Sustained release theophylline in nocturnal asthma

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SUMMARY Twice daily sustained release theophylline gave satisfactory steady serum theophylline concentrations in asthmatic children aged 7 to 14 years. The children showed improvement in symptoms, less frequent waking at night, reduced use of beta agonist inhalers, and improved early morning peak flows while being treated with this preparation. There was no improvement in peak flow at other times, but the patients recorded increased use of beta agonists during the placebo period.

Asthmatic symptoms in children are often particularly troublesome at night and after exercise. The alleviation of these symptoms has been hampered by the short duration of action of most available preparations, both in aerosol and oral form. This has prevented satisfactory control during the long interval between doses during the night, which may be longer in children than adults. Similarly, with these preparations plasma drug concentrations vary during the day which may result in inadequate control of symptoms, particularly after exercise.

Sustained action theophylline preparations give more stable plasma concentrations throughout the day and the night, and so can be used to control these symptoms.^{1,2} In addition, the twice daily dosage regimen is convenient and aids compliance.

Methods

Trial design. The study was a double blind crossover trial with slow release theophylline and an indistinguishable placebo preparation given in a random order, each for a two week period. There was a run up period of one week during which a standard dose of theophylline 14 to 19 mg/kg/day (Nuelin SA) was taken in a divided dose as a combination of 175 mg and 250 mg tablets with breakfast and with a bed time snack. The active and placebo tablets were individually packed by Riker Laboratories and dispensed by the pharmacy according to a code which selected whether the active drug was taken in the first or second period of the study.

On the fourth day of the run up period a serum theophylline concentration was measured five hours after the morning dose. If this was in the range of 10 to 15 mg/l it was accepted. If the concentration was less than 10 mg/l the dose was increased approp-

riately, providing it was tolerated. Serum concentrations were measured in duplicate using an EMIT enzyme immunoassay (Syva Ltd) on an EMIT 5000 laboratory system.³

The patients continued taking disodium cromoglycate or beclomethasone by inhalation if they were already established on these drugs. Each patient was allowed to use a beta agonist inhaler as required.

Patient selection. Children aged 7 to 14 years of age who were able to use the peak flow meter, to swallow the tablets, and to keep a diary of symptoms, peak flows, and beta agonist usage were selected provided that they suffered from nocturnal symptoms sufficient to wake them at least twice each week or frequently showed morning dips in peak flow. These patients also complained of exercise induced bronchospasm. Consent was obtained from the parents and children.

Patient evaluation. The children kept a daily symptom diary recording wheeze, tightness, and cough which they graded as none, mild, moderate, or severe. They also recorded peak flow using a mini Wright Peak Flow Gauge on arising, on returning home from school, at bed time, and during any episodes when they awoke at night. They recorded each time they used their beta agonist inhaler, and made notes of any suspected side effects and of any unusual events that occurred each day.

Blood was taken by venepuncture or autolet, as preferred by the patient, on the last day of each two week period in the patient's home before the morning dose and again five hours after the morning dose.

Results

Thirteen children entered the trial and 10 (cases 3 to 12) completed it fully. The first two failed to keep adequate daily record diaries during the first fortnight. The remaining children were given a diary to keep in the run up period while their individual dose of theophylline was being calculated. The thirteenth child was withdrawn when he was admitted to hospital during an acute asthmatic attack. This occurred 36 hours after starting the placebo fortnight, after he had been well during the previous fortnight on the active medication.

Serum theophylline concentrations. The mean daily dose of theophylline was 17.3 mg/kg. This produced a theophylline concentration before dosage of mean (SD) 9.86 (2.75) mg/l (Table 1). Two patients (cases 5 and 10) had low theophylline concentrations on day 4 of the run up period but they experienced symptoms of nausea and tremor on the next higher

dose and so were kept on the lower dose. Two patients (cases 8 and 9) had a greater concentration before the morning dose than afterwards. Presumably this reflected either more rapid metabolism of the drug during the day or slower absorption of the sustained release drug at night, with a peak occurring near 12 hours.⁴

Apart from the two patients (cases 5 and 10) who complained of nausea and tremor on the next higher dose, no other patient complained of any side effects while taking either the active or placebo preparation.

