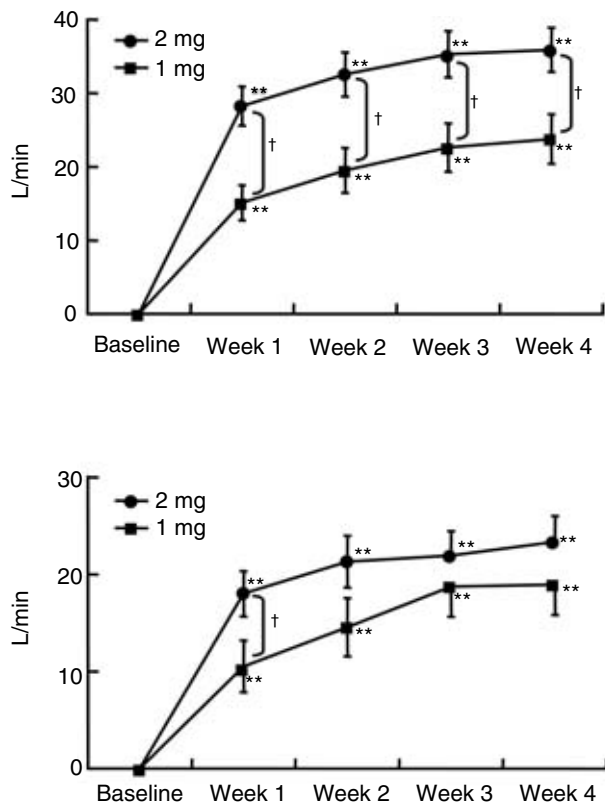
Fig. 1 Increase in morning PEF (upper panel) and evening PEF (lower panel) after administration of tulobuterol tape. Symbols and bars represent means and SE, respectively. **Significant difference between the point and baseline ($P <$ 0.01). †Significant difference between 1 mg treatment group (square) and 2 mg treatment group (circle) ($P <$ 0.05).

ing the run-in period, the same dosage and method of administration were continued throughout the trial to prevent bias. In addition, the same dosage of inhaled corticosteroids and rescue use of inhaled short-acting β2-agonists were continued throughout the trial. No patient experienced exacerbation of asthma or an upper respiratory tract infection during the 4-week period prior to the study.

STATISTICAL ANALYSIS

The primary efficacy variable was morning PEF. The mean morning PEF value during the final week of the treatment period was compared with that during the last week prior to randomization. Improvement was compared between the two groups using Wilcoxon's two-sample test. Secondary efficacy measures consisted of changing PEF, asthma symptoms, disturbance of activities of daily living (ADL) and sleep, and supplemental use of β2-agonists. Weekly averages (mean ± standard deviation (SD)) of PEF in each group were obtained during the final week of the run-in period and throughout the treatment period. Stu-

dent's two-sample test was used to compare changes in PEF from baseline values between the two groups, and Student's one-sample test to compare changes in PEF during the treatment period from baseline in each group. For asthma symptoms, disturbance of ADL and sleep, and supplemental β2-agonists use, the t-test and paired t-test were used for analyses of differences between the two groups and within each group, respectively. All statistical tests were two-side at an a level of 0.05.

RESULTS

DEMOGRAPHICS

A total of 116 patients used tapes containing tulobuterol at a dose of 1 mg/day and 123 patients at a dose of 2 mg/day. As shown in Table 1, the two treatment groups had similar demographic and clinical characteristics at baseline.

PEF

Mean baseline morning PEF was comparable between the two groups (328.4 L/min *vs.* 332.4 L/min in the 1 mg/day and 2 mg/day groups, respectively). During the 4-week treatment period, patients in the 2 mg/day group had significantly greater increases in mean morning PEF (35.9 L/min) compared with the 1 mg/day group (23.8 L/min, $p < 0.05$). Significantly greater improvements in morning PEF (Fig. 1, upper panel) were noted in the 2 mg/day group within the first week of treatment, and the superior bronchodilating properties of the 2 mg/day dose remained significantly greater than those of the 1 mg/day dose throughout the study period. Significantly greater improvements in evening PEF (Fig. 1, lower panel) were noted in the 2 mg/day group within the first week of treatment, and the bronchodilating effects of 2 mg/day were persistently stronger than those observed with the 1 mg/day dose throughout the treatment period, though the differences between them were not statistically significant.

ASTHMA SYMPTOMS, DISTURBANCE OF ADL AND SLEEP, AND SUPPLEMENTAL USE OF β2-AGONISTS

Asthma symptoms, disturbance of ADL and sleep, and supplemental use of β2-agonists over the 4-week study period are shown in Table 2. In both groups, the number of symptom-free days significantly increased compared with the baseline value, although the number of symptom-free nights did not. Although patients in neither group reported disturbance of ADL or sleep at baseline, the number of days with disturbance of sleep per week was significantly decreased in the 1 mg/day group compared with baseline. In both groups, daytime and nighttime supplemental use of β2-agonists significantly decreased from baseline, and the number of rescue-free days and nights significantly increased from baseline.

