The H₂-Receptor Antagonist Era in Duodenal Ulcer Disease

I.N. MARKS, M.B., Ch.B., F.R.C.P., F.A.C.G.

Gastrointestinal Clinic, Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa

Received September 1, 1992

This paper reviews the remarkable impact of H₂-receptor antagonists on duodenal ulcer management. The development and the scientific rationale of these agents are presented, and efficacy and safety aspects in the short- and long-term treatment of duodenal ulcer disease discussed. Attention is focused on the possible role of “acid rebound” in ulcer relapse following the withdrawal of therapy and on the clinical relevance of prolonged suppression of acid secretion in patients on long-term therapy.

HISTORICAL ASPECTS OF ULCER THERAPY

The medical treatment of peptic ulcer has undergone some interesting changes since Pliny extolled the virtues of the “milk of an asse or cow” in the first century A.D. Frequent milk feeds, immortalized by the Sippy regime in the early twentieth century and the Winkelstein milk drip in the mid-1930s, was considered standard ulcer treatment until as recently as 20 years ago. This therapeutic approach has always been closely linked with the use of antacids. Celsus used neutralizing earths for abdominal distress in the first century A.D., Brinton employed bicarbonate preparations in the mid-1850s, and insoluble, non-absorbable antacids provided the basis of ulcer therapy from the mid-1920s [1].

The time-honored use of antacid and milk regimens was challenged, over the years, by a number of provocative approaches based largely on current prejudice and, later, by the diligent pharmacologic exploration of folklore remedies such as cabbage juice, potatoes, liquorice, and seaweed. Jean Cruveilhier’s case report of the management of a bleeding ulcer in 1830 (Table 1) provides an interesting cameo of medicine in a bygone era but, above all, offers a melancholy warning regarding the limitation of all forms of medical treatment in the management of bleeding peptic ulcers. Continental workers, during the post-World War II period, used blood transfusions alternating with subcutaneous novocaine, electro-coagulation of the pre-frontal lobe, and other remedies such as ichthyol, and ingenious workers in the West tried stilbestrol [2], subcutaneous secretin, gastric freezing, and gastric irradiation with equal enthusiasm. Douthwaite recommended cannabis indica in 1947 for ulcer patients to “lend enchantment to the dietary” and Gefarnil, a cabbage-juice extract, enjoyed a short vogue before being superseded by carbenoxolone sodium, a derivative of liquorice root. This mucosal strengthening agent, with a seemingly impeccable scientific rationale, was hailed as a major therapeutic breakthrough in 1968. It was regarded by some as the “yardstick of a well-proved medical treatment,” but was abandoned shortly after, when it was appreciated that the drug carried with it the hazards of hypertension, edema, and potentially lethal hypokalemia [3]. One hesi-


### TABLE 1
Medical Treatment of Bleeding Peptic Ulcer c. 1830

| Date       | Description                                      |
|------------|--------------------------------------------------|
| April 15, 1830 | RECURRENCE OF EPIGASTRIC PAIN                     |
| April 30   | HAEMATEMESIS; carried to Charité                  |
|            | • Bleeding precluded by gross anaemia             |
|            | • Mustard plasters to feet                        |
| May 1      | SMALL HAEMATEMESIS ONLY                          |
|            | • 20 leeches to epigastrium                      |
|            | • Mustard plasters to calves                      |
|            | • Rice eau de Kabel & syrup of quinces           |
|            | • Diet                                            |
| May 2      | ISQ                                              |
|            | • 20 leeches to anus                             |
|            | • Mustard plasters                               |
|            | • Same drink                                      |
|            | HAEMATEMESIS—DEATH                               |

**AUTOPSY:** LESSER CURVE GASTRIC ULCER
OPENING OF BRANCH OF CORONARY ARTERY

Jean Cruveilhier (1791–1874)

tates to reflect on the fact that the drug was endorsed by the leading British gastroenterologists of the day. Xylamide, an alleged mucosal protective agent, was tried without much success, and amylopectin sulphate, a synthetic polysaccharide with an antipeptic effect, suffered the same fate [4].