Subjective assessment at home. The first four days of each fortnight were discounted to allow a 'wash out' period. For the remaining 10 days the symptoms of wheeze, cough, and tightness were allocated 0, 1, 2, or 3 points for each day, corresponding to no, mild, moderate, or severe symptoms, to give an overall symptom score for each patient (Table 2). The mean symptom score during the active treatment 10 days

Table 1 Serum theophylline concentrations

Case No	Sex	Age (yrs)	Weight (kg)	Total dose (mg/day)	Dose (mg/ml)	Serum theophylline concentrations (mg/l)		Variation
						On arising*	Midday†	
1	M	10	30.0	500	16.7	8.4	9.6	1.2
2	F	13	60.0	850	14.2	10.0	16.0	6.0
3	F	11	39.5	600	15.2	9.2	10.0	0.8
4	F	7	21.5	350	16.3	9.2	12.3	3.1
5	M	11	39.5	600	15.2	5.6	8.4	2.8
6	F	12	38.0	600	15.8	12.3	13.4	1.1
7	F	10	21.6	500	23.6	10.9	11.9	1.0
8	M	11	27.0	500	18.5	12.0	8.8	3.2
9	M	12	28.5	600	21.1	14.5	12.2	2.3
10	M	14	30.0	500	16.7	5.5	7.5	2.0
11	F	10	30.0	500	16.7	11.0	19.4	8.4
12	M	12	39.5	700	17.7	9.7	9.9	0.2
Mean (SD)		11	33.76	566.7	17.3	9.86 (2.75)	11.67 (3.59)	2.67

*Trough concentration: Blood taken in morning 12 hours after evening dose and on arising immediately before morning dose.

†Peak concentration: Blood taken at 5 hours after morning dose.

Conversion—traditional units to SI: theophylline 1 mg/l≈5.6 μmol/l.

Table 2 Analysis of patient diaries of last 10 days of each 2 week period

Case No	Sex	Age (yrs)	Symptom score		Frequency of occasions when awake at night		No of doses of beta agonist		Peak flow (l/min) on arising		Peak flow (l/min) after school		Peak flow (l/min) at bedtime	
			Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo
3	F	11	9	9	0	0	16	31	310	270	290	280	310	280
4	F	7	25	47	0	1	2	12	180	170	180	180	170	180
5	M	11	28	28	9	12	17	93	160	110	220	190	190	170
6	F	12	13	13	0	0	32	33	310	280	290	300	300	290
7	F	10	14	35	1	4	9	23	270	180	240	220	240	230
8	M	11	13	40	0	2	10	24	230	210	220	210	210	210
9	M	12	2	17	1	5	30	26	300	315	310	330	320	340
10	M	14	40	46	0	1	2	9	230	180	240	300	220	290
11	F	10	5	27	2	7	10	25	290	170	300	140	250	150
12	M	12	5	34	0	0	1	8	320	300	380	320	350	300
Mean		11	15.4	29.6	1.3	3.2	12.9	28.4	260	218	267	247	328	316

was 15.4 compared with 29.6 during the placebo 10 days. This was significant on a paired *t* test ($P < 0.01$).

During the 10 days active treatment period the mean number of times the patient was awoken at night, recorded a peak flow, and used a beta agonist was 1.3 compared with 3.2 during the placebo 10 days. This was significant on a paired *t* test ($P < 0.01$).

Objective assessment at home. During the active 10 day treatment period the mean number of beta agonist doses per day was 1.29 compared with 2.84 in the placebo 10 days giving a paired *t* test value of 2.21 ($P < 0.1$). Mean peak flows for morning, afternoon, and bed time are shown in Table 2. There was no significant difference between the active and placebo treatment periods in the afternoon and evening mean peak flows. There was a difference, however, in the early morning peak flow on a paired *t* test ($P < 0.01$).

Discussion

This study showed that sustained action theophylline reduced symptoms of cough, wheeze, and tightness in a group of children suffering from perennial asthma. The number of occasions on which the children awoke at night and required relief from a beta agonist fell significantly. There was a trend to reduction in the usage of a beta agonist inhaler while taking theophylline. There was a significant improvement in morning peak flow while on the active treatment.

A similar significant fall in symptom scores on theophylline treatment was found by Wilson and Silverman.⁵ They did not find that the use of beta agonist inhalers fell during theophylline treatment.

Sustained action oral theophylline clearly has much to offer asthmatic children by reducing their symptoms through maintaining adequate blood concentrations throughout the day and night on a simple and memorable twice daily drug regimen. The mean dose required was 17.3 mg/kg. This is less than that used by Wilson and Silverman,⁵ thus no

patient had serum concentrations greater than 20 mg/l. The mean serum concentration before dosage was 9.86 mg/l. In only two patients did this concentration fall below 8 mg/l, and neither of these patients could tolerate an increased dose. Both these patients, however, still had greater peak flows on arising when taking theophylline, and reduced their use of beta agonists during the period on active treatment. The mean variation before and after dosage was only 2.67 mg/l, showing fairly even plasma concentrations during the 24 hour period. One patient, however, (case 11) showed a 76% rise in the concentration after dosage compared with the value beforehand. Variable individual pharmacokinetics were observed by Ellis *et al*⁶ and partly for this reason a more restricted normal range of 10 to 15 mg/l for serum theophylline concentrations is advocated when treating children as outpatients rather than the conventionally accepted range of 10 to 20 mg/l.³ Furthermore, this study showed good clinical response to the lower range. This should reduce the chance of toxic concentrations occurring when single drug concentrations are used in dosage guidance.

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