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Effect of the new H_2-receptor antagonist ranitidine on plasma prolactin levels in duodenal ulcer patients

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Ranitidine is a new histamine H_2-receptor antagonist which has different chemical features to cimetidine; principally the central imidazole ring of histamine has been replaced by a furan ring. Ranitidine is 4–10 times as potent as cimetidine on a molar basis in inhibiting gastric acid secretion in man (Domschke & Domschke 1980). The intravenous administration of cimetidine stimulated prolactin secretion (Carlson & Ippoliti 1977; Burland et al 1979; Macaron et al 1979) whereas the standard oral treatment did not (Van Thiel et al 1979; Nelis & Van de Meene 1980). The present study investigated the effect of oral ranitidine treatment on plasma prolactin levels in duodenal ulcer patients.

Consecutive outpatients with endoscopically proven duodenal ulcer (and free of systemic disease) were allocated to either ranitidine hydrochloride, one tablet (150 mg) twice a day, or to matching placebo, one tablet twice a day, according to a randomized double-blind design. Patients were permitted to take antacid tablets when necessary. No patients had been on neuroleptic agents and none had taken cimetidine in the previous four weeks. Patients underwent endoscopy at the beginning of the trial; they made a second visit after two weeks of therapy and a third after four weeks when endoscopy was again performed. (The clinical aspects of the trial (Marks & Wright, in preparation) will be reported elsewhere.) Blood was drawn at the first, second and third visits (between 09.00 h and 11.00 h) and the plasma was assayed for prolactin (by a radioimmunoassay kit purchased from Diagnostic Products Corporation, Los Angeles) and for ranitidine (by the method of Carey & Martin 1979). The results were analysed by non-parametric statistical tests.

There were 19 males (mean age: 33·1 years) and 6 females (mean age 31·5 years) in the ranitidine group and 20 males (mean age: 38·6 years) and 9 females (mean age: 39·0 years) in the placebo group. There were no significant changes in prolactin levels over the four weeks of treatment within either the ranitidine or the placebo groups (Table) and no significant differences emerged between the ranitidine and placebo groups at any of the three visits (Table). Spearman's rank correlation coefficient was obtained between the plasma ranitidine and the plasma prolactin concentrations in the male patients only (the female sample was too small): this was 0·28 at 2 weeks (not significant) and 0·19 at 4 weeks (not significant).

Oral ranitidine treatment (300 mg daily) therefore did not influence plasma prolactin levels in patients with duodenal ulceration. Our findings confirm the clinical trial data of Berstad et al (1980) and the intravenous ranitidine study of Nelis & Van de Meene (1980). Furthermore, in vitro experiments demonstrated that ranitidine had no dopaminergic effects and did not alter prolactin by any action on the pituitary (Yeo et al 1980). All these results refute the suggestion of Carlson & Ippoliti (1977) that the blockade of H_2-receptors produces raised prolactin levels. Sharpe et al (1980) found that another H_2-antagonist (oxmetidine HCl SK & F-92994) with similar physio-

Table 1. Effect of ranitidine and placebo on plasma prolactin concentrations.

	Plasma prolactin (ng ml^{-1})			
	Baseline*	2 weeks*	4 weeks*	P**
Ranitidine group				
Males (n = 19)	15 (5–19)	9 (2·5–15)	9 (5–15)	n.s.
Females (n = 6)	6·5 (6–10)	7 (6–7)	8·5 (6–13)	n.s.
Placebo group				
Males (n = 20)	8 (2–13·5)†	7 (1–9)†	8·5 (6–11·5)†	n.s.
Females (n = 9)	10 (4·0–14·5)†	6 (0–10)†	9 (3·0–15·5)†	n.s.

* Prolactin expressed as median (interquartile range).
** Friedman's two-way analysis of variance.
n.s. = not significant.
† n.s. when compared against corresponding values in the ranitidine group (Wilcoxon sum of ranks test).

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chemical properties to cimetidine also failed to raise prolactin in healthy volunteers after intravenous injection. They speculated that the specific effect of cimetidine on prolactin was due to a particular feature of the cimetidine molecule itself.

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The stimulation of lysosomal enzyme secretion from human polymorphonuclear leucocytes by leukotriene B_4

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The structure of LTB_4 (isomer III), a metabolite of arachidonic acid formed after initial lipoxygenase action, has been confirmed as 5(*S*),12(*R*)-dihydroxy-6-*cis*-8-*trans*-10-*trans*-14-*cis*-eicosatetraenoic acid (Corey et al 1980). Its principal biological activities in vitro are to stimulate the aggregation and movement (chemokinesis and chemotaxis) of leucocyte cell types (Smith 1981) and it is equipotent to the complement-derived peptide C5a, and to the synthetic cytotaxin FMLP, formyl-methionyl-leucyl-phenylalanine (Bray et al 1981). A further effect of cytotaxins on leucocyte function in vitro is degranulation and the release of lysosomal enzymes. One group of workers (Goetzl & Pickett 1980) found that LTB_4 (isomer III) is only approximately one third as active as the chemotactic peptides, C5a and FMLP, in stimulating lysosomal enzyme release while others (Palmer et al 1981) reported that the leukotriene was apparently as active as FMLP. We have therefore studied the effects of LTB_4 (isomer III) and FMLP, separately and in combination, on the release of β-glucuronidase and lysozyme from human peripheral polymorphonuclear leucocytes (PMNs). In addition we have examined the effects of the closely related slow reacting substances, LTC_4 and LTD_4, in the system.

Cell suspensions (>98% PMNs) were prepared from 100 ml samples of heparinized blood, obtained by venepuncture from normal male subjects, aged 25 to 40 years, by dextran sedimentation, Ficoll Hypaque separation and hypotonic lysis of residual red cells (Walker et al 1979). The cells were resuspended at a concentration of 1×10^7 cells ml^{-1} in Eagle's Minimum Essential Medium (MEM) buffered to pH 7·4 with HEPES. LTB_4 (isomer III) was prepared as described previously (Ford-Hutchinson et al 1980), FMLP and cytochalasin B (Sigma Chemical Co.) were dissolved in dimethylsulphoxide (DMSO) and serial dilutions were made in MEM. The final concentration of DMSO never exceeded 0·05%. In each experiment 0·25 ml aliquots of the cell suspension were incubated in a shaking water bath for 15 min at 37 °C with cytochalasin B (final concentration of 5 μg ml^{-1}). LTB_4 (isomer III), FMLP, LTC_4 or LTD_4 were added in 0·25 ml MEM to give the final concentrations described in Table 1 and the incubation was continued for a further 15 min. The mixtures were then removed, centrifuged for 10 min at 300 *g* and lyosyme, β-glucuronidase and lactate dehydrogenase activities measured in the supernatants by conventional methods (Smolelis & Hartsell 1943; Fishman et al 1967; Anon 1970). The results (Table 1) are expressed as a percentage of the total enzyme recovered from cells exposed to 0·2% (v/v) Triton X 100.

FMLP caused a dose-dependent release of the two lysosomal enzymes over the range 10^{-9} to 10^{-6} M, the ED50s being $2·5 \times 10^{-8}$ M and 2×10^{-8} M for β-glucuronidase and lysozyme respectively. LTB_4 (isomer III) produced a much weaker response and LTC_4 and LTD_4 were without effect

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