mean values for each patient are shown in Table 1, and values greater than 1.5 are indicated. The ratio was greater than 1.5 in six of twelve patients demonstrating dose-dependent pharmacokinetics. This phenomenon occurred with the final dosage increment at the upper section of the therapeutic range in five of the six patients. One patient who had nausea was included in this group and it is likely that this phenomenon occurred in the other patient with nausea, although some patients will have unwanted effects with serum levels within the therapeutic range. The incidence of dose-dependent pharmacokinetics in this study is similar to that (40%) observed in a much larger group of patients with chronic lung disease receiving conventional twice daily doses of slow release theophylline (Marlin *et al.*, 1980). Large increments in serum theophylline levels can readily place a patient into the toxic range with the concomitant high risk of adverse effects.

This study has shown that patients with chronic lung disease may be safely stabilized by serum level monitoring on single daily dose theophylline with a slow release preparation. A safe commencing

evening dose is 375 mg which will produce a peak serum theophylline level near to the lower section of the therapeutic range. Dosage increments should not exceed 125 mg/day because of the high incidence of dose-dependent pharmacokinetics. The dose may be increased at weekly intervals in accord with the serum level, but should be reduced immediately if unwanted effects occur. A single daily dosage regimen would be expected to improve patient compliance in drug taking without increasing the risk of unwanted effects. This treatment may be beneficial for patients with symptoms occurring predominantly during the night and early morning.

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SALIVA THEOPHYLLINE CONCENTRATIONS AFTER A SINGLE ORAL DOSE

Theophylline is widely used in the treatment of obstructive respiratory disorders but because of significant interindividual differences in elimination half-

life (Ogilvie, 1978) and possible dose dependent alterations in the kinetics of the drug (Lesko, 1979) it is thought necessary to individualise patients' drug

Table 1 The regression lines calculated for the regression of serum theophylline concentration on saliva theophylline concentration at the four time points. The method of Deming (1943) was used which allows for the imprecision of measurement of both variables.

Time (h)		<i>r</i>
3	Serum theophylline = $3.67 \times \text{saliva theophylline} - 3.41$	0.326
4	Serum theophylline = $3.26 \times \text{saliva theophylline} - 2.18$	0.485
5	Serum theophylline = $2.80 \times \text{saliva theophylline} - 1.31$	0.618
6	Serum theophylline = $2.14 \times \text{saliva theophylline} + 0.09$	0.811

regimens. Serum or plasma theophylline concentrations in the range 10 to 20 mg l⁻¹ are usually effective. It has been shown that two well chosen plasma samples are sufficient to estimate the elimination half-life of theophylline (Bonora *et al.*, 1980) and recently using intravenous aminophylline, Plavsic *et al.* (1981) have demonstrated that saliva concentrations could replace these serum measurements.

Although the degree of correlation between saliva and serum theophylline concentrations has been shown to be variable (Boobis *et al.*, 1979; Koysooko

et al., 1974; Lena *et al.*, 1980) the ease of obtaining saliva rather than blood, makes it worthy of further investigation. In this study we have investigated the possibility of estimating theophylline half-life after a single oral dose of aminophylline using saliva drug measurements with a view to develop a procedure which could be used at outpatients to determine the correct dose for maintenance therapy.

Twelve males and seven females volunteered to participate in the study. The subjects were healthy and weighed between 42 and 80 kg and were aged

Figure 1 Scatter-grams of serum v saliva theophylline concentration at 3, 4, 5 and 6 h after a single oral dose of aminophylline.

between 21 and 33 years. After an overnight fast each received aminophylline B.P. orally in a dose of 3–5 mg kg⁻¹ of body weight. At 3, 4, 5 and 6 h after this administration 5 ml blood samples were taken into plain glass tubes and simultaneous saliva samples were obtained. Salivary flow was stimulated by chewing parafilm and salivary flow rate was measured by the weight difference in the preweighed collection tubes. After centrifugation serum and saliva samples were stored frozen at –20°C until analysis by EMIT.

The mean saliva/serum theophylline ratio was 0.46 ± 0.12 (s.d.) and although there were marked inter-individual differences the mean varied little with time. The degree of correlation between serum and saliva theophylline concentrations altered markedly with time, the correlation coefficient, *r*, increasing from 0.33 (*P* > 0.1) at 3 h to 0.81 (*P* < 0.001) at 6 h. The method of Deming (1943) and Smith *et al.* (1980) was used to calculate the slope and intercept to the regression line, serum on saliva, at each time point. It was found that the slope decreased while the intercept increased with time (Table 1). The individual scattergrams are shown in Figure 1. The saliva/serum theophylline ratio was unrelated to the salivary flow rate.

The original aim of this study was to provide a simple method of calculating theophylline half-life in patients on oral therapy and thereby predict a dose of theophylline which would maintain an individual

serum level within the therapeutic range, but because of the low correlation between serum and saliva theophylline levels at earlier time points this would prove impractical. It is probable that variations between subjects in the rates of absorption and distribution of theophylline contribute to this early lack of correlation. However Koup *et al.* (1979) and Slattery *et al.* (1980) have demonstrated that only one plasma concentration of theophylline is required accurately to predict a patient's maintenance dose. It might therefore be possible to use one saliva theophylline concentration measured 6 h after a single oral dose in the same fashion, since our results suggest that at that time serum theophylline concentration can be predicted from salivary concentration with some accuracy. It is intended to investigate this possibility further.

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ESTIMATION OF TRANSCORTIN CONCENTRATION BY MEASUREMENTS OF PLASMA PROTEIN-BINDING OF PREDNISOLONE AND BY ELECTROIMMUNODIFFUSION

Since the binding of prednisolone to plasma proteins occurs at transcortin and albumin, prednisolone exhibits nonlinear kinetics in the therapeutic dose

range (Jusko *et al.*, 1980; Frey *et al.*, 1980, 1981). Therefore, the concentrations of albumin and transcortin are mandatory for the interpretation of pred-