SERUM LEVEL MONITORING OF A NEW SLOW RELEASE THEOPHYLLINE FORMULATION IN PATIENTS WITH CHRONIC LUNG DISEASE

G.E. MARLIN, M.A. BUTCHER, J.A. KLUMPP & P.J. THOMPSON

Respiratory Investigation Unit, Concord Hospital, Sydney, N.S.W., Australia

- 1 Serum theophylline levels were performed in 26 patients with chronic lung disease receiving rapid release theophylline (125 mg 6 hourly) and 28 patients receiving slow release theophylline (250 mg 12 hourly) under steady state conditions.
- 2 For rapid release theophylline the mean $\pm$ s.d. serum theophylline levels at 0 and 2 h were 41.0 ± 21.7 and $52.3 \pm 20.9 \mu\text{mol l}^{-1}$ respectively and for slow release theophylline at 0, 4 and 6 h 43.7 ± 25.5 , 50.9 ± 23.0 and $51.7 \pm 26.4 \mu\text{mol l}^{-1}$ respectively.
- 3 Serum theophylline monitoring with slow release theophylline was performed in 70 patients with chronic lung disease. The initial dose was 250 mg administered 12 hourly.
- 4 The mean $\pm$ s.d. steady state serum theophylline level achieved was $76.0 \pm 18.8 \mu\text{mol l}^{-1}$ and the mean $\pm$ s.d. dose to produce this level was $9.4 \pm 2.3 \text{ mg kg}^{-1} \text{ day}^{-1}$. There was no correlation between dosage and serum theophylline level.
- 5 Sixty percent of patients required a dosage change for stabilization (375 to 1000 mg/day). Seventeen patients reported unwanted effects (nausea or tremor), which either settled quickly or resolved with dosage reduction.
- 6 Serum theophylline levels were obtained at different dosages in 44 patients and 18 patients demonstrated dose-dependent kinetics.
- 7 An initial dose of 500 mg/day is recommended and dosage increments should not exceed 125 mg/day with monitoring by serum theophylline levels.

Introduction

Oral theophylline is widely used for the management of chronic airways obstruction in patients with asthma. The bronchodilator effect of theophylline is directly related to the logarithm of the plasma concentration (Mitenko & Ogilvie, 1973; Levy & Koysooko, 1975; Marlin, Harris, Klumpp & Rutland, 1979). A therapeutic range for plasma theophylline of 55 to $110 \mu\text{mol l}^{-1}$ has been defined with toxicity common above $110 \mu\text{mol l}^{-1}$ (Jenne, Wyze, Rood & MacDonald, 1972; Ogilvie, 1978; Weinberger, 1978). However, the elimination rate of theophylline in man is variable and may be influenced by numerous factors including age, bodyweight, smoking habits, diet, drugs, cardiac and hepatic disease. This necessitates serum theophylline monitoring during maintenance oral treatment if the therapeutic range is to be achieved and toxicity avoided.

Rapidly dissolving theophylline formulations are absorbed quickly and possess very high bioavailability, but may result in high peak-trough differences and require six hourly dosing (Ginchansky & Weinberger, 1977; Wyatt,

Weinberger & Hendeles, 1978). This may not provide sufficient control of symptoms and frequent daily dosing may lead to poor patient compliance. Slow release theophylline formulations have been introduced recently with the purpose of providing stable serum theophylline levels with a more convenient dosage schedule.

This study reports 1) a comparison of serum theophylline levels during steady state conditions with rapid and slow release theophylline and 2) a serum theophylline monitoring survey in clinical practice in patients with chronic lung disease.

Methods

Patients

Seventy six patients (70 males and six females), aged from 51 to 83 years, were included in this study. All patients had chronic, partially reversible airways obstruction due either to asthma (nine patients),

