

## Effects of withdrawal of sustained-release theophylline in patients with chronic obstructive lung disease

T. AAMODT,<sup>1</sup> R. DAHLE<sup>2</sup> & O. HORGEN<sup>1</sup>

Division of Pulmonary Diseases, <sup>1</sup>Vestfold Central County Hospital, Tønsberg and <sup>2</sup>Ostfold Central County Hospital, Fredrikstad, Norway

In a double-blind, cross-over study, sustained-release theophylline was withdrawn to determine whether the drug was still effective after long-term treatment. Twenty adult out-patients with stable, chronic obstructive lung disease and who had been on continuous long-term treatment for at least 6 months, were studied. Lung function, plasma theophylline concentration, symptom score, number of nocturnal dyspnoea attacks, requirement for additional beta<sub>2</sub>-stimulant aerosol, and side effects, were recorded before withdrawal, after withdrawal and after reinstitution of treatment. When theophylline was withdrawn, all parameters were significantly worsened, but after reinstitution of treatment they all improved significantly. The results show that sustained-release theophylline remains effective after at least 6 months' continuous treatment in adult patients.

*Key words:* adults; chronic obstructive lung disease; delayed-action preparations; drug tolerance; theophylline; long-term treatment.

*Accepted for publication 15 March 1988*

Sustained-release theophylline is now extensively used for long-term, maintenance treatment of chronic obstructive lung disease. Theophylline has been shown to have substantial clinical effect in many controlled, but short duration clinical studies. There are, however, few studies which have evaluated long-term treatment, and the results from these appear contradictory. The development of tolerance has been described in some reports of prolonged theophylline administration (5), and Katz et al. (4) found that many children require an increase in theophylline plasma concentration in order to maintain the same clinical benefit after continuous treatment for 2 months. It has also been suggested that a change in theophylline clearance over time can occur (3), and that development of tolerance could be due to autoinduction of theophylline metabolism (2).

In contrast, Pedersen & Nathan (6) have concluded that long-term treatment with theophylline in children remains effective for at least

1 year and Tinkelman et al. (8) found no evidence of tolerance in adults after 12 weeks.

The present study was undertaken to determine the efficacy of theophylline after continuous long-term treatment in adult patients.

### MATERIAL AND METHODS

Twenty-one adult out-patients (9 males, 12 females) with stable, chronic obstructive lung disease were selected for the study. They were aged 22-65 years (mean 48.1) and suffered from obstructive lung disease 2-36 years (mean 11.4). The mean FEV<sub>1</sub> was 2.03 l (range 0.59-3.59). Thirteen patients used continuous systemic corticosteroid therapy, and 14 continuous local corticosteroid therapy. The patients had used sustained release theophylline for 7-38 months (mean 19.8) with a mean daily dose of 10.0 mg/kg body weight (range 5.2-14.0 mg/kg) and a mean plasma theophylline concentration of 65.5 µmol/l (range 32-102 µmol/l on entering the study).

Patients with uncompensated heart failure, hepatic, renal or gastro-intestinal disease, and pregnant women, were excluded as were patients receiving allopurinol, phenobarbital, erythromycin, cimetidine or diuretics. Informed consent was obtained from all patients in accordance with the Helsinki Declaration of 1975.

The study was conducted over 4 consecutive weeks. All patients received sustained-release theophylline, as Nuelin Depot, during weeks 1 and 4 while the two middle weeks were used for the double-blind, cross-over study. Patients were randomly allocated to receive either Nuelin Depot or a matching placebo preparation in week 2 and then crossed over to the alternative regime in week 3. For the double-blind part of the study, active and placebo

tablets were packed so that each patient received the same individualized maintenance dose as taken prior to entering the study. The tablets were taken at the same time every morning and evening with a 12-h interval. Throughout the study the patients were not allowed to take other xanthine-containing medication or oral beta-adrenoceptor stimulants. Established therapy with corticosteroids was maintained at a constant dose. All patients were allowed to use their bronchodilator aerosol as required, but were instructed to record the number of inhalations they needed.

Pulmonary function was measured as forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV<sub>1</sub>) using a Vitalograph dry spirometer and peak expiratory flow (PEF)

Table 1  
Lung function tests. Mean  $\pm$  SEM ( $n = 20$ )

|                  | FVC<br>(litres) | FEV <sub>1</sub><br>(litres) | PEF <sup>a</sup><br>(litres/min) | PEF <sup>b</sup><br>(litres/min) |
|------------------|-----------------|------------------------------|----------------------------------|----------------------------------|
| On theophylline  | 3.10**          | 2.02**                       | 333*                             | 294**                            |
| Before placebo   | + 0.22          | + 0.17                       | + 25                             | + 20                             |
| Off theophylline | 2.65            | 1.60                         | 282                              | 270                              |
| Placebo          | + 0.21          | + 0.14                       | + 26                             | + 20                             |
| On theophylline  | 2.94**          | 1.89**                       | 319*                             | 288*                             |
| After placebo    | + 0.21          | + 0.15                       | + 22                             | + 20                             |

<sup>a</sup> 4 h after morning dose in doctor's office

<sup>b</sup> In the morning before dose at home

\*  $P < 0.05$  (compared with placebo)

\*\*  $P < 0.01$  (compared with placebo)

Table 2

Consumption of beta<sub>2</sub>-adrenoceptor stimulant aerosol, episodes of nocturnal attacks of dyspnoea and plasma theophylline concentration. Mean  $\pm$  SEM ( $n = 20$ ).

