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

G Fink, C Kaye, J Sulkes, U Gabbay, S A Spitzer

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 PO₂, 8:91 ± 8:59 kPa, PCO₂, 5:38 ± 5:56 kPa). The incremental exercise study showed improvement in maximal work rate (86-5 ± 75:0 watts) and maximal ventilation (VEmax) (46-7 ± 43:0 l/min). The dyspnoea index on maximal effort (VEmax/MVVO₂), 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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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 Kohten). 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 (\(V_{O_2}\)max), heart rate (HR), respiratory rate, and ventilation. From these values maximum oxygen pulse (\(V_{O_2}\)max/HR) and dyspnoea index (\(V_{max}/MVV\)) were calculated. Anaerobic threshold was determined by locating the change in the \(V_{E}/V_{O_2}\) slope.*

### 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 FEV₁, 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 \(P_{A02}\) and \(P_{AC02}\) 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, \(V_{O2}\)max/kg increased by 12.1% (\(p<0.001\)). Heart rate at maximal effort also increased (\(p<0.01\)), and \(V_{E}\)max increased by 11.2% (\(p<0.001\)). The dyspnoea index at maximal effort (\(V_{E}/V_{max}/MVV\)) 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
Anaerobic HR of HR at rest (ml/kg/min) (1/min) Vo2max rate of predicted
O1 rate (beat/min) (1/min)

Vo2max = maximum oxygen consumption; HR = heart rate; Vemax = maximal ventilation.
*p values relate to placebo vs theophylline calculated by paired t test. There was no significant difference between baseline and placebo. p < 0.05 was considered significant.

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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

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Placebo</th>
<th>Theophylline</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work rate (watts)</td>
<td>75.5 (15.0)</td>
<td>75.0 (14.5)</td>
<td>86.5 (16.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vo2max (l/min)</td>
<td>253 (260)</td>
<td>255 (240)</td>
<td>265 (160)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vo2max (% of predicted)</td>
<td>15.0 (3.9)</td>
<td>14.0 (3.4)</td>
<td>16.6 (4.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anaerobic threshold (% of predicted Vo2max)</td>
<td>50.6 (6.5)</td>
<td>50.6 (6.3)</td>
<td>50.6 (5.9)</td>
<td>NS</td>
</tr>
<tr>
<td>O2 pulse (Vo2/HR)</td>
<td>81.7 (8.2)</td>
<td>81.4 (7.7)</td>
<td>83.1 (9.4)</td>
<td>NS</td>
</tr>
<tr>
<td>HR at rest (beat/min)</td>
<td>85.0 (8.7)</td>
<td>86.0 (9.2)</td>
<td>90.6 (8.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HR at maximum effort (1/min)</td>
<td>82.1 (11.3)</td>
<td>81.7 (11.9)</td>
<td>87.0 (10.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Vemax (l/min)</td>
<td>41.8 (10.6)</td>
<td>42.0 (10.4)</td>
<td>46.7 (14.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyspnea index (Vemax/MVV, %)</td>
<td>90.6 (9.0)</td>
<td>92.1 (8.6)</td>
<td>90.3 (8.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Vo2max = maximum oxygen consumption; HR = heart rate; Vemax = maximal ventilation.
*p values relate to placebo vs theophylline calculated by paired t test. There was no significant difference between baseline and placebo. p < 0.05 was considered significant.

8 Jenne JW. Theophylline is no more obsolete than "two puffs qid" of current beta, agonists. Chest 1990;98:3-4.
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