chronic bronchitis with asthma (21 patients) or chronic bronchitis and emphysema (46 patients). There were 12 life non-smokers, while past smoking history was mild (less than 20 pack years) in nine patients, moderate (20 to 50 pack years) in 29 patients and heavy (greater than 50 pack years) in 26 patients. Current smoking habits were mild (less than 10 cigarettes/day) in nine patients, moderate (10 to 20 cigarettes/day) in nine patients and heavy (greater than 20 cigarettes/day) in one patient, while 57 patients had not smoked for at least 3 months prior to the study. The patients were receiving various combinations of drugs for maintenance treatment of airways obstruction including prednisone in various doses (41 patients), salbutamol by pressurized aerosol (76 patients), beclomethasone dipropionate (47 patients), oral theophylline preparations (38 patients) and sodium cromoglycate (4 patients). There were 17 patients with right heart failure, four with left heart failure and three with biventricular failure controlled by drug treatment. Forty patients gave a history of other diseases which included ischaemic heart disease (16), essential hypertension (6), gout (8), peptic ulcer (4), arthritis (3), osteoporosis (2), epilepsy (2), alcoholic cardiomyopathy (1), hepatic cirrhosis (1), diabetes mellitus (1), pulmonary tuberculosis (5), hiatus hernia (1), diverticulitis (1), peripheral vascular disease (1), prostate carcinoma (1) and multiple sclerosis (1). Two patients had previous liver biopsies, one showing early hepatic cirrhosis and the other fatty change. Concomitant drug therapy taken by the patients included digoxin (20), frusemide (25), thiazide diuretic (8), potassium supplement (19), amiloride (5), allopurinol (6), methyl dopa (4), spironolactone (4), nitrazepam (9), glyceryl trinitrate (4), diazepam (2), oxazepam (5), indomethacin (2), phenytoin (2), isoniazid (4), sorbide nitrate (2), bromhexine (2), ibuprofen (2), tetracycline (2), doxycycline (4), and amoxycillin (12), while there was one patient taking each of the following drugs, debrisoquine, warfarin, insulin, thyroxine, phenylbutazone, chlorthalidopoxide, amitriptyline, dexamphetamine, pentaerythritol tetranitrate, verapamil, stilboestrol, mixogen, trifluoperazine, demazin, clonidine, Gaviscon, mylanta, nicotiny alcohol, aspirin, mutabon, ethambutol, rifampicin and pyridoxine. The alcohol intake of the patients was nil in 18, mild (less than 70 g/day) in 34, moderate (70 to 100 g/day) in 16 and heavy (greater than 100 g/day) in eight. Routine haematological and biochemical profiles were performed in each patient. For patients had polycythaemia and one patient anaemia. There were 28 patients with abnormal biochemistry including 25 with raised lactic acid dehydrogenase, seven with raised glutamic oxaloacetic transaminase, two with raised alkaline phosphatase and two with reduced albumin. Ten patients were considered to have

impaired hepatic function on the basis of abnormal biochemistry or pathology.

Study one

Thirty eight patients, hospitalized for various reasons, entered the first phase of the study when it was considered that their clinical condition and treatment had stabilized. Twenty-six of these patients had been receiving oral theophylline, a rapid release microfinned formulation (Nuelin, 125 mg tablet, 3 M Riker Laboratories), administered 125 mg six hourly for at least 3 days. All other drugs were continued at maintenance doses. Venous blood samples were taken for serum theophylline estimations immediately before and 2 h after a dose on 1 (six patients) and 2 days of treatment (20 patients). Fourteen of these patients were transferred to slow release theophylline (Nuelin R250, 250 mg tablet, 3M Riker Laboratories) and a further 14 patients were commenced on this preparation which was administered 250 mg twelve hourly. Serum theophylline levels were estimated in these 28 patients after at least 5 days of treatment from venous blood samples collected immediately before and 4 and 6 h after a dose on 1 day (22 patients), 2 days (four patients) and 3 days (two patients). In all patients drug taking was supervised directly by hospital staff.

Study two

There were 70 patients admitted to the clinical monitoring second study phase, 32 from the first study and 38 further patients, all of whom were now attending a hospital out-patient clinic for respiratory disease. They had been commenced or had been transferred from another theophylline preparation to slow release theophylline administered 250 mg twelve hourly. All other drugs were continued at maintenance doses. The patients returned after they had received slow release theophylline for at least 7 days for the first serum theophylline estimation, a venous blood sample being taken 4 to 6 h after the morning dose. Each patient was given a chart to indicate the time at which each dose was taken for drug compliance to be checked. Dosage changes were implemented according to serum theophylline levels, which were repeated after an interval of at least 7 days on the new dose. More than one steady state serum theophylline level was determined when possible on a particular dose at 7 day intervals or more. The patients were told that nausea may occur if the dose was too high. They were instructed to report nausea or any other unwanted effect considered by the patient to be related to the introduction of this theophylline preparation and to reduce the dose (e.g.