The therapeutic turmoil of the late 1960s reflected the profound lack of any meaningful advance in the understanding of the duodenal ulcer diathesis and, in general, treatment continued to be governed by the well-worn equation of ulcer etiology—acid pepsin aggression versus impaired mucosal resistance. This approach provided the rationale for the development of potent acid inhibitors on the one hand and effective mucosal protective ulcer-healing agents on the other. Recent appreciation of the importance of *H. pylori* in the etiology of duodenal ulcer disease and, in particular, its role in duodenal relapse, has resulted in a shift in emphasis from the healing of the ulcer to the possible cure of the disease. The therapeutic pendulum continues to swing.

**DEVELOPMENT OF H2-RECEPTOR BLOCKERS**

The fundamental discovery by Black and co-workers [5] of the so-called H2-receptors, identified by the selective antagonist burinamide, was of profound importance in unraveling the physiology of histamine and gastrin. It also ushered in a new era of ulcer therapeutics. Burinamide was neither sufficiently potent nor well enough absorbed after oral administration to warrant further clinical study. Modification of burinamide to yield less polar, more active H2-receptor antagonists, however, led in turn to metiamide [6] and cimetidine [7]. The former, while active by mouth and
clinically effective, showed evidence of bone-marrow toxicity and immunological changes [8] and was withdrawn from further clinical study.

By a happy accident of timing, cimetidine, the potent H₂-receptor blocker, was developed at about the same time as the fiber-duodenoscope became generally available, and the concept of controlled clinical trials firmly established. The unequivocal superiority of cimetidine over placebo in short-term duodenal ulcer healing was soon confirmed by a series of superbly orchestrated, worldwide, endoscopically controlled studies. The scientific appeal and convincing short-term effect of cimetidine prompted Wormsley to state, in 1977, that “it is already possible to conclude that the H₂-receptor blockers make all other medical treatment of duodenal ulcer obsolete.” The effect of cimetidine and, with it, realization of the financial potential of the ulcer market, set the scene for an ongoing race for the newer competitive H₂-receptor blockers and, indeed, the pharmaceutical breaching of both the outer and inner bastions of the parietal cell. Ranitidine became available in 1980, and famotidine, nizatidine, and roxatidine were introduced in many countries over the next few years. There can be no class of drug that has been researched so thoroughly.

CHEMISTRY

The H₂-receptor antagonists are characterized by two functional groups—an aromatic ring system and a polar (unchanged at physiological pH) planar group—which are connected by a flexible chain. The chemical structures of the currently available H₂-receptor antagonists are shown in Fig. 1. Cimetidine is an imidazole derivative, ranitidine and nizatidine belong to the basically substituted furans and
thiazoles, respectively, famotidine is a member of the guanidino-thiazole group, and roxatidine belongs to the aminoalkylphenoxy series. The approximately equipotent daily dose of these agents, shown in Table 2, ranges from 40 mg for famotidine to 800 mg for cimetidine. Molecular modeling studies suggest that the increased potency of famotidine, on a weight basis, is due to its greater H$_2$-receptor affinity [9].

TABLE 2
Dosages for Ulcer Therapy of Currently Available H$_2$-Receptor Antagonists

| H$_2$-Receptor Antagonist | Ulcer Therapy Dose (mg/day) |
|---------------------------|-----------------------------|
| Cimetidine                | 800                         |
| Ranitidine                | 300                         |
| Famotidine                | 40                          |
| Roxatidine                | 150                         |
| Nizatidine                | 300                         |

EFFICACY AND DURATION OF SHORT-TERM THERAPY

Duodenal ulcer healing studies show that approximately 70 to 80 percent of ulcers will be healed after four weeks' treatment with an H$_2$-receptor antagonist and that 90 to 95 percent will be healed after eight weeks. The McMaster group defined three primary determinants of healing derived from antisecretory data: the degree and duration of suppression of 24-hour intragastric acidity, and the length of treatment. They noted that a longer duration of antisecretory effect and/or a longer duration of treatment are of greater importance than potency of acid suppression for duodenal ulcer healing [10,11].

