PAPERS AND SHORT REPORTS

Plasma theophylline concentrations, six minute walking distances, and breathlessness in patients with chronic airflow obstruction

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Abstract

Twenty patients with chronic bronchitis were given incremental dosages of a new slow release preparation of theophylline and observed for its effect on lung function and exercise tolerance. Measurements were made subjectively by using visual analogue scales and objectively using six minute walking distances and spirometry. The study was placebo controlled and had a double blind randomised design.

In the dosages used (200, 400, 600, and 800 mg) theophylline produced no significant improvement in forced expiratory volume in one second or forced vital capacity, and there was no overall improvement in peak expiratory flow rate. Similarly, neither effort tolerance nor degree of breathlessness appeared to be influenced by the drug, even when unacceptably high dosages were used. By contrast, placebo yielded a 7% increase in the six minute walking distance.

From these results it seems difficult to justify the routine, indiscriminate use of theophylline for chronic bronchitis.

Introduction

Methylxanthines are routinely prescribed for patients with chronic bronchitis, yet their efficacy in this condition is not established. Small dose related improvements in spirometric function have been reported with short[1] and more long term treatment but such benefits are not always found.[2]

There is also evidence that aminophylline may improve the contractility of skeletal[3 4] and diaphragmatic[5] muscle. This raises the possibility that these drugs might reduce the susceptibility of the muscles of the inspiratory apparatus to muscular fatigue.[5] Such fatigue may play an important part in the effort dyspnoea so commonly encountered in patients with chronic bronchitis.

Surprisingly few studies have observed the effect of theophylline on this effort intolerance, and even these have produced conflicting results.[6 7] I report the effects of incremental dosages of a new slow release theophylline preparation (Uniphyllin Unicontin) on pulmonary function and everyday exercise measured both subjectively (visual analogue scales) and objectively (six minute walking distances)[8] in 20 patients with chronic bronchitis.

Patients and methods

The 20 patients had a mean age of 66 years (range 45-75), a mean height of 169 cm (range 150-185), and a mean weight of 58 kg (range 35-97); their mean forced expiratory volume in one second (FEV_1) was 0·8 l (range 0·3-1·5). The patients were studied on six occasions over three weeks. The table lists the individual measurements of lung function carried out at the start of the study without medication. Patients with any feature of chronic asthma, as suggested by one or more of the following factors, were excluded: wide variation in spirometric values, sputum or blood eosinophilia, history of atopy, or improvement >20% in peak expiratory flow rate (PEFR) or FEV_1 with β_2 agonists. All subjects had previously been heavy cigarette smokers and satisfied the standard Medical Research Council criteria for chronic bronchitis. After selection 14 subjects were considered to have abnormally low diffusion constants (KCO <68% of predicted), indicating accompanying emphysema (table).

Patients were instructed to withhold all oral and inhaled bronchodilator drugs at least 12 hours before the study. Only inhaled β_2 agonists were allowed during the study period between study days, and these were not allowed in the 12 hours before each corridor walk. After two practice walks each patient performed two further walks on a different day, which were recorded as baseline values. Patients were given incremental dosages of oral theophylline (Uniphyllin Unicontin) 200, 400, 600, and 800 mg or matched placebo tablets in a double blind randomised sequence. All tablets were given as a single daily dosage at 2200 on the eve of the study days. Patients were studied 12 hours later.

Venous blood was withdrawn for plasma theophylline assay. PEFR, FEV_1, forced vital capacity (FVC), and heart rate were recorded followed by the first six minute corridor walk.[8] Breathless-

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ness was rated immediately after exercise using a 100 mm vertical visual analogue scale (0 = no dyspnoea, 100 = maximum tolerable dyspnoea), which the patients marked for themselves. After a rest period of one hour the spirometric and walking tests were repeated.

Data from both walks on each study day were subjected to standard techniques for correlation, regression, and analysis of variance.

Results

Recognised side effects associated with theophylline were commonly encountered. Eight subjects complained of gastrointestinal disturbance with the 600 mg dose, and the 800 mg increment was not given to four of these. Of the 16 subjects given 800 mg, 14 developed similar side effects or others—namely, insomnia or headache. Two subjects felt too unwell to perform exercises after the 800 mg increment. All subjects completed the protocol as far as and including the 600 mg incremental dose, and those results were submitted for statistical analysis.

Theophylline dosage correlated closely with plasma theophylline concentrations measured 12 hours later ($r^2 = 0{\cdot}9$) and accounted for 40% of the variation of theophylline values ($p < 0{\cdot}01$). Plasma concentrations, however, varied among subjects ($p < 0{\cdot}01$), with ranges for each incremental dose of oral theophylline as follows: 200 mg, 3-11 mg/l; 400 mg, 5·0-19·9 mg/l; 600 mg, 8-31 mg/l; 800 mg, 14-42 mg/l (n = 16).