500 to 375 mg/day; doses above 500 mg/day to the previous level) immediately and report to the clinic as soon as practical. The patients were considered stabilized when as near as possible to the therapeutic range (55 to 110 $\mu\text{mol l}^{-1}$) for serum theophylline was achieved with no unwanted effects.

Theophylline assay

Serum theophylline levels were determined by radioimmunoassay (RIA) (Clinical Assays), an assay specific for theophylline with minimal cross-reactivity

towards other xanthine derivatives (e.g. % cross-reactivity: theophylline 100, caffeine 5.0). Thirty samples were selected randomly for assay by both RIA and high pressure liquid chromatography (HPLC) in a double-blind study. There was no significant difference between the results and the correlation coefficient was 0.92 ($P < 0.001$) ($\text{HPLC} = 1.06\text{RIA} + 0.06$). The correlation coefficient for 30 randomly selected duplicate assays by RIA was 0.99 ($P < 0.001$).

Results

Study one

The mean $\pm$ s.d. serum theophylline levels for the patients receiving rapid release and slow release theophylline are shown in Table 1. With rapid release theophylline there was a significant difference between the 0 and 2 h serum theophylline levels ($P < 0.01$). The serum theophylline levels for slow release theophylline at 4 and 6 h were significantly higher than at 0 h ($P < 0.01$), but did not differ significantly from each other. There were no unwanted effects reported.

Study two

The mean $\pm$ s.d. steady state serum theophylline level achieved in 67 patients was $76.0 \pm 18.8 \mu\text{mol l}^{-1}$ (range: 47.3 to $129.3 \mu\text{mol l}^{-1}$). The mean $\pm$ s.d. dose to produce this level was $9.4 \pm 2.3 \text{ mg kg}^{-1} \text{ day}^{-1}$ (range: 5.6 to $14.2 \text{ mg kg}^{-1} \text{ day}^{-1}$). There was no correlation between dosage and serum theophylline level ($r = 0.02$, $P > 0.1$). The number of patients stabilized on a particular theophylline dosage (mg/day) is shown in Table 2. A dosage change was indicated in 60% of patients. The two unwanted effects reported by the patients were nausea and muscle tremor and their incidence is shown in Table 3. Of the 14 patients who complained of nausea, three gave a history of previous gastric symptoms, one

Table 1 The mean $\pm$ s.d. serum theophylline levels for 26 patients receiving rapid release theophylline (125 mg 6 hourly) and 28 patients receiving slow release theophylline (250 mg 12 hourly under steady state conditions).

	<i>Rapid release theophylline</i>		
	<i>0 h</i>	<i>2 h</i>	
Mean $\pm$ s.d. serum theophylline level ($\mu\text{mol l}^{-1}$)	41.0 ± 21.7	52.3 ± 20.9	
	<i>Slow release theophylline</i>		
	<i>0 h</i>	<i>4 h</i>	<i>6 h</i>
Mean $\pm$ s.d. serum theophylline level ($\mu\text{mol l}^{-1}$)	43.7 ± 25.5	50.9 ± 23.0	51.7 ± 26.4

Table 2 The daily dosage of oral slow release theophylline required to produce therapeutic serum theophylline levels in 67 patients with chronic lung disease.

Dosage (mg/day)	Number of patients
375	5
500	27
625	13
750	19
1000	3

Table 3 The incidence of unwanted effects in 70 patients receiving slow release theophylline.

Dosage (mg/day)	Number of patients	Nausea	Unwanted effect Tremor	Both	Outcome
500	6	4	2	—	2—withdraw 1—transitory 3—resolved with dosage reduction
750	10	8	1	1	1—withdraw 9—resolved with dosage reduction
1000	1	1	—	—	1—resolved with dosage reduction
Total	17	13	3	1	

with hiatus hernia and one with peptic ulcer. However, it was considered on clinical grounds that the nausea in these patients was drug related. There were 13 patients in whom a serum theophylline level was determined at the time of the unwanted effects. The mean $\pm$ s.d. serum theophylline level in these patients was $105.7 \pm 26.7 \mu\text{mol l}^{-1}$ (range: 64.8 to $148.5 \mu\text{mol l}^{-1}$) and the mean $\pm$ s.d. dosage which produced this level was $10.1 \pm 3.0 \text{ mg kg}^{-1} \text{ day}^{-1}$ (range: 8.1 to $18.6 \text{ mg kg}^{-1} \text{ day}^{-1}$).

