SYMPTOMS AND PEAK EXPIRATORY FLOW RATE: RESPONSE TO A SLOW RELEASE THEOPHYLLINE PREPARATION

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SYNOPSIS

The development of sustained release preparations of theophylline hopes to overcome the problem of early morning exacerbations of symptoms and signs in certain asthmatic children by maintaining stable plasma theophylline levels without increase in dosage frequency. We investigated the efficacy of one such preparation, Euphylline retard mite, on 10 asthmatic children with early morning deterioration of symptoms and peak expiratory flow rates. Our results suggest that Euphylline produces significant improvement in the early morning symptoms and peak expiratory flow rates ($p < 0.05$, $p < 0.001$ respectively), and the mean difference between evening and morning peak expiratory flow rates is significantly smaller during Euphylline therapy ($p < 0.001$). Although plasma levels of theophylline remain fairly stable in between doses, the mean peak plasma level (8.1 μgm/ml) is lower than the usual therapeutic range. It is worth while therefore to subject Euphylline to a more detailed and better controlled study.

INTRODUCTION

The occurrence of diurnal variations of symptoms and airway resistance in certain asthmatic children (1,2) has caused considerable concern to the patients, parents and the clinicians. Most of the bronchodilator drugs have short half lives and therefore do not effectively control the exacerbation of symptoms in the early morning after a single dose before going to bed. The development of sustained-release preparations of theophylline attempts to overcome this problem of early morning deterioration of symptoms and airway resistance by maintaining stable theophylline levels within the therapeutic range without increase in the number of doses administered (3,4).

Our study aims to evaluate the effect of Euphylline retard mite, a slow-release theophylline preparation, in controlling symptoms and peak expiratory flow rate in a group of asthmatic children with early morning deterioration of symptoms and airway resistance.

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MATERIALS AND METHODS

10 children with moderately severe bronchial asthma were selected for study after informed consent from their parents. Their ages ranged from 5 years to 10½ years and there were 9 males and 1 female. Their history of bronchial asthma varied from 2 years to 7½ years and they were all on some form of prophylactic bronchodilator therapy for control of their asthmatic symptoms. Table 1 shows the type of medication each child was on before starting on the slow-release theophylline therapy. Though their symptoms were well controlled in the day they continued to experience nocturnal or early morning symptoms of cough, with or without breathlessness and wheezing. Each child was taught how to use the Mini Wright's Peak Flow Meter in the mother's presence. Each mother was required to score the child's daily symptoms of cough, breathlessness and wheezing on a printed form (Table 2) and record subjectively the degree of severity of each symptom as follows:-

None = 0 Moderately bad = 2
Little = 1 Severe = 3

The symptoms were scored three times each day i.e. in the night (during sleep), in the early morning (on waking up) or during the rest of the day. The peak expiratory flow rate (PEFR) for each child was also measured in the early morning (on waking up) and in the evening just before going to bed, using the Mini Wright's Peak Flow Meter. The child was required to make 3 measurements and the best of the 3 readings was recorded.

Each child was reassessed two weeks from the day the study started during which they continued with their usual bronchodilator therapy. During the period of study the subject should not develop any respiratory tract infection which would then exclude him from the study. During this period of study no patient experienced any severe asthmatic attack.

At the end of the 2 weeks of study each patient was given Euphylline retard mite, a slow-release preparation of theophylline in film-coated tablet form. Each tablet contained 140.9 mg of theophylline monohydrate and 75.5 mg ethylenediamine dihydrochloride. The dosages prescribed averaged 8 mg per kilogram body weight per dose and this was administered twice a day every 12 hourly for a period of 2 weeks. The patients also continued with their previous medication with the exception of drugs containing theophylline. The symptoms and PEFR were scored as before. At the end of the 2 weeks each child was reassessed in the Asthma Clinic. During this visit the trough blood level of theophylline was obtained before the child started on his morning dose of Euphylline retard mite, which was about 12 hours after the previous dose. Following this

