PLASMA THEOPHYLLINE CONCENTRATIONS IN ASTHMATIC CHILDREN RECEIVING A TWICE DAILY THEOPHYLLINE PREPARATION

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SYNOPSIS

A slow-release theophylline (SRT) preparation given to 20 asthmatic children at a mean dose of 6.6 mg/kg/12 hourly resulted in sustained mean plasma theophylline concentration in the range of 5.2-8.3 μg/ml in the children. Increment in dosage is necessary to achieve therapeutic concentration between 10-20 μg/ml. There is wide interpatient variation in the plasma theophylline concentration such that individualisation of dosage is needed for optimal treatment of childhood asthma with SRT. The manufacturer's recommended dose of 5-8 mg/kg/12 hourly is a safe initial dose but needs to be increased if no symptomatic improvement occurs.

INTRODUCTION

Recent years have seen renewed interest in theophylline being used in the prophylactic management of children with chronic asthma. This has come about due to the development of sustained-released theophylline (SRT) preparation which allows a 12 hoursly dosing interval instead of the usual 6 with ordinary theophylline. (1) With SRT, compliance, particularly in children, is encouraged. Some of the slow-release formulations have been shown to reliably maintain sustained serum theophylline concentrations in the range of 10-20 g/ml necessary for reducing asthmatic symptoms

without causing significant side effects. (1, 2, 3) To achieve this therapeutic range, the dose for a 12 hourly SRT preparation for children is about 10 mg/kg/dose. Because of its narrow therapeutic index, it is essential to check plasma theophylline concentration after commencement of the drug to ensure that they are in the accepted therapeutic range.

In developing countries, facilities for measurement of plasma theeophylline concentrations are often not available. Moreover, in the out-patient situation, such measurements are inconvenient and often impractical. The practice, therefore, is either to avoid using SRT altogether for fear of toxicity or to use SRT in dosages based on the manufacturer's recommendation.

The purpose of this present study is to determine whether one SRT preparation (Theodur, Astra, Sweden) given at the manufacturer's recommended dose of 5-8 mg/kg/dose will result in adequate plasma concentration in Singapore children.

PATIENTS AND METHODS

Twenty children with asthma attending the Chest Clinic of the University Department of Paediatrics, Singapore General Hospital, were studied. There were 18 boys and 2 girls, with ages ranging from 5 to 15 years (mean 9.7 years). Sixteen of them were Chinese, 3 Indians and 1 Malay. All children were on regular salbutamol, the majority by inhalation and 5 required steroids as well. They were prescribed SRT in addition to their regular medication because nocturnal cough and/or wheeze persisted. The purpose of the study was explained to the child and a parent.

Theodur is marketed in Singapore as 200 mg and 300 mg tablets. Each is scored and can be halved so as to allow better dosage titration. Each child was given a dose as close to 5-8 mg/kg/12 hourly as the strength of the tablet, whole or halved, would allow. This dose was then taken twice daily at 8 am and 8 pm for at least 4 days prior to the study. Each child reported to and was lodged in the hospital before 8 am in the morning of the study. An indwelling heparinised cannula or "butterfly needle" was inserted into a hand or forearm vein. The 8 am dose of Theodur was served. Blood for plasma theophylline measurement was taken just before the 8 am dose and thereafter at 3 hour intervals for the next 12 hours.

The plasma theophylline concentrations were measured in duplicates using EMIT (R) enzyme immunoassay (Syva Ltd). The Quality Control programme of the American Association for Clinical Chemistry was used.

