REVIEW ARTICLE

The management of peptic ulcer disease in the 1990s

J. A. Louw, I. N. Marks

Perceptions regarding the effective management of peptic ulcer disease have changed dramatically over the past few years. Healing of the ulcer crater is no longer a problem and the real challenge of management is now the prevention of the almost inevitable ulcer relapse.

While the pathogenetic model of acid-pepsin aggression versus mucosal resistance has provided a rationale for the use of either acid-inhibitory or mucosal-protective therapy for ulcer healing, peptic ulcers are now increasingly being seen as *Helicobacter pylori*-related (the majority), NSAID-related (an important minority) and, less commonly, purely 'acid-related'.[1] Acceptance of these aetiological factors now provides the basis for an effective short- and long-term management strategy for peptic ulcer disease.

Short-term healing

The agents used in ulcer healing can be categorised as either manipulators of the acid/pepsin milieu, i.e. inhibitors of acid secretion, antacids or drugs that enhance the mucosa's capacity to resist acid/pepsin aggression (mucosal protective agents).

Acid-neutralising agents

Antacids are widely used by patients with dyspepsia. Their once unchallenged role in peptic ulcer therapy, however, has been seriously undermined by the impact of the newer anti-secretory agents. Although there is little doubt that antacids are capable of healing duodenal ulcers, the optimal dose has not been defined. Peterson *et al.*[2] showed that a large-dose antacid regimen with an acid-neutralising capacity (ANC) of 1 008 mmol/day (15 ml antacid = 20 - 40 mmol) was superior to placebo in healing duodenal ulcer. Subsequent studies suggested that antacid dosages with an ANC of about 120 - 160 mmol/day may be effective in ulcer healing, but an ANC of less than 100 mmol/day has been shown to be ineffective. The antacid formulation (liquid or tablet) does not appear to affect efficacy.[2] Available evidence also suggests that gastric ulcer healing rates are comparable to those achieved with the H_2-receptor antagonists (cimetidine and ranitidine) when treatment is continued for 6 - 12 weeks.[3]

Our own experience is that antacids (ANC = 166 mmol/day) are significantly less effective in healing duodenal ulcers

Gastro-intestinal Clinic and Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town

J. A. Louw, M.B. CH.B., M.MED. (INT.), F.C.P. (S.A.)

I. N. Marks, B.SC, M.B. CH.B., F.R.C.P., F.A.C.G.

after 4 weeks of therapy, when compared with ranitidine 300 mg at night, but that this difference is not significant after 8 weeks of therapy. In this study, however, we were unable to demonstrate a difference in the frequency of gastric ulcer healing at 4 and 8 weeks.[4] These data indicate that unselected duodenal ulcer patients may require greater acid-neutralising doses of antacids than suggested in some previous studies.

Inhibitors of acid secretion

These drugs act on the various processes involved in the control of acid secretion. The muscarinic blockers act by selectively blocking the cholinergic receptors of the stomach. The H_2-receptor antagonists, until recently the most potent acid-inhibiting agents, act by blocking the parietal H_2-receptor. The most recent additions to the list of anti-secretory agents are the 'proton pump inhibitors' (PPIs). These drugs target the parietal H^+-K^+-ATP-ase proton pump and block it irreversibly. The PPIs, of which omeprazole, lansoprazole and pantoprazole are currently available locally, are the most potent inhibitors of acid secretion available. As ulcer healing rates have been shown to be directly related to the degree of acid suppression over a 24-hour period,[5] it is not surprising that these agents are claimed to have excellent healing efficacy.

Mucosal protective agents

These agents heal ulcers without affecting acid secretion. They include sucralfate, a basic aluminium salt of sucrose octasulphate, and the colloidal bismuth agents, all of which have a complex mode of action on the mucosa and ulcer base. These drugs are of particular interest in that initial ulcer healing with these agents has been shown to delay duodenal ulcer relapse significantly when compared with the H_2-receptor antagonists.[6,7] The reason for this is not clear, but an improved quality of healing of the ulcer scar, a lack of acid rebound (found after cessation of H_2-receptor antagonist therapy) and an anti-*H. pylori* effect have all been suggested to explain this finding.

Misoprostol, the prostaglandin analogue in clinical use, is included in this group although there is evidence that its acute healing effect may be linked to its ability to suppress acid secretion.[8]

Ulcer healing rates

Most currently available drugs have excellent healing rates. The PPIs are clearly more effective than the other agents in short-term healing and show 2-week healing rates of around 70 - 80% (traditionally considered the 4-week H_2-receptor antagonist healing rate). Non-healing at 4 weeks occurs in about 5% of duodenal ulcers. Gastric ulcer healing rates lag behind, and longer treatment periods are generally needed.

