PLASMA THEOPHYLLINE LEVELS IN ASTHMATIC CHILDREN IN SINGAPORE A PRELIMINARY STUDY

H S Lee
T E Ngiam

SYNOPSIS

The peak plasma theophylline level in 15 paediatric asthmatic children (2-11 years old), given the usual standard dosage schedule of choline theophyllinate i.e., 14.1 (SEM = 0.91) mg theophylline/kg/day, was found to be 6.8 (SEM = 0.96) μg/ml. Only 2 out of the 15 patients achieved peak level within the therapeutic range of 10-20 μg/ml. The mean steady state level expected from 1 mg/kg/day for the patients was 0.51 (SEM = 0.07) μg/ml. The t½ of theophylline after I.V. infusion of aminophylline in 3 other patients was found to vary from 3-5 hours.

Since both the t½ of the theophylline and the steady state level expected from 1 mg/kg/day in our Asian population have been found to be similar to those that have been reported in Caucasians. We attributed the ineffectiveness of choline theophyllinate in our patients to the subtherapeutic level of theophylline caused by insufficient dosage of the drug.

INTRODUCTION

Theophylline at plasma concentration of 10-20 μg/ml has been reported to be effective and safe in controlling the symptoms of chronic asthma (1). Without the parallel guidance from plasma theophylline measurements it is very difficult to adjust the dosages so as to achieve the therapeutic levels in the patients. Interpatient variation in plasma level into the subtherapeutic or toxic range can be attributed to the alteration in metabolism and elimination of theophylline in different individuals. Ellis, Koysooko and Levy (2) has established that elimination of theophylline in children is more rapid than in adults. When elimination of theophylline is rapid, fluctuations between the peak and trough levels will be pronounced especially with plain uncoated tablets, as reported by Ginchansky and Weinberger (3).

Department of Pharmacology
Faculty of Medicine
National University of Singapore
Kent Ridge
Singapore 0511

H S Lee, Ph D

Department of Paediatrics
Medical Faculty
National University of Singapore

T E Ngiam, MBBS, M Med (Paed)

In Singapore, children with chronic asthma attending the Paediatrics Department of the National University of Singapore in the Singapore General Hospital are usually given oral choline theophyllinate at standard dosage schedules; namely 100 mg 8 hourly for the smaller children, 200 mg 8 hourly for the bigger children; and some were given 100 mg, 100 mg and 200 mg for the night dose. With these schedules, the drug choline theophyllinate was found to be not too effective. It was difficult for the pediatricians then to increase the dosage for the patients without the help of plasma theophylline measurements since toxic levels of theophylline can produce seizures with unconsciousness that can be lethal. Now, with therapeutic drug monitoring being available, paediatricians can individualize dosages for their patients effectively.

It is our intention in this preliminary study to report the peak plasma theophylline concentration measured in our asthmatic patients given oral choline theophyllinate with the standard dosage schedules during the initiation stage of plasma theophylline monitoring. We also determined the half-life of theophylline in a few other patients given intravenous infusion of aminophylline.

METHODS

Fifteen patients who have been on long-term choline theophyllinate (Jed Chemie) were included in this study. 66% of them were Chinese and 33% non-Chinese Asians. Their ages ranged from 2 to 11 years old. They received the various standard dosage schedules namely 100 mg 8 hourly for the smaller children, 200 mg 8 hourly for the bigger children and some received 100 mg, 100 mg and 200 mg for the night dose. Blood was sampled 2-3 hours after the morning dose.

Three patients who were admitted into the hospital with acute asthmatic attacks were selected for theophylline half-line estimation. They were given aminophylline injection (prepared by the Government Pharmaceutical Department) at a dose of 5 mg/kg. The calculated volume of aminophylline injection was diluted with 20 ml of sterile Normal Saline and infused intravenously into the patient over 20 min. Blood samples were collected before infusion, immediately, 0.5, 1, 3, and 5 hours after infusion.

Blood samples (0.4 ml) were collected in heparinised microcentrifuge tubes and transported in ice to the laboratory. Plasma samples obtained from the blood samples were assayed in duplicate for theophylline using the EMIT^{R} — aad (Syva) enzyme immunoassay method.

The preparations used, choline theophyllinate 100 mg, 200 mg sugar-coated tablets and aminophylline injections were estimated for theophylline available using the same EMIT^{R} method. Choline theophyllinate tablets were found to contain 60-62% of theophylline and aminophylline injections contained 79% theophylline. According to The Extra Pharmacopoea (Martindale), theophylline contents in choline theophyllinate and aminophylline are about 64% and 78-84% respectively.

RESULTS

Table 1 shows the peak plasma concentrations of theophylline in 15 patients on long term choline theophylline. The daily oral dose of theophylline (calculated as theophylline available from the tablets) administered to the children varied between 9.1 to 19.5 mg/kg with a mean of 14.1 (SEM = 0.91) mg/kg. The plasma theophylline obtained in these patients 2-3 hours after administration ranged from 2.7 to 15.5 μg/ml with a mean of 6.8 (SEM = 0.96) μg/ml.