Lung function values in 20 patients with chronic bronchitis

Case No	FEV_1 (l)	FVC (l)	TLC (l)	KCO% pred
1	0·5	2·0	7·9	68
2	0·7	3·6	6·4	55
3	0·8	2·4	5·2	60
4	1·1	2·6	5·6	85
5	1·0	3·0	6·1	42
6	1·5	3·2	7·4	58
7	1·1	3·7	7·6	35
8	0·5	1·6	7·1	73
9	0·7	2·4	6·3	53
10	0·6	2·4	7·5	68
11	0·3	1·7	7·8	62
12	0·8	2·1	6·4	50
13	0·5	2·9	5·4	62
14	0·3	1·5	5·8	88
15	0·9	3·0	6·1	42
16	0·9	2·8	7·5	50
17	0·8	2·8	7·6	35
18	1·0	2·8	7·1	74
19	0·7	1·7	6·1	58
20	0·5	1·6	7·5	65

FEV_1 = Forced expiratory volume in one second. FVC = Forced vital capacity. TLC = Total lung capacity (helium dilution technique). KCO% pred = Diffusion constant as percentage of predicted (single breath carbon monoxide technique).

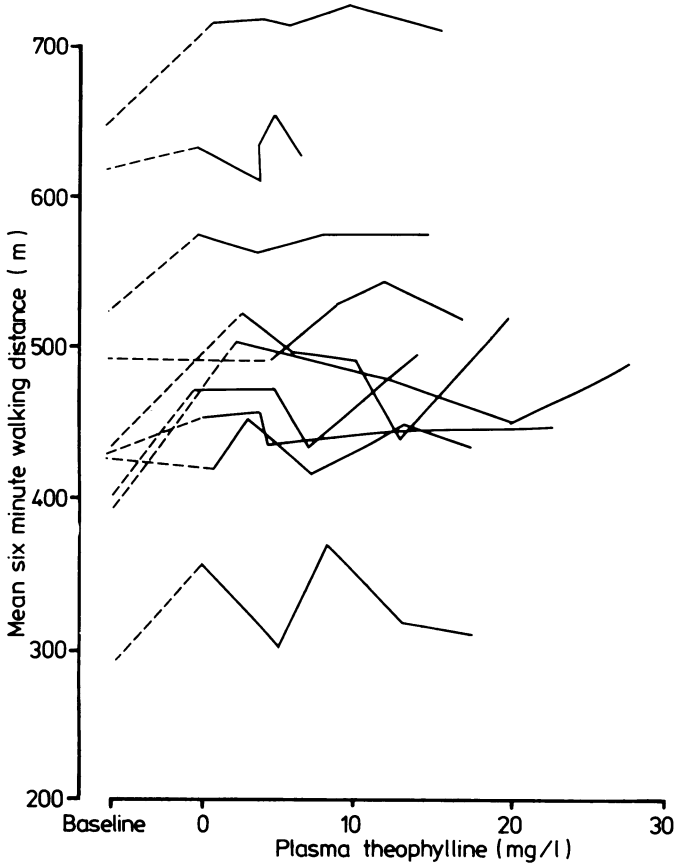

FIG 1—Mean six minute corridor walking distances (m) at baseline and 12 hours after incremental dosages of oral slow release theophylline 200, 400, 600, and 800 mg or placebo (0 mg) in cases 1-10. (Data in cases 11-20 (fig 2) shown separately for clarity.)

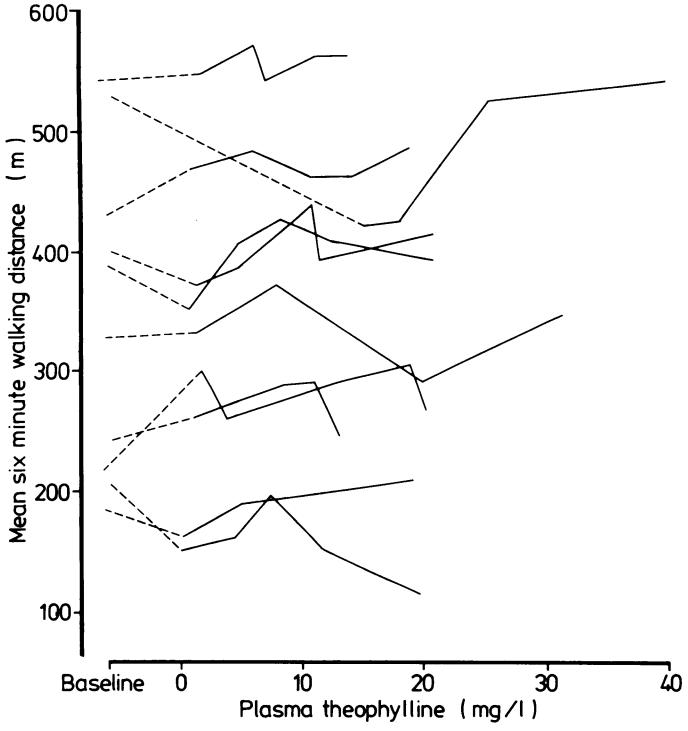

FIG 2—Mean six minute corridor walking distances (m) at baseline and 12 hours after incremental dosages of oral slow release theophylline 200, 400, 600, and 800 mg or placebo (0 mg) in cases 11-20.

