

Long-Term Treatment with Oral Sustained-Release Theophylline

A Double-Blind, Controlled Study

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The treatment of chronic asthma with a sustained-release theophylline preparation was evaluated in a placebo controlled, 2×4 week, randomised, double-blind study. The dose which would give serum theophylline levels in the range of 10–20 mcg/ml had been previously determined for each patient. This individualisation of dosage resulted in 80% of the patients having serum concentrations within the 10–20 mcg/ml therapeutic range. The average daily dose taken by males was 998.55 mg (range 700–1175 mg) and by females 778.1 (range 500–1000 mg).

Of the 33 patients who completed the study 28 had less asthma during the theophylline period, four did not respond and one did better during the placebo period. No serious side effects were reported. During theophylline therapy, patient's requirements for aerosol bronchodilators were significantly reduced.

Key words: asthma; long-term treatment; sustained-release; theophylline.

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Oral theophylline is widely used for the treatment of chronic asthma and the importance of maintaining a therapeutic blood level has been stressed during the last decade. Recent studies have shown that therapeutic serum levels are easily and safely achieved by sustained release tablets given twice daily (3, 12, 15, 16, 18, 19, 21, 26).

Although theophylline has been used in the treatment of asthma for longer than both beclomethasone and sodium cromoglycate, in contrast to the latter agent, whose value in the prophylaxis of childhood asthma is well documented, (1, 2, 7–10, 27) few studies have been reported which demonstrate the usefulness of theophylline in long-term treatment.

The aims of this study were, 1) to assess the clinical value of theophylline treatment objectively by comparison with placebo, and 2) to obtain an impression of the range of dosage required to produce therapeutic serum levels in

long-term treatment when theophylline is administered twice daily utilising a slow-release preparation.

METHODS AND PATIENTS

Study design

The study design is summarised in Figs. 1 and 2. Before entering the study all patients were required to give their informed consent. The study consisted of two parts:

An "open"-dose evaluation phase during which the theophylline dose required to give a plasma concentration within the therapeutic range of 10–20 mcg/ml was determined.

A randomised, double-blind, cross-over study of 4 week's duration on active sustained-release theophylline and 4 weeks of an exactly matching placebo preparation.

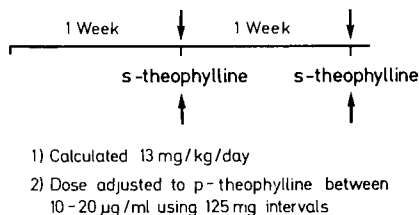
"Open" - dose evaluation phase

Fig. 1. Diagram of trial design for the open, dose evaluation phase. Dose given during week 1 calculated at 13 mg/kg/day. Dose given during second week adjusted according to plasma concentrations achieved in week 1.

After this procedure had been completed, the patients entered a "wash-out period" of at least 1 week during which they received no theophylline.

The duration of the double-blind, cross-over trial was 8 weeks. During the first 4 weeks the patients were randomly allocated to receive either the active drug or a matching placebo tablet in the same dosage. In the second period of 4 weeks they were "crossed-over" to the alternative regimen.

Active and placebo tablets for the double-blind phase of the study were pre-packed to

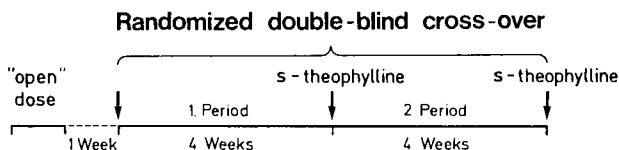


Fig. 2. Diagram of double-blind study. Patients randomly allocated to receive sustained-release theophylline or matching placebo tablets.

For the first week of the open, dose-evaluation phase all patients were given a "calculated dose" of 13 mg/kg/day (29) given as "Nuelin" Retard. Patients not previously treated with theophylline were given an "induction dose" of 500 mg per day for the first 3 days of this phase. Dosage was then increased in these patients to 13 mg/kg/day for days 4, 5, 6 and 7. The patients were instructed to take the morning dose at home on day 8 at 0800 h before attending hospital for blood sampling at 1300 h, – that is 5 h after the morning dose when they were expected to be in "steady-state". This procedure was not necessarily used for patients already receiving theophylline treatment but these patients too had their dosage changed to establish a steady-state at a dosage of 13 mg/kg/day. If the serum theophylline concentration was between 10 and 20 mcg/ml the patient was given the same daily dose throughout the second, double-blind phase of the study. If the serum level was above or below these limits, the dose was adjusted and the patients received a further 7 days' treatment at their "adjusted dosage".

permit easy and accurate dispensing and to ensure the integrity of the double-blind design. Patients were allocated – by the findings during the open dosage evaluation phase – to a dosage closest to their individual requirements. Thus, a patient requiring 700 mg theophylline per day was randomly allocated to a pre-prepared pack containing either 4 weeks' supply of active or 4 weeks' supply of placebo tablets at his own individually determined 700 mg dosage requirements.