Specific primary healing problems

Resistant ulceration, previously defined as the failure of a duodenal ulcer to heal after 3 months of treatment with an H_2-receptor antagonist, is a rarity in the PPI era. When present, the clinician should consider the possibility of a non-peptic ulcer, and exclude (surreptitious) NSAID use and the Zollinger-Ellison syndrome.

The NSAID-associated ulcer. As a rule, these ulcers heal similarly to non-NSAID ulcers, if the offending drug is stopped. Healing while on NSAIDs may be problematic, but preliminary data suggest that this is best achieved with the PPIs.[9]

Can the current excellent healing efficacy be improved?

Although effective, the excellent healing rates achieved with modern drugs come with a hefty price tag. One way of reducing this would be to shorten the duration of therapy. In this regard, the PPIs have an obvious advantage. It is worth noting that, although *H. pylori* eradication has been studied primarily as a factor determining ulcer relapse, there is now some evidence that *H. pylori* eradication enhances duodenal ulcer healing rates.[10] This approach needs to be studied.

Long-term management of peptic ulcer disease

The long-term management strategy of peptic ulcer disease is aimed at the reduction or abolition of ulcer relapse and the prevention of potentially fatal complications. Therapy should, of course, be safe and affordable. Various strategies have been developed to manage the possibility of ulcer relapse. Primary ulcer healing with mucosal protective agents has been shown to delay duodenal ulcer relapse and maintenance therapy, either 'on demand', repeated courses thereof or the more satisfactory continuous maintenance therapy, has proved successful in preventing ulcer relapse. Long-term maintenance data are available, and these show remission rates as high as 80% (5-year follow-up, symptomatic ulceration) and a clear beneficial effect on the incidence of bleeding;[11] the natural history of the disease is not affected by this approach, however, and the ulcers will relapse once maintenance is stopped.

The safety and relative efficacy of this approach have led to the virtual demise of elective peptic ulcer surgery; the ease with which healing is usually achieved has practically removed the 'ulcer resistant to medical therapy' from the list of indications for elective surgery, while the policy of a 'pill a day keeps the surgeon at bay' has considerably reduced the need for surgery for recurrent ulceration. It remains to be seen whether surgeons' fairly recent acquisition of minimally invasive (i.e. laparoscopic) surgical skills will have any significant effect on this mindset.

Appreciation of the value of successful *H. pylori* eradication in reducing the liability to ulcer relapse, however, has led to a swing away from maintenance therapy.

H. pylori is a Gram-negative, micro-aerophilic, flagellated (motile) organism, able to penetrate gastric mucus, preferring to live under it and uniquely adapted to do so. The organism was first cultured a mere 10 years ago[12] and data collected since then have given the impression that the organism is an important player in peptic ulcer and, in particular, duodenal ulcer disease. Acceptance of this belief is based not on any specific understanding of the organism's role in the pathogenesis of ulcer disease, but

rather on the dramatic improvement in ulcer relapse rates observed when the infection is effectively treated. This has been demonstrated best in duodenal ulcer disease, with a number of authors claiming cure following successful eradication of the organism. The overall, prospectively studied 12-month relapse rates in patients in whom the organism was effectively eradicated is around 10%, with most recent studies claiming near 0% 12-month relapse rates in cured duodenal ulcer patients.[13] Although the data are more limited, studies of gastric ulceration have also documented a marked beneficial effect of *H. pylori* eradication on gastric ulcer relapse rates.[14]

Several key questions with regard to the management of *H. pylori*-positive ulcer patients remain to be answered, however. Firstly, we need to establish how long the protective effect of eradication lasts. Most studies indicate that a subject will be protected for as long as he/she remains uninfected, making reinfection the most important determinant of eventual relapse.[15] Although the mode of transmission of the organism is not known, it is likely to be some form of person-to-person spread (oral-oral spread is currently favoured), which makes the population carrier rate an important theoretical risk factor for reinfection. While this is low, and appears to be age-related in developed countries, the African experience indicates that the carrier rate is high.[16] Fortunately, our experience in an ongoing study suggests that the short-term (12-month) reinfection rate following successful eradication is not significantly different from the 0,5 - 2% per annum reinfection rate reported in studies from developed countries.

A more important practical consideration relates to the choice of appropriate eradication therapy. Effective treatment is defined as 'eradication', i.e. the absence of the organism a minimum of 4 weeks after anti-*H. pylori* therapy is stopped. The organism has proved to be particularly difficult to eradicate, with no single agent achieving acceptable eradication rates. Combination therapy has therefore become the standard approach.

