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ORIGINAL ARTICLE

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 β2-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 β2-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 β2-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 β2-agonist, transdermal therapeutic system, tulobuterol tape

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 β2-agonists salmeterol and formoterol should be used as "controllers" and the inhaled short-acting β2-agonists as "relievers".[1-4]

Tulobuterol tape is the first long-acting transdermal preparation of a β2-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 β2-agonist, while in the United States and Europe the most frequently used long-acting β2-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-