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Effect of theophylline on exercise performance in patients with severe chronic obstructive pulmonary disease

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Abstract

Background **– Theophylline is a well known bronchodilator which has been used for more than 50 years in the treatment of obstructive pulmonary diseases. In patients with severe chronic obstructive pulmonary disease whose cardiopulmonary performance is limited by their ventilatory capacity the administration of theophylline may improve exercise performance.**

Methods **– A randomised, placebo controlled, double blind, crossover trial was conducted in 22 patients with severe but stable disease. The patients (mean age 68 years) were studied before and after one month of placebo and one month of treatment with a sustained release preparation of theophylline administered orally. The theophylline dose was adjusted until a blood level above 55·5 μmol/l was achieved. The two treatments were administered in random order and separated by a two week washout period. After theophylline was administered for one month a mean level of 68·2 μmol/l was achieved. Pulmonary function tests, arterial blood gas measurements, maximal voluntary ventilation (MVV), and an incremental exercise test were performed before (baseline) and at the end of the first and second month of treatment.**

Results **– Pulmonary function tests showed no improvement in the flow parameters but showed an improvement in MVV after treatment with theophylline. Pulmonary gas exchange was improved after theophylline (resting arterial P_{O_2} 8·91 *v* 8·59 kPa, P_{CO_2} 5·38 *v* 5·56 kPa). The incremental exercise study showed improvement in maximal work rate (86·5 *v* 75·0 watts) and maximal ventilation ($\dot{V}E$max) (46·7 *v* 43·0 l/min). The dyspnoea index on maximal effort ($\dot{V}E$max/MVV), anaerobic threshold, and oxygen pulse remained unchanged. Resting and exercise heart rate were higher after theophylline.**

Conclusions **– Theophylline improved cardiorespiratory performance in these patients with severe chronic obstructive pulmonary disease mainly by increasing the ventilatory capacity.**

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Theophylline continues to be widely used in the treatment of obstructive lung diseases and may improve the ventilatory capacity by its bronchodilator effect and possibly by an effect on respiratory muscle performance.[1–5] Murciano *et al*[3] in a randomised controlled trial of theophylline in patients with severe chronic obstructive pulmonary disease (COPD) found an improvement in respiratory function and dyspnoea which they related to improved respiratory muscle performance. Marsh *et al*[5] found a delay in skeletal muscle fatigue during progressive exercise at therapeutic concentrations of theophylline, suggesting an enhancement of the oxidative capacity of the muscle. The purpose of the present study was to further assess the possible effect of improved respiratory function on exercise performance in patients with COPD in a randomised, placebo controlled, double blind, crossover trial. The hypothesis was that any improvement in respiratory function would improve exercise performance in subjects limited by their ventilatory capacity.

Methods

Twenty two patients (17 men and five women of mean (SD) age 68 (3) years) with severe but stable COPD were studied. All were smokers or former smokers. Baseline measurements before inclusion in the protocol included pulmonary function indices, arterial blood gases, maximal voluntary ventilation (MVV), and an incremental exercise test. Most patients had been previously receiving theophylline on a long term basis. All other medications, including corticosteroids given by inhalation and other bronchodilators, were continued as before. Theophylline was withdrawn two weeks before the baseline studies, and theophylline blood levels were determined on the day of the initial baseline study. Only patients with an FEV_1 of 50% or less of predicted were included; those with known cardiac disease or in whom cardiac disorders were shown on the baseline incremental exercise test were excluded.

Patients received either theophylline (Theotrim, Trima Laboratories, Israel) or an identical placebo in a random fashion. Those weighing less than 60 kg received an initial dose of 200 mg twice daily, and those weighing more than 60 kg received 300 mg twice daily. After the first week theophylline blood levels were determined and the dose was adjusted if the level was below 55·5 μmol/l. This adjustment was repeated until all patients had a

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blood level above 55·5 μmol/l. After one month pulmonary function tests, MVV, arterial blood gas measurements, and an incremental exercise test according to the Wasserman protocol[6] were performed. Pulse oximetry was recorded continuously during exercise. After a washout period of two weeks a crossover trial was performed in the same fashion as described above: those patients previously on theophylline received placebo and vice versa. After another month the tests were repeated. Precautions were taken to ensure that all patients on theophylline had blood levels above 55·5 μmol/l.

