Ranitidine does not potentiate mediator release from human lung *in vitro*

Extracellular histamine inhibits antigen-induced histamine release from human basophils *in vitro*, apparently via H₂-receptors since it is antagonized by metiamide and burimamide (Lichtenstein & Gillespie, 1975). If there are H₂-receptors on human pulmonary mast cells which modulate histamine release via a similar mechanism, then H₂-receptor antagonists may potentiate antigen-induced release of histamine and leukotrienes with potential adverse effects in asthmatic patients receiving these drugs for unrelated disorders such as peptic ulcers (Henry, 1984). However, in experiments with human lung fragments *in vitro* (Platshon & Kaliner, 1978), single concentrations (50 µM) of cimetidine or metiamide did not significantly alter the immunological release of histamine and slow-reacting substance of anaphylaxis, which is now known to comprise leukotrienes (Samuelsson, 1980).

Ranitidine is a new H₂-receptor antagonist which is five times more potent than cimetidine (Daly *et al.*, 1981). It may be preferable for the treatment of peptic ulcers because it does not have the inhibitory effects on hepatic drug metabolism which occur with cimetidine (see Henry, 1984). The present experiments were performed to determine the effects of ranitidine, over a wide concentration range, on the release of histamine and leukotrienes from human lung fragments.

Macroscopically normal human lung tissue was obtained from operative specimens removed from patients undergoing resections for lung cancer. Lung fragments which were sensitized and challenged with *Dermatophagoides pteronyssinus* extract as described previously (Hughes *et al.*, 1983) were pre-incubated with ranitidine (0.01–100 µmol/l) at 37°C for 15 min before antigen challenge. The release of histamine and leukotrienes was determined by spectrofluorimetric assay and bioassay respectively as described (Hughes *et al.*, 1983).

Following antigen challenge the release of histamine was 30.5 ± 5.1% (mean ± s.e. mean, *n* = 6 lung specimens) of original tissue histamine content and the release of leukotrienes was equivalent to 2.25 ± 0.87 nmole/ml leukotriene E₄ (mean ± s.e. mean, *n* = 4). Ranitidine, over a wide concentration range, had little effect on antigen-induced mediator release (Table 1).

Table 1 Effects of ranitidine on antigen-induced mediator release from human lung *in vitro*. Values are mean ± s.e. mean

Concentration (µmol/l)	% Control	
	Histamine	Leukotrienes
0.01	100.3 ± 2.4 (4)†	98.0 ± 6.8 (4)
0.1	98.4 ± 2.2 (4)	83.3 ± 12.5 (4)
1	98.2 ± 4.0 (6)	85.8 ± 5.3 (6)*
10	106.2 ± 4.8 (5)	92.9 ± 5.1 (5)
100	103.4 ± 2.9 (5)	96.6 ± 7.0 (5)

†Figures in parentheses denote number of lung specimens

**P* < 0.05

None of the concentrations of ranitidine significantly altered the release of histamine. Only one concentration of ranitidine (1 µmol/l) significantly reduced leukotriene release compared with control values (*P* < 0.05, paired *t*-test, *n* = 6).

The present results, which have shown that the potent histamine H₂-receptor antagonist, ranitidine, does not alter the immunological release of histamine from human lung tissue, support the earlier findings of Platshon & Kaliner (1978), suggesting that human pulmonary mast cells do not possess functional histamine H₂-receptors. Thus it is evident that there are fundamental differences between these mast cells and human basophils in which it appears that histamine H₂-receptors are responsible for feedback inhibition of histamine release (Lichtenstein & Gillespie, 1975).

In general, the effects of ranitidine on leukotriene release resembled its effects on histamine release. Although one concentration (1 µmol/l) of ranitidine significantly reduced leukotriene release, the biological interpretation of this finding remains uncertain because the effect was small and not apparently concentration-dependent (Table 1). It has been suggested that lipoxygenase products of arachidonic acid have a facilitatory role in histamine release (Peters *et al.*, 1981) but the presence of histamine as a requirement for the synthesis and release of lipoxygenase products such as leukotrienes has not been documented.

The plasma concentrations of ranitidine in patients taking therapeutic doses range from

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-