Duodenal Ulcer and Gastroesophageal Reflux Disease Today: 
Long-Term Therapy — A Sideways Glance

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Acid-peptic disease is widely considered conquered or controlled, future advances being refinements of existing treatments rather than radical new developments. Yet controversies remain and developments have yet to be made.

**Duodenal ulcer:** Daily maintenance treatment with the anti-secretory drugs, histamine H₂ receptor antagonists and proton pump blockers, controls duodenal ulcer effectively, markedly reducing relapse rate at one year after treatment from about 75 percent to 15 to 20 percent (and to about 10 percent on proton pump blockers). In contrast, *Helicobacter pylori* eradication with a one to two week course of treatment yields prolonged remission or cure. The consequent reduction in drug costs in individual patients, however, has been exceeded by increasing community use on the more expensive proton pump blockers for the treatment of gastroesophageal reflux disease. The marked decline in elective surgery since the introduction of histamine H₂ receptor antagonists is commonly attributed to the power of these drugs. The fall, however, had started much earlier, indicating that the decline is due to changing natural history. In contrast, complication rates remain unaltered. An increasing proportion of newly diagnosed duodenal ulcer patients are elderly, and more of them now present for the first time with complications (in this center, about 40 percent), which consequently cannot be forestalled. Thus, duodenal ulcer disease is likely to remain a problem and in many will be a serious illness.

**Gastroesophageal reflux disease:** The proton pump blockers have revolutionized the treatment of gastroesophageal reflux disease. In clinical trials they have proven markedly superior to the histamine H₂ receptor antagonists in healing (at eight weeks, 80 to 90 percent vs. 50 to 60 percent), symptom relief, prevention of relapse on maintenance therapy and cost-effectiveness. However, several issues remain. The prevalence of gastroesophageal reflux disease seems to be rising and is now probably the commonest acid-peptic disease encountered in the West. Most clinical trials comparing proton pump blockers vs. histamine H₂ receptor antagonists have been done in patients with erosive esophagitis, whereas the majority (50 to 60 percent) of patients with gastroesophageal reflux disease have milder, generally non-erosive, disease. The therapeutic gain of proton pump blockers diminishes in mild disease so may not be worth the higher drug costs. This is an important area for investigation. The majority of patients with erosive esophagitis relapse when treatment is stopped (about 75 percent at one year). Relapse is markedly reduced (to 20 to 25 percent) by daily maintenance treatment with proton pump blockers. Mild disease relapses less often, so long-term therapy by intermittent treatment may prove acceptable and more cost-effective than maintenance treatment. This strategy remains unexplored in trials. The ideal profile of an anti-secretory drug for intermittent treatment would combine rapid onset of action (similar to histamine H₂ receptor antagonists) with powerful effect (as with proton pump blockers). The new class of drug, the reversible proton pump blocker (e.g., BY841) approaches this requirement.

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bAbbreviations: H₂RA, Histamine H₂ receptor antagonists; PPB, proton pump blockers; DU, Duodenal ulcer; GERD, Gastroesophageal reflux disease; NSAID, Non-steroidal anti-inflammatory drugs.
INTRODUCTION

A common perception of the treatment of acid-peptic disease is that it is a "dead subject"! There are no major issues left in therapy; with few exceptions newer treatments will result at most only in marginal improvement, if not in efficacy and safety then in lower cost. This viewpoint is understandable in the light of the spectacular advances in therapy made with the development of proton pump blockers (PPB) and anti-Helicobacter pylori treatment regimes.

While agreeing with much of this sentiment, I believe there are issues that remain. The purpose of this provocative and personal viewpoint is to draw attention to these matters. Two areas have been selected: duodenal ulcer (DU) and gastroesophageal reflux disease (GERD).

DUODENAL ULCER

Anti-secretory therapy: The story so far

By the late 1980s, virtually all patients with DU could be successfully managed with the histamine H2 receptor antagonists (H2RA). About one-third needed daily maintenance treatment; these patients had frequently relapsing disease (arbitrarily three or more relapses per year) or had suffered complications and often were elderly. The remaining two-thirds, younger, fitter patients with milder, uncomplicated disease, could be managed effectively with intermittent treatment at lower cost [1, 2].

Results from several studies on long-term maintenance treatment with low dose H2RA confirmed their continued efficacy (for as long as the patients remained on treatment) [3-7], the cumulative symptomatic relapse rate at one year off therapy (or on placebo) being 50 to 80 percent compared with only five to 20 percent on treatment. Most relapses on therapy occur in the first two years; after five years the relapse rate in two studies was only 28 percent on 400 mg cimetidine nightly [4] and 39 percent on 150 mg ranitidine nightly [7]. However, in the longest follow-up study so far, the relapse rate on 150 mg ranitidine nightly after nine years was a mere 13 percent [5]. Interruption of treatment is followed by relapse (cumulatively, about 80 percent at five years) [8]; i.e., the disease is only controlled, not cured, the benefit lasting only for as long as the patient continues treatment ("once he's stopped the drug, he starts where he left off" as a thoughtful editorial written as far back as 1978 put it) [9]. However, from early days there were reports that maintenance treatment lasting from one to five years may alter the natural history of the disease, reflected by reduced relapse rate (compared with the pre-treatment pattern) when therapy is stopped [10, 11].

