Combined treatment with sustained-release theophylline and beta₂-adrenoceptor-stimulating agents in chronic childhood asthma

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Abstract

The effect of adding theophylline to treatment with a beta₂-adrenoceptor stimulant was studied in 18 asthmatic children in a double-blind cross-over trial. Most patients were taking cromolyn sodium (cromoglycic acid) or beclomethasone aerosol, or both. A sustained-release preparation of theophylline was administered in individually titrated doses, producing a mean plasma theophylline concentration of about 8 µg/ml. Statistically significant improvements were found during the theophylline treatment in symptom score, consumption of beta₂ stimulants in aerosol form, and morning peak expiratory flow rate and forced expiratory volume in one second. There was also a reduced need for emergency-room treatment during the theophylline period. Reported side effects were few and mild and were similar during the theophylline and placebo periods. Of the 17 patients who completed the trial, 14 preferred theophylline and three expressed no preference between theophylline and placebo.

Adding submaximal doses of sustained-release theophylline to treatment with a beta₂ stimulant gave further relief of asthmatic symptoms without appreciable side effects, suggesting that the drug combination has a favourable therapeutic index.

Introduction

Beta₂-adrenoceptor-stimulating agents are potent bronchodilators. High dosage however, is restricted by dose-related side effects, mainly skeletal muscle tremor.^{1,2} If a subtoxic dose of a beta₂ stimulant does not control asthmatic symptoms, it seems logical to add theophylline, since in-vitro experiments have shown that theophylline inhibits the phosphodiesterase enzymes of human bronchial muscle in lower concentrations than in skeletal muscle.³ These data suggest that the combination may give a potentiated therapeutic effect with no more side effects than with beta₂ stimulants alone. Furthermore, results of single-dose studies in adult asthmatics indicate that there may be therapeutic advantages in combining an oral beta₂ stimulant with theophylline.^{3,4} Nevertheless, no long-term trials have apparently been conducted to determine the possible advantages of this drug combination in maintenance treatment of chronic bronchial asthma.

We have studied the effect of adding theophylline to treatment with a beta₂ stimulant in children with chronic asthma; most of the children were also receiving cromolyn sodium (cromoglycic acid) or beclomethasone aerosol, or both. Individually

titrated doses of a sustained-release preparation of theophylline (Theo-Dur, AB Draco, Sweden) were used.

Patients and methods

Twelve boys and six girls with a median age of 11 years (range 7-14) were selected for the trial. All had moderate to severe chronic allergic asthma and were well known to the investigators. Their asthma was relatively stable at the time of the study (September to May). Reversibility of bronchial obstruction was shown by a 15% or greater improvement in forced expiratory volume in one second (FEV₁) 20-30 minutes after inhaling 0.3 mg salbutamol. None of the patients had cardiac, renal, or hepatic disorders, nor any other relevant medical disease. Informed consent was obtained from the patients and their parents. The study was approved by the local ethics committee.

The study was designed as a double-blind cross-over trial comprising two two-week periods. Treatment periods were randomised, each patient receiving theophylline or placebo in identical preparations. Before the first treatment period the dose of theophylline was titrated individually for each patient to give a plasma theophylline concentration of 7-15 µg/ml as measured four hours after the morning dose (which is the mean time for the peak plasma concentration at steady state in adults⁵) after at least four days of treatment. The drug was administered twice daily, at about 8 am and 8 pm. Only whole or half tablets were used.

During each treatment period the patients kept a daily diary, recording symptoms (see table I), medication, peak expiratory flow rates (PEFR) in the morning and evening before the theophylline dose, and any side effects. Specific side effects were sought by questionnaire after completing the study (see table IV). At the end of each treatment period (day 14) blood samples were taken for plasma theophylline determinations and FEV₁ and PEFR measured. PEFR was measured with a Mini-Wright peak flow meter, and FEV₁ with a dry spirometer (Vitalograph). For both FEV₁ and PEFR the highest value in three measurements was used.

All patients took terbutaline (n = 16) or salbutamol (n = 2) tablets in the generally recommended dosage—namely, 45-96 (mean 70) µg/kg body weight thrice daily or 47-53 (mean 50) µg/kg body weight thrice daily respectively—throughout the study. All except two were also using a terbutaline (n = 3) or salbutamol (n = 13) aerosol, administered as required. Eleven children were receiving cromolyn sodium and four beclomethasone aerosol; these medications were kept constant throughout. Most patients had been receiving standard theophylline tablets, which were stopped one day before entry to the trial.

