Medical treatment of peptic ulcer disease: Should the emphasis be altered in view of laparoscopic surgery?

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ABR THOMSON. Medical treatment of peptic ulcer disease: Should the emphasis be altered in view of laparoscopic surgery? Can J Gastroenterol 1994;8(3):199-204. In the past H2-receptor antagonist era, there was initially a lull as more and more 'me-too' drugs were developed. Then came the excitement of the proton pump inhibitors and the controversy of the pros and cons of moderate versus potent acid inhibition. The most recent explosion of knowledge has been in the discussion of pH versus Helicobacter pylori, but on the horizon is lurking the promise of the resurgence of the surgical option.

Key Words: Laparoscopic surgery, Management, Peptic ulcer disease

TRAITEMENT MEDICAL DE L'ULCÈRE GASTRO-DUODÉNAL. LA CHIRURGIE LAPAROSCOPIQUE INDICE-T-ELLE UNE NOUVELLE VOIE?

RÉSUMÉ : Au cours de la récente époque anti-H2, on a d'abord connu une période lente avant que n'apparaissent de nouveaux médicaments toujours plus nombreux. Puis, vinrent les inhibiteurs de la pompe à protons, qui ont soulevé l'enthousiasme et la controverse au sujet des avantages et des inconvénients de l'inhibition modérée ou marquée de l'acidité. Les découvertes les plus récentes portent sur le pH versus Helicobacter pylori, mais on note à l'horizon les promesses que pourraient receler les interventions chirurgicales.

THE NUMBER OF SURGICAL PROCEDURES performed on patients with peptic ulcer disease has declined dramatically in the past 20 years. This decline was associated with, but not entirely explained by, the introduction in the mid-1970s of, first, cimetidine and then other H2-receptor antagonists such as ranitidine, famotidine and nizatidine (1,2). With the current possibility of reducing intragastric hydrogen ion (H+) concentration by greater than 99% via proton pump inhibitors such as omeprazole, one might have hoped that peptic ulcer disease would be a condition of the past. This has not occurred. One might also have wondered whether the medical management of peptic ulcer disease would completely replace surgical therapy of peptic ulcer disease, but that too has not occurred because of the problems of ulcer resistance, recurrence, drug complications and cost. With the benefits of minimal access surgery on the close horizon, these potential drawbacks of medical therapy need to be examined in closer detail, and need to be examined against the background of the possibility of curing peptic ulcer disease with eradication of commonly associated Helicobacter pylori infections.

RESISTANCE

While the H2-receptor antagonists and proton pump inhibitors are effective in healing duodenal and benign gastric ulcers, there remains a small group of peptic ulcer disease patients who are apparently resistant to therapy. The mechanisms of this resistance have not been established, and while some patients respond when switched from one H2-receptor antagonist to another, others only heal when switched from
an H2-receptor antagonist to another therapeutic agent, such as a proton pump inhibitor. The recent report of Lauritsen et al (3) has shown that 100% of more than 1000 patients with duodenal ulcers healed after a course of omeprazole, so there may prove to be relatively few duodenal ulcer patients who do not heal on omeprazole.

Ulcer symptoms do not necessarily occur when the ulcer is present (4). The complications of hemorrhage and perforation may be independent of whether the ulcer has been clinically apparent or silent (5). In persons taking nonsteroidal anti-inflammatory drugs (NSAIDs), hemorrhage from the silent ulcer is frequent (4). Persons with a past history of peptic ulcer disease who are present with complicated silent ulcers are resistant when using this definition (6), and even patients on maintenance therapy may develop silent ulcers (7,8).

The problem of 'resistance' to the usual therapeutic doses of ulcer-healing drugs has been reviewed (9,10). Duodenal ulcers are defined as 'resistant' or 'refractory' if they are unhealed after treatment with the usual healing doses of H2-receptor antagonists after eight weeks; less than 10% of duodenal ulcers are resistant when using this definition (11). When ulcers fail to heal, a number of diagnostic considerations must be undertaken (12). In the patient who has been on H2-receptor antagonists for eight weeks, persistence of symptoms is not necessarily associated with persistence of ulceration. If persistent ulceration is confirmed on endoscopy, it is important to assess the patient's compliance, use of NSAIDs or smoking, the possible previous presence of a larger ulcer (which takes longer to heal than a small ulcer), gastric hypersecretory state or a persistent H pylori infection (13,14).