Packs were prepared containing tablets providing 500, 700, 850, 1000 and 1175 mg of theophylline or placebo per day. Patients were allocated to receive dosage from the pre-prepared pack which was nearest to their individual "calculated" or "adjusted" dose.

The preparation used was a sustained-release preparation ("Nuelin" Retard, 175 mg and 250 mg tablets) which was given twice daily.

Before entering the study all patients had filled out diary cards for at least 1 month. They measured and recorded their own peak expiratory flow (PEF) every morning and night with a Wright Mini-meter. In addition they were in-

structed to take a reading every time they felt a need for additional bronchodilatation. If the PEF was less than 60% of the highest PEF which the patient could perform, he or she was to take one puff of a β_2 -agonist spray. Five minutes later PEF was again to be measured and if the reading was over "60%-value" no more bronchodilator was to be taken. If, on the other hand, the PEF after bronchodilatation was still lower than the "60%-value", another puff of β_2 -agonist aerosol was to be taken and this procedure repeated until the PEF was greater than the 60% value. In the immediate pre-study period theophylline was withheld but the use of β_2 -agonist inhalers was permitted up to 10 puffs per day. In this pre-study period it was therefore possible to establish that the patient was in a stable phase of the disease and to assess his usual consumption of an aerosol β_2 stimulant preparation.

At the end of each 4-week period patients were seen in the out-patient clinic where blood was taken for serum theophylline assay and the diary card was scrutinised for recorded side effects.

Patients

The patients who took part in the study were all adults between 18 and 65 years with perennial asthma, but who were otherwise healthy. The other criteria for selection were the need to take at least four puffs a day of a β_2 -agonist inhaler, and improvement in FEV_1 greater than 20% following two puffs of an isoprenaline inhaler, a PEF greater than 200 l/min and the mental ability to satisfactorily complete a diary card.

RESULTS

Sixty-one patients agreed to enter the study. Thirty-three of these were randomly entered into the formal, double-blind study period after their competence in the completion of the diary card had been accepted and the daily doses of medicines other than the β_2 -agonists had been regulated so that the need for inhalation

Table 1

Anthropological data and the duration of asthma

		Male	Female
Number of patients		17	16
Age (years)	mean	46.0	38.1
	range	26-64	17-59
Weight (kg)	mean	79.6	60.4
	range	64-97	48-79
Height (cm)	mean	176	165
	range	162-188	158-178
Duration of asthma (years)			
	mean	17.9	13.9
	range	2-50	1-32

Table 2

Number of patients with b-eosinophilia and increased IgE in the blood. Treatment denotes amount of corticosteroid employed, whereas the description of asthma denotes number of patients employing the different levels of corticosteroids

		Male	Female
Serum-IgE	< 263 U/ml	8	12
	> 263 U/ml	9	4
Eosinophils	< 250 Mill/l	6	3
	> 359 Mill/l	11	13
Asthma	No daily medicine	0	0
	Daily medicine - no corticosteroid	3	3
	Local corticosteroid (spray)	11	7
	Systemic corticosteroid	3	6
Treatment	Oral steroids (5 to 12 mg/day)	3	6
	Beclomethasone (8 to 12 puffs/day)	14	13
	No steroid	3	3

of aerosol sprays was between 4 and 10 puffs per day. Nine out of the 28 patients who did not start the double-blind study just stayed away without giving a reason. Six patients suffered

Table 3

Average theophylline dose given to obtain a serum level between 10 and 20 mg/l, and the number of patients receiving the different theophylline dosages

		Male	Female
Theophylline dose	Mean	12.5	12.9
(mg/kg/day)	SD	1.2	2.3
Dose		Number of patients	
		Male	Female
500 mg/day		0	2
700 mg/day		1	4
850 mg/day		4	9
1000 mg/day		7	1
1175 mg/day		5	0

Table 4

Side effects. Most of the side effects persisted for about a week

	Active	Placebo
Nausea, vomiting, diarrhoea, pain	6	2
Headache, tiredness	10	4
Tachycardia	2	0

from other diseases and three continued to change their medication without permission. Three did not use beta₂-agonist sprays at least 4 times daily and two patients could not learn to complete the diary card satisfactorily. Five failed to complete the trial for various other reasons.

