0.1–1 $\mu\text{mol/l}$ (McNeil *et al.*, 1981). Therefore, the concentrations used in our experiments approximated to the likely intrapulmonary concentrations in patients taking the drug for treatment of peptic ulcers. The present results obtained with ranitidine, and previous findings with cimetidine and metiamide (Platshon & Kaliner, 1978), indicate that drugs belonging to this class are unlikely to potentiate immunological mediator release in patients with asthma. Moreover, the conclusions from these *in vitro* studies are consistent with clinical observations of Leopold *et al.* (1979), who found that cimetidine, in daily oral doses of 1 g for 1 week, did not

cause deteriorations in peak flow rates or symptom scores and did not alter the severity of exercise-induced asthma.

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J. M. HUGHES, J. P. SEALE &
D. M. TEMPLE

*Department of Pharmacology, University of
Sydney, N.S.W. 2006, Australia*

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Influence of chronic dosing on theophylline clearance

Before accepting the statement of Efthimiou *et al.* (1984) in their paper on 'Influence of chronic dosing on theophylline clearance' saying that the therapeutic implications of their results are basic, some points must be raised concerning pharmacokinetics.

There are at least two reasons why the results of this study should be interpreted with caution. Firstly, the sampling time over 8 h after an oral dose yields only 6–7 h period for the determination of the terminal half-life. With a mean half-life of 7 to 8 h, as reported in that study, this is clearly too short for an accurate estimate of the apparent elimination rate constant. Secondly, the design of the intravenous study was such that the results are biased towards the clearance values obtained during the oral study. Differ-

ences between oral and intravenous clearances of more than 30% may have been missed. In the intravenous study, a loading dose was chosen to achieve a serum concentration that would be expected at steady-state with the clearance value found in the oral study. The observation time on a constant infusion rate was only about 1 h (disregarding the early distribution of about 30 min). This is too short for confirmation of steady-state even if multiple samples are obtained. Assuming a half-life of 8 h, the change in the serum concentration within 1 h is only about 10% of the difference between the current concentration and the steady-state value. In case of a difference between oral and intravenous clearances of, say, 30% the expected systematic shift in serum concentration during the observa-

tion period would be only 3% of the initial value, which is well within the assay error. Thus, concentration-dependent changes of theophylline clearance cannot be excluded as a possible cause for the differences in oral clearance that were observed between the single dose and chronic dose studies.

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S. VOŽEH & F. FOLLATH
Division of Clinical Pharmacology, Department of Medicine, University Hospital, Kantonsspital, CH-4031 Basel, Switzerland

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Influence of chronic dosing on theophylline clearance

Vožeh & Follath (1985) have given two reasons in criticizing our exclusion of concentration dependence as a possible mechanism for the difference in oral clearances of theophylline (Efthimiou *et al.*, 1984).

The first criticism, regarding the short sampling time compared with the terminal half-life, is valid when applied to the oral clearance determined from the first single oral dose. This criticism does not, however, apply to the oral clearance determined after chronic dosing because the calculation was performed on data obtained during a dosage interval at steady-state. The doubt regarding the oral clearance determined after the first single dose was, however, one of the reasons we repeated the clearance determination using intravenous infusion of theophylline and plateau drug levels.

The second criticism is based on the false premise that the intravenous loading dose was chosen on the basis of the clearance value found in the oral study. The size of the loading dose determines the plasma drug concentration at the end of the 20 min loading infusion and, as Vožeh & Follath (1985) point out, for some time thereafter. Thus, Vožeh & Follath (1985) argue that basing the intravenous loading dose on the oral clearance value will bias the apparent intravenous clearance value obtained towards the oral clearance value. The premise of this argument is false because, as stated in our paper (Efthimiou *et al.*, 1984), the intravenous loading dose was calculated for each subject using a volume of distribution of 0.5 l/kg, which is a

literature value. The oral clearance value was used only in the calculation of the maintenance infusion rate and not the loading dose. Thus, the observed plateau theophylline levels and the resultant intravenous clearance values were not biased by the oral clearance values.

Inspection of our data shows that there was no systematic pattern in plasma levels following the loading dose in the intravenous clearance studies. In the acute phase, after the intravenous loading dose plasma theophylline levels approached steady-state from above in four subjects (subjects 1, 2, 4 and 5) and from below in the other two subjects. Similarly, in the chronic phase, steady-state was approached from above in four subjects (subjects 1–4) and from below in the other two subjects. This rules out the likelihood that there was a systematic deviation in the measured plateau levels from the 'true' plateau levels, as suggested by Vožeh & Follath (1985). Thus, concentration dependent changes in theophylline clearance may reasonably be excluded as the cause for the differences in oral clearance.

D. J. MORGAN & K. RAYMOND
Victorian College of Pharmacy, 381 Royal Parade, Parkville, Victoria, Australia 3052

A. J. McLEAN
Department of Clinical Pharmacology, Alfred Hospital, Prahran, Victoria, Australia 3181

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