Table 2 Baseline and mean change from baseline in symptom scores and β-stimulant use over 4 weeks of treatment with 1 mg or 2mg Tulobuterol tape

Variables	Treatment Groups					p Value (t-test)
	1 mg (n = 116)		2 mg (n = 123)			
	Baseline	Change	Baseline	Change		
No. of symptom-free days per week	4.10 (0.29)	*0.65 (0.23)	4.11 (0.27)	*0.52 (0.20)		1.000
No. of symptom-free nights per week	4.58 (0.28)	0.56 (0.22)	5.18 (0.24)	0.27 (0.20)		1.000
No. of days not disturbed ADL per week	6.21 (0.18)	0.07 (0.15)	6.43 (0.15)	0.10 (0.12)		1.000
No. of nights not disturbed sleep per week	6.26 (0.17)	*0.48 (0.17)	6.50 (0.13)	0.04 (0.09)		0.100
No. of rescue-free days per week	4.62 (0.26)	**0.99 (0.18)	4.66 (0.25)	**0.97 (0.18)		1.000
No. of rescue-free nights per week	5.72 (0.22)	**0.54 (0.17)	5.58 (0.22)	*0.47 (0.16)		1.000
No. of puffs per week	6.43 (1.16)	** − 2.68 (0.61)	5.14 (1.05)	* − 2.01 (0.67)		1.000
No. of puffs per week (night time)	1.70 (0.33)	* − 0.80 (0.28)	2.12 (0.38)	* − 0.83 (0.31)		1.000

Date are presented as the mean (SE). Baseline value is the average for the 7 days immediately prior to treatment with tulobuterol-tape.
*: $p < 0.05$ (student's paired t-test) compared with Baseline. **: $p < 0.01$ (student's paired t-test) compared with Baseline.

There was no difference between groups in daytime and nighttime supplemental use of β2-agonists and numbers of rescue-free days and nights.

ADVERSE EFFECTS AND SYMPTOMS ASSOCIATED WITH ASTHMA

The percentages of patients reporting at least one drug-related adverse event, except skin reaction at treatment sites, were comparable in the two groups (14.7% in the 1 mg/day group and 13.8% in the 2 mg/day group). The drug-related adverse events most frequently reported were palpitations (7% in the 1 mg/day group and 6% in the 2 mg/day group) and tremor (3% in the 1 mg/day group and 6% in the 2 mg/day group). All other drug-related events, occurring in > 1% of patients, were chest pain, headache and thirst in the 1 mg/day group and facial flushing and thirst in the 2 mg/day group. The percentages of patients reporting local adverse reactions were also comparable in the two groups (24.1% in the 1 mg/day group and 18.7% in the 2 mg/day group). The local adverse events most frequently reported were itching (16% in the 1 mg/day group and 14% in the 2 mg/day group), redness (10% in the 1 mg/day group and 4% in the 2 mg/day group), and dermatitis (8% in the 1 mg/day group and 2% in the 2 mg/day group). Pain was reported in the 2 mg/day group as a local event occurring in < 1% of patients. No patient exhibited symptoms associated with mild increase in CPK, although increase in CPK was observed in 10% and 12% of patients in the 1 and 2 mg/day groups, respectively. In both groups, only 1 patient withdrew from the study due to exacerbation of asthma.

DISCUSSION

In the present study, we compared the effects of 4-week treatment with 1 mg/day or 2 mg/day of tulobuterol tape once a day in patients with persistent asthma which was not fully controlled despite regular inhalation of corticosteroids. We found that tulobuterol tape at both 1 mg/day and 2 mg/day significantly increased the mean morning and night PEF throughout the treatment period, compared with baseline values. We therefore conclude that tulobuterol tape acts as a long-acting β2-agonist that can be used in the treatment of persistent asthma, since it has add-on effects when administered together with inhaled corticosteroids.

Although tulobuterol is a short-acting β2-agonist with regard to its affinity of binding to receptors, tulobuterol tape is a sustained-release preparation that uses a transdermal therapeutic system. Peak concentration of tulobuterol in the blood was found in the early morning and effective concentration in the blood is maintained for 24 hours, when it is applied at bedtime once daily.[5] Crompton *et al.* reported that once-daily oral bambuterol is a convenient and alternative to twice-daily inhaled salmeterol for treating nocturnal asthma.[23] Therefore, regardless of their affinity of binding to β2 receptors, it appears that β2-agonists, which have long-term bronchodilating effects, behave as long-acting β2-agonists in the treatment of asthma.

Since we used improvement of PEF as the primary outcome measure in the present study, patients were enrolled when their PEF increased by ≥ 15% after inhalation of short-acting β2-agonists at the usual doses during the run-in period and/or their mean PEF at bedtime was ≥ 15% higher than that in the morning during the week before randomization. As a consequence, many patients were asymptomatic and inhaled a few supplemental β2-agonists during the run-in period. This might be the reason for the lack of significant decreases in improvement of asthmatic symptoms and disturbance of ADL and sleep throughout the 4-week study, although supplemental daytime

and nighttime use of β2-agonists significantly decreased in both groups.

A double-blind comparative study of tulobuterol tape with tulobuterol hydrochloride tablets has confirmed that tulobuterol tape is superior in clinical efficacy to the conventional oral preparation of tulobuterol, with milder and less frequent systemic adverse effects such as palpitations and tremors.[6] Tulobuterol tape possesses several advantages over inhaled preparations, including availability for use in infants and elderly individuals who cannot inhale drugs, simple confirmation of drug use by visual inspection of applied tape, and good compliance because of its once-daily regimen. The 2003 Japanese Asthma Prevention and Management Guidelines recommended that tulobuterol tape be used as a long-term controller agent for persistent asthma. Although, in our previous clinical study, tulobuterol tape did not exhibit decrease in efficacy and had no severe adverse events with long-term administration over 1 year,[24] we need to examine the effects and adverse effects of the tape for a prolonged period.

In summary, tulobuterol tape exerted add-on effects to inhaled corticosteroids. Although both the 1 and 2 mg/day tapes significantly increased mean morning and night PEF compared with baseline values, the increase in mean morning PEF was significantly greater in the 2 mg/day group. No patient experienced serious adverse events during the study. Neither the nature nor the incidence of adverse events differed significantly between the two groups. We conclude that tulobuterol tape is a convenient and effective long-acting β2-agonist for the treatment of persistent asthma.

ACKNOWLEDGEMENTS

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