In the event of a respiratory tract infection the trial was interrupted without breaking the code (with two exceptions, see Results). The interrupted two-week period was run again from the beginning once the patient's condition had returned to normal.

Plasma (50 µl) was obtained by finger prick. Plasma concentrations of theophylline were determined by a gas chromatographic mass spectrometric method,⁶ which entailed a combined extraction and derivatisation step and the use of deuterated theophylline as internal standard.

Standard computer programs were used for statistical calculations. Student's paired *t* test (two-sided) was used for testing significance. Only the results from days 4-14 in each period were used, as patients were considered not to be in steady state until day 4.

Results

Seventeen of the 18 patients completed the study. The other patient deteriorated noticeably during the first few days (placebo period), and the code had to be broken and additional oral treatment given. The parents then withdrew the patient from the study.

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Emergency-room treatment with inhalation of high doses of salbutamol or injections of adrenaline, or both, was required for five patients during the placebo period, but for none during the theophylline period. Two of the five patients had definite or probable respiratory tract infection, and the study was therefore interrupted and completed later. Two of the remaining three patients improved with treatment and continued the study without interruption. The third patient was admitted for further treatment and the code had to be broken; the whole trial was repeated a few months later. Four other patients (three during the theophylline period and one during the placebo period) interrupted the study because of respiratory tract infection and completed it later. These patients did not require emergency-room treatment.

Table I shows the mean symptom scores during days 4-14. The scores were significantly better during the theophylline period with respect to physical activity and breathlessness during the day. Medication scores during days 4-14 showed a significantly ($p < 0.05$) reduced consumption of β_2 stimulants in aerosol form during the theophylline period compared with the placebo period. The mean numbers of inhalations a day were 2.1 (SD 2.2) and 3.0 (SD 2.7), respectively. The mean within-person difference between the two periods was 0.83 (SEM 0.30) inhalations a day.

TABLE I—Mean symptom scores (days 4-14)*

Symptom	Theophylline (SD)	Placebo (SD)	Within-person difference between periods (SEM)	Significance
Daytime:				
Breathlessness	1.5 (0.38)	1.7 (0.58)	0.26 (0.11)	$p < 0.05$
Cough	1.3 (0.35)	1.4 (0.28)	0.10 (0.07)	NS
Physical activity	1.6 (0.36)	1.8 (0.35)	0.21 (0.09)	$p < 0.05$
Night-time:				
Breathlessness	1.2 (0.33)	1.3 (0.35)	0.10 (0.06)	NS
Cough	1.3 (0.35)	1.4 (0.33)	0.07 (0.09)	NS
Sleep	1.9 (0.46)	1.9 (0.39)	0.02 (0.11)	NS

NS = Not significant.

*Symptom scores graded 1-4: 1 = no symptoms; 2 = mild symptoms; 3 = moderate symptoms; 4 = severe symptoms. For physical activity and sleep: 1 = better than normal; 2 = normal; 3 = moderately impaired; 4 = severely impaired.

The mean morning PEFR during days 4-14 was higher ($p < 0.05$) with theophylline (275 l/min (SD 83)) than with placebo (253 l/min (SD 82)). The mean within-person difference between the periods was 20.8 l/min (SEM 9.3). The mean evening PEFRs (297 l/min (SD 71) during theophylline; 288 l/min (SD 77) during placebo treatment) did not differ significantly (mean within-person difference 5.0 (SEM 9.8)). The morning (8 am, predose) FEV₁ on day 14 was higher ($p < 0.01$) during the theophylline period (table II), while the values three and five hours after the dose did not differ significantly between the periods. Salbutamol aerosol increased the FEV₁ similarly during the two periods (table II).

The mean dose of theophylline administered was 8.9 mg/kg body weight twice daily (range 5.4-13.6). Mean plasma theophylline concentrations on day 14 were 8.1 (SD 2.2), 8.3 (SD 1.7), and 8.9 (SD 2.0) μ g/ml before and three and five hours after the dose, respectively.