Earlier reports had suggested that ulcer healing, once initiated, may continue despite withdrawal of the H$_2$-receptor antagonist. Johannessen et al. [12] treated duodenal ulcer patients with cimetidine for four weeks or cimetidine for one week followed by placebo for three weeks. The four-week healing rate in both groups was 68 percent. Lance and Gazzard [13] had previously studied two groups of patients with duodenal ulcer treated with cimetidine for six weeks or cimetidine given until they became asymptomatic (about two weeks). The relapse rates after three months were similar in both groups. It is difficult to reconcile the findings in these two relatively small studies with those of the more substantial McMaster analyses.

DOSAGE REGIMENS

The recommended dosage regimen of cimetidine has evolved from the four times daily (qds) to the twice daily (bd) and eventually a single daily dose, whereas the dosage regime of ranitidine has evolved from the bd to a single nocturnal dose. The switch to once-a-day dosing, prompted by the potential threat of once-a-day dosing with the newer H$_2$-receptor antagonists and omeprazole, was justified on the grounds of better compliance and the need to achieve better control of nocturnal acid secretion.

The concept of selective suppression of nocturnal acid secretion is applied widely in the marketing of H$_2$-receptor antagonists [14]. Clinical studies, however, suggest that morning or evening dosing with full doses of these drugs achieves comparable
duodenal ulcer healing rates [15–19]. The data thus suggest that selective suppression of nocturnal acid secretion is not essential for duodenal ulcer healing, and that a prolonged period of acid inhibition during the day may suffice.

By the same token, Merki et al. [20] showed that early evening dosing with a full dose of an H₂-receptor antagonist produces a more profound decrease of 24-hour intragastric acidity than a similar dose taken at bedtime, but studies confirming the advantage of this early evening regimen in terms of ulcer healing are still awaited.

RELAPSE RATES

Recurrent rates following initial duodenal ulcer healing with an H₂-receptor antagonist—of the order of 70–90 percent in one year—were appreciably higher than those reported in the pre-cimetidine era. Langman [21], in his review on the long-term course of duodenal ulcer, reported relapse rates of 20–45 percent after about five years, and Spiro [22] regarded duodenal ulcer as a tame disorder which "did not seem to require perpetual therapy from the physician or eternal vigilance from its owner." These differences could perhaps be reconciled with the fact that approximately 25 percent of endoscopic recurrences are unassociated with symptoms, and that clinically mild relapses account for a proportion of the remainder.

The reported increase also raised the question as to whether the H₂-receptor antagonists do not, in themselves, invite a higher relapse rate [3]. Relapse rates after initial treatment with colloidal bismuth agents are appreciably, and often significantly, lower than those following initial treatment with an H₂-receptor antagonist, and a similar advantage has been reported in most studies in patients healed initially with sucralfate [23]. The reason for the trend toward lower relapse rates following ulcer healing with mucosal protective agents is not clear. The antimicrobial action of the colloidal bismuth agents against H. pylori, discussed elsewhere in this symposium, is clearly a factor, and differences in the quality of ulcer healing following treatment with an H₂-receptor antagonist and the mucosal protective agents may have some relevance. A third possibility relates to the concept of "acid rebound" following treatment with an H₂-receptor antagonist [24].

REBOUND ACID HYPERSECRETION

The evidence for a rebound increase in gastric acid secretion after withdrawal of H₂-receptor antagonists is strong in control subjects and in duodenal ulcer patients in remission [25–31]. The data in all but one [32] of the studies in patients following successful treatment of an active duodenal ulcer is less convincing [33–37], but this finding may be linked with the tendency for acid secretory responses to fall with ulcer healing. Sucralfate healing is consistently associated with a significant decrease in all acid secretory parameters, whereas responses after healing with an H₂-receptor antagonist show little change over pre-treatment levels. The failure of the acid secretory responses to fall, despite ulcer healing, has been construed as evidence of H₂-receptor antagonist-related "acid rebound" [34].