The plasma theophylline levels in these patients were low considering that these were the expected peak values. Only 2 out of the 15 (13%) achieved levels within the therapeutic range of 10-20 ug/ml. 9 out of 15 (60% had levels between 5-10 μg/ml and 4 out of 15 (27%) were found to have levels below 5 μg/ml.

When the ratio between the plasma level obtained (μg/ml) and the daily dose administered (mg/kg) was worked out to obtain the steady state level expected from 1 mg/kg/day for each patient, it was found to vary between 0.15 to 1.15 μg/ml with a mean of 0.51 (SEM = 0.07) μg/ml. Correlation of the steady state level expected from 1 mg/kg/day with the age of patient (Fig. 1) showed no fixed pattern indicating pronounced interpatient variation in children between 2-11 years old in the selected group. However, one can see that for the steady state level produced by 1 mg/kg/day to be above 0.6 μg/ml the age of the child was eight or above.

Fig. 2 shows the plasma concentration time plots of theophylline in 3 patients given intravenous infusion of 5 mg/kg aminophylline. The plasma samples of these patients taken before the infusion were found to contain undetectable or very low amounts of theophylline (0-0.9 μg/ml). The half-lives of theophylline in these 3 patients were between 3-5 hours.

DISCUSSION

With the standard dosage schedules used, the daily dosage worked out to give a mean of 14.1 mg/kg, this is much lower than the dosage recommended by Zaske et al (4) for optimum therapy; they gave the guidelines of 28 and 23.2 mg/kg/day of aminophylline in younger and older children respectively. Wyatt et al (5) also recommended similar dosage guidelines, that is, 24.1 mg/kg/day theophylline for children under 9 years. It was therefore not surprising that the mean peak plasma theophylline concentration in our children was found to be only 6.8 μg/ml; of course this explains why the choline theophyllinate was observed to be not too effective in controlling the symptoms of chronic asthma.

Although the steady state level expected from 1 mg/kg/day was highly variable, the mean 0.51 μg/ml was similar to that in children as described in 'The Therapeutic Window' (6). The results also showed that values above 0.6 μg/ml occurred only in older children, those who are eight and above, indicating lower requirements of theophylline in older children.

The half-lives of theophylline in our children who required IV aminophylline infusion were quite short, 3-5 hours; but they are comparable to those reported by Kadlec et al (7). Although only three patients were investigated, there seems to be a trend to show that the half-life of theophylline increased with age. The plasma level of theophylline in these three patients before IV infusion were very low or undetectable, perhaps the cause of their acute asthmatic attacks was due to poor compliance of the oral choline theophyllinate.

From what we have gathered from the results, we can optimise therapeutic efficacy of theophylline with the

Table 1

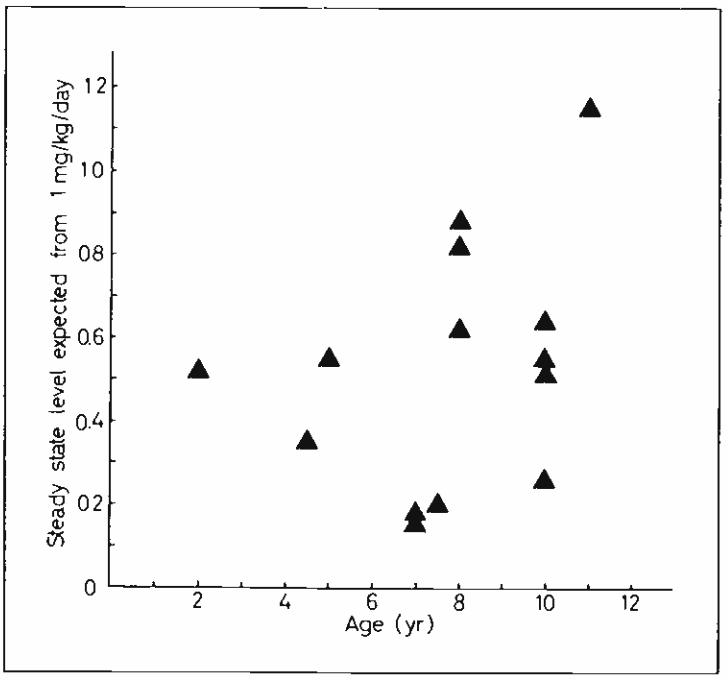
PEAK PLASMA THEOPHYLLINE LEVELS AFTER ORAL ADMINISTRATION OF CHOLINE THEOPHYLLINATE