There was no statistically significant correlation between six minute distances and theophylline dose ($r^2 = 0{\cdot}1$) or plasma theophylline concentrations ($r^2 = 0{\cdot}08$) (figs 1 and 2). These variables accounted for 0·1% and 0% (not significant (NS)) of the variation in these corridor walks. A significant increase in six minute distances (mean 21 m) was seen between baseline and placebo walks ($p < 0{\cdot}05$; paired t test). The order of walks accounted for 3·5% (NS) of the variation in six minute distances; thus the later walks did not influence the results as might be expected from a training or experience effect.

There was no significant correlation between either the dose or the resultant plasma theophylline concentration and the breathlessness accompanying these exercises ($r^2 = 0{\cdot}2$ and $r^2 = 0{\cdot}18$ respectively). Dose of theophylline accounted for 0·6% (NS) and plasma theophylline concentration 0% (NS) of the variation in these dyspnoea scores.

In this series theophylline produced no significant improvement in either FEV_1 or FVC. Overall PEFR similarly showed no improvement, although in a few patients a beneficial effect was seen. In the analysis of variance there was therefore a significant patient-theophylline interaction factor which accounted for 14% of the total variation in PEFR.

Heart rates increased with plasma theophylline concentrations ($p < 0{\cdot}01$), mean increases of 0·74/min (before exercise) and 0·62/min (after exercise) being recorded per unit mg/l rise in plasma theophylline value.

Discussion

The six minute corridor walk[8] is an accurate, routine standard test of effort tolerance in patients with respiratory disease. Use of the test and the design of this study appeared to have been satisfactory in that variations in walking distances were not prejudiced by walking order, experience, or training effects. Patients were selected carefully so as to exclude only those who might be considered as suffering from chronic asthma. The population studied was therefore representative of patients whom we commonly encounter with chronic bronchitis due to cigarette smoking.

As with some single dose studies of theophylline in chronic bronchitis[2] the incremental dosages used here produced no useful improvement in spirometric values. Neither effort tolerance nor concomitant dyspnoea appeared to be influenced by the drug, even when unacceptably high dosages were used. The results were similar for those subjects who showed small improvements in PEFR and for those with or without accompanying emphysema.

Leitch *et al* reported a 6% improvement in 12 minute distances with oral slow aminophylline.[6] Their results, however, were not confirmed or reproduced by Eaton *et al* in patients with chronic airflow obstruction, who did show significant improvement in spirometric function with oral theophylline.[7] Interestingly, my results show that an improvement of 7% can be obtained with placebo alone.

Nineteen of the 20 subjects in this study with chronic bronchitis had previously been prescribed long term oral theophylline, and the use of the drug in this condition is common practice. The role of theophylline in chronic bronchitis appears to be less controversial than before, but the routine, indiscriminate use of the drug in these patients seems difficult to justify.

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How soon after myocardial infarction should plasma lipid values be assessed?

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Abstract

Because acute myocardial infarction may affect plasma lipid concentrations it is commonly recommended that assessment of these concentrations should be delayed until about three months after the acute event. A study was therefore conducted of fasting plasma lipid concentrations in 58 patients with acute myocardial infarction. Measurements were made during their stay in hospital (days 1, 2, and 9) and three months later.

Triglyceride concentrations remained unchanged throughout. Values of total cholesterol, low density lipoprotein, and high density lipoprotein all fell significantly between the first two days and day 9. Total cholesterol and low density lipoprotein also showed significant falls between days 1 and 2. Nevertheless, fasting plasma lipid concentrations showed no significant difference at any time during the first 48 hours from values measured three months later. After the infarction 26 patients changed to eating less fat or less energy, or both. More patients had hypercholesterolaemia in the first 48 hours than at three months.

These results suggest that lipid state may be assessed as accurately, and possibly more accurately, during the first 48 hours after acute myocardial infarction than at three months.

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Introduction

Current clinical convention dictates that because acute myocardial infarction may affect plasma lipid concentrations lipid measurement for the detection of hyperlipidaemia should be deferred until two to three months after the acute event.[1-4] We have re-examined the effect of acute myocardial infarction on plasma lipid values to see if these can be meaningfully assessed during the hospital admission.

Patients and methods

We studied 58 patients who survived for three months after myocardial infarction. All had been admitted to the coronary care