motility. With this method, we have demonstrated that the maximal stimulatory concentration of caffeine ranges from 10^{-3} to 10^{-2} mol/l and the response varies from sample to sample.

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C.Y. HONG, D.M. CHAPUT DE SAINTONGE & P. TURNER

Department of Clinical Pharmacology, St Bartholomew's Hospital, London EC1A 7BE

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ORAL SUSTAINED-RELEASE AMINOPHYLLINE IN MEDICAL INPATIENTS

We read with interest the paper by Ramsay, Mackay, Eppel & Oliver (1980) on the use of oral sustained-release aminophylline in medical inpatients. It has been previously reported that 5–15% of patients may experience gastrointestinal toxicity at plasma levels below 20 $\mu\text{g/ml}$ (Ogilvie, 1978).

Only two patients (patients 12 and 16) included in the study had uncomplicated asthma.

We were surprised that patients 2 and 3 had their dose increased when they had already exhibited clinical toxicity at the lower dose; this was particularly disturbing in patient 3 whose plasma level was already above 20 $\mu\text{g/ml}$ at the lower dose and rose to 50 $\mu\text{g/ml}$ on the higher dose.

Five patients (Nos. 2, 3, 8, 14 and 15) experienced toxicity at the lower dose of 450 mg/day. Two of these

patients (Nos. 3 and 15) had plasma levels in excess of 20 $\mu\text{g/ml}$. In the other three patients, all of whom were over 60 years in age, heart failure was a major clinical problem. All of them were on diuretics and two were also receiving digoxin.

A further three patients (Nos. 5, 7 and 9) experienced toxicity at the higher dose of 900 mg/day. These three patients also had the problems of age, cardiac failure and its therapy.

Although the authors were unable, in this small sample, to demonstrate a statistically significant relationship between age, heart failure or diuretic treatment and toxicity, the occurrence of nausea at levels lower than 20 $\mu\text{g/ml}$ in patients with these complicating factors is not surprising. An interpretation of the findings in this study would be that

toxicity occurs at lower plasma levels in patients of advanced years with heart failure who are receiving diuretics and/or digoxin. We do not believe that the findings of this paper are relevant to the treatment of younger patients with uncomplicated asthma.

We suggest that the main conclusions which can be drawn from this study are—

1. The indication for oral theophylline should be carefully reviewed, particularly in patients where a diagnosis of asthma has not been made and complicating factors such as cardiac failure, diuretic and digoxin therapy are present.
2. Patients on theophylline should be monitored carefully for clinical toxicity and should have their

plasma levels measured. The dose should not be increased if clinical toxicity and/or a high plasma level is obtained.

3. The plasma levels at which nausea appear may well be lower in elderly patients with complicating factors such as congestive cardiac failure.

J.W. PATERSON & KENNETH F. ILETT

Department of Pharmacology, The University of Western Australia, Nedlands, Western Australia 6009

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ORAL SUSTAINED-RELEASE AMINOPHYLLINE IN MEDICAL INPATIENTS

I thank Professor Paterson and Dr Ilett for their comments (Paterson & Ilett, 1981). Our aim was to examine the safety and efficacy of the oral aminophylline formulation when it was prescribed according to the manufacturer's recommendations, and without the benefit of plasma theophylline levels. That is the way the drug is used in the United Kingdom. The data sheet indications are 'for the treatment and prophylaxis of bronchospasm associated with asthma, emphysema and chronic bronchitis (and) in the treatment of cardiac asthma and left ventricular or congestive cardiac failure'. Our results suggest that the recommended dosage is unsafe when applied to consecutive general medical inpatients with these indications for treatment. I agree that the findings are not relevant to young patients with uncomplicated asthma, and the indications for oral aminophylline should indeed be reviewed carefully. I hope that the manufacturer and the regulatory authority will do just that. They might also consider whether the data sheet gives sufficient emphasis to the dangers of theophylline toxicity.

Patients 2 and 3 had the dose of aminophylline increased after experiencing mild and transient symptoms at the lower dose. At that stage of the study we were not fully aware of the danger, and this sequence of events could happen very easily in ordinary practice in this country. The high plasma theophylline level in patient 3 was not available to us at the time (by design), and again this would be the case in ordinary practice. It is possible that sick elderly patients experience toxicity at lower plasma theophylline levels than the young, but I know of no evidence that this is so, and our data are insufficient to answer the question.

L.E. RAMSAY

University Department of Therapeutics, Royal Hallamshire Hospital, Sheffield S10 2JF

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