Several views have been advanced to identify the cause of "acid rebound" following treatment with an H₂-antagonist. "Upregulation" of the H₂-receptors has been suggested [27], but appropriate H₂-receptor counts have not been performed. Hypergastrinemia induced by prolonged acid inhibition has also been suggested as a possible mechanism for acid hypersecretion after withdrawal of therapy, but studies with various H₂-receptor antagonists have shown that the raised gastrin levels during
therapy revert to normal before rebound acid hypersecretion becomes apparent [28]. It is not known whether the development of "tolerance" during treatment [38,39], defined as the decreased effectiveness of H₂-receptor blockade with time, translates into "acid rebound" once treatment is withdrawn.

The clinical relevance of "acid rebound" after treatment with an H₂-receptor antagonist cannot be excluded, despite the transient nature of this phenomenon. Available data suggest that the majority of relapses occur within the first few months following documented ulcer healing and withdrawal of treatment [40], and a close correlation between acid secretory status after duodenal ulcer healing and early relapse has been reported [41,42]. The tantalizing possibility that *H. pylori* and various mediators associated with inflammation and duodenitis may play a role in this phenomenon is yet to be investigated.

**LONG-TERM STRATEGY**

Chronic duodenal ulcer is a relapsing disease, and it is generally accepted that a long-term treatment strategy is required for the majority of patients. Appreciation of the value of continuous low-dose treatment with an H₂-receptor antagonist in reducing the liability to relapse established the concept of maintenance therapy—and added a new dimension to the management of duodenal ulcer. The dilemma was aptly expressed in the title of an editorial in *The British Medical Journal* in 1978 [43]: "Cimetidine for ever (and ever and ever...?)" Some sceptics [3] likened cimetidine to an unsuccessful marriage—"a moment of bliss and a life-time of maintenance." They went further. The rationale of treating all ulcer patients with maintenance therapy after initial ulcer healing was questioned on the grounds of cost, possible long-term side effects, and, indeed, efficacy. Although maintenance treatment with ranitidine is marginally superior to that with cimetidine [44], one-year relapse rates with H₂-receptor antagonists are usually of the order of 30 percent. Furthermore, relapse rates on stopping maintenance therapy are similar to those found in patients after short-term healing [45].

There are other therapeutic options. Some patients with less aggressive disease are treated with recurrent full-dose courses for each relapse (intermittent treatment) [46], while others take the drug for a few days on an ad hoc basis for symptomatic relief (on-demand treatment) and report to their doctors only in the event of persistent or severe symptoms. The hazard of an increased incidence of complications with the latter two options has not been fully evaluated. Maintenance treatment with cimetidine may be cost-effective in the first two years after duodenal ulcer healing [47], but there is no consensus on this regimen [48].

The place of maintenance treatment with an H₂-receptor antagonist in patients with a history of frequent and severe relapses and in the elderly with a history of complications appeared, until recently, to be unassailable. This orthodox approach is now being challenged by an increasing appreciation of the role of *H. pylori* in duodenal ulcer relapse, and by remarkable developments in mini-access surgery. There is strong evidence that eradication of *H. pylori* is associated with a dramatic reduction, and virtual elimination, of ulcer relapse [49], and many workers are of the opinion that *H. pylori* eradication is the preferred option in all patients being considered for maintenance therapy—or elective duodenal ulcer surgery. Laparoscopic vagotomy may yet prove a significant and cost-effective alternative to mainte-
nance therapy in patients with aggressive duodenal ulcer disease in whom *H. pylori* eradication cannot be achieved.

**SAFETY ASPECTS**

The H$_2$-receptor antagonists have a remarkable safety record, surprising in view of the strategic location of the H$_2$-receptors in other organs [50].

*Side Effects*

Headache, nausea, dizziness, constipation, vomiting, and abdominal pain are rarely encountered; anti-androgenic side effects such as gynecomastia and impotence have been recorded in patients receiving large doses of cimetidine or, even less commonly, ranitidine. Central nervous system side effects in the elderly, such as mental confusion, restlessness, agitation, and depression, have also been reported in patients treated with cimetidine or ranitidine [9].

