THE EFFECT OF DIET UPON SERUM CONCENTRATIONS OF THEOPHYLLINE

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1 Eight patients with airways obstruction were investigated to determine if dietary components had any significant effect upon serum concentrations of theophylline when taking a slow release formulation.

2 A high carbohydrate, low protein diet, given for 1 week, resulted in the area under the concentration time curve for 12 h being 33.3% greater than a high protein low carbohydrate diet given under the same conditions.

3 In contrast to two previous studies no significant effect upon the elimination half-life was detected after changing from one diet to the other and an effect of dietary components upon absorption and/or distribution needs to be considered.

4 Morning and afternoon trough levels were significantly different from each other on both diets suggesting that theophylline kinetics are different at night.

5 Individualising of theophylline dosing is particularly needed when treating patients on a varied dietary intake.

Keywords theophylline diet pharmacokinetics

Introduction

Theophylline is used in many countries of the world for the treatment of airways obstruction. It has a narrow therapeutic range and for any prescribed dose many factors can significantly affect the steady-state serum concentration achieved (Ogilvie, 1978). The dietary intake of those receiving theophylline is highly variable and yet its potential to alter serum theophylline concentrations has been relatively unexplored. Several investigations carried out in both animals and in normal volunteers have suggested that high protein diets can stimulate the hepatic cytochrome enzyme systems involved in theophylline metabolism (cytochrome P448) (Kappas *et al.*, 1976). We have investigated the effect of dietary intake upon the steady-state serum concentrations of slow release theophylline in patients with airways obstruction by contrasting the effect of a high carbohydrate, low protein diet with that of a high protein, low carbohydrate diet.

Methods

Eight patients who had been admitted for treatment of airways obstruction were studied. They were pre-

scribed theophylline (Nuelin SA Riker) 10 mg kg⁻¹ day⁻¹ in two equally divided doses given by one of the investigators at 09.00 h and 21.00 h each day. After they had been on this dose for a minimum of 1 week and when their mean peak expiratory flow rates were stable they were allocated to one of two diets. These were a low carbohydrate high protein diet (CHO 51.3%, protein 30%, fat 18.7%) and a high carbohydrate low protein diet (CHO 75.6%, protein 5.9%, fat 18.5%). For each individual the total calorific intake per day for both diets was identical, with the mean intake being 2,250 (s.d. 400.9) calories per day. Both diets excluded cruciferous vegetables which on their own are thought to be inducers of hepatic enzymes (Pantuck *et al.*, 1979). The patients were randomly allocated to commence on one of the two diets, four to the high CHO diet and four to the high protein diet. Each diet was given over a 1 week period, in hospital, under the supervision of the dietetic department.

At the end of 1 week, and after the usual morning dose had been taken, the steady-state serum concentrations of theophylline were assessed over a 24 h period. The morning dose on this day was taken with 200 ml of water 15 min after the commencement of

a standard breakfast (CHO 68%, protein 15%, fat 17%). No food or beverage was consumed for the next 4 h. Serum samples were obtained at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h with the evening dose of theophylline being omitted. No caffeine containing foods or beverages were consumed during the period of serum sampling. All other medications were taken at their usual times and kept constant throughout the study. Blood samples were also taken for full blood count and liver and renal function.

Following this, and in order to provide a washout period of 1 week, the patients returned to their 'normal diet' either at home or in hospital. During this week the daily carbohydrate, fat and protein intake of each individual was assessed by the use of dietary diary cards. Each individual was given detailed instructions on how to use them and supervised in this respect by one of the investigators. The mean intake per day was carbohydrate 54.3% (s.d. 7.4%), protein 23.2% (s.d. 3.2%) and fat 21.5% (s.d. 4.2%) with the mean calorific value being 2058 (s.d. 838.7) calories.

