Archives of Disease in Childhood, 1986, **61,** 1024–1026

Slow release theophylline in preschool asthmatics

S P CONWAY AND W T HOULSBY

University Department of Paediatrics and Child Health, The General Infirmary at Leeds

SUMMARY A double blind crossover trial with active or placebo slow release theophylline (Slo-phyllin) in children with asthma aged up to 4 years is described. Although no difference in symptom scores was shown, other differences in favour of active treatment were noted. We conclude that this preparation is of benefit in the management of the wheezing preschool child. The value of symptom scores as an index of clinical improvement is discussed.

Theophylline can be an effective drug for less severe chronic perennial asthma in older children[1 2] and is widely prescribed for the preschool child, especially when beta$_2$ sympathomimetics have failed to control symptoms. It is said to be easily administered. The bronchodilator effect is related to plasma concentration.[3] Interindividual variations in plasma concentration for a given dose and intraindividual variations in concentrations during a 24 hour period are well recognised in children.[4] There is, however, little information on its use or effectiveness in the preschool child.

Assessment of outpatient anti-asthmatic treatment in the young child is difficult. Respiratory function tests, if they can be used at all, are not reliably reproducible. Recourse is made to parental opinion, often formalised by the use of a diary card for symptom scores. The aims of this study were to assess whether twice daily slow release theophylline, prescribed as closely as possible to the manufacturer's recommendations, was effective in controlling asthmatic symptoms in the preschool child and to examine the value of the symptoms score in assessing clinical improvement.

Patients and methods

Children aged up to 4 years diagnosed as having asthma were enrolled into the study, after acute admission or outpatient referral, with a wheezing illness. In each case there was a history of recurrent wheezing or coughing episodes resolving either spontaneously or with treatment. No other cause for these symptoms was found. They were given Slo-phyllin (Lipha Pharmaceuticals Ltd) or placebo in a double blind crossover study for 24 weeks. Active and placebo periods alternated at six weekly intervals, the child being allocated to the initial active or placebo treatment at random. Throughout the study a beta$_2$ sympathomimetic was prescribed to be taken when necessary for symptoms of cough or wheeze. Additional treatment—for example, steroids—was at the discretion of the general practitioner or admitting hospital doctor.

Parents scored symptoms of cough, wheeze, daytime activity and night time symptoms daily on a 4 point ordinal scale where a maximum score of 3 was obtained for maximal symptoms. Use of additional medication and comments were also recorded. No run in period was used. The scores from the last five weeks of each six week period were studied, however, to avoid a carry over effect. The effectiveness of the treatment was judged by change in symptom scores, use of additional medication, number of hospital admissions for acute attacks of asthma, and parental preference.

Statistical analysis was by paired *t* test and Wilcoxon signed rank test for non-parametric data.

Results

Twenty nine children were entered into the study; six were lost to follow up, three refused to take the drug, and four were non-compliant as judged by negligible theophylline concentrations in the active treatment period. The records of the 16 remaining children were studied. Mean age at entry was 2·6 years (range 10 months to 4 years). Fourteen had a family history of atopy and nine had had eczema. Mean age at onset of symptoms was 1·1 years (range <1 to 36 months) and frequency of symptoms varied from several times weekly (eight) to weekly (three) or less than once weekly (five). Ten had had previous admissions to hospital for asthma.

Mean (SD) theophylline dose was 10·3 (2·0) mg/kg/dose (range 7·6–14·3 mg/kg/dose); mean

Table 1 *Comparison of symptom scores in active and placebo treatment periods in children up to 4 years of age with asthma*

Score	*Treatment*		*Mean difference*	*95% Confidence interval*	*p Value**
	Active (mean (SD))	*Placebo (mean (SD))*			
Total	57·8 (55·1)	55·3 (53·4)	−2·6	−24·6, 29·7	0·73
Daytime	42·8 (40·9)	41·4 (39·8)	−1·4	−18·8, 21·6	0·74
Night time	15·0 (15·1)	13·8 (14·9)	−1·2	−6·3, 8·7	0·75

*Wilcoxon signed rank test.

plasma concentration of theophylline measured three to five hours postdose was 9·1 (2·1) mg/l (range 6·4–13·2 mg/l). Side effects, consisting of mild gastrointestinal symptoms, were seen in two patients and settled on reduced dosage. Behavioural and sleep disturbances were not noted.

No difference in symptom scores was found between active and placebo treatment periods for either total daily scores or for separate scores for daytime and night time symptoms (Table 1). There were similar numbers of consultations of general practitioners, days when bronchodilators were used, and prescriptions issued for steroids or antibiotics during the active and placebo periods (Table 2).

One child was admitted to hospital during the active treatment period, but five children were admitted during the placebo period (four once and one twice).

Table 2 *Comparison between active and placebo treatment periods in children up to 4 years of age with asthma*

	Treatment	
	Active	*Placebo*
General practitioner consultations	10	14
Additional use of bronchodilators (patient days)	240	223
Courses of steroids prescribed	2	3
Courses of antibiotics prescribed by general practitioners	9	9
Admission to hospital with asthma	1	6
Parental opinion of period in which child was better controlled	8	0

Parental opinion sought before the randomisation code had been broken was that their child had been better controlled during the active treatment period in eight cases. In the remaining eight there was no preference. No parent thought that the placebo treatment was superior. When the symptom scores were classified according to parental preference, however, there was a significant improvement in scores in the active treatment period in those children whose parents preferred the active treatment and a significant deterioration in symptom scores in the active treatment period in those whose parents had no preference (Table 3).