*Drug Interactions*

Several drug interactions have been recorded in patients receiving cimetidine. These include interactions with theophylline, warfarin, phenytoin, propanolol, metopropol, diazepam, and lidocain. It is suggested that cimetidine inhibits the hepatic metabolism of these and other drugs by binding directly to cytochrome p-450, a major component of the mono-oxygenase system, thus reducing the substrate interactions with other drugs. Caution should therefore be exercised in prescribing cimetidine to patients on these drugs. The interaction between ranitidine and cytochrome p-450 is much lower than that between cimetidine and cytochrome p-450, and it does not appear to occur with famotidine [9].

Interference with the gastric alcohol dehydrogenase (ADH) system by certain H$_2$-receptor antagonists during acute alcohol intake may increase the systemic bioavailability of alcohol and raise peak blood alcohol levels by as much as 20 percent. This reaction applies particularly to cimetidine and, to a lesser extent, nizatidine [51,52].

*Suppression of Acid Secretion*

The ongoing debate regarding the effect of sustained pharmacologic suppression of acid secretion has focused largely on the relevance of acid secretion in health and disease and, in particular, the possible risk of gastric cancer. These concerns put the brake on the development of the unsurmountable or irreversible H$_2$-antagonist and stalled, for a while, the clinical trials with omeprazole. They have also prompted an enquiry as to the feasibility of somewhat less potent, reversible proton pump inhibitors.

Acid is required to facilitate peptic digestion of food and foreign antigens, favors the release of vitamin B$_{12}$ from food, increases Fe$^{+++}$, Ca$^{+++}$, and trace metal solubility and absorption and, as important, provides a barrier against infectious agents. It is well established that a decrease of intragastric acidity leads to intragastric bacterial colonization [53,54], and this condition, in turn, may expose the patient to the risk of enteric infections. This problem is minimal with present dose regimens of H$_2$-receptor antagonists, but drug regimens which inhibit acid secretion over the full 24-hour period may be another matter. Patients in the post-operative or intensive-care setting represent an important risk group. Such patients may suffer an increased
incidence of nosocomial pneumonia and sepsis as a result of gastric bacterial colonization due to pharmacologic suppression of gastric acidity in stress ulcer prophylaxis [55].

Putative mechanisms linking prolonged acid suppression with gastric cancer have been comprehensively reviewed by Soybel and Modlin [56]. The lingering hypothesis that intragastric bacterial overgrowth may lead to raised gastric nitrite and N-nitroso levels does not appear to have any clinical relevance in patients on current H₂-receptor antagonist dosage regimens, and the relatively modest rise in serum gastrin levels consequent upon acid suppression in this setting is hardly a matter of concern.

A third mechanism relates to the finding of epithelial proliferation and neoplastic transformation in rats treated with a variety of potent candidate H₂-receptor antagonists. Tiotidine caused dysplasia or neoplasia in the distal stomach, SKF 93479 elicited focal hyperplasia and hyperkeratosis of the forestomach, and lupitidine produced squamous carcinomas of the stomach. The absence of such changes in experimental animals treated with the currently used H₂-receptor antagonists suggests that carcinogenic potential is linked to the structural properties of individual agents rather than to their efficacy in inhibiting acid secretion [56].

QUO VADIS

The hitherto dominant position of H₂-receptor antagonists in ulcer therapy—they accounted for no less than 85 percent of all ulcer tablets used in the U.S.A. in 1989—is currently being challenged by the irreversible proton pump inhibitors, on the one hand, and by evolving concepts on the role of H. pylori in duodenal ulcer disease on the other [57]. These and other factors such as mucosal protection, growth factors, and the possible development of less potent, reversible proton pump inhibitors promise to keep the ulcer debate active, but the efficacy, safety, and long track record of the H₂-receptor blockers should ensure their place in duodenal ulcer therapy for many years to come. History has taught us, however, that nothing is sacrosanct in ulcer therapeutics.