After being on their 'normal diet' for 1 week they were crossed over to the alternate test diet. This was again in hospital and for 1 week. Serum concentration assessments were then repeated under the same conditions as on the first occasion. All serum concentrations were assayed blind. The assays were performed in duplicate by the Emit (Syva) method using a centrifugal fast analyser (Kampa *et al.*, 1979).

Information was collected about the patients' age, sex, smoking habits, other medications and disease states. The study was approved by the hospital's Ethics Committee and written informed consent was obtained from each patient.

The area under the concentration time curve

(AUC) was determined by the linear trapezoidal rule for areas and the elimination half-life ($t_{1/2}$) was derived from the terminal portion of the log concentration time curve for each subject. All statistical analyses were performed using Student's paired *t*-test.

Results

Five of the eight patients were male and three were female with a mean age of 44.5 years (range 17–69). The mean weight was 66 kg (range 40–80) and the mean dose given was 656 mg (range 500–1000 mg) which was equivalent to 9.9 mg kg⁻¹ day⁻¹. The patients were taking regular doses of salbutamol and beclomethasone by aerosol. Other drugs being taken included cimetidine (1), prednisolone (5), spironolactone (1) and phenytoin (1). One patient was a smoker of 6–10 cigarettes per day. No significant biochemical or haematological abnormalities were detected.

The mean serum drug levels with s.e. mean, the mean differences and associated *P* values are shown in Table 1. Table 2 shows the mean and s.e. mean for the time to peak concentration (t_{max}), peak serum concentration (C_{max}), $t_{1/2}$, AUC (0 to 12 h) and peak to trough differences. Significantly higher serum concentrations occurred after the carbohydrate diet at 1, 3, 4, 8 and 12 h and the AUC was similarly significantly increased after the carbohydrate diet by 33.3%. The evening trough serum concentrations were significantly lower than the morning trough serum concentrations on both test days as seen in Table 3. No other parameters were significantly different between the two test days and no side effects were reported.

Table 1 The serum concentrations of theophylline ($\mu\text{g/ml}$) obtained after a high carbohydrate diet and after a high protein diet; $n = 8$ with s.e. mean, the mean differences and *P* values.

	Time (h)									
	0	0.5	1	2	3	4	6	8	12	24
CHO										
Serum theophylline	11.0	10.5	11.3	11.6	11.8	11.6	12.3	11.2	9.0	4.7
s.e. mean	1.6	1.7	1.8	1.9	1.8	1.8	2.1	1.8	1.4	0.9
Protein										
Serum theophylline	9.0	8.6	8.5	8.5	8.8	9.3	9.7	8.2	6.3	3.5
s.e. mean	1.4	1.4	1.3	1.1	1.3	1.5	1.8	1.4	1.0	0.8
CHO – Protein										
<i>P</i> value	< 0.1	< 0.1	< 0.05	< 0.1	< 0.05	< 0.05	< 0.1	< 0.05	< 0.01	< 0.1

Table 2 The mean values for $C_{\max}$, $t_{\max}$ (h), $C_{\max}$ trough, AUC, $t_{1/2}$, $n = 8$ for high carbohydrate and high protein diets with their mean differences, P values and s.e. mean (in brackets).

	CHO	Protein	Difference	P value
$C_{\max}$ ($\mu\text{g/ml}$)	12.9 (2.0)	10.3 (1.7)	2.6 (1.0)	< 0.1
$t_{\max}$ (h)	3.3 (0.7)	3.8 (0.9)	-0.5 (0.7)	> 0.1
$C_{\max}$ -trough ($\mu\text{g/ml}$)	4.1 (0.8)	4.1 (0.7)	0.0 (0.7)	> 0.1
AUC ($\mu\text{g ml}^{-1}$ 12 h)	133.3 (21.1)	100.0 (16.3)	33.3 (12.6)	< 0.05
$t_{1/2}$ (h)	12.8 (2.3)	14.0 (1.9)	-1.2 (2.2)	> 0.1

Table 3 Mean theophylline concentrations ($\mu\text{g/ml}$) at 0 and 12 h (morning and afternoon troughs), the mean differences, appropriate P values and s.e. mean (in brackets).

