Short reports

Effect of practical timing of dosage on theophylline blood levels in asthmatic children treated with choline theophyllinate

The bronchodilator effect of theophylline has been known for over 50 years, but although it has been widely used both intravenously and rectally in the treatment of acute asthma, its use as an oral bronchodilator has been limited by inadequate knowledge of the correct dosage of the oral preparations. The therapeutic level of theophylline is generally considered to be between 10 and 20 µg/ml (Turner-Warwick, 1957; Jenne *et al.*, 1972), although sub-optimal bronchodilation can be achieved with levels of 5 µg/ml or less (Maselli *et al.*, 1970; Nicholson and Chick, 1973). Serious toxicity with levels of less than 20 µg/ml has not been reported, but when this level is exceeded, nausea and vomiting become increasingly common (Jenne *et al.*, 1972; Jacobs *et al.*, 1974; Zwillich *et al.*, 1975). Convulsions usually occur at high levels but may not be preceded by other symptoms.

Pharmacokinetic studies have shown that the mean biological half-life of theophylline is 3.7 hours (Ellis *et al.*, 1976), and so on this basis a 6-hour dose regimen seems reasonable. This, however, is not at all suitable for the treatment of children outside hospital because of its inconvenience.

The purpose of this study was to try and establish a suitable regimen for the treatment of asthmatic children at home using choline theophyllinate, a compound containing 64% theophylline, which is available in both liquid and tablet form and hence very suitable for children.

Patients

Twenty children were studied. All were moderately severe asthmatics with perennial symptoms who were considered to need continuous long-term treatment. All were studied as hospital inpatients. They were divided arbitrarily into two groups. The mean age of the 9 children in group A was 6.9 years (range 1.4-14.5 years), and of the 11 in group B was 6.7 years (range 3.4-10.3 years).

Methods

For the period of the study, the children did not receive tea, which contains theophylline.

Group A. These children were given choline theophyllinate in a dosage of as near as possible 8 mg/kg per dose qds (mean 7.9 mg/kg, range 7.2-8.7 mg/kg), starting with half the dose on the first day to try and minimise nausea. The doses were given at 0800 h, 1300 h, 1700 h, and 2100 h, times considered suitable for administration outside hospital. On the third day of the study serum levels were measured 2 hours after each dose and before the 0800 h dose the following morning.

Group B. These children were given choline theophyllinate in a dosage of as near as possible 10 mg/kg per dose tds (mean 9.7 mg/kg, range 8.6 mg/kg-10.7 mg/kg), starting on the first day with half the dosage. In this group the times of administration were 0800 h, 1600 h, and 2100 h. On the third day serum levels were measured 2 hours after each dose, immediately before the 1600 h dose and before the 0800 h dose the following morning.

Method of theophylline measurement

The theophylline was measured by high-pressure liquid chromatography on a minimum of 25 µl of serum or plasma obtained by finger-prick or from an indwelling intravenous needle. Theobromine and caffeine do not interfere with the measurement (cf. the method of Schack and Waxler, 1949) and so chocolate, coffee, and cola were not restricted for the period of the study. Sulphamethoxazole, however, in high quantities does interfere with the measurement. A result can be obtained within 15 minutes.

Results

Three children had to be withdrawn from the study: one from group A, who was vomiting on the first day, and one from group B who was vomiting on the second day. Neither child had serum levels above 10 µg/ml at the time of vomiting. A third child was withdrawn because he was concomitantly taking

trimethoprim-sulphamethoxazole and this interfered with the method of measurement.

Group A. The results for group A are shown in Table 1. The mean 2-hour postdose levels all fall

Table 1 *Theophylline levels of group A patients ($\mu\text{g/ml}$ serum)*

Case no.	Times of estimation (h)				
	Before 0800	1000	1500	1900	2300
1	13	20	19	18	19
2	7	13	14	20	19
3	4	8	9	9	10
4	6	15	13	17	16
5	5	10	14	15	16
6	7	13	13	10	15
7	6	12	18	19	17
8	2	9	12	14	12

within the therapeutic range and no level exceeded 20 $\mu\text{g/ml}$. The mean pre-0800 h level was 6 $\mu\text{g/ml}$ (range 2–13 $\mu\text{g/ml}$). The difference between the maximum and minimum peak levels for each child ranged between 2 and 7 $\mu\text{g/ml}$.

Group B. The results for group B are shown in Table 2. All 2-hour postdose levels are within the

Table 2 *Theophylline levels of group B patients ($\mu\text{g/ml}$ serum)*

Case no.	Times of estimation (h)				
	Before 0800	1000	1600	1800	2300
1	2	10	3	9	12
2	7	14	9	15	16
3	4	10	5	13	16
4	5	17	4	19	19
5	7	14	9	15	14
6	5	14	7	17	19
7	8	15	6	12	13
8	6	13	6	10	12
9	3	10	6	9	10

therapeutic range. The mean pre-0800 h level was 5 $\mu\text{g/ml}$ (range 2–8 $\mu\text{g/ml}$). The mean pre-1600 h level was 6 $\mu\text{g/ml}$ (range 3–9 $\mu\text{g/ml}$). The difference between the maximum and minimum peak levels for each child range between 1 and 6 $\mu\text{g/ml}$.

Discussion

This study has shown that choline theophyllinate in a dose of either 8 mg/kg per dose daily or 10 mg/kg per dose tds will produce 2-hour postdose levels within the therapeutic range. However, in both cases

the pre-0800 h level was outside the therapeutic range for most children, as was the pre-1600 h level in the tds regimen. It remains to be seen whether this is important.

No child in either study had levels $>20 \mu\text{g/ml}$ or any evidence of serious toxicity, but 2 children did vomit with blood levels $<10 \mu\text{g/ml}$ and had to be withdrawn from the study. We have also confirmed the intrasubject variability of theophylline levels in response to similar doses and emphasise the desirability of measurement of blood levels.

Summary

Two dosage schedules, 8 mg/kg per dose daily and 10 mg/kg per dose tds of choline theophyllinate were evaluated in asthmatic children. The times of the doses were considered the most practical for use outside hospital. Theophylline levels were measured 2 hours after each dose and were satisfactory in both schedules. The levels before the first dose of the day were, however, unsatisfactory. We emphasise the desirability of measuring blood levels in any patient receiving a theophylline compound.

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