REFERENCES

1. Lam SK: Antacids: The past, the present and the future. In Bailliere’s Clinical Gastroenterology, Vol 2. Edited by DW Piper. London, UK, Bailliere Tindall, 1988, pp 641–654
2. Truelove SC: Stilboestrol, phenobarbitone and diet in chronic duodenal ulcer. Brit Med J 2:559–561, 1960
3. Marks IN: A sceptical view of medical treatment. In Topics in Gastroenterology 7. Edited by SC Truelove, CP Willoughby. Oxford, UK, Blackwell, 1979, pp 111–129
4. Bockus HL: Management of uncomplicated peptic ulcer. In Gastroenterology. Third Edition. Vol 1. Edited by HL Bockus. Philadelphia, PA, Saunders, 1974, pp 674–709
5. Black JW, Duncan WAM, Durant CJ, Ganellin CR, Parsons ME: Definition and antagonism of histamine H₂-receptor. Nature 236:321–326, 1972
6. Black JW, Duncan WAM, Emmett JC, Ganellin CR, Hesselbo T, Parsons ME, Wylie JM: Metiamide—an orally active histamine H₂-receptor antagonist. Agents & Actions 3:133–134, 1973
7. Brimblecombe RW, Duncan WAM, Durant CJ, Emmett JC, Ganellin CR, Parsons ME: Cimetidine—a non-thiourea H₂-receptor antagonist. J Int Med Res 3:86–88, 1975
8. Annotation. Cimetidine, publicity and safety. Lancet i:129, 1977
9. Schunack W: Pharmacology of H₂-receptor antagonists: An overview. J Int Med Res 17 (Supplement 1):9A–16A, 1989
10. Burget DW, Chiverton SG, Hunt RH: Is there an optimal degree of acid suppression for healing of duodenal ulcer? A model of the relationship between ulcer healing and acid suppression. Gastroenterology 99:345–351, 1990
11. Hunt RH: Pathophysiology of peptic ulcer: Role of acid in ulcerogenesis and healing. In Mechanisms of Peptic Ulcer Healing. Edited by F Halter, A Garner, GNJ Tytgat. Dordrecht, The Netherlands, Kluwer, 1991, pp 173–182
12. Johannessens T, Kristensen P, Sandbakken P, et al: One and four weeks cimetidine treatment for duodenal ulcer. Scand J Gastroenterol 20 (Supplement 113):47, 1985
13. Lance P, Gazzard BG: Controlled trial of cimetidine for symptomatic treatment of duodenal ulcers. Br Med J 286:937–939, 1983
14. Gledhill T, Howard OM, Buck M, Paul A, Hunt RH: Single nocturnal dose of an H2-receptor antagonist for the treatment of duodenal ulcer. Gut 24:904–908, 1983
15. Lucke W, Marks IN, Adams G, Newton K, Wallace I: Comparison of nocturnal with morning dose of ranitidine 300 mg in short-term duodenal ulcer healing. S Afr Med J 75 (Supplement June 3): 11, 1989
16. Zaterka S, Massuda HK, Eisig JN, Chinzon D, Bettarello A: Is the inhibition of nocturnal gastric acid secretion the most important factor in duodenal ulcer treatment? A comparison between the effectiveness of single morning and nocte doses of ranitidine 300 mg. Rev Hosp Clin Fac Med Sao Paulo 44:185–188, 1989
17. Bianchi-Porro G, Parente F: Single morning dose versus bedtime dose of ranitidine in duodenal ulcer healing. Hepato-Gastroenterol 25:44, 1988
18. Bianchi-Porro G, Parente F, Sangaletti O: Inhibition of nocturnal acidity is important but not essential for duodenal ulcer healing. Gut 31:397–400, 1990
19. de Pretis G, Dobrilla G, Ferrari A, Fontana G, Maiolo F, Marenco G, Menardo G, Pallini P, Rossini FP, Saggio: Comparison between single morning and bedtime doses of 40 mg famotidine for the treatment of duodenal ulcer. Aliment Pharmacol Therap 3:285–291, 1989
