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Research Article

Effect of Transdermal Tulobuterol Patch on the Physical Activity in Eight Male Subjects with Chronic Obstructive Pulmonary Disease

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- COPD
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Abstract

Background: Improvement of daily physical activity (PA) is important for the management of chronic obstructive pulmonary disease (COPD) because PA is the strongest predictor of all-cause mortality from COPD. Bronchodilator is recommended by guidelines for the management of COPD, although the effects of bronchodilators on PA are not well understood. We evaluated the effects of a transdermal beta2-adrenoceptor agonist patch, tulobuterol, on the PA of COPD, and the factors that could affect the improvement of PA.

Methods: Eight stable male COPD subjects, without any other diseases that might suppress PA and who were not treated with a beta2-adrenoceptor agonist, were recruited. The PA, which was measured with a triaxial accelerometer for 2 weeks, pulmonary function tests and incremental shuttle walking tests (ISWT) were measured before and after 4-week treatment with transdermal tulobuterol.

Results: The transdermal tulobuterol significantly improved the duration of PA at ≥3.5 metabolic equivalents (METs), though it did not improved the mean intensity of PA evaluated by a METs•hours score at ≥3.0 METs. The % change of the duration of PA at ≥3.5 METs was 34.5±33.0% and not correlated with the % changes of ISWT or any values of the pulmonary function tests.

Conclusions: The transdermal tulobuterol could improve the duration of relatively high intensity PA in patients with COPD. As such an improvement was not reflected by the exercise capacity or pulmonary function tests, PA should be measured directly and objectively for a better prognosis of COPD.

INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) are often limited in their daily physical activity (PA), and the level of PA is related to the decline of lung function [1], hospitalizations [2,3] and mortality [4]. Therefore, PA for patients with COPD has received increasing clinical interest and is considered an important target for the management of COPD.

Recently, motion sensors, especially accelerometers, have been used instead of questionnaires, which are less objective and reliable [5], to quantify the PA in patients with COPD [6-10]. The Actimarker®, (Panasonic, Osaka, Japan) a well-validated, compact-sized triaxial accelerometer, can monitor the intensity of PA, and can continuously monitor activity for more than 1 month [11].

The Global Initiative for Chronic Obstructive Lung Disease recommends the use of long-acting bronchodilators, such as anticholinergics, beta2-adrenoceptor agonists, and methylxanthines, for the management of stable COPD patients [12]. The transdermal tulobuterol patch was developed in Japan as the world's first long-acting beta2-adrenoceptor agonist in a patch formulation. This formulation of tulobuterol was designed to maintain the drug level at constant, effective concentrations over a 24-hr period when applied once daily [13,14] Administered this way, tulobuterol exerts its effect through the systemic circulation and provides a lower maximum blood concentration, resulting in fewer systemic adverse effects.

The efficacy of this drug on pulmonary function, dyspnea and quality of life in patients with COPD was reported [15,16]. However, the effect of the transdermal tulobuterol on the PA of COPD is not clearly understood. Therefore, we conducted a pilot study to evaluate the efficacy of transdermal tulobuterol on the PA in patients with COPD by monitoring their activity with an Actimarker®, and by assessing the factors that could affect improvements in PA.

Table 1: Anthropometric characteristics and baseline pulmonary function measurements of eight male COPD subjects

Age	72.3± 10.9
BMI (kg/m²)	21.9+ 1.4
Smoking [non/ex/curr]	0/ 8/0
[pack-years]	55.9+ 36.7
COPD Stage (I /II/ III/ IV)	3/3/2/0
Pulmonary function tests	
FVC (L)	3 63± 0.91
$FEV_{1.0}$ (L)	1.90+ 0.58
$FEV_{1.0}$ /FVC (%)	52.6+ 12.2
$FEV_{1.0}$ % pred (%)	69.5± 20.2
FRC (L)	4.08+ 1.02
RV (L)	2.49+ 0.48
TLC (L)	6.25+ 1.29
IC/TLC	34.4+ 5.4
DLCO (mL/min/mmHg)	16.6+ 3.6
DLCO/V_A (mL/min/mmHg/L)	3.68 ± 0.88

BMI = body mass index; non = non smoker; ex = ex smoker; curr = current smoker; FVC = force vital capacity; $FEV_{1.0}$ = forced expiratory volume in one second; % pred = % of predicted; FRC = functional residual capacity; RV = residual capacity; TLC = total lung capacity; DLCO = pulmonary carbon monoxide diffusing capacity; V_A = alveolar volume

MATERIALS AND METHODS

Subjects

Eight stable male COPD subjects, without any other diseases that might suppress PA and who were not being treated with a beta2-adrenoceptor agonist, were recruited from among the outpatients of Wakayama Medical University Hospital. COPD was diagnosed as postbronchodilator forced expiratory volume in one second ($FEV_{1.0}$) / forced vital capacity (FVC) <0.7. The patients had not had any other pulmonary diseases such as asthma or bronchiectasis [12]. The numbers of patients with stage I, II, III, and IV were 3, 3, 2 and 0, respectively. At baseline, two patients had received no medication, 5 had received long acting muscarinic receptor antagonist and 1, long acting muscarinic receptor antagonist with inhaled glucocorticoid (Table 1).