Only few and mild side effects were reported spontaneously during the study (table III), and there was no difference between the theophylline and placebo periods. The same was true when specific side effects were sought by questionnaire after the study (table IV).

On completion of the trial the patients were asked which treatment they preferred. Fourteen of the 17 patients preferred the theophylline treatment, three expressed no preference, and none preferred the placebo. This difference was highly significant ($p < 0.001$; Wilcoxon's signed rank test).

Discussion

In this study adding sustained-release theophylline in submaximal dosage to treatment with a β_2 stimulant (which in most cases was being given concomitantly with cromolyn sodium or beclomethasone aerosol, or both) relieved clinical symptoms of chronic childhood asthma. Statistically significant differences between theophylline and placebo periods in favour of theophylline were noted in symptom score for physical activity and breathlessness during the daytime; consumption of β_2 stimulants in aerosol form; morning PEFR and FEV₁

TABLE II—Forced expiratory volume in one second (FEV₁) measured on day 14 (results expressed as means)

Time	FEV ₁ (l)				FEV ₁ (% of expected value for height ¹⁴)	
	Theophylline (SD)	Placebo (SD)	Within-person difference between periods (SEM)	Significance	Theophylline (SD)	Placebo (SD)
8 am before dose	1.70 (0.63)	1.49 (0.58)	0.22 (0.07)	$p < 0.01$	74 (26)	65 (25)
11 am 3 h after dose	1.87 (0.62)	1.84 (0.58)	0.06 (0.09)	NS	81 (23)	80 (25)
1 pm 5 h after dose	1.89 (0.71)	1.73 (0.50)	0.20 (0.11)	NS	82 (26)	75 (24)
1.30 pm 30 min after 0.3 mg inhaled salbutamol	2.15 (0.71)	2.07 (0.63)	0.13 (0.12)	NS	94 (30)	90 (20)

NS = Not significant.

TABLE III—Spontaneously reported side effects

Symptom	Theophylline	Placebo
Headache	1	
Nausea	1	1
Abdominal pain	1	1
Irritability		1
Difficulty in falling asleep		1

All side effects were mild and of short duration (one to three days).

TABLE IV—Side effects sought by questionnaire*

Symptom	Theophylline	Placebo
Tremor	3	3
Nausea	1	1
Abdominal pain	2	3
Nervousness	1	

*Questions asked were: Did any of the following side effects occur: tremor; nausea; abdominal pain; nervousness? Alternatives given for each symptom were: no; yes, some; yes, much. For all side effects reported "yes, some" was chosen.

values; and treatment preferred by the patients. Furthermore, five patients needed treatment in the emergency room during the placebo period compared with none during the theophylline period. This difference, however, was not significant.

Symptom score for physical activity and breathlessness—The improvements in symptom scores were numerically small and might appear clinically unimportant. Nevertheless, the scores were quite low even during the placebo period (see table I), leaving little room for improvement. This may partly explain the lack of significant improvement in nightly symptom scores.

Consumption of β_2 stimulants—The more frequent use of β_2 stimulant aerosol during the placebo period (40% more than with theophylline) must have tended to diminish any difference in other variables between the two periods caused by theophylline. This adds to the significance of the improvements in symptom score and respiratory function during the theophylline period.

PEFR and FEV₁—The β_2 stimulants used in this study (terbutaline and salbutamol) have a duration of effect of about six hours after oral ingestion. Hence a nightly dose interval of

about 10 hours, as used by our patients, leaves the early-morning unprotected. It is also a common clinical observation that many asthmatic patients have symptoms during these hours. Our data suggest that sustained-release theophylline protects the whole night and relieves the early-morning symptoms.

Preferred treatment—Fourteen of the 17 patients who completed the study preferred theophylline and none the placebo; three gave no preference. Since chronic asthma has a variable course which tends to obscure the effects of treatment, we find these figures most convincing.

Theophylline concentrations in the plasma showed considerable stability during the dose interval, with mean values varying between only 8.1 and 8.9 µg/ml. This supports findings^{7,8} that the sustained-release preparation tested here may be administered every 12 hours in asthmatic children. The mean dose of theophylline was 8.9 mg/kg body weight twice daily (range 5.4–13.6). This finding of an approximately 2.5-fold difference in the maintenance dose of theophylline agrees with other data.⁹ It is probably explained by the pronounced interindividual differences in elimination rate that are known to exist.