Failure of conventional doses of H2-receptor antagonists to inhibit gastric acid secretion has been reported in some duodenal ulcer patients (15). The inhibitory effect of H2-receptor antagonists on 24 h intragastric pH profiles may be less in nonresponders than in responders (16). This cannot be the entire explanation for resistance to H2-receptor antagonist treatment because some patients may develop nocturnal achlorhydria on H2-receptor antagonists and yet still not heal (17,18).

Therapeutic manipulations that have been used to treat resistant ulcers include: higher than 'normal' doses of H2-receptor antagonists; use of 'normal' doses of H2-receptor antagonists for longer periods (15,19,20); or switching from an H2-receptor antagonist to a proton pump inhibitor (21), to colloidal bismuth subcitrate (22) or to a prostaglandin analogue (23). If there is H pylori infection associated with a duodenal ulcer, one therapeutic approach is to use triple antibiotic therapy or omeprazole plus amoxicillin. In the patient who has not healed with H2-receptor antagonists and who has a highly selective vagotomy, the incidence of recurrence of duodenal ulcers is 10 times greater than if the ulcer were not resistant (24).

**RECURRENTNESS**

Once acute therapy has been discontinued, peptic ulcer disease recurs at a rate of approximately 80% per year, and 90% of ulcers relapse within two years of healing irrespective of the initial ulcer healing therapy (25). This rate of recurrence can be reduced with the continuous administration of H2-receptor antagonists, but despite maintenance therapy, some patients will have a symptomatic recurrence and some will have an asymptomatic recurrence. The rates of duodenal ulcer recurrence may prove to be even lower with maintenance therapy using a proton pump inhibitor. Most of these recurrent ulcers will heal when the dose of maintenance medication is increased to approximately twice the high levels of H2-receptor antagonists needed for acute therapy.

Wormsley (26) has outlined the different methods of treating ulcers: the variants of therapy with anti-ulcer drugs range from demand (taking a few tablets of an anti-ulcer drug for a few days while symptoms persist) to periodic (taking a few tablets at specific intervals, such as weekends or seasonally), through intermittent, relapsing each symptomatic relapse with standard courses of anti-ulcer drugs given for one to two months to long term, continuous (maintenance) treatment.

Weekend therapy with ranitidine 300 mg may be comparable with continuous use of ranitidine 150 mg at night-time (27). Seasonal treatment with ranitidine in March and April and again in September and October results in relapse rates almost twice as high over 24 months of therapy, compared with continuously treated patients (28). Giving therapy for symptomatic relapse (intermittent treatment) has been discussed (29); its potential contraindications extend to include most patients with relapsing ulcer disease.

Are agents other than H2-receptor antagonists useful for maintenance therapy? Sucralfate may be effective for maintenance therapy in duodenal ulcers (30,31) but not for gastric ulcers (32). Pirenzepine is of limited use for maintenance therapy (33). The results of a large multicentre maintenance trial of omeprazole in patients with duodenal ulcers will soon be available.

American views of maintenance therapy have been analyzed (34). It remains controversial whether duodenal ulcers 'burn out' over time (34,35). In any case, maintenance therapy should be continued for at least one year (36). When point prevalence rates of recurrence of duodenal ulcers during maintenance therapy are assessed, the cumulative rate of recurrence is 48% after 12 months, and 71% of these recurrences are painless (8).

With cimetidine maintenance treatment, symptomatic relapse occurs in 17.2% of duodenal ulcer patients during the first year, 9.6% in the second year and 8.8% in the third year (37). In another study of patients with duodenal or gastric ulcers maintained on cimetidine for as long as six years, life-table analysis showed that the cumulative symptomatic relapse rates for duodenal ulcers were 13, 19, 24, 26 and 28% during the first five years (38). Thus, maintenance therapy may reduce the risk of ulcer recurrence, but even better maintenance therapy would be desirable.

While maintenance therapy may reduce the risk of ulcer recurrence, does it reduce the risk of complications? Yes — over a three-year period of mainte-
nance therapy, the cumulative rate of ulcer hemorrhage during periods without active treatment was approximately 15% compared with an incidence of ulcer bleeding during six years of continuous maintenance therapy of approximately 1.3% (39).