Protocol

Patients with COPD wore an Actimarker® the whole day, except while bathing, for 2 weeks and performed pulmonary function tests and incremental shuttle walking tests (ISWT) on the last day of the PA measurement. They were additionally treated with transdermal tulobuterol (2mg/day) and then evaluated for their PA after 4 weeks from the beginning of treatment and performed pulmonary function tests and ISWT on the last day of PA measurement. Written informed consent was obtained from all participants, and the study was approved by the local ethics committee (Committee: IRB committee of Wakayama Medical University, approval number: 968).

Assessment of PA

The Actimarker® is a small (74.5mm x 13.4mm x 34.0mm) and lightweight (36.0g) accelerometer that is worn only at the waist and can be continuously monitored for over one month. It collects the data of triaxial acceleration at 20Hz, and the standard deviation of the data for one minute is defined as the mean value of acceleration. The value of metabolic equivalents (METs) is calculated from the linear regression formula produced by the relationship between the mean value of acceleration and the METs measured using a respiratory gas metabolic system [17,18].

Actimarker® was already validated for evaluating the PA of COPD in terms of the intensities [11]. The physical activities on rainy days and holidays were found to be significantly reduced [11,19,20], and repeatability was obtained when the number of measured days was 3 or more [11]. Furthermore, when the average daytime and nighttime temperature was lower than 2.5, there was a significantly greater reduction in the likelihood of patients going outdoors. When the average temperature was between 2.5 °C and 27.0°C, the difference of the time patients

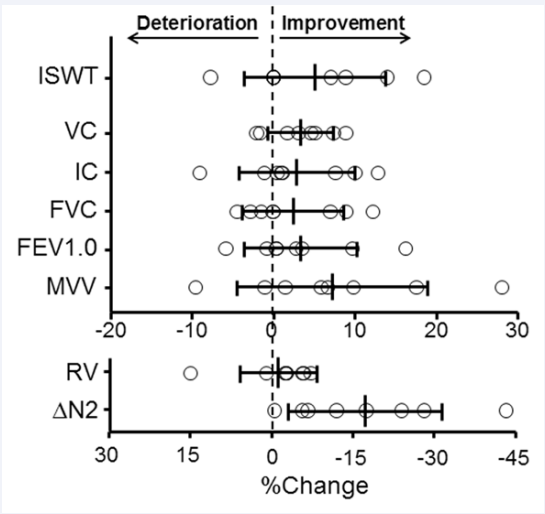

Figure 1 % change in ISWT and pulmonary function tests. ISWT = incremental shuttle walking test; VC = vital capacity; IC = inspiratory capacity; FVC = forced vital capacity; FEV1.0 = forced expiratory volume in one second; MVV = maximal voluntary ventilation; RV = residual volume; ΔN2 = the slope of phase III of the single-breath nitrogen test. Vertical lines indicate mean±SD.

Table 2: Changes in pulmonary function measurements and ISVVT of eight male COPD subjects by transdermal tulobuterol.

	n	Pretreatment	Post-treatment	p-value
ISWT (m)	8	515.0±123.2	536.3±111.7	0.313
VC (L)	8	3.68±0.92	3.81±0.96	0.055
IC (L)	8	2.08±0.27	2.14±0.31	0.232
FVC (L)	8	3.63±0.91	3.69±0.80	0.563
$FEV_{1.0}$ (L)	8	1.90±0.58	1.94±0.54	0.233
FRC (L)	8	4.08±1.02	4.11±0.97	0.641
RV (L)	8	2.49±0.48	2.46±0.50	0.233
TLC (L)	8	6.25±1.29	6.35±1.44	0.547
MVV (L)	8	69.8±26.1	73.0±23.8	0.148
DLco(mL/min/mmHg)	8	16.6± 3.6	16.4± 4.3	0.844
ΔN_2	8	3.19±1.27	2.72±1.30	0.014

ISWT = total distance of incremental shuttle walking test; VC = vital capacity; IC = inspiratory capacity; FVC = forced vital capacity; $FEV_{1.0}$ = forced expiratory volume in one second; MVV = maximal voluntary ventilation; DLCO = diffusing capacity for carbon monoxide; RV = residual volume; ΔN_2 = the slope of phase III of the single-breath nitrogen test. Data are presented as mean ± SD.

going outdoors was less than 10% [21]. So, in order to obtain a representative value of daily PA, we extracted the data only from days with average temperatures between 2.5-27.0°C that were also 3 non-rainy weekdays during the 2 weeks of monitoring. The first and last days of measurement were excluded because data of whole day were not obtained. The mean values of the duration of PA from the extracted 3 days are employed as the representative PA in the patients with COPD.