20. Merki H, Witzel L, Harre K, Scheurle E, Neumann T, Rommel J: Single dose treatment with H2-receptor antagonists: Is bedtime administration too late? Gut 28:451–454, 1987
21. Langman MJS: The long term course of peptic ulcer. In Topics in Gastroenterology 7. Edited by SC Truelove, CP Willoughby. Oxford, UK, Blackwell, 1979, pp 99–109
22. Spiro HM: Should we take duodenal ulcer so seriously? J Clin Gastroenterol 1:199–200, 1979
23. Marks IN: Sucralfate: Efficacy and basis for therapy. In Ulcer Disease: Investigation and Basis for Therapy. Edited by EA Swabb, S Szabo. New York, Marcel Dekker, 1991, pp 263–285
24. Marks IN, Johnston DA, Young GO: Acid secretory changes and early relapse following duodenal ulcer healing with sucralfate, ranitidine, antacids and omeprazole. In Mechanisms of Peptic Ulcer Healing. Edited by F Halter, A Garner, GNJ Tytgat. Dordrecht, The Netherlands, Kluwer, 1991, pp 273–281
25. Aadland E, Berstad A: Parietal and chief cell sensitivity to histamine and pentagastrin stimulation before and after cimetidine treatment in healthy subjects. Scand J Gastroenterol 14:933–938, 1979
26. Frislid K, Aadland E, Berstad A: Augmented postprandial gastric acid secretion due to exposure to ranitidine in healthy subjects. Scand J Gastroenterol 21:119–122, 1986
27. Jones DB, Howden CW, Burget DW, Silletti C, Hunt RH: Alterations of H2-receptor sensitivity in duodenal ulcer patients after maintenance treatment with an H2-receptor antagonist. Gut 29:890–893, 1988
28. Fullarton GM, McLaughlan G, MacDonald A, Crean GP, McColl KEL: Rebound nocturnal hypersecretion after four weeks treatment with an H2-receptor antagonist. Gut 30:449–454, 1989
29. Nwokolo CU, Smith JTL, Pounder RE: Rebound intragastric hyperacidity occurs following dosing with cimetidine, nizatidine and famotidine. Gastroenterology 96:A369, 1989
30. Fullarton GM, MacDonald AMI, McColl KEL: Rebound hypersecretion after H2-antagonist withdrawal—a comparative study with nizatidine, ranitidine and famotidine. Aliment Pharmacol Therap 5:391–398, 1991
31. Prewett EJ, Hudson M, Nwokolo CU, Sawyer AFM, Pounder RE: Nocturnal intragastric acidity during and after a period of dosing with either ranitidine or omeprazole. Gastroenterology 100:873–877, 1991
32. Kummer AF, Johnston DA, Marks IN, Young GO, Tigler-Wybrandi NA, Bridger S: Changes in nocturnal and peak acid outputs after DU healing with sucralfate or ranitidine. Gut 33:175–178, 1992
33. Aadland E, Berstad A: Parietal and chief cell sensitivity to pentagastrin stimulation before and after cimetidine treatment for duodenal ulcer. Scand J Gastroenterol 14:111–114, 1979
34. Marks IN, Young GO, Tigler-Wybrandi NA, Bridger S, Newton KA: Acid-secretory response and parietal cell sensitivity in patients with duodenal ulcer before and after treatment with sucralfate or ranitidine. Am J Med 86 (Supplement 6A):145–147, 1989
35. Johnston DA, Marks IN, Young GO, Tigler-Wybrandi NA, Bridger SA: Duodenal ulcer healing and
acid secretory responses to modified sham feeding and pentagastrin stimulation. Aliment Pharmacol Therap 4:403-410, 1990
36. Savarino V, Mela GS, Zentilin P, Sumberzaj A, Bonifacino G, Celle G: Lack of gastric acid rebound after stopping a successful short-term course of ranitidine in duodenal ulcer patients. Am J Gastroenterol 86:281-284, 1991