Sonnenberg (40) developed a Markov chain to study the long term outcome of maintenance with H2-receptor antagonists, intermittent treatment with H2-receptor antagonists and proximal gastric vagotomy. With maintenance treatment, the rate of complications and the number of deaths related to ulcers were slightly higher than after proximal gastric vagotomy, but because the few deaths from this procedure occur at treatment start, the loss of life-years during maintenance treatment exceeded that of proximal gastric vagotomy only after 20 years. Thus, 'surgical maintenance therapy' with proximal gastric vagotomy may be a useful option for the patient requiring prolonged suppression of gastric acidity.

HELICOBACTER PYLORI

Many duodenal or gastric ulcer patients are faced with the prospect of remaining on medication for the rest of their lives. In some persons the tendency for ulcer recurrence may be the result of persistence of an infection with H pylori. Strong evidence suggesting causation of duodenal ulcers by H pylori has been reviewed (41). H pylori is found in more than 90% of persons with duodenal ulcers (42-46), but in about one patient in 10, duodenal ulcers will occur in the absence of H pylori (demonstrated with the methods currently available). The eradication of H pylori is associated with the healing of gastritis (44), and a marked reduction in the rate of recurrence of duodenal ulcers (43,47-51).

Ulcers may recur in patients who do not have H pylori infection, and patients with H pylori do not necessarily have ulcers or ulcer recurrences (43,49). Eradication of H pylori using tetracycline 2 g, metronidazole 750 mg and bismuth subsalicylate five or eight tablets (151 mg bismuth/tablet) plus ranitidine 300 mg in patients with duode-

Figure 1) Life-table recurrence of duodenal and gastric ulcers for one year after successful healing with ranitidine alone or triple therapy plus ranitidine (adapted with permission from Graham et al Ann Intern Med 1992;116:70)

nal or gastric ulcers is associated with much lower rates of ulcer recurrence at 48 weeks (Figure 1). Life-table analysis demonstrates that patients whose ulcers have healed but who continue to have H pylori infection have a 95% chance of developing a recurrent ulcer by the end of one year. For patients whose H pylori infection is eradicated, the risk of ulcer recurrence is less than 10%.

Interestingly, if H pylori infection is cleared in patients with duodenal ulcers, smoking does not appear to pose a risk for ulcer recurrence (51). Unfortunately, compliance with the available complicated three- or four-agent treatment therapies remains a problem (52). Also, the long term safety of bismuth needs to be clarified; bismuth levels in urine remain elevated for weeks after therapy with bismuth-containing compounds (53). Unfortunately, in vitro sensitivity of H pylori to antibiotics does not predict drug efficacy in vivo (54,44). Recurrent H pylori infection may occur rapidly after initial clearance (44), and the strain that emerges is usually identical to the original infecting strain (56). If H pylori is absent six weeks after completion of therapy (eradication), cultures will usually remain negative after one year (49). Thus, it is possible that ulcer disease – and not just ulcers – may be cured by treating the H pylori infection effectively. If this hypothesis is confirmed in future studies, then medical or surgical maintenance therapy may become a thing of the past. And the need to consider today's tomorrow – minimal access surgery – for surgical maintenance therapy may also become a thing of the past.

COMPlications

There is a small potential for complications arising from continuous use of H2-receptor antagonists or proton pump inhibitors. For example, there may be interference with the metabolism of some medications, and there often is mild hypergastrinemia (the biological significance of which is unknown). Intestinal acidity is decreased more by omeprazole (94%) than after proximal gastric vagotomy (78%), but plasma gastrin concentrations are increased more after proximal gastric vagotomy (+284%) than during treatment with omeprazole (+186%) (57). There is no evidence that H2-receptor antagonists or proton pump inhibitors cause gastric cancer; postcimetidine surveillance for up to 10 years does not indicate an increased incidence of carcinoma of the stomach.
or esophagus (58). Case-control studies have also suggested that long term use of H2-receptor antagonists does not predispose to gastric cancer (59). Gastric surgery may be associated with the later development of stump cancer, but the relative risk of postgastric surgery carcinoma is highly disputed.