TABLE 1

CLINICAL DATA OF ASTHMATIC CHILDREN

Patient	Sex*	Age(yrs)	Ethnic+ Group	Duration of Asthma	Treatment ≠
CCC	M	6	C	5 yrs 8 mths	Aminophylline supp. Choledyl tab. Ventolin tab. Prednisolone tab.
MBAJ	M	8	M	5 yrs	Ventolin tab.
IL	M	8½	I	7½ yrs	Ventolin tab. Choledyl tab.
SM	F	10½	I	3 mths	Choledyl tab.
LYM	M	9	C	6 yrs	Ventolin tab.
TCY	M	5	C	?	Ventolin tab. Choledyl tab.
LCS	M	7	C	3 yrs	Ventolin tab. Choledyl tab. Intal inhaler
DD	M	5	I	4 yrs	Choledyl tab. Ventolin tab.
YPY	M	6	C	2 yrs	Ventolin tab. Choledyl tab.
DVC	M	9	C	6 yrs	Ventolin Becotide } inhaler Intal inhaler Aminophylline supp.

* F = Female; M = Male
\+ C = Chinese; I = Indian; M = Malay
≠ Becotide® = Beclomethasone dipropionate, inhaler; Choledyl® = Oxytriphylline; Intal® = Disodium cromoglycate; Ventolin ® = Salbutamol sulphate

TABLE 2

SYMPTOM SCORES AND PEFR MEASUREMENTS

				1	2	3	4	5	6	7	8	9	10	11	12	13	14
	Year	Month	Date														
NIGHT (while sleeping)	Cough	None ..... 0 Little ..... 1 Moderately bad ..... 2 Severe 3															
	Breathless or Wheezing	None ..... 0 Little ..... 1 Moderately bad ..... 2 Severe 3															
EARLY MORNING (1 hr before and after waking)	Cough	None ..... 0 Little ..... 1 Moderately bad ..... 2 Severe 3															
	Breathless or Wheezing	None ..... 0 Little ..... 1 Moderately bad ..... 2 Severe 3															
DAYTIME	Cough	None ..... 0 Little ..... 1 Moderately bad ..... 2 Severe 3															
	Breathless or Wheezing	None ..... 0 Little ..... 1 Moderately bad ..... 2 Severe 3															
7. METER Best of 3 blows (Before Medication)		Early Morning															
		Evening															
8. DRUGS No. of doses actually taken during the past 24 hours		Name of Drugs	Dose Ordered														
9. Comments																	

he took his usual morning dose of Euphylline and 4 to 5 hours later the peak blood level of theophylline was obtained. Serum theophylline levels were analysed using the method of high pressure liquid chromatography (5). During the 2 weeks of Euphylline treatment the patient could return to the clinic should be develop severe asthmatic attacks or symptoms of fever, gastrointestinal or central nervous system disturbances which might be side effects resulting from hypersensitivity to Euphylline or an overdosage of theophylline.

RESULTS

During the period of study, none of the children developed severe asthmatic attacks or complained of symptoms related to hypersensitivity or overdosage of theophylline.

The clinical data of the children, including the bronchodilator treatment they were on are tabulated in Table 1.

Table 3 shows the mean clinical scores of the children with and without sustained release theophylline therapy. The mean morning score (20 ± 11), though not significantly different from the night scores (12 ± 10) during the period without theophylline, shows deterioration as compared to the night score. When the children were on Euphylline, the clinical scores show improvement compared to those without the therapy. The mean morning score (10 ± 9) is significantly different from that before Euphylline was instituted ($t = 2.1$, $p < 0.05$).