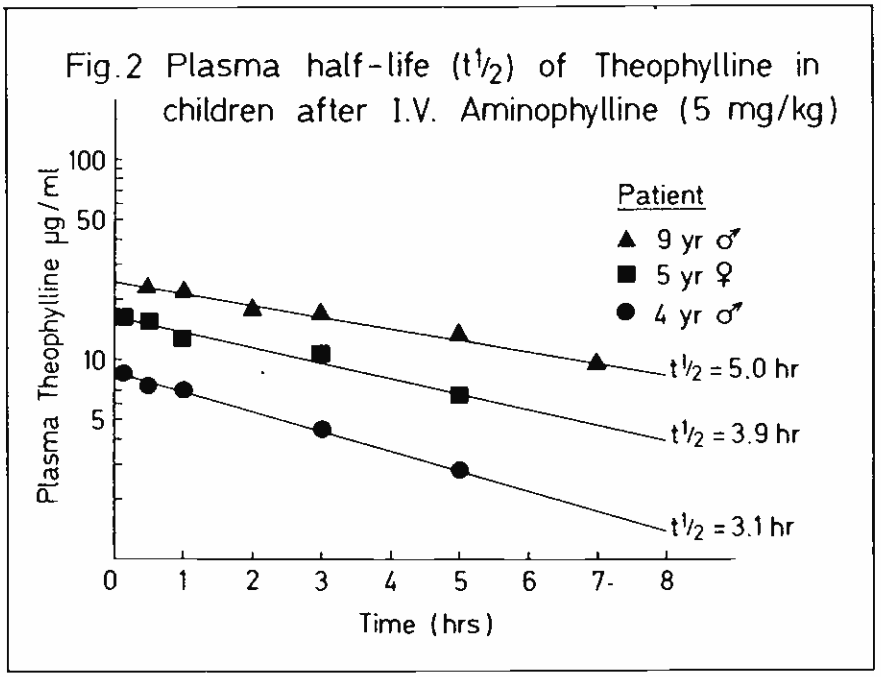
PATIENT	AGE/SEX	DOSE* (mg/kg/day)	LEVEL (ug/ml)	SS (ug/ml) EXPECTED FROM 1 mg/kg/day
1	5.0/M	10.9	6.0	0.55
2	10.9/F	9.8	5.0	0.51
3	8.0/M	15.4	9.6	0.62
#4	4.5/M	16.4	5.8	0.35
#5	8.0/M	15.4	13.5	0.88
#6	7.0/M	18.5	2.7	0.15
7	2.0/F	9.8	5.1	0.52
8	9.0/M	19.5	6.5	0.32
9	7.5/M	15.7	3.2	0.20
10	7.0/M	18.7	3.6	0.19
#11	11.9/F	13.5	15.5	1.15
#12	10.9/F	15.4	8.4	0.55
13	8.0/F	9.7	8.0	0.82
14	10.0/F	13.7	3.6	0.26
15	10.0/M	9.1	5.8	0.64
Range	2.0-11.0	9.1-19.5	2.7-15.5	0.15-1.15
Mean	7.8	14.1	6.8	0.51
S.D.	2.46	3.54	3.7	0.28
n	15.0	15.0	15.0	15.0
S.E.M.	0.64	0.91	0.96	0.07

* Dose is calculated as theophylline available

\# non-Chinese Asian

SS Steady state level





LEGENDS

Fig 1. Relationship between steady state level expected from 1 mg/kg/day of oral theophylline and the age of the patients.
Fig 2. Plasma level-time plots of theophylline in 3 patients given aminophylline (5 mg/kg) IV infusion.

▲ 9 yr ♂, ■ 5 yr ♀, • 4 yr ♂

help of plasma theophylline measurements by (1) increasing the dosage of choline theophyllinate; (2) increasing the dosage frequency from 8 hourly to 4 or 6 hourly. However, increasing the dosing frequency may result in poorer compliance.

We are now initiating the use of sustained release preparation of theophylline in children and are currently monitoring and evaluating the efficacy of the different sustained release preparations available in the local market for use in our asthmatic children.

REFERENCES

1. Hambleton G, Weinberger M, Taylor J et al. Comparison of cromoglycate (cromolyn) and theophylline in controlling symptoms of chronic asthma. *Lancet* 1977; i: 381-5.
2. Ellis EF, Koysooko R, Levy G: Pharmacokinetic of theophylline in children with asthma. *Pediatrics* 1976; 58: 542-7.
3. Ginchansky E and Weinberger M: Relationship of theophylline clearance to oral dosage in children with chronic asthma. *J. Pediatrics* 1977; 91: 655-60.
4. Wyatt R, Weinberger M, Hendeles L. Oral theophylline dosage for the management of chronic asthma. *J. Pediatrics* 1978; 92: 125-30.
5. Zaske DE, Miller KW, Strem EL, Austrian S, Johnson PB. Oral aminophylline therapy increased dosage requirement in children. *JAMA* 1977; 237: 1453-5.
6. Syva Monitor 1978 (No. 1): The Therapeutic Window — Theophylline.
7. Kadlec GJ, Le Thanh HA, Jarboe CH, Richards D, Karibo JM Theophylline half-life in infants and young children. *Annals of Allergy* 1978; 40: 303-10.