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A 21-DAY DOUBLE-BLIND STUDY OF THE EFFECT OF ADDING SUSTAINED-RELEASE THEOPHYLLINE (NUELIN SA) TO INHALED SALBUTAMOL IN PATIENTS WITH ASTHMA

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Summary

The effect of adding sustained-release theophylline tablets (Nuelin SA) in a dose of 350 and 700 mg daily to regular treatment with inhaled salbutamol was assessed in a double-blind cross-over study in 19 patients with reversible airways obstruction.

In this combination, oral theophylline, even in the relatively low dose of 350 mg a day, produced a significant additional improvement in lung function. Subjectively, patients showed a preference for the combination of theophylline and inhaled salbutamol compared with the beta-stimulant alone.

Introduction

Barclay et al. (1981) demonstrated additive effects by the addition of inhaled salbutamol to intravenous aminophylline in patients with chronic bronchitis but Blumenthal (1980) showed no difference in the response of asthmatic children to oral aminophylline, oral salbutamol and a combination of half the dose of each.

Marlin et al. (1979) demonstrated an additive effect between oral theophylline and inhaled rimiterol occurring over an 8-hour period in adult asthmatic patients. In a comparative trial of combination therapy (Sahay & Chatterjee 1980) oral aminophylline and inhaled salbutamol on demand controlled asthmatic symptoms but with a relatively high incidence of side-effects.

The present study was designed to assess the effects on lung function of sustained-release theophylline (Nuelin SA), given in combination with regular inhalations of salbutamol in adult asthmatic patients.

Patients and Methods

Seventeen male and two female patients aged 24–72 (mean 55) years completed a 21-day, double-blind, cross-over study. All patients entering the trial had less than 70% of predicted normal one-second forced expiratory volume (FEV_1) and at least 15% reversibility of airways obstruction after receiving two inhalations of a β_2-stimulant aerosol. None of the patients was pregnant or had renal, liver or cardaic disease, but smokers were not excluded. Five patients

receiving stable doses of steroids and one patient receiving cromoglycate continued this therapy unchanged. All other bronchodilator treatment was discontinued 3 days before patients attended the clinic for the initial lung function tests.

On Day 1 basal measurements of peak expiratory flow rate (PEFR), forced vital capacity (FVC) and FEV_1 were recorded before 1000 hours. Patients were then instructed to take two inhalations of salbutamol 100 μg, at 0800, 1300, 1800 and 2300 hours each day throughout the study until the final measurements at 1400 hours on Day 21. Patients were also given a 7-day supply of tablets and instructed to return to the clinic at the same time the following week.

Each patient was allocated to receive each of the following three 7-day treatment regimens in random order:

Placebo and theophylline 175 mg, one tablet of each twice daily (350 mg/day); or
Placebo and theophylline 175 mg, one tablet of each twice daily for 3 days, followed by theophylline 175 mg, two tablets twice daily for 4 days (700 mg/day); or
Placebo, two tablets twice daily.

The doses were individually packed and labelled and were taken at 1000 and 2200 hours daily.

On Days 7, 14 and 21 patients attended the clinic. Pulmonary function was measured and a blood sample taken before the morning dose was given. These procedures were repeated at 1400 hours when near-peak serum theophylline levels were expected.

Analysis of serum theophylline levels was made using Enzyme Multiplied Immunoassay Technique (Koup & Brodsky 1978).

Results

The mean lung function measurements on Day 7 of each treatment period are shown in Table I. The differences between the values shown for each theophylline/salbutamol combination and the salbutamol/placebo treatment regimens were analysed using paired *t*-test differences (Armitage 1980).

At 0900 hours, 1 hour after salbutamol but before administration of theophylline, there was a statistically significant additional improvement in PEFR, FVC and FEV_1 compared with salbutamol from the lower dose but not from the high dose of theophylline.

At 1400 hours, 1 hour after salbutamol and 4 hours after theophylline there was a statistically significant additional improvement in PEFR, FVC and FEV_1 from high dose theophylline and in PEFR and FEV_1 from low dose theophylline.