Table 4 shows the comparison of PEFR before and during Euphylline therapy. The mean morning and evening PEFR show significant difference between each other ($z = 4.8$, $p < 0.001$) before Euphylline as contrast to the difference observed during Euphylline therapy ($z = 1.29$, $p > 0.05$). Furthermore the difference in mean morning PEFR before and during Euphylline is statistically highly significant ($z = 5.28$, $p < 0.001$). Comparison of the differences between evening and morning PEFR (mean ± SD) (Table 5) shows that with Euphylline the difference (31 ± 31 L/min) is significantly smaller than that before Euphylline (45 ± 35 L/min),

Table 3

COMPARISON OF BIWEEKLY TOTAL CLINICAL SCORES (MEAN ± SD) OF 10 ASTHMATIC CHILDREN

	Clinical Scores		Significance of Difference
	Morning	Night	
Without Euphylline (n = 9)	20 ± 10	12 ± 9	t = 1.78 df = 16 $p > 0.05$
With Euphylline (n = 9)	10 ± 9	8 ± 7	t = 0.53 df = 16 $p > 0.05$
Significance of Difference	t = 2.10 df = 16 $p < 0.05$	t = 0.99 df = 16 $p > 0.05$	

TABLE 4

COMPARISON OF PEAK EXPIRATORY FLOW RATES (PEFR) (MEAN ± SD) OF 10 ASTHMATIC CHILDREN

	PEFR (L/min)		Significance of Difference
	Morning	Evening	
Without Euphylline	(n = 125) 183 ± 58	(n = 128) 218 ± 58	z = 4.80 $p < 0.001$
With Euphylline	(n = 126) 222 ± 59	(n = 130) 232 ± 65	z = 1.29 $p > 0.05$
Significance of Difference	z = 5.28 $p < 0.001$	z = 1.83 $p > 0.05$	

TABLE 5

COMPARISON OF DIFFERENCES BETWEEN EVENING AND MORNING PEAK EXPIRATORY FLOW RATES (PEFR) (MEAN + SD)

	PEFR (Evening-Morning) (L/min)
Without Euphylline (n = 124)	45 + 35
With Euphylline (n = 125)	31 + 31
Significance of Difference	z = 3.34 $p < 0.001$

$p < 0.001$.

Measurements of the peak and trough plasma levels of theophylline during the study show that there was no difference between the mean trough value (6.0 ± 2.6 μgm/ml) and the mean peak value (8.1 ± 3.7 μgm/ml), $p > 0.05$.

DISCUSSION

The occurrence of nocturnal symptoms in some asthmatic children has prompted the search for drugs that do not require increase frequency of administration but at the same time are able to alleviate the early morning symptoms after the last evening dose. The development of Euphylline retard mite for paediatric bronchial asthmatics is to hopefully achieve this purpose. It is a sustained-release preparation containing 140.9 mg of theophylline monohydrate, the active bronchodilator component, per tablet. Various sustained-released preparations of theophylline have been shown to be effective in relieving bronchospasm and in improving pulmonary function in adult asthmatics (2,6,7). Some also

achieve a stable plasma theophylline level during the interval between doses (1). Our study, though suffering from the setbacks of being an open trial, has shown encouraging results using Euphylline retard mite in several children with nocturnal or early morning symptoms of asthma. The significantly better early morning clinical score is further supported by a significant improvement in the early morning PEFR while on theophylline therapy. The fact that the mean difference between evening and morning PEFR before Euphylline is significantly larger than the difference observed while on Euphylline ($p < 0.001$) is further suggestive of the efficacy of this drug.

We have observed that although the dosages of Euphylline prescribed (8 mg/kg body weight/dose) tended to be higher than that recommended by the manufacturer (5 mg/kg body weight/dose), the peak plasma value remained lower than the usual therapeutic serum concentration of 10 to 20 μgm/ml (8,9). However, despite this fact, the study has shown promising results. Although there seems to be much individual variations in the release and absorption of theophylline (10), the trough and peak plasma levels of our patients have remained fairly stable.

In conclusion, our study has revealed encouraging results that Euphylline retard mite may be effective in ameliorating nocturnal and early morning symptoms of asthmatic children, even though the peak plasma level of theophylline does not seem to reach the accepted therapeutic range. In view of these, it therefore calls for a better controlled trial in order to determine exactly the efficacy and bioavailability of theophylline in this slow-release theophylline preparation.

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