Assessment of physiological properties

The lung function was evaluated by CHESTAC-8800 DN type (Chest Ltd., Tokyo, and Japan) according to the recommendations of the American Thoracic Society / European Respiratory Society [22]. ISWT was performed according to Singh's method (Japanese license number: 410) [23].

Table 3: Changes of physical activity of eight male COPD subjects by transdermal tulobuterol.

Intensity of Activity	n	Pretreatment	Post-treatment	p-value
METs·hr score	8	2.43±1.61	2.77±1.99	0.547
≥ 2.0 METs (min)	8	227.7±90.6	237.3±77.4	0.547
≥ 2.5 METs (min)	8	104.9±40.2	108.0±52.4	0.742
≥ 3.0 METs (min)	8	41.9±23.0	46.4±29.6	0.383
≥ 3.5 METs (min)	8	13.2±20.3	16.1±23.9	0.021

METs = metabolic equivalents. Data are presented as mean ± SD.

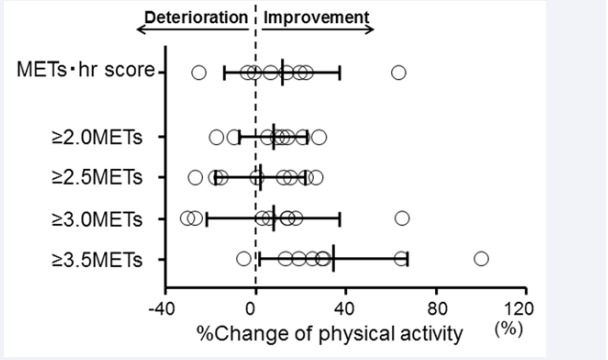

Figure 2 % change in physical activity. METs = metabolic equivalents. Vertical lines indicate mean±SD.

Table 4: Relationship between % change of physical activity (>3.5METs) with ISWT or pulmonary function measurements of eight male COPD subjects by transdermal tulobuterol.

	n	r-value	p-value
ISWT (m)	8	0.708	0.058
VC (L)	8	0.691	0.069
IC (L)	8	-0.024	0.977
FVC (L)	8	0.719	0.058
$FEV_{1.0}$ (L)	8	0.310	0.462
RV (L)	8	0.452	0.268
MVV (L)	8	0.262	0.619
ΔN_2	8	-0.214	0.536

ISWT = total distance of incremental shuttle walking test
VC = vital capacity; IC = inspiratory capacity; FVC = forced vital capacity
$FEV_{1.0}$ = forced expiratory volume in one second; RV = residual volume
MVV = maximal voluntary ventilation
ΔN_2 = the slope of phase III of the single-breath nitrogen test.

Statistical analysis

Analyses were performed using GraphPad Prism 5 (GraphPad Software, Inc., CA, USA). Wilcoxon signed rank test was used for the comparisons of PA, pulmonary functions and ISWT between before and after treatment with the transdermal tulobuterol. Spearman's correlation was used for the relationship between % change of PA and that of ISWT and pulmonary function tests by transdermal tulobuterol. Comparisons were considered significant for p values of 0.05 or less.

RESULTS AND DISCUSSION

Improvement of pulmonary function and ISWT

Though most of patients showed improvements in ISWT and pulmonary function tests by treatment with the transdermal tulobuterol (Figure 1), these parameters were not significantly improved except for the slope of phase III of the single-breath nitrogen test (ΔN_2) (p=0.014) (Table 2).

The duration of PA at ≥3.5 METs was significantly improved by treatment with the transdermal tulobuterol (p=0.021) (Table 3). The improvement rate (% change) of the duration was 34.5±33.0% (Figure 2). However, that at ≥2.0, ≥2.5 and ≥3.0 METs, and the mean intensity of PA evaluated by a MET•hours score at ≥3.0 METs were not improved (Table 3, Figure 2).

The % change of the duration of PA at ≥3.5 METs with tulobuterol treatment had a tendency to correlate with the % changes of ISWT (p=0.058), but not significant, and was not significantly correlated with the % changes of any values of the pulmonary function tests (Table 4).