Sixteen of the patients were females, 11 of whom had never smoked and only one of whom still smoked each day. Four of the 17 men were smokers and six had never smoked. For anthropometric data, see Table 1. The values of eosinophils and IgE are shown in Table 2 together with the additional medication given to the patients during the study.

The average daily use of beta₂-agonist inhalers during the last 7 days of each of the two periods was compared using a paired t-test for

each patient. The patient was categorised as a responder in the period where he or she used significantly ($P < 0.05$) fewer inhalations. If the patients developed status asthmaticus in *one* of the periods he or she was automatically categorised as a responder to the alternative medication.

Twenty-eight of the 33 patients who completed the study were responders in the theophylline period. One patient was a responder in the placebo period and in the four other cases the results were equivocal. Six of the responders to theophylline developed status asthmaticus, which was treated in the hospital emergency room, during the period when they were receiving placebo.

The other 22 responders reduced their daily intake of inhaled bronchodilator therapy from an average of 8.9 puffs per day in the placebo period to 4.6 puffs per day in the period when sustained-release theophylline was being taken.

The different dosages of theophylline taken by the patients are shown in Table 3. On average, the females received 778.1 mg/day divided into two daily doses and the males received 998.5 mg/day.

The side effects which occurred in both the theophylline period and the placebo period are listed in Table 4. These side effects were mild and usually short-lived, lasting about 1 week, and could appear at the beginning or at the end of the period.

Theophylline serum concentrations

During the active treatment period six patients had serum values between 5 and 10 mcg/ml, 26 patients values between 10 and 20 mcg/ml and one patient had a plasma concentration of 29.1 mcg/ml. On the last day of the placebo period all the patients had theophylline levels of less than 0.1 mcg/ml.

DISCUSSION

There is ample published evidence that sustained-release preparations are capable of giving serum theophylline concentrations in the range which is considered to be therapeutic (3,

12, 14, 15, 16, 18, 19, 21, 26) namely between 10 and 20 mcg/ml. This was confirmed in the present study in which serum levels were in the therapeutic range at the end of 4 weeks' treatment in the majority of cases.

In six patients serum concentrations were below the expected level but compliance by the other 27 patients was obviously beyond question. The necessity for good compliance by asthmatic patients during theophylline therapy has been stressed in recent years (5, 24).

In four out of the six patients who had serum theophylline concentrations of less than 10 mcg/ml, the concentration was only slightly less at 9.0 mcg/ml. In one other patient, who surprisingly was classified as a responder to the placebo period, the serum concentration was 8.3 mcg/ml. The sixth patient's serum concentration was 5.1 mcg/ml. These few low serum concentrations cannot be explained by the patients' smoking habits (13, 20).

The individualised dosage of theophylline given in this study appears to have been both effective and safe in terms of clinical response, serum theophylline concentrations and the incidence of side effects. In other studies the serum level has usually exceeded 30 mcg/ml before severe side effects have appeared (11, 30).

Published studies comparing the effect of theophylline with other regimens are rare. It is, however, clear that the addition of ephedrine to adequate doses of theophylline gives little or no additional benefit in the long-term treatment of asthma (6, 25). It has also been shown that addition of cromoglycate to theophylline treatment is of limited value (10). The addition of theophylline to β_2 -agonists given orally may confer benefit but the side effects of these agents have been shown to be additive when both are given by mouth (4). It is logical to use theophylline as complementary therapy to inhaled β_2 -adrenergic stimulants to achieve an additional bronchodilator effect with an increase in side effects (17, 23, 28).

As has been shown by the results of the present study, the use of theophylline as a "base-line treatment" in asthma can significantly reduce the need for sympathomimetic inhaled bronchodilators.

CONCLUSION

It is concluded that theophylline given as a sustained-release preparation is effective and relatively trouble-free in the long-term treatment of asthma. When theophylline is given alone, dosages of about 750 mg/day for women and about 1000 mg/day for men, appear to be optimum.

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