RESULTS

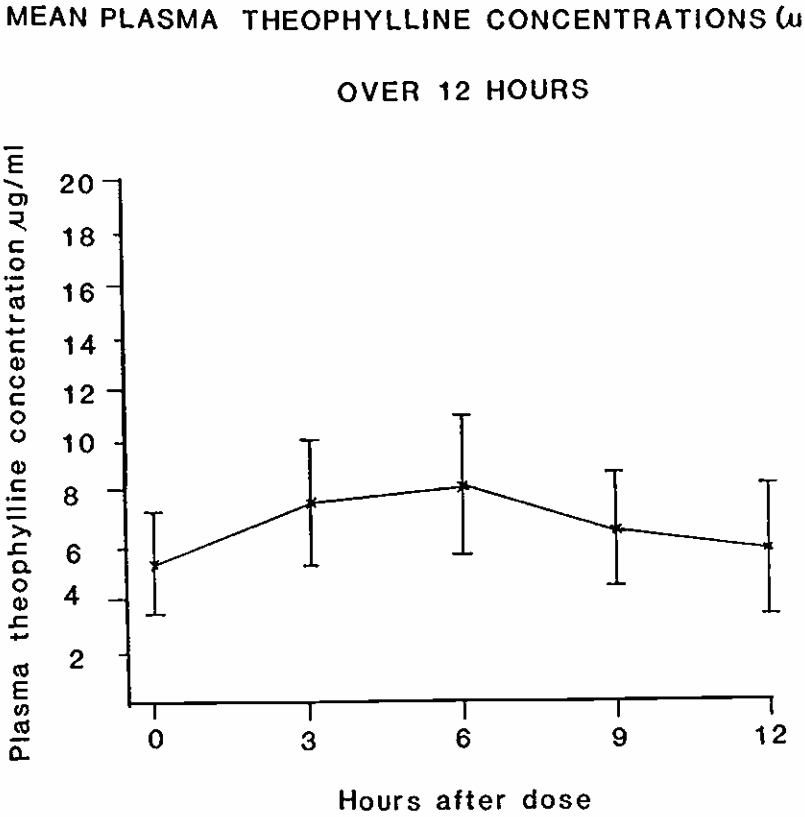
Table 1 lists the Theodur dose for each patient and the plasma theophylline concentrations obtained during the 12 hour period. The mean theophylline dose prescribed was 6.6 ± 1.1 mg/kg/12 hourly. This dosage resulted in a mean 6-hour post-dose plasma theophylline concentration of 8.3 ± 2.6 μg/ml. No patient had peak concentrations exceeding 15 μg/ml. Figure 1 shows the mean plasma theophylline concentrations for all the patients.

TABLE I
PLASMA THEOPHYLLINE CONCENTRATIONS (μg/ml) OVER A 12-HOUR PERIOD

Patient No.	Sex	Age (Yrs)	Dosage (mg/kg)	Hours after dosage					Diff. bet. peak-trough concentration	% Fluctuation*
				0	3	6	9	12		
1	M	8	7.0	3.7	10.8	8.8	6.8	ND+	6.8	183
2	M	7	8.7	3.7	10.8	10.6	8.0	6.6	5.1	89
3	M	5	7.9	5.7	6.6	3.9	1.5	1.0	5.6	560
4	M	8	6.7	4.5	5.7	7.5	3.2	2.1	5.4	257
5	M	10	6.9	7.3	4.9	8.8	5.6	3.1	5.7	183
6	M	10	4.8	5.1	6.0	7.1	9.1	7.0	4.0	78
7	M	15	5.1	4.5	4.4	7.8	6.8	4.8	3.4	73
8	M	7	5.4	2.4	6.5	6.0	4.6	4.0	4.1	170
9	M	9	8.7	4.9	9.4	6.7	5.8	5.8	4.5	92
10	M	12	6.8	6.2	7.7	5.6	6.3	8.7	1.5	55
11	M	9	6.3	4.3	5.7	6.7	4.7	2.1	4.6	219
12	M	12	4.6	6.8	10.5	11.7	8.2	5.8	5.9	102
13	M	10	5.7	8.8	10.2	10.5	9.6	9.4	1.7	19
14	M	12	7.1	6.9	8.8	14.8	10.3	6.9	7.9	114
15	F	11	6.5	5.0	9.0	10.4	8.8	6.5	5.4	108
16	M	10	7.1	5.6	5.0	5.3	5.0	5.2	0.6	12
17	M	12	6.6	4.7	10.2	10.2	8.0	5.8	5.5	117
18	M	11	6.6	0.7	2.5	4.8	5.4	7.5	6.8	971
19	M	10	7.7	8.2	6.4	10.0	7.3	10.3	3.7	61
20	F	6	6.5	3.1	5.9	9.4	5.4	2.7	6.7	248
Mean		9.7	6.6	5.2	7.3	8.3	6.5	5.5	4.7	185.6
SD		2.4	1.1	1.9	2.4	2.6	2.2	2.5	1.9	220.4
n		20	20	20	20	20	20	19	20	20

* % fluctuation is calculated from $\frac{\text{peak-trough plasma concentration}}{\text{trough plasma concentration}} \times 100$

+ ND = Not Done



The mean difference between peak and trough plasma theophylline concentration (ΔtL) is 4.7 ± 1.9 µg/ml. But the mean percent fluctuation

$$\left[\frac{\text{peak} - \text{trough plasma concentration}}{\text{trough plasma concentration}} \times 100\right] \text{in}$$

plasma concentration was 185.6%.

Four children reported sleep difficulties while 2 reported gastric irritation when first commenced on Theodur. These 2 side effects, however, were mild and tolerable. The study was not designed to assess the efficacy of Theodur in relief of symptoms and thus no objective assessments in improvement of symptoms were made. But 12 children reported symptomatic improvement soon after commencement of the SRT.

