

Correspondence

Alteration of H₂ receptor sensitivity in duodenal ulcer patients

SIR,—The important study by Jones *et al* (*Gut* 1988; 29: 890–3) has highlighted the problem of rebound acid hypersecretion and, in the process, brought the concept of up-regulation of H₂ receptors into the ambit of the clinical gastroenterologist. Appreciation of the high relapse rates after ulcer healing with a potent H₂-receptor blocker gave rise to the notion that such treatment may be followed by 'rebound hypersecretion'. This nagging suspicion was supported by elegant studies carried out by the Berstad group in control subjects,^{1,2} but its occurrence in the duodenal ulcer setting awaited confirmation.^{3–5} It is against this background that the McMaster study, in a small group of healed duodenal ulcer patients, should be viewed. They found increased acid secretory responses to graded doses of an intravenous infusion of the H₂ agonist impromidine after three months maintenance treatment with ranitidine. They also reported an enhanced antisecretory effect of a single intravenous bolus of ranitidine. The study, however, is not without certain methodological limitations.

First, all patients were 'pretreated' with ranitidine 150 mg nocte for three days and the baseline and second tests were carried out 10 hours after the last dose of ranitidine. It is thus probable that the drug was still present in the plasma at the time of testing.^{2,6} This, it may be argued, would have had an equally inhibitory effect on both tests. There is, however, another possibility which might conceivably have influenced the interpretation of the data. Could the acid inhibitory effect of the ranitidine after three days 'pretreatment' have been appreciably greater than that after three months treatment? Hyman *et al*⁷ in their report on ranitidine tachyphylaxis in children, noted a mean inhibition of the maximal acid secretory response of 89% after two days and a mere 24% after two to four weeks treatment with this drug. One can but speculate as to whether the significantly higher responses after maintenance ranitidine in the McMaster study do not, in part at least, reflect a gradual escape from the effect of ranitidine rather than an increase in the number of H₂ receptors. The accentuated antisecretory effect of an iv bolus of ranitidine at the end of the study is more difficult to reconcile with ranitidine tachyphylaxis. It is not clear, however, whether this accentuation was significant (Table, $p=0.05$), or not (Figure, $p=0.06$). In any event, their finding contrasts with that of Prichard *et al*⁸ who showed a significant decrease ($p<0.025$) in the effectiveness of an iv bolus of ranitidine in

reducing pentagastrin stimulated acid secretion in patients on longterm ranitidine therapy. Their results were comparable with those of similar studies with cimetidine,⁹ and more in keeping with the concept of H₂-receptor blocker tachyphylaxis.

The second point relates to the lack of endoscopic control of possible asymptomatic recurrences during the course of the study. The Dundee group¹⁰ reported endoscopic recurrences in no fewer than 28% of patients within two months of entry into a maintenance study with ranitidine 150 mg nocte after duodenal ulcer healing. Ulcer recurrences, albeit asymptomatic, may well have influenced the results of the McMaster study. There is good evidence that patients with an active duodenal ulcer have increased parietal cell responsiveness and sensitivity,^{11,12} and that the latter diminishes with ulcer healing.^{13–16} It is conceivable, therefore, that inclusion of a few patients who developed a recurrence at the time of the second test may have exaggerated any increase in parietal cell responsiveness to impromidine.

These comments do little to detract from the seminal contribution of the McMaster workers in the evolution of our thinking on 'rebound hypersecretion' and up-regulation of H₂ receptors after profound acid inhibition. The Glasgow group have reported rebound nocturnal acid hypersecretion after four weeks treatment with nizatidine 300 mg nocte in patients with previous duodenal ulceration,¹⁷ the Cape Town group^{15,16} have shown that the decrease in acid secretory responses on duodenal ulcer healing is more marked in sucralfate than in ranitidine treated patients, and the CURE, UCLA group¹⁸ found increased acid secretory responses after four weeks treatment with omeprazole in a mixed group of duodenal ulcer patients. These changes are not unique to man, and Coruzzi and Bertaccini¹⁹ have recently shown a transient increase in parietal cell sensitivity in the conscious cat after ranitidine given for one month. Bertaccini has for long championed the concept of up-regulation of the H₂ receptors,²⁰ but the McMaster group have focussed attention on its clinical relevance.

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Reply

SIR, — We should like to thank Professor Marks for his kind and interesting remarks which focus on the two questions of tachyphylaxis and rebound hypersecretion which may or may not be related. Neither of these questions formed the primary objective of our study.

Professor Marks concludes that the study by Prichard *et al*¹ and the brief abstract by Hyman *et al*² show tachyphylaxis to continued H₂-receptor antagonist administration. In these studies the gastric secretory response to pentagastrin or a peptone meal was altered by a course of ranitidine showing reduced effectiveness on the peak and maximal acid output. This could have resulted from several possible mechanisms other than tachyphylaxis, which could not be determined by the methodologies used in these studies. The possibilities include a change in the parietal cell mass or the secretory drive, and/or an increase or decrease in the density or affinity of any of the four recognised receptors for the gastric parietal cell.

Our study showed an enhanced effect of ranitidine on the H₂-receptor but whether there were changes in any other modalities was never addressed. The response of the gastrin and/or cholinergic receptors might for example have been paradoxical? The accentuated effect of an intravenous bolus of ranitidine at the end of the study, as Professor Marks concedes, cannot be reconciled with tachyphylaxis.

Prichard *et al* and Hyman *et al* used pentagastrin as their secretagogue which raises two immediate problems with interpretation. H₂-receptor antagonist inhibition of pentagastrin stimulated acid secretion is non-competitive^{3,4} and the secretagogue action of pentagastrin is indirect *via* ECL and other cells.

The Prichard study¹ should have been able to detect an increase in BAO and MAO if the parietal cell mass increased with treatment and an accompanying decreased response to ranitidine. Even if this had been present, however, it could have been masked by the lack of a ranitidine pretreatment at the beginning of the study. This was corrected in our study and although Professor Marks asks whether the effect of ranitidine . . . three days pretreatment could have been greater than after three months