	Morning trough	Afternoon trough	Difference	P value
High CHO	11.0 (1.6)	9.0 (1.4)	2.0 (0.6)	< 0.02
High protein	9.0 (1.4)	6.3 (1.0)	2.7 (0.6)	< 0.01

Discussion

Food can affect drug absorption and elimination in many different ways. The mechanisms by which it does this include alterations to gastric and intestinal transit times, alterations in the concentration of pancreatic enzymes and bile, the stimulation of hepatic oxidative enzymes and the preferential binding of drugs to food (Boxenbaum, 1982; Welling, 1979). However the influence of food and diet upon theophylline metabolism has received only limited investigation. The previous studies on the effect of diet on theophylline pharmacokinetics have shown that a high protein diet increases the elimination rate of the drug. These studies used rapid release theophylline and examined either normal volunteers or children and made no comment on the effect of diet upon absorption (Feldman *et al.*, 1980; Kappas *et al.*, 1976). However the sites of absorption for rapid release and slow release tablets are certain to be different and the effect of a particular diet upon the theophylline levels achieved may well depend upon the formulation used.

The results we obtained in patients with airways obstruction have confirmed that a high carbohydrate diet leads to higher serum levels than those achieved after a high protein diet. There was a significant increase in the amount present in the serum over the first 12 h (AUC 0–12 h increased by 33.3%) and more than half of the mean serum levels were significantly different. With the data obtained we were unable to detect any difference between the two diets with respect to the half-life. This contrasts with the work of Kappas *et al.* (1976) and Feldman *et al.* (1980) who both obtained significant differences between the two diets for $t_{1/2}$. However, unlike our patients who were investigated in a balanced randomised crossover de-

signed study, the subjects in both of these studies were all placed on a high protein diet prior to a high CHO diet and this may have contributed to the differences observed. Other contributing factors include: the longer washout period in our study, the longer period of exposure to the diets in the other two studies and the higher age level in our group of patients.

Throughout the investigation period one of our patients was on cimetidine which is known to inhibit the action of liver cytochrome enzyme systems (Jackson *et al.*, 1981). Cimetidine would tend to nullify the effect of any enzyme induction by a high protein diet and in accord with this his $t_{1/2}$ was similar on both diets. However when on the carbohydrate diet he had an increase in his AUC of over 65%. The results of this patient and the group as a whole suggest that the diets affect theophylline absorption or distribution rather than elimination. Nuelin SA is reported to have a bioavailability of greater than 95% (Svedmyr *et al.*, 1979) and therefore inhibition of absorption with the high protein diet seems more likely than an enhancement of absorption with the high CHO diet. The mechanism for this is not clear although proteins and amino acids have been reported to block the mucosal absorption of levodopa (Gillespie *et al.*, 1973), and propoxyphene is preferentially absorbed after a carbohydrate diet as opposed to a protein diet (Wagner *et al.*, 1972).

The importance of these results to clinical practice is worthy of further investigation as food may cause serum levels to change by up to 34%. People on unusual diets or living in non-western environments or countries may need doses of theophylline quite different to those normally prescribed. Patients in hospitals rarely consume their normal diet and may depart substantially from their normal carbohydrate and protein intake. Consequently fine adjustment of theophylline dosage should be left till the patient has returned home to his normal diet.

Diet had no obvious effect on the differences seen between morning and afternoon trough levels. On both diets the morning trough levels were significantly higher than the afternoon trough levels ($P < 0.02$) further supporting the concept of different kinetics during the night (Thompson *et al.*, 1981).

This study and those of Kappas *et al.* (1976) and Feldman *et al.* (1980) provide evidence that for any

given dose of theophylline dietary components can have a major effect upon the serum levels achieved. The mechanism of action of these dietary components is probably multifactorial and involves both degradation and absorption. Further specific single dose studies on diet and the absorption of slow release tablets are required.

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