There were 44 patients in whom serum theophylline levels were obtained at different doses ranging from 250 to 1000 mg/day. These doses were taken in equally divided doses 12 hourly except for the 375 mg (250 mg morning and 125 mg evening) and 625 mg doses (375 mg morning and 250 mg evening). For 60 observations in these patients, the % change in serum theophylline level and the % dosage change was calculated and expressed as a ratio (% change in serum theophylline/% change in dose). If this ratio exceeded 2.0, this was considered to indicate non-linear or dose-dependent kinetics. The results of patients in whom a 375 or 625 mg dose was involved in the only dosage increment were omitted because of the uneven dosing. When more than one serum theophylline level was available for a particular dose (39 observations), the highest value was used in the calculations. There were 18 patients (41%) in whom this ratio exceeded 2.0 and the individual dosage and serum theophylline level changes and ratios are shown in Table 4. These ratios deviated significantly from linearity (ratio = 1.0) ($P < 0.001$).

Repeat serum theophylline levels were performed at intervals of more than 7 days on the same dosage in 55 patients. There were 62 dosage regimens and 141 serum theophylline levels performed. The mean serum theophylline level for each patient on each dosage was calculated. The % deviation of each serum theophylline estimation from the mean value in each patient was determined. The mean $\pm$ s.d. % deviation for all patients was $15.6 \pm 14.4\%$. The correlation coefficient between serum theophylline levels on the same dosage at weekly intervals was 0.68 ($P < 0.001$).

The patients were grouped according to the presence or absence of a particular clinical feature and the mean $\pm$ s.d. serum theophylline levels and dosages for these patient groups are shown in Table 5, but there were no significant differences found.

Discussion

The rapid and slow release theophylline preparations used in this study have been shown to possess equivalent and very high bioavailability (Jonkman, Berg, Schoenmaker, Greving, De Zeeuw & Orie, 1979; Svedmyr, Mellstrand & Svedmyr, 1979). Both single dose and steady state pharmacokinetic studies have been performed with these formulations and indicate that approximate peak serum theophylline levels will occur at 2 h with rapid release and 4 to 6 h with slow release theophylline (Marlin, Hartnett, Berend & Hackett, 1978; McDevitt, Elwood &

Table 4 The mean $\pm$ s.d. serum theophylline levels and theophylline dosages in 67 patients with various medical disorders and treatments.

<i>Medical disorder of treatment</i>	<i>Number of patients</i>	<i>Serum theophylline ($\mu\text{mol l}^{-1}$)</i>	<i>Dosage ($\text{mg kg}^{-1} \text{ day}^{-1}$)</i>
With heart failure	22	78.3 ± 15.8	8.6 ± 2.1
Without heart failure	45	75.1 ± 20.4	9.7 ± 2.3
Severe airways obstruction ($\text{FEV}_1 < 1\text{l}$)	37	77.2 ± 18.5	10.0 ± 2.2
Mild ($\text{FEV}_1 > 2\text{l}$) and moderate ($\text{FEV}_1: 1\text{--}2\text{l}$) airways obstruction	30	74.5 ± 19.4	8.7 ± 2.2
With abnormal biochemistry	26	77.1 ± 20.5	8.8 ± 2.0
With normal biochemistry	41	75.5 ± 18.2	9.7 ± 2.4
Impaired liver function	8	72.1 ± 12.4	8.5 ± 2.6
Moderate and heavy alcohol	18	74.2 ± 19.4	8.4 ± 2.5
Mild alcohol	49	76.4 ± 19.0	9.8 ± 2.3
Non-smokers	11	81.5 ± 20.4	9.2 ± 2.1
Previous smokers	56	75.1 ± 18.6	9.4 ± 2.4
Currently smoking	17	74.6 ± 20.8	9.3 ± 2.6
Not currently smoking	50	76.2 ± 18.4	9.4 ± 2.2
Previous theophylline	37	78.6 ± 18.8	9.8 ± 2.2
No previous theophylline	30	73.2 ± 18.9	8.8 ± 2.3
Oral corticosteroids	35	76.8 ± 16.5	9.1 ± 2.1
No oral corticosteroids	32	75.4 ± 21.5	9.9 ± 2.7

Table 5 The dosage changes, serum theophylline level changes and the ratios of % change in serum theophylline/% change in dose for 18 patients who demonstrated dose-dependent kinetics (ratio ≥ 2.0).

