drugs, a few patients may respond. Others have found drowsiness to be a prominent side-effect of ketotifen (Dyson & McKay, 1980; Prowse, 1980), but at a dose of 1 mg twice daily only one of the 25 patients in this study complained of it.

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PHARMACOKINETICS OF A SINGLE EVENING DOSE OF SLOW RELEASE THEOPHYLLINE IN PATIENTS WITH CHRONIC LUNG DISEASE

Slow release theophylline preparations administered twice daily may be safely used for control of airways obstruction in patients with chronic lung disease (Marlin *et al.*, 1980). However, the theophylline dose requires individualizing for each patient because of variable theophylline clearance due to the interaction of factors such as severe airways obstruction, left and right heart failure, hepatic disease and smoking (Piafsky *et al.*, 1977a, b; Powell *et al.*, 1977; Powell *et al.*, 1978; Vicuna *et al.*, 1979) and also because some patients may demonstrate dose-dependent kinetics (Marlin *et al.*, 1980). Many patients with airways obstruction have symptoms predominantly during the night and early morning (Turner-Warwick, 1977). The purpose of this study was to evaluate the pharmacokinetics of slow release theophylline with the total daily dose requirement administered as a single evening dose.

Twelve male patients, aged 50 to 82 years, hospitalized for an acute exacerbation of airways obstruction were selected for this study after their condition had stabilized and their consent obtained. Nine patients had chronic bronchitis and emphysema, three chronic bronchitis with asthma, four right heart failure controlled with appropriate therapy and all had severe airways obstruction with FEV₁ less than 50% of predicted normal value. All patients were previous moderate smokers (10 to 30 cigarettes/day) for many years, but only four were smoking during the three months prior to the study. The patients gave a history of other diseases which included ischaemic heart disease (2), chronic renal impairment (2), gout (2), hypothyroidism (2), peptic ulcer (1), hypertension (1) and bronchial carcinoma (1). The patients were receiving various medications including salbutamol aerosol (12), oral corticosteroids (8), beclomethasone dipropionate (7) and theophylline (9) and all were continued during the study at maintenance doses.

There were no patients with impaired biochemical hepatic function.

The dose of slow release theophylline (Nuelin SR 250, 3M Riker Laboratories, 250 mg tablet) was selected on the basis of weight, clinical factors influencing theophylline clearance, previous dosage requirements or previous serum theophylline estimations. Seven patients received 750 mg, two 625 mg, two 500 mg and one 875 mg (5 to 12 mg kg⁻¹ day⁻¹) as a single evening dose at 2100 h. All patients had received this dosage for more than five days and nine patients had been changed from previous theophylline dosage schedules. On the study day venous blood samples for serum theophylline level estimations (radioimmunoassay, Clinical Assays) were taken immediately before dosage and after at 2, 4, 6, 8, 12, 16, 20 and 24 h.

The mean $\pm$ s.e. mean serum theophylline levels for all the patients are shown in Figure 1. The mean $\pm$ s.e. mean peak theophylline concentration was 99.2 ± 7.0 $\mu\text{mol l}^{-1}$ and the mean $\pm$ s.e. mean time to reach this peak concentration was 10.0 ± 0.7 h. The mean $\pm$ s.e. mean peak-trough serum theophylline level difference was 54.2 ± 5.9 $\mu\text{mol l}^{-1}$. There were no unwanted effects reported by the patients during the study although in four patients serum theophylline levels exceeded 110 $\mu\text{mol l}^{-1}$ (highest level—145.8 $\mu\text{mol l}^{-1}$). There was no clinical or pulmonary function evidence of deterioration of airways obstruction, although in ten patients serum theophylline levels fell below 50 $\mu\text{mol l}^{-1}$ at one or two sampling times during the 24 h period. However, the study was not specifically designed to assess the clinical efficacy of this dosage schedule.

Single dose and steady state studies with this slow release theophylline preparation have shown that peak serum levels usually occur between 4 and 6 h after the morning dose (McDevitt, Elwood & Russell,

Figure 1 The mean $\pm$ s.e. mean serum theophylline levels before and at various times for 24 h after a single dose of slow-release theophylline administered at 21.00 h to twelve patients with chronic lung disease after a period of five or more days on this dosage schedule.

1979; Svedmyr, Mellstrand & Svedmyr, 1979). This study shows that the time to peak concentration is longer at night indicating that the rate of absorption is slowed presumably because of factors including reduced autonomic and humoral activity and patient posture and immobility. Serum theophylline levels were maintained within the therapeutic range for most of the 24 h period and in all patients during the early hours of the morning and upon waking. The bronchodilator effect of theophylline is directly related to the logarithm of the serum concentration (Marlin *et al.*, 1979) and thus therapeutic serum

theophylline levels during the night and early morning might contribute to the control of symptoms during these times. Milledge & Morris (1979) have shown slow release theophylline (450 mg twice daily) to provide benefit in nocturnal asthma but with a significant incidence of unwanted effects, although there was no serum level monitoring. Fairfax, McNabb, Davies & Spiro (1980) have demonstrated improved morning lung function but no change in the overnight fall in peak expiratory flow rate in patients with chronic asthma with a single evening 450 mg dose of slow release theophylline, but serum levels were suboptimal. This study provides pharmacokinetic support for the use of single evening doses of slow release theophylline and further studies are required in patients with chronic lung disease to assess the clinical efficacy of this dosage schedule in controlling nocturnal and early morning symptoms of airways obstruction. For patients with a prolonged serum theophylline half-life, single daily dose therapy may be adequate to provide stable serum levels within the therapeutic range during both day and night. This therapy would be expected to improve patient compliance in drug taking and the appropriate dose should be selected on the basis of serum theophylline level monitoring.

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