There was a reduction in symptom scores between the first and second active or placebo treatment periods, which was independent of order of randomisation.

Discussion

We have shown no significant alteration in symptom scores in children of up to 4 years with asthma who received Slo-phyllin at a dose close to the maximum recommended by the manufacturers (it is our experience that children are usually prescribed considerably less than this by general practitioners).

It is probable, none the less, that the drug as currently recommended is of benefit in relieving asthmatic symptoms in children under 4 years of age. There were fewer admissions to hospital of children taking the active treatment; of the six children admitted because of mild attacks of asthma, five were taking placebo, one of whom was admitted

Table 3 *Comparison of symptom scores in active and placebo treatment periods with reference to parental preference. No parent preferred the placebo period*

Score	*Parents prefer active treatment*		*Parents have no preference*	
	Mean difference in symptom score	*p Value*	*Mean difference in symptom score*	*p Value*
Total	21·2	0·03	−26·3	0·02
Daytime	14·6	0·06	−17·4	0·02
Night time	6·6	0·01	−8·6	0·04

twice. While 50% of parents thought that their child was better when taking the active treatment, none thought that placebo was superior. These observations indicate a clinically important improvement with active treatment.

In those subjects whose parents thought their child was improved during the active treatment period there was a significant decrease in symptom scores during this period. The children recognised by their parents as benefiting from active treatment tended to be those with lower overall scores, suggesting that children with milder asthma benefited most from this form of treatment, as has been suggested previously.[5]

Although the blood concentrations of theophylline achieved were within the range thought to be effective,[3] others have recommended that concentrations of 10–20 mg/l should be maintained.[2] It is possible that larger or more frequent doses than are currently recommended by the manufacturers would be more effective for the preschool child, who is known to eliminate the drug more rapidly, but close monitoring of blood concentrations would be necessary.

Although Slo-phyllin is said to be easy to give, the beaded capsule contents being simply disguised in food, seven out of 23 (30%) of the children in this study did not or would not take the prescribed drug. Others have reported similar problems.[5] The observed trend towards an improvement in symptoms with time indicates that any child on regular prophylaxis should have regular critical review of the need for such treatment.

This study has highlighted some of the problems of using the symptom score as an index of severity of asthma. Parentally derived symptom scores have a wide numerical range, because of the wide variation in observers. The power of this study to detect a fairly small change in score—for example, 15%—is low. A study population of 800 would have been needed to show a change of this size with 80% power at $p=0{\cdot}05$. Although a distinct preference for the active treatment was shown by parents, and this was borne out by a significant improvement in symptom scores in the group whose parents preferred the active treatment, there was an equally significant change in symptom scores in the opposite direction in the group whose parents showed no preference—yet they should, all other factors being equal, have preferred the period of treatment with placebo. By asking parents to complete a diary for symptom scoring they are probably made to concentrate on some of the important symptoms, but parental preference is probably determined by additional unidentified factors that must have a stronger influence.

It therefore remains possible that benefit from active treatment in other children was not recognised because of deficiencies in the symptom score as a tool in clinical assessment. There are several other reasons why this may be so. Decisions as to the efficacy of treatment rely on impressions of dyspnoea and severity of wheeze. Even the older sufferer may not perceive important airways obstruction, and there is no means of identifying the poor perceiver except by objective tests of lung function.[6] Paediatric practice is further hindered by the perceiver being at one remove from the sufferer. Intrinsic to the symptom score is a total reliance on subjective parental responses. While many parents may be sensitive to the level of their child's respiratory difficulty, others are known both to underestimate its severity, with possibly the eventual production of permanent chest deformity, and to over react to mild attacks when objective assessment shows little or no evidence of lower airways obstruction.[7]

The optimum method of assessment of preschool children with asthma has yet to be established.

We thank Lipha Pharmaceuticals Ltd for generous financial support.

References

1 Hambleton G, Weinberger M, Taylor J, *et al.* Comparison of cromoglycate and theophylline in controlling symptoms of chronic asthma. *Lancet* 1977;i:381–5.

2 Weinberger MM, Bronsky EA. Evaluation of oral bronchodilator therapy in asthmatic children. *J Pediatr* 1974;**84:**421–7.

3 Rachelefsky GS, Katz RM, Siegel SC. A sustained release theophylline preparation: efficacy in childhood asthma with low serum theophylline. *Ann Allergy* 1978;**40:**252–7.

4 McKenzie S, Baillie E. Serum theophylline levels in asthmatic children after oral administration of two slow-release theophylline preparations. *Arch Dis Child* 1978;**53:**943–6.

5 Wilson N, Silverman M. Controlled trial of slow release aminophylline in childhood asthma: are short term trials valid? *Br Med J* 1982;**284:**863–6.

6 Rubinfeld AR, Pain MCF. Perception of asthma. *Lancet* 1976;i:882–4.

7 McNicol KN, Williams HB. Spectrum of asthma in children. I Clinical and physiological components. *Br Med J* 1973;**iv:**7–11.

Correspondence to Dr S P Conway, University Department of Paediatrics and Child Health, The General Infirmary at Leeds, Clarendon Wing, Leeds LS2 9NS, England.

Received 9 June 1986