Patient	Dosage change (mg/day)	Serum theophylline level change ($\mu\text{mol l}^{-1}$)	% change in serum theophylline/% change in dose
1	500-750	24.2-126.5	8.5
	500-625	24.2-47.3	2.0
	625-750	47.3-126.5	8.4
2	500-750	27.5-143.0	8.4*
3	500-750	24.8-115.5	7.3*
4	500-750	23.7-95.7	6.1*
	500-625	23.7-52.8	4.9
	625-750	52.8-95.7	4.1
5	500-750	27.0-99.0	5.3*
6	500-750	35.2-121.0	4.9*
	500-625	35.2-60.5	2.9
	625-750	60.5-121.0	5.0
7	500-750	37.4-126.5	4.8*
	500-625	37.4-71.5	3.6
	625-750	71.5-126.5	3.9
8	500-750	31.4-89.1	3.7*
9	500-750	33.0-85.3	3.2*
10	500-750	40.7-101.8	3.0*
11	500-750	46.2-112.8	2.9*
12	500-1000	25.3-90.8	2.6*
	500-750	25.3-79.8	4.3
	750-1000	79.8-90.8	0.4
13	500-750	33.0-73.7	2.5*
14	500-750	23.7-51.7	2.4*
15	500-750	68.8-148.5	2.3*
16	500-750	44.0-90.8	2.1*
17	250-500	37.4-115.5	2.1*
18	500-750	31.4-63.3	2.0*

* Ratio at highest dosage change

Russell, 1979; Svedmyr *et al.*, 1979). Although both interpatient and inpatient variability in the rate of drug absorption will occur, it is considered that these sampling times would provide an estimate of peak serum theophylline for a clinical monitoring survey in a large group of patients when a single sampling time is desirable practice. McDevitt *et al.* (1979) also showed in healthy subjects that trough serum theophylline levels did not increase from the second day with rapid release and from the third day with slow release theophylline. The present study demonstrated no significant difference between the trough serum theophylline levels with the two preparations. The two hour-trough and six hour-trough differences of 11.3 and 8.0 $\mu\text{mol l}^{-1}$ with rapid and slow release theophylline respectively were small and not significantly different. Although multiple sampling was not performed in this study, a similar steady state pharmacokinetic profile is suggested by these results. However, with slow release theophylline this has been achieved with a more convenient dosage schedule. A dosing interval of 12 h should improve

patient compliance. Only twelve of the 28 patients reached therapeutic serum theophylline greater than 55 $\mu\text{mol l}^{-1}$ with 500 mg slow release theophylline, indicating the need for dosage increase in the other 16 patients. These results and those of other workers (McDevitt *et al.*, 1979; Svedmyr *et al.*, 1979) indicate the potential of this slow release theophylline for producing near constant steady state serum theophylline levels. These levels would be expected to produce a continual degree of bronchodilatation. Such regular bronchodilator treatment is necessary for patients with chronic airways obstruction.

The profiles of the patients in the clinical monitoring survey indicate numerous factors which might interact to influence theophylline clearance. Hepatic disease, left and right heart failure and severe airways obstruction all reduce theophylline clearance (Zwillich, Sutton, Neff, Cohen, Matthay & Weinberger, 1975; Weinberger, Matthay, Ginchansky, Chidsey & Petty, 1976; Jenne, Chick, Miller & Strickland, 1977; Jusko, Koup, Vance, Schentag & Kuritzky, 1977; Piafsky, Sitar, Rangno & Ogilvie, 1977a & b;