Pulmonary function tests were performed on a Jaeger Transferscreen II. MVV was performed with the patient breathing maximally into the pneumotachograph for a period of 10 seconds and multiplied to obtain a one minute value. The incremental exercise study was performed on a cardiopulmonary exercise unit which included an electronically braked cycle ergometer (Ergoline 800), a pneumotachograph and a gas analyser module (CPX Med Graphics), and a computer (Mitsubishi MP 286). Pulse oximetry was recorded continuously by an S-100 pulse oximeter (Simed). The subjects were connected to an ECG (6353 Cardiofax Nihon Kohden). After a three minute rest period the subjects performed unloaded pedalling at a cycle speed of 60 rpm. The work rate was progressively increased by 10 watts/minute in a ramp programme until the subject could no longer maintain a cycle frequency of 40 rpm. The data of the incremental exercise test were recorded breath by breath and included work rate, maximum oxygen consumption ($\dot{V}O_2max$), heart rate (HR), respiratory rate, and ventilation. From these values maximum oxygen pulse ($\dot{V}O_2max/HR$), and dyspnoea index ($\dot{V}Emax/MVV$) were calculated. Anaerobic threshold was determined by locating the change in the $\dot{V}E/\dot{V}O_2$ slope.[6]

Table 1 Anthropometric data and theophylline levels after one month of treatment with theophylline in 22 patients with chronic obstructive pulmonary disease

Variable	*Mean (SD)*
Age (years)	68·5 (3·3)
Weight (kg)	71·1 (10·8)
Height (cm)	169·0 (9·1)
Theophylline levels (μmol/l)	68·2 (9·4)

Table 2 Mean (SD) pulmonary function data for 22 patients with chronic obstructive pulmonary disease measured before (baseline) and one month after administration of placebo or theophylline

	Baseline	*Placebo*	*Theophylline*	*p value**
FVC (l)	2·30 (0·5)	2·28 (0·46)	2·38 (0·55)	<0·05
FVC (% predicted)	65·3 (10·1)	65·0 (9·9)	67·4 (9·6)	<0·05
FEV_1 (l)	1·06 (2·8)	1·05 (2·8)	1·1 (3·3)	NS
FEV_1(% predicted)	38·3 (8·6)	37·9 (8·7)	39·6 (8·0)	NS
MVV (l/min)	46·1 (9·0)	45·7 (9·4)	51·7 (10·8)	<0·0001
MVV (% predicted)	41·5 (8·3)	41·3 (8·3)	46·4 (10·0)	<0·0001

FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; MVV = maximum voluntary ventilation.
* p values relate to placebo *v* theophylline calculated by paired *t* test. There was no significant difference between baseline and placebo. $p < 0·05$ was considered significant.

Table 3 Mean (SD) arterial blood gas values in 22 patients with chronic obstructive pulmonary disease measured before (baseline) and one month after administration of placebo or theophylline

	Baseline	*Placebo*	*Theophylline*	*p value**
Pao_2 at rest (kPa)	8·61 (0·83)	8·59 (0·80)	8·91 (0·77)	<0·05
$Paco_2$ (kPa)	5·53 (0·40)	5·56 (0·44)	5·38 (0·41)	<0·05
O_2 saturation at rest (%)	95·4 (2·3)	95·8 (2·1)	96·7 (1·9)	<0·05
O_2 saturation at maximum effort (%)	95·0 (1·9)	94·9 (2·2)	96·1 (2·2)	<0·05

Pao_2, $Paco_2$ = arterial oxygen and carbon dioxide tension.
* p values relate to placebo *v* theophylline calculated by paired *t* test. There was no significant difference between baseline and placebo. $p < 0·05$ was considered significant.

STATISTICAL ANALYSIS

The results were expressed as mean (SD). The paired *t* test was used to compare the mean pulmonary function test results, arterial blood gas tensions, and cardiopulmonary exercise test results between the baseline values and placebo and between the values obtained after one month of placebo with those obtained after one month of treatment with theophylline. Probability values $\leq 0·05$ were considered statistically significant.

Results

The anthropometric data and theophylline levels are summarised in table 1. The mean plasma theophylline level in the theophylline period on the day of the study was 68·2 (9·4) μmol/l. During treatment with placebo the plasma theophylline levels in each patient remained below 5·5 μmol/l. Table 2 compares the effect of one month of treatment with theophylline and placebo on ventilatory parameters. Theophylline improved forced vital capacity (FVC) by 4·4% ($p < 0·05$) and MVV by 13·1% ($p < 0·0001$). The FEV_1 improved, but not significantly.

The effects on arterial blood gas levels and oxygen saturation of one month of treatment with theophylline compared with placebo are shown in table 3. The mean Pao_2 and $Paco_2$ at rest, as well as oxygen saturation at rest and at maximal effort, improved significantly after the administration of theophylline compared with placebo ($p < 0·05$).