Few and mild side effects were reported during the study, with no difference between the theophylline and placebo periods. The most common adverse effects with oral theophylline are gastrointestinal, which are dose-related.^{10,11} The virtual absence of gastrointestinal disturbances in this study may be explained by the sustained-release formulation used or the comparably low steady-state plasma theophylline concentrations, or both.

That adding sustained-release theophylline in submaximal dosage to treatment with beta₂ stimulants relieved asthmatic symptoms without any side effects suggests that this combination has a favourable therapeutic index. Most of our patients had plasma theophylline concentrations below the recommended therapeutic range of 10–20 µg/ml.¹¹ In several studies, however, some bronchodilating effect and relief of asthmatic symptoms have been observed with plasma concentrations of only 5–10 µg/ml in patients treated with theophylline alone.^{12–14} From these data and ours, and since the bronchodilating effect of theophylline and beta₂ stimulants is at least additive,^{3,4,15} we consider it reasonable to aim at theophylline concentrations of 6–10 µg/ml in patients receiving this

drug combination. If the effect is not satisfactory, an increased dose of theophylline may be tried.

This study was supported by AB Draco, Lund, Sweden.

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(Accepted 30 January 1981)

NETTLES are so well known, that they need no description; they may be found by feeling, in the darkest night.

This is also an herb Mars claims dominion over. You know Mars is hot and dry, and you know as well that Winter is cold and moist; then you may know as well the reason why Nettle-tops eaten in the Spring consume the phlegmatic superfluities in the body of man, that the coldness and moistness of Winter hath left behind. The roots or leaves boiled, or the juice of either of them, or both made into an electuary with honey and sugar, is a safe and sure medicine to open the pipes and passages of the lungs, which is the cause of wheezing and shortness of breath, and helps to expectorate tough phlegm, as also to raise the imposthured pleurisy; and spend it by spitting; the same helps the swelling of the almonds of the throat, the mouth and throat being gargled therewith. The juice is also effectual to settle the palate of the mouth in its place, and to heal and temper the inflammations and soreness of the mouth and throat. The decoction of the leaves in wine, being drank, is singularly good to provoke women's courses, and settle the suffocation, strangling of the mother, and all other diseases thereof; it is also applied outwardly with a little myrrh. The same also, or the seed provokes urine, and expels the gravel and stone in the reins or bladder, often proved to be effectual in many that have taken it. The same kills the worms in children, eases pains in the sides, and dissolves the windiness in the spleen, as also in the body, although others think it only powerful to provoke venery. The juice of the leaves taken two or three days together, stays bleeding at the mouth. The seed being drank, is a remedy against the stinging of venomous creatures, the biting of mad dogs, the

poisonous qualities of Hemlock, Henbane, Nightshade, Mandrake, or other such like herbs that stupify or dull the senses; as also the lethargy, especially to use it outwardly, to rub the forehead or temples in the lethargy, and the places stung or bitten with beasts, with a little salt. The distilled water of the herb is also effectual (though not so powerful) for the diseases aforesaid; as for outward wounds and sores to wash them, and to cleanse the skin from morpew, leprosy, and other discolourings thereof. The seed or leaves bruised, and put into the nostrils, stays the bleeding of them, and takes away the flesh growing in them called polypus. The juice of the leaves, or the decoction of them, or of the root, is singularly good to wash either old, rotten, or stinking sores or fistulous, and gangrenes, and such as fretting, eating, or corroding scabs, manginess, and itch, in any part of the body, as also green wounds, by washing them therewith, or applying the green herb bruised thereunto, yea, although the flesh were separated from the bones; the same applied to our wearied members, refresh them, or to place those that have been out of joint, being first set up again, strengthens, dries, and comforts them, as also those places troubled with aches and gout, and the defluxion of humours upon the joints or sinews; it eases the pains, and dries or dissolves the defluxions. An ointment made of the juice, oil, and a little wax, is singularly good to rub cold and benumbed members. An handful of the leaves of green Nettles, and another of Wallwort, or Deanwort, bruised and applied simply themselves to the gout, sciatica, or joint aches in any part, hath been found to be an admirable help thereunto. (Nicholas Culpeper (1616–54) *The Complete Herbal*, 1850.)