Mangione, Imhoff, Lee, Shum & Jusko, 1978; Powell, Vozeh, Hopewell, Costello, Sheiner & Riegelman, 1978; Vicuna, McNay, Ludden & Schwertner, 1979). The patients were receiving numerous drugs and various quantities of alcohol which might interfere with hepatic enzyme activity and theophylline clearance. Long-term theophylline therapy and dietary methylxanthines may inhibit theophylline metabolism (Caldwell, Lancaster, Monks & Smith, 1977), but smoking will increase theophylline clearance (Hunt, Jusko & Yurchak, 1976; Powell, Thiercelin, Vozeh, Sansom & Riegelman, 1977; Pfeifer & Greenblatt, 1978; Powell *et al.*, 1978). In the present study no single factor was found to significantly affect theophylline clearance (Table 5) and undoubtedly there were many factors operating in a particular patient.

The variability of serum theophylline levels on the same dosage observed in this study may have been related to changes in clinical status not detectable or changes in treatment or smoking habits not reported. Other factors contributing to this variability include changes in the rate of drug absorption and unreported changes in drug compliance, either dosage or time of administration. However, there was a significant positive correlation between duplicate levels.

Several regimens for maintenance oral theophylline treatment in adults have been recommended. Piafsky & Ogilvie (1975) suggested an initial dose of $9.6 \text{ mg kg}^{-1} \text{ day}^{-1}$ which could be increased with monitoring to an optimal dose of $19.2 \text{ mg kg}^{-1} \text{ day}^{-1}$ if tolerated. Zaske, Miller, Strem, Austrian & Johnson (1977) considered that projected dose requirements for trough serum concentrations of $55 \mu\text{mol l}^{-1}$ would be $12.4 \text{ mg kg}^{-1} \text{ day}^{-1}$. Wyatt *et al.* (1978) indicated a safe, commencing dose would be the lesser of $16 \text{ mg kg}^{-1} \text{ day}^{-1}$ or 400 mg/day and found a mean weight-adjusted dose to be $13.4 \text{ mg kg}^{-1} \text{ day}^{-1}$. These studies were all performed with rapid release theophylline preparations and no details were given regarding the patients' clinical profiles. In the present study of patients with chronic lung disease and other concomitant disorders, an initial dose of 500 mg/day proved satisfactory. Only six patients had unwanted effects and although two withdrew from the study, in the others the symptoms either settled quickly or resolved with dosage reduction. If 375 mg/day had been the initial dose, no unwanted effects would have occurred. However, as only five patients were finally

stabilized on this dose, the majority of patients would have required a further weekly visit for monitoring, which may have resulted in delay of symptom control. The mean dosage of $9.4 \text{ mg kg}^{-1} \text{ day}^{-1}$ is lower than in other reported adult studies and reflects the clinical profiles of these patients.

The high incidence of dose-dependent kinetics in these patients was not expected. The serum theophylline variability in this study may have contributed to these findings, but there were no patients in whom there was recognized poor compliance and all remained in a stable clinical condition with no changes in treatment. Dose-dependent kinetics of a lesser degree has been observed occasionally in adults (Jenne *et al.*, 1972; Mitenko & Ogilvie, 1973; Nicholson & Chick, 1973) and children (Weinberger & Ginchansky, 1977). Biphasic elimination from very high theophylline levels ($550 \mu\text{mol l}^{-1}$) has been reported (one adult, two children) (Jacobs & Senior, 1974; Weinberger & Ginchansky, 1977; Kadlec, Janboe, Pollard & Sublett, 1978), but this was not confirmed by Vaucher, Lightner & Walson (1977) in three children. Caldwell *et al.* (1977) have demonstrated Michaelis-Menten kinetics for the elimination of the major metabolite of theophylline and the clearance of theophylline would thus be expected to be dose-dependent. Patients with lower clearance rates would be expected to have a higher incidence of dose-dependent kinetics. However, changes in absorption rate as well as elimination rate might have contributed to the results of the 18 patients in this study and theophylline pharmacokinetics in such patients requires further investigation.

This study demonstrates the safe use of slow release oral theophylline in patients with chronic lung disease and other disorders which may influence theophylline clearance. An initial dosage of 500 mg/day is recommended. Dosage increments should be sufficiently small to allow for disproportionate serum level increases and should not exceed 125 mg/day . The dosage of theophylline requires individualizing for each patient with serum theophylline level monitoring.

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