37. Johnston DA, Marks IN, Young GO, Tigler-Wybrandi NA, Bridger SA, Zak J: Acid secretory responses and parietal cell sensitivity following duodenal ulcer healing with omeprazole, sucralfate and Maalox. Am J Med 91 (Supplement 2A):91S–94S, 1991
38. Nwokolo CU, Smith JTL, Gavey C, Sawyer A, Pounder RE: Tolerance during 29 days of conventional dosing with cimetidine, ranitidine, famotidine or nizatidine. Alim Pharmacol & Therap 45:29-46, 1990
39. Wilder-Smith CH, Halter F, Ernst T, et al: Loss of acid suppression during dosing with H2-receptor antagonists. Alim Pharmacol & Therap 45:15-28, 1990
40. Johnston DA, Marks IN: Relapse rates after duodenal ulcer healing—apples or pears? Gut 30:1299–1300, 1989
41. Marks IN, Young GO: Changes in acid secretory response and parietal cell sensitivity on healing predict early relapse in patients with duodenal ulcer. Am J Gastroenterol 83:1075(A), 1988
42. Yanaka A, Muto H: Increased parietal cell responsiveness to tetragastrin in patients with recurrent duodenal ulcer. Dig Dis Sci 33:1459-1465, 1988
43. Editorial. Cimetidine for ever (and ever and ever . . . . . . )? Br Med J i:1435–1436, 1978
44. Gough KR, Korman MG, Bardhan RD, et al: Ranitidine and cimetidine in prevention of duodenal ulcer relapse—a double-blind, randomised, multicentre, comparative trial. Lancet ii:659–662, 1984
45. Gudmand-Høyer E, Jensen KB, Krag E: Prophylactic effect of cimetidine in duodenal ulcer disease. Br Med J i:1095–1097, 1978
46. Bardhan KD: Intermittent treatment of duodenal ulcer with cimetidine. Br Med J ii: 20–22, 1980
47. Pym B, Sandstead J, Seville P, Byth K, Middleton WRJ, Talley NJ, Piper DW: Cost effectiveness of cimetidine in maintenance therapy in chronic gastric and duodenal ulcer. Gastroenterology 99:27–35, 1990
48. Freshton JW: On demand treatment for duodenal ulcers: Has its time come? (Editorial.) Am J Gastroenterol 85:241–242, 1990
49. Tytgat GNJ: Helicobacter pylori and duodenal ulcer disease. In Mechanism of Peptic Ulcer Healing. Edited by F Halter, A Garner, GNJ Tytgat. Dordrecht, The Netherlands, Kluwer, 1991, pp 283–294
50. Bertaccini G, Coruzzi G: Extragastric H2-receptors. J Clin Gastroenterol 5 (Supplement 1):57-70, 1983
51. Cabaliera J, Baraana E, Radamilans M, Lieber CS: Effects of cimetidine on gastric alcohol dehydrogenase activity and blood ethanol levels. Gastroenterology 96:388–392, 1989
52. Guram M, Holt S: Are ethanol-H2-receptor antagonist interactions relevant? Gastroenterology 109:4A81, 1991
53. Ruddel WSJ, Axon ATR, Findlay JM, Bartholomew BA, Hill MJ: Effect of cimetidine on gastric bacterial flora. Lancet i:672–674, 1980
54. Stockbruegger RW: Bacterial overgrowth as a consequence of reduced gastric acidity. Scand J Gastroenterol 20 (Supplement 111):7–16, 1985
55. Driks MR, Craven DE, Celli BR, et al: Nosocomial pneumonia in intubated patients given sucralfate as compared with antacids or histamine type 2 blockers. N Engl J Med 317:1376–1382, 1987
56. Soybel DI, Modlin IM: Implications of sustained suppression of gastric acid secretion. Am J Surg 163:613–622, 1992
57. Lomas RW, Smith JL: Medical treatment of peptic ulcer disease. Current Opinion in Gastroenterology 8:934–940, 1992