|                  | No. of inhalations | No. of nocturnal attacks | Plasma theophylline concentration ( $\mu$ mol/l) |
|------------------|--------------------|--------------------------|--------------------------------------------------|
| On theophylline  | 67.4*              | 3.0*                     | 68.8                                             |
| Before placebo   | + 13.3             | + 1.0                    | + 5.1                                            |
| Off theophylline | 83.7               | 4.4                      | 0                                                |
| Placebo          | + 16.8             | + 1.3                    | + 0                                              |
| On theophylline  | 58.2*              | 2.3*                     | 67.0                                             |
| After placebo    | + 10.3             | + 0.8                    | + 5.4                                            |

\*  $P < 0.05$  (compared with placebo)

using a Wright Peak Flow Meter. Measurements were made at the clinic, 3–4 h post dosing on the last day of each study week. The best of three measurements was used for analysis.

Throughout the study the patients themselves measured their pre-dose PEF at home each morning using a Mini-Wright Peak Flow Meter. Patients were provided with diary cards on which they recorded, daily, their home-measured PEF, the number of acute attacks of nocturnal dyspnoea, the total number of inhalations of bronchodilator aerosol they had needed and the frequency of any side effects. At the end of each study week the patients were asked to evaluate their respiratory symptoms on a visual analogue scale.

Blood samples were drawn 4 h after dosing on the last day of each study period. The plasma was deep-frozen and stored until the study was completed, when the plasma theophylline concentration was determined using an enzyme multiplied immunoassay (EMIT).

In the statistical analyses we used the measurements from the theophylline periods just before and after the placebo period as well as measurements taken during the placebo period. All quantitative data are presented as mean  $\pm$  SEM. The results were analysed by Student's paired t-test and analysis of variance. Since the results of the two tests were similar, only the results of the t-test are reported. Results corresponding to probabilities  $< 0.05$  were considered statistically significant.

## RESULTS

Twenty-one patients were entered into the study, 20 patients completed since one had to be withdrawn because of an acute, severe bronchial infection.

The results of pulmonary function tests at hospital and at home, patients' additional bronchodilator aerosol usage, the number of nocturnal attacks and theophylline plasma concentrations are shown in Tables 1 and 2 as mean values  $\pm$  SEM.

All measured parameters were statistically significantly improved ( $P < 0.05$ ) in the theo-

phylline periods compared with the placebo period. There were no significant differences between measured parameters before withdrawal and after reinstitution of theophylline therapy. When theophylline treatment was withdrawn, pulmonary function deteriorated as shown by a mean decrease of 14.5%, 20.8% and 15.3% in FVC, FEV<sub>1</sub> and PEF, respectively. During the placebo period, nocturnal attacks of dyspnoea increased by 46.7% even though the number of doses of aerosol bronchodilators was increased by 24.2%.

When theophylline treatment was reinstituted after the withdrawal week, there was a mean increase of 10.9%, 18.1% and 13.1% in the lung function parameters and nocturnal attacks of dyspnoea were reduced by 47.7% together with a 30.5% reduction in the patients' requirements for additional aerosol bronchodilators. Analysis of the patients' subjective evaluation of bronchial symptoms on the visual analogue scale showed that 16 patients felt significantly better during the theophylline periods compared with placebo, two were unchanged and two felt worse despite their significantly decreased need of beta<sub>2</sub> bronchodilator aerosols. The 13 patients treated with systemic corticosteroids did not differ from the whole group.

## DISCUSSION

When sustained-release formulations of theophylline were introduced they were regarded as a major advance in the treatment of asthma (7). One of their advantages was that unacceptably wide, trough-to-peak fluctuations in plasma concentration during the dosing interval could be minimised or avoided. However, stable plasma concentrations could be disadvantageous if they increase the possibility of patients developing treatment tolerance. Although sustained release preparations have been available for several years, only a few long-term studies have been made, most of them on children. We therefore undertook this study to determine whether theophylline remained an effective bronchodilator after long-term therapy with sustained-release tablet preparations in adult patients.

If the efficacy of theophylline is reduced after long-term therapy it could be anticipated that when the drug was withdrawn there would either be no change or a limited and minor worsening of the patient's condition. Similarly, when theophylline treatment was reinstituted, the patient's condition would be expected to improve significantly provided the withdrawal period was of sufficient duration.

Our results have shown that there was a statistically significant worsening of all the parameters used to evaluate the patients' condition during the withdrawal period. Analysis of the measured observations was supported by the patients' subjective evaluation of their condition: 16 of 20 reported that they felt better during the theophylline phases. The individual results showed that two patients seemed to derive no benefit at all from theophylline. Theoretically, this lack of response could indicate a development of tolerance in these two patients. However, a more likely explanation is that the patients had probably never shown any substantial bronchodilator response to theophylline on the doses they had previously been receiving. Unfortunately, we could not check this since no records were available of our patients' response when treatment with sustained release theophylline was first started.

In a recently published long-term study (1) Billing et al. showed that half of the 20 adult patients they studied were "non-responders" in terms of improved bronchodilation, and suggested that "responders" and "non-responders" may represent two groups of asthmatics with differences in the aetiology of airway obstruction.

## CONCLUSION

Our study has shown that sustained-release theophylline is an effective bronchodilator and that

its usefulness does not diminish during long-term maintenance treatment of adult patients.

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Address:

Terje Aamodt, M.D.  
Division of Pulmonary Diseases  
Vestfold Central County Hospital  
3100 Tønsberg  
Norway

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