DISCUSSION

We demonstrated that the transdermal tulobuterol patch significantly improved the duration of PA at ≥3.5 METs, though it did not improve the duration at ≥2.0, ≥2.5 and ≥3.0 METs, or the mean intensity of PA. The degree of this improvement was not correlated with the degree of improvement in ISWT or pulmonary function tests.

Daily PA, evaluated by questionnaires or motion sensors, is reduced in patients with COPD compared with healthy subjects [8,24-28]. It also constitutes an independent prognostic factor for mortality and hospitalization due to severe exacerbations [4,29], and is the strongest predictor of all-cause mortality in patients with COPD [30]. The improvement of PA could be one of the most important issues for the management of COPD.

Several studies showed that the PA of COPD was improved with rehabilitation [26,31-34]. The mean levels of PA are most effectively increased when a bronchodilator is combined with pulmonary rehabilitation [35,36], but they are not increased by a bronchodilator alone in patients with COPD [37]. In the current study, though the mean intensity of PA was not improved by transdermal tulobuterol, consistent with a previous report, the duration of PA at ≥3.5 METs, a relatively high intensity, was significantly improved. The difference between current results and previous report might be attributed to the difference of index of PA. Vorrink et al. reported that patients with COPD have

a significantly reduced intensity, duration, and counts of PA when compared to healthy control subjects. The average percentage of PA of COPD patients vs. controls was: for intensity, 75%, for duration 57%, and for PA counts, 56%. This suggests that the mean intensity of PA seems to be less affected by COPD than the duration and counts [38]. Accordingly, the mean intensity of PA might be less sensitive as an index to detect the effect of a bronchodilator than the duration of PA. The accelerometer, which can measure the duration of PA in terms of intensity, might be better employed for the evaluation of PA improvement by medical intervention.

Transdermal tulobuterol was developed in Japan as the world's first long acting beta2-adrenoceptor agonist in a patch formulation. This formulation of tulobuterol was designed to maintain drug levels at constant, effective concentrations over a 24-hr period when applied once daily [13,14]. Administered this way, tulobuterol exerts its effect through the systemic circulation and provides a lower maximum blood concentration, resulting in fewer systemic adverse effects, such as palpitation and tremor, than oral formulations. It was reported that the transdermal tulobuterol resulted in improvements in FEV1.0, FVC and inspiratory capacity (IC) after dosing compared with those at baseline, and the values of the area under the curve of FEV1, FVC and IC during the transdermal administration of tulobuterol were 2.98±1.05, 1.81±0.98, 0.75±0.85 L•hr, respectively [39]. Transdermal tulobuterol is as effective as or better than the inhaled salmeterol for the management of stable COPD, with significant effects on the quality of life [16]. Furthermore, the adherence is greater with the transdermal tulobuterol than with inhaled bronchodilators in patients with COPD [40, 41].

In the current study, the % change of the duration of PA at ≥3.5 METs with transdermal tulobuterol treatment was not significantly correlated with the % changes of ISWT or any values of pulmonary function tests. PA, leg activity and 6 min walking distance are improved by rehabilitation in patients with COPD, but the changes of PA were not correlated with the changes in muscle strength or walking distance [26]. The improvement of PA which is the strongest predictor of all-cause mortality [30] should be one of the most important issues for the management of COPD. As the changes of PA by medical intervention could not be detected by exercise capacity or pulmonary function tests, the PA in patients with COPD should be measured directly and objectively.

For the measurement of daily PA in patients with COPD, accelerometers have been used [6-8] instead of less reliable questionnaires [5]. The Actimarker® is a well-validated triaxial accelerometer that can be used to evaluate the mean intensity of PA, and the duration of PA in terms of intensity and walking count [11]. As daily PA easily varies according to the day, the selection of suitable days for evaluation is very important to extract representative values of PA. We selected days taking into account the weather, holiday, air temperature [11,21], and number of days for analysis (3 days) that could provide repeatability when measured by the Actimarker® [11]. With this procedure, more reliable values of representative PA could be obtained.

There are several limitations that need to be addressed. First, the number of recruited patients was small. A larger study is required to clarify the effect of the transdermal tulobuterol on PA in patients with COPD. Secondly, though the study subjects had not been diagnosed as having comorbidities, subclinical conditions including cardiovascular dysfunction, depression, osteoporosis, or muscular weakness were not completely excluded. The influence of comorbidities and muscular weakness on the PA in patients with COPD should be elucidated in future studies.

CONCLUSIONS

The transdermal tulobuterol could improve the duration of relatively high intensity PA in patients with COPD. As this improvement was not reflected by the exercise capacity or pulmonary function tests, PA should be measured directly and objectively for a better prognosis of COPD.

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