Table 4 shows the cardiopulmonary exercise data for the placebo and theophylline periods. Work rate increased by 15·3% ($p < 0·001$) and, as a result, $\dot{V}O_2max/kg$ increased by 12·1% ($p < 0·001$). Heart rate at maximal effort also increased ($p < 0·01$), and $\dot{V}Emax$ increased by 11·2% ($p < 0·001$). The dyspnoea index at maximal effort ($\dot{V}Emax/MVV$) did not change. No significant difference was found between baseline and placebo values in the pulmonary function parameters, arterial blood gas values, and cardiopulmonary exercise data.

Discussion

After one month of treatment with slow release theophylline a significant improvement in ventilatory capacity was noted which, in turn, induced a significant improvement in exercise performance. The possible mechanisms that account for these beneficial effects must be related to the pharmacological effects of the drug.

Theophylline is an established bronchodilator and is mainly used for diminishing airway

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Table 4 Mean (SD) cardiopulmonary exercise data in 22 patients with chronic obstructive pulmonary disease measured before (baseline) and one month after administration of placebo or theophylline

	Baseline	Placebo	Theophylline	p value*
Work rate (watts)	75·5 (15·0)	75·0 (14·5)	86·5 (16·7)	<0·001
$\dot{V}O_2$max (l/min)	1073 (263)	1066 (242)	1195 (334)	<0·001
$\dot{V}O_2$max (% of predicted)	66·2 (14·2)	65·7 (12·4)	73·8 (16·4)	<0·001
$\dot{V}O_2$max (ml/kg/min)	15·0 (3·7)	14·9 (3·4)	16·8 (4·7)	<0·001
Anaerobic threshold (% of predicted $\dot{V}O_2$max)	51·0 (6·5)	49·0 (6·3)	50·6 (5·9)	NS
O_2 pulse ($\dot{V}O_2$/HR) (% of predicted)	81·7 (8·8)	81·4 (7·9)	83·1 (9·4)	NS
HR at rest (beat/min)	85·0 (8·7)	86·0 (9·2)	90·6 (8·9)	<0·01
HR at maximum effort (% of predicted)	82·1 (11·3)	81·7 (11·9)	87·0 (10·9)	<0·01
$\dot{V}E$max (l/min)	41·8 (10·6)	42·0 (10·4)	46·7 (14·5)	<0·001
Dyspnoea index ($\dot{V}E$max/MVV, %)	90·6 (9·0)	92·1 (8·6)	90·3 (8·1)	NS

$\dot{V}O_2$max = maximum oxygen consumption; HR = heart rate; $\dot{V}E$max = maximal ventilation.
* p values relate to placebo *v* theophylline calculated by paired *t* test. There was no significant difference between baseline and placebo. $p < 0.05$ was considered significant.

resistance,[1 7-9] although this effect is small in patients with COPD.[10-12] In our study FEV_1 improved by an insignificant 4·8% compared with 13% reported by Murciano *et al.*[3] This improvement was unlikely to increase exercise performance to the magnitude achieved in our patients.

A prominent finding in our study was the improvement in ventilatory capacity as determined by measurement of the MVV. This improvement, which increased the respiratory reserve of our ventilatory limited patients, is the probable cause of the greater exercise performance, as manifested by the rise in $\dot{V}O_2$max and work rate. The improvement in MVV may be related to either a direct positive inotropic effect of theophylline on the respiratory muscles[5 13-15] or its action via a central stimulatory pathway,[16 17] or both. There are indications that both mechanisms may have a role in the enhancement of the ventilatory capacity and exercise performance in patients with COPD given theophylline preparations.[3 5 7 11 16 18] The controversy concerning these two mechanisms cannot be settled by our study, and depends on whether the origin of diaphragmatic fatigue is predominantly central or predominantly peripheral (myogenic).[13]

The slight rise in Pa_{O_2} and decrease in Pa_{CO_2} during rest and the rise in oxygen saturation during rest and exercise on theophylline treatment has already been reported by Vereen *et al*[19] and is attributed to an increase in ventilation induced by the central stimulatory effect of the drug.

In conclusion, we speculate that the improvement in workload capacity and in the resultant $\dot{V}O_2$max is related to the improvement in the ventilatory capacity as expressed by the significant increase in MVV following the administration of slow release theophylline. Whatever the mechanism, slow release theophylline in therapeutic doses may be beneficial in improving exercise tolerance in patients with severe COPD.

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