DISCUSSION

This study shows that plasma theophylline concentration in the therapeutic range of 10-20 µg/ml were generally not achieved in Singapore children when given Theodur at the dose of 5-8 mg/kg/12 hourly. Only 8 of the 20 children achieved a peak concentration of 10 µg/ml and above and in 5 of them, the therapeutic concentration was sustained for at least 3 hours. The adjustment of the dosage to 10 mg/kg/12 hourly in the majority of the patients would probably result in the trough concentration above 10 µg/ml without resulting in peak concentration above 20 µg/ml.

The mean difference between peak and trough plasma theophylline concentration of 4.7 µg/ml in this study is apparently consistent with other studies which reported a value of 4.5 µg/ml and 5.2 µg/ml. (3, 4) However, the percent fluctuation of concentration is the more accurate method of comparing peak-trough concentration. (4) When this is looked at, the mean percent fluctuation of Theodur in this study is 183.1%, much higher than figures of 65.8% and 38% quoted in other studies. (4, 5) There may be several reasons for this. Steady state plasma theophylline concentrations may not have been achieved in some of the children even though the study was undertaken at least 4 days after commencement of Theodur. Secondly, compliance is suspected in one child (patient 18) who registered a predose level of 0.7 µg/ml. It is probable that he forgot to take his 8 pm dose the night before. There is also the wide interpatient variability in absorption and clearance of theophylline. For example, at the same dosage of 7.1 mg/kg, patient 14 exhibited 114.4% fluctuation in theophylline concentration while patient 16 exhibited 12% fluctuation.

There is evidence to suggest that therapeutic responses are achieved when plasma theophylline concentrations are above 5 µg/ml. (6, 7) In one study, satisfactory control was achieved in children with concentrations lower than 10 µg/ml. (8) While it is true that some bronchodilator effect occurs at lower plasma concentration of theophylline, other studies suggest that control of asthma and stabilisation of the hyperactive airways in asthma are most pronounced at levels above 10 µg/ml. (2, 9) In situations where measurement of plasma theophylline concentration is not possible or impractical, the following scheme for commencement of SRT in asthmatic children may be adopted. Theodur is given at an initial dose of 5-8 mg/kg/12 hourly. This dose will result in a sustained plasma theophylline concentration above 5 µg/ml for at least 9 hours in more than half the children (Table 1). If symptomatic improvement occurs, the dose is continued. If not, stepwise increment at intervals of 3-4 days up to 10 mg/kg/12 hourly can be made, providing the increased dose is tolerated.

By starting SRT at low doses, transient side effects of insomnia and nausea may be minimised or avoided. The dose should not exceed 10 mg/kg/12 hourly without estimation of the peak serum concentration which occurs from 3-6 hours post dose (Fig. 1). Following the evening dose of Theodur, the peak concentration will occur at a time when night symptoms are likely.

Theodur may then be useful in the management of children with nocturnal asthma.

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REFERENCES

1. Weinberger M, Hendeles L: Slow-release theophylline: Rationale and basis for product selection. N Engl J Med 1983; 308: 760-4.
2. Weinberger M, Bronsky: Evaluation of oral bronchodilator therapy in asthmatic children. J Pediatr 1974; 84: 421-7.
3. Kelly HW, Murphy S: Efficacy of a 12 hour sustained release preparation in maintaining therapeutic serum theophylline levels in asthmatic children. Pediatr 1980; 97-102.
4. Menendez R, Kelly HW, Howick J, et al: Sustained-release Theophylline: Pharmacokinetic and therapeutic comparison of 2 preparation. Am J Dis Child 1983; 137: 469-73.
5. Weinberger M, Hendeles L, Weng L, et al: Relationship of formulation and dosing interval to serum theophylline concentration in children with chronic asthma. J Pediatr 1981; 99: 145-52.
6. Mitenko PA, Ogilvie RI: Rational intravenous doses of theophylline. N Engl J Med 1973; 86: 789-93.
7. Levy G, Kaysooko R: Pharmacokinetic analysis of the effect of theophylline on pulmonary function in asthmatic children. J Pediatr 1975; 86: 789-93.
8. Rachelefsky GS, Katz RM, Siegel SC: A sustained release theophylline preparation: Efficiency in childhood asthma with lower serum theophylline. Ann Allergy 1978; 40: 252-7.
9. Pollock J, Kelchel F, Casper D, Weinberger M: Relationship of serum theophylline concentration to inhibition of exercise-induced bronchospasm and comparison with Cromolyn. Pediatr 1977; 60: 840-4.