'Triple therapy' is probably the most widely used form of combination therapy, and consists of a bismuth preparation — we use Denol (Brocades Pharma (Riker)) 120 mg — taken four times daily combined with metronidazole 400 mg three times daily and a second antibiotic, usually tetracycline, 500 mg four times daily, or amoxycillin, 500 mg four times daily. These tablets need to be taken for 14 days to achieve optimal results. Although side-effects occur in 20 - 30% of patients treated, the efficacy of this combination in Western society is around 90% and is determined mainly by patient compliance.[17] In Africa, however, metronidazole resistance is common, and in some regions, almost universal. While there is some evidence that 2-week triple therapy will eradicate the majority of resistant organisms, metronidazole resistance remains a concern. Bismuth has been considered an essential component of this so-called triple therapy. We have used sucralfate with equal success, however, while others have used ranitidine, also with excellent results.[10,18]

More recently omeprazole, one of the PPIs, was used in combination with an antibiotic. Although none of the PPIs studied so far can eradicate the organism on its own, clinical studies have clearly demonstrated a suppressive effect of omeprazole on *H. pylori*,[19] while both omeprazole and lansoprazole possess anti-*H. pylori* effects *in vitro*.[20] The combination used most commonly at present is that of omeprazole and amoxycillin. The dosages of both the PPI and amoxycillin vary considerably, and tend to be high, while the eradication rates vary from 0% to approximately 80%. Although this combination makes a lot of sense from a therapeutic point of view (antibiotic efficacy is enhanced in the stable pH and the ulcer is healed while the disease is cured), a number of questions remain unanswered. Firstly, the optimal dose and dosage schedule of PPI remain to be determined. The recommendation at present is for double-dose omeprazole, taken as 20 mg twice daily. Secondly, the optimal dosage and dosing frequency of amoxycillin need to be determined. At present, a minimum of 2 g/day is recommended, given either as 1 g twice daily or 500 mg four times daily. Patient compliance is obviously an important consideration, but we need to determine whether the twice-daily dosing schedule (with high peak levels) is in fact more effective than the multiple dosing schedule (with stable steady-state levels, presumably). Thirdly, the timing of the antibiotic component of this combination therapy needs clarification. The limited data available suggest that the antibiotic and PPI should be started concurrently, as pre-treatment with the PPI may reduce eradication efficacy.[21] The reason for this is unclear, and further studies are needed. Fourthly, the antibiotic component of this combination has also not been settled; there is some interest in the use of the new-generation macrolides, which have low-frequency dosage schedules, are acid-resistant and have good tissue penetration. A preliminary report on the use of one such agent, clarithromycin, in combination with omeprazole has been very encouraging,[22] but some concern has been expressed about the organism's becoming resistant to clarithromycin.[1] Finally, the PPIs themselves have to be investigated to determine whether their anti-*H. pylori* effect is class- or molecule-specific; although there appear to be differences in the *in vitro* efficacy of these drugs against *H. pylori*, we have to determine whether this is in fact the case in the clinical setting, as *in vitro* efficacy has not translated into clinical benefit in the case of antibiotics used so far.

Whom to 'eradicate'

This important question was addressed at a recent consensus meeting of the National Institutes of Health (NIH).[23] Their recommendation is that all patients with peptic ulceration be treated with antimicrobials, whether at first presentation or while on maintenance therapy. They further recommended, prudently in our view, that patients with peptic ulceration complicated by bleeding should be kept on maintenance therapy, until more data become available regarding the effect of eradication on complicated peptic ulcer disease. Unfortunately, while the NIH guidelines clearly identify patients who should be treated, no clear-cut recommendations with regard to the optimal therapy emerged. NSAID-associated ulcers also need to be managed by maintenance therapy, if a long-term management strategy is needed, as there are no data to show that *H. pylori* eradication is effective in reducing ulcer recurrence in these patients. Present evidence suggests that acid suppression therapy is effective in preventing NSAID-associated duodenal ulceration, while the prostaglandin analogues are effective in preventing NSAID-associated gastropathy, and both gastric and duodenal ulceration.

Conclusion

Ulcer healing is not a problem, thanks to the excellent drugs available to us; the trend will probably continue toward shorter-course therapy. *H. pylori* is increasingly implicated in the pathogenesis of duodenal ulcer relapse, and also seems to influence gastric ulcer relapse rates, although we do not understand its role in the pathogenesis of the ulcer diathesis. Eradication therapy, which seems to be evolving from the complicated triple therapy regimen to the PPI and antibiotic combination regimens, needs to be considered in all patients eligible for the various forms of maintenance strategies. The goalposts are shifting, however, and we foresee the incorporation of *H. pylori* eradication into the primary healing therapy of ulcers, thereby possibly harnessing the improved effect of eradication on healing while the ulcer diathesis is cured. It is also clear that, because of the extremely variable efficacy, the simplistic PPI dual therapy approach to eradication will probably be replaced by the use of a PPI combined with at least two antibiotics.