The mean steady-state trough and 'peak' (measured 4 hours after dosing) serum theophylline levels produced on Day 7 by the sustained-release preparation were respectively 4.27 (± 0.44) and 6.0 (± 0.44) μg/ml after 350 mg and 9.38 (± 1.30) and 11.16 (± 1.47) μg/ml after 700 mg daily.

At the end of each treatment period 18 of the patients were asked to comment on the effect of each treatment. Their replies (Table II) showed a preference for theophylline over placebo but little difference in preference for the two doses of theophylline.

Four patients recorded undesirable effects which may have been due to the treatment. One patient reported reflux oesophageal acidity and palpitations with the higher dose and loose bowels with the lower dose regimens. The other three reports, one of tremor, one of nausea and headache and one of slight indigestion were associated with the maximum dosage combination of theophylline 700 mg together with salbutamol 800 μg daily.

Table I. Mean effect on lung function of adding sustained-release theophylline 350 mg (T350) and 700 mg (T700) to salbutamol 800 μg (S) daily (n = 19)

	Day 7 – 0900 hours							*Day 7 – 1400 hours*						
	S plus placebo	*S plus T350*	*Difference*	*P**	*S plus T700*	*Difference*	*P**	*S plus placebo*	*S plus T350*	*Difference*	*P**	*S plus T700*	*Difference*	*P**
PEFR (l/min) ± SEM	281 24.2	311 23.8	30	< 0.01	302 24.3	21	NS	288 22.6	312 25.2	24	< 0.01	312 25.3	24	< 0.01
FVC (litres) ± SEM	3.07 0.26	3.33 0.26	0.26	< 0.001	3.16 0.26	0.09	NS	3.07 0.24	3.19 0.24	0.12	NS	3.23 0.23	0.16	< 0.001
FEV_1 (litres) ± SEM	1.61 0.18	1.76 0.18	0.15	< 0.01	1.68 0.19	0.07	NS	1.58 0.16	1.72 0.18	0.14	< 0.001	1.79 0.17	0.21	< 0.001

* Paired t-test.

Mean pretreatment base values (± SEM): PEFR 269 (22.9) l/min, FVC 2.04 (0.26) litres, FEV_1 1.51 (0.16 litres).

Table II. Analysis of subjective assessment of the three treatment regimens

Comparison	*Number of patients who felt better*	*No difference*
Theophylline 350 mg + salbutamol	10	
v.		6
Placebo + salbutamol	2	
Theophylline 700 mg + salbutamol	10	
v.		5
Placebo + salbutamol	3	
Theophylline 350 mg + salbutamol	6	
v.		9
Theophylline 700 mg + salbutamol	3	

Discussion

Combinations of xanthines and beta-stimulants in the treatment of asthma appear to offer the prospect of more satisfactory control of symptoms without increasing side-effects. However most studies have used aminophylline intravenously, have been short-term or single-dose studies or have been in children. In a previous study we showed that oral sustained-release aminophylline combined with inhaled salbutamol controlled asthmatic symptoms but with a relatively high incidence of side-effects. The present study was designed to assess the effect of combining multiple doses of inhaled salbutamol and oral theophylline in adult asthmatics.

The modest theophylline dose of 350 mg daily produced mean trough and peak serum levels of 4.27 (± 0.44) and 6.0 (± 0.44) μg/ml respectively. Although these values are below the accepted therapeutic range of 10–20 μg/ml they were associated with a significant improvement in lung function over that produced by salbutamol alone. Thus even the lower mean trough serum theophylline value in combination with salbutamol was associated with a significantly better PEFR ($P < 0.01$), FVC ($P < 0.001$) and FEV_1 ($P < 0.01$) than after inhaled salbutamol alone.

The unexpected absence of significant further improvement in lung function at 0900 hours from the high dose of theophylline may be related to poor compliance by patients who experienced troublesome side-effects, three of whom had relatively low plasma theophylline levels. The overall low level of side-effects in this study may be a reflection of the small trough to peak fluctuations in serum theophylline levels achieved by the slow-release formulation or possibly of the absence of ethylene diamine from the sustained-release preparation chosen.

We conclude that sustained-release theophylline as Nuelin SA 350 mg or 700 mg daily, when added to two inhalations of salbutamol given four times daily produces a significant additional improvement in lung function.

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