Cimetidine may reduce serum cortisolation concentrations (which may be reversed by taking ascorbic acid [60]), an effect not seen with ranitidine. Cimetidine inhibits the plasma aldosterone response to angiotensin II, whereas this does not occur with ranitidine (61). H2-receptor antagonists may rarely cause a disturbance of cardiac rhythm (62). Famotidine, but not cimetidine or ranitidine, may have a small negative inotropic effect on cardiac performance (63). The hepatic cytochrome P450 enzyme systems are inhibited in varying degrees by the different H2-receptor antagonists and by omeprazole (64,65), but the clinical importance of this interaction, while noteworthy, may be small.

While initial reports suggested that genotoxicity might be associated with the use of omeprazole (66,67), methodological considerations have been raised and differences between studies may be based, in part, on the species of rat used (68-72). A technique using hydroxyurea has suggested a weak positive genotoxicity effect of omeprazole at a dose of 100 mg/kg (73), but omeprazole did not affect 3H-thymidine uptake in purified parietal cells (74). It is unlikely that omeprazole has a significant genotoxicity effect.

Cimetidine and ranitidine, but not famotidine, may inhibit gastric alcohol dehydrogenase slightly (75-77), but the differences are small and the clinical significance is unlikely to be important (78). If H2-receptor antagonists are abruptly stopped there may be a brief period of rebound of gastric acid hyperacidity, particularly at nighttime (79); this lasts for less than one week and may not be clinically important.

**SURGERY: RECURRENCE, REOPERATION AND DEATHS**

Proximal gastric vagotomy is widely practised to treat peptic ulcer disease except in cases of prepyloric ulcers, pyloric obstruction, and combined duodenal and gastric ulcers (80). The 10- to 20-year postoperative recurrence rate varies widely and has been reported to be 15%, with 80% of the recurrences occurring within five years and no recurrences after 13 years (81). Others have noted a 12% recurrence rate after 10 years (82). A five- to 15-year follow-up after proximal gastric vagotomy demonstrated a recurrence rate of 11% (83); 71% of these recurrences occurred in the first five years, with only one recurrence in 200 patients occurring later than 10 years after surgery. However, late recurrences do sometimes occur (84). Kaplan-Meier estimates of the probabilities of recurrence at five and 10 years after proximal gastric vagotomy performed at the Mayo Clinic were 6 and 12% for duodenal ulcers, 16% for gastric ulcers, and 12 and 39% for pyloric and prepyloric ulcers. The endoscopic recurrence rate after proximal gastric vagotomy when patients were followed five to 10 years gave a total recurrence rate of 13.9%, with 24.3% recurrence rate for pyloric ulcers and 28.8% for prepyloric ulcers (85). However, the recurrence rate was low, only 2.9%, because most of the ulcer recurrences were treated satisfactorily with cimetidine. Thus, patients with postoperative recurrence of duodenal or gastric ulcers will be candidates for H2-receptor antagonists or proton pump inhibitor therapy, and some persons may need low dose maintenance therapy for five to 10 years.

Selective vagotomy and pyloroplasty, proximal gastric vagotomy alone and proximal gastric vagotomy plus pyloroplasty give similar outcome results (86), with an overall death rate less than 1%, a three-year ulcer recurrence rate of 8.3% and a reoperation rate of 7.5%. Recurrences may be eight times more frequent after proximal gastric vagotomy than after Billroth I resection (87).

The mortality rates associated with elective or urgent surgery are higher in older than in younger persons (88). For this reason, the decision to use medical therapy or to avoid surgical therapy must be influenced by the patient's age.

**COST-EFFECTIVENESS**

The three important criteria for comparing different types of treatment of the same disease are mortality, morbidity and cost (89). While maintenance therapy is effective for most individuals, the therapy is expensive (approximately $500/year in Canada). In the United States, proximal gastric vagotomy is more expensive than medical therapy, but is the least expensive therapeutic option in Germany (90). Canadian figures are not available. Laparoscopic selective vagotomies have been performed (91,92). With the prospect of markedly reducing the duration of hospital stays via minimal access surgery, the cost factor of surgery may become even less, and the surgical option for the long term suppression of acid secretion to maintain healing of duodenal and gastric ulcers may become even more desirable in the future. This is, of course, unless peptic ulcer disease can be cured by effectively eradicating H pylori!
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