REFERENCES

1. Graham DY. Treatment of peptic ulcers caused by *Helicobacter pylori*. *N Engl J Med* 1993; **328:** 349-350.
2. Peterson WL, Sturdevant RAL, Frankel HD, Richardson CT, Isenberg JI, Elashoff JD. Healing of duodenal ulcer with an antacid regimen. *N Engl J Med* 1977; **297:** 341-345.
3. Marks IN, Schmassmann A, Halter F, *et al.* Antacid therapy today. *Eur J Gastroenterol Hepatol* 1992; **4:** 977-983.
4. Winter TA, Louw JA, Wright J, *et al.* Antacids vs ranitidine in peptic ulcer healing. *S Afr Med J* 1992; **82:** 41.
5. Jones DB, Howden CW, Burget DW, Kerr GD, Hunt RH. Acid suppression in duodenal ulcer: a meta-analysis to define optimal dosing with antisecretory drugs. *Gut* 1987; **28:** 1120-1127.
6. Lee FI, Samloff IM, Hardman M. Comparison of tri-potassium di-citrato bismuthate tablets with ranitidine in healing and relapse of duodenal ulcers. *Lancet* 1985; **1:** 1299-1302.
7. Lam SK, Hui WM, Lam WY, *et al.* Sucralfate overcomes adverse effect of cigarette smoking on duodenal ulcer healing and prolongs subsequent remission. *Gastroenterology* 1987; **92:** 1193-1201.
8. Debas HT, Mulholland MW. Drug therapy for peptic ulcer disease. *Curr Probl Surg* 1989; **Jan:** 9-54.
9. Howden CW, Holt S. Acid suppression as treatment for NSAID-related peptic ulcers. *Am J Gastroenterol* 1991; **86**(12): 1720-1722.
10. Hentschel E, Brandstätter G, Dragosics B, *et al.* Effect of ranitidine and amoxicillin plus metronidazole on the eradication of *Helicobacter pylori* and the recurrence of duodenal ulcer. *N Engl J Med* 1993; **328:** 308-312.
11. Penston JG. Maintenance treatment versus no treatment in patients with duodenal ulcer disease. *Scand J Gastroenterol* 1990; **25:** suppl 177, 42-51.
12. Marshall BJ. The *Campylobacter pylori* story. *Scand J Gastroenterol* 1988; **23:** suppl 146, 58-66.
13. Axon AR. Duodenal ulcer: the villain unmasked? *BMJ* 1991; **302:** 919-920.
14. Graham DY, Lew GM, Klein PD, *et al.* Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric and duodenal ulcer. *Ann Intern Med* 1992; **116:** 705-708.
15. Borody TJ, George LL, Brandl S, Andrews P, Jankiewicz E, Ostapowicz N. Smoking does not contribute to duodenal ulcer relapse after *Helicobacter pylori* eradication. *Am J Gastroenterol* 1992; **87**(10): 1390-1393.
16. Louw JA, Jaskiewicz K, Girdwood AH, *et al. Helicobacter pylori* prevalence in non-ulcer dyspepsia — ethnic and socioeconomic differences. *S Afr Med J* 1993; **83:** 169-171.
17. Graham DY, Lew GM, Malaty HM, *et al.* Factors influencing the eradication of *Helicobacter pylori* with triple therapy. *Gastroenterology* 1992; **102:** 493-496.
18. Louw JA, Zak J, Lucke W, *et al.* Triple therapy with sucralfate is as effective as triple therapy containing bismuth in eradicating *Helicobacter pylori* and reducing duodenal ulcer relapse rates. *Scand J Gastroenterol* 1992; **27:** suppl 191, 28-31.
19. Louw JA, Zak J, Jaskiewicz K, *et al.* Omeprazole may clear, but does not eradicate, *Helicobacter pylori*. *Eur J Gastroenterol Hepatol* 1992; **4:** 481-485.
20. Megraud F, Boyanova L, Lamouliatte H. Activity of lansoprazole against *Helicobacter pylori*. *Lancet* 1991; **337:** 1486.
21. Labenz J, Geynes E, Ruhl H, Borsh G. Efficacy of omeprazole and amoxicillin to eradicate HP. *Am J Gastroenterol* 1992; **87**(9): 1271.
22. Mendelson M, Greaves R, Logan R, Hegarty Baron J, Misiewics J. Eradication of *H. pylori* with clarithromycin and omeprazole. *Gut* 1992; **33**(2): suppl, S27.
23. NIH consensus conference. *Heliobacter pylori* in peptic ulcer disease. *JAMA* 1994; **272:** 65-69.

Accepted 3 June 1993.