Although symptomatic relapse rate was much reduced on maintenance treatment (see above), periodic endoscopic checks in asymptomatic patients showed that silent but active disease was common: for every patient with symptomatic recurrence, another would have silent disease. Thus the treatment seemed more effective in preventing symptom recurrence than in controlling the disease process [4, 12]. H2RA maintenance therapy at a higher (healing) dose (e.g., 0.8 to 1 g cimetidine, 0.3 g ranitidine) showed still further reduction in relapse rates in some studies [13] but not in others [14].

Maintenance therapy with PPB is effective, as would be predicted from the powerful anti-secretory effect, although there are few studies comparing them against H2RA [15-20]. One such study is our own investigation in very aggressive DU; cumulative relapse on 150 mg ranitidine at one year was 54 percent compared with 19 percent on 10 mg omeprazole [21]. One reason for the dearth of comparative studies is that interest has shifted to H. pylori treatment to achieve long-term control.

Prolonged maintenance therapy with H2RA has proven safe, and there is no reason to believe the same will not apply to the PPB. The main drawback, however, is the
inconvenience of daily (probably permanent) treatment and the expense. Examples of approximate annual drug costs in the U.S. are: 400 mg cimetidine (generic) nightly, $74.34; 150 mg ranitidine nightly, $251.01; 10 mg omeprazole daily, $389.02; 20 mg omeprazole daily, $691.27.

Intermittent treatment aims at rapidly relieving symptoms and healing the ulcer in each relapse without attempting to suppress the disease over the long term. Contrary to earlier views, the majority of patients have fewer than two relapses per year, so each episode can be treated with a short healing course of H2RA as and when needed [1]. Intermittent treatment with omeprazole gave even better results than with cimetidine [22]. Though the number of relapses over the next 12 months was similar in both treatment groups, as expected, the remission period, i.e., the number of days not receiving treatment for relapse, was significantly longer in patients treated with omeprazole than with cimetidine (272 vs. 175 days; p < .01). Using a complex decision analysis and statistical model based on clinical trial data comparing omeprazole and ranitidine, the likely outcome over a five-year period was calculated. The predicted number of relapses was a median of four (range 0 to 9) in both groups. However, judged by other criteria, omeprazole had significant advantages over ranitidine: less likelihood of requiring a change to maintenance therapy for slow healing or frequent relapses (15 percent vs. 26 percent) or of elective surgery for unhealed ulcer (1.6 percent vs. 7.2 percent), and lower direct costs, i.e., paid by the patients or society (17,645 vs. 19,965 Swedish crowns, 1992 prices).

Finally, a variant of intermittent treatment is "symptomatic self-care," the objective of which aims to relieve symptoms only, the patient titrating his/her own intake of tablets. This strategy is suited for patients with mild disease [24] (i.e., patients with infrequent, short-lived, easily controlled symptoms and without a history of ulcer complications).

**ANTI-HELiCOBACTER pylori THERAPY**

This novel treatment exploded into the recently-stabilized world of ulcer control with anti-secretory therapy and has rapidly and radically changed management. Successful bacterial eradication holds the glittering prospects of short-term treatment giving prolonged remission and probably cure. This, in turn, would prevent ulcer complications. By removing the need for maintenance treatment, huge savings in drug costs would be made [25]. Have these come to pass?

**The proven benefits of H. pylori eradication**

**The long-term outcome: Cure:** The early promise of prolonged DU remission after *H. pylori* eradication based on studies with one or two year follow-up [26, 27] has recently been confirmed in two studies with longer follow-up: 5.1 to 7.6 years (mean: 6.5 years) [28] and 1.4 to 10.9 years (mean: 4.7 years) [29]. Recrudescence and re-infection rates are low, probably between one to two percent per year [30, 31]. This minority is at risk of re-ulceration and needs further eradication therapy or maintenance treatment. For the majority, it seems reasonable to assume further anti-secretory therapy for ulcer disease is no longer required once the organism has been eradicated.

**The abolition of complications:** Three studies have shown significant reduction of re-bleeding after successful *H. pylori* eradication in patients with peptic ulcer. In a small study (n = 31), 29 percent re-bleed on maintenance 300 mg ranitidine vs. none after *H. pylori* eradication [32]; in another (n = 66), 38 percent bled again after failed *H. pylori* eradication but none after successful treatment [33]. In the largest study (n = 125), 12 percent bled on maintenance 150 mg ranitidine or 20 mg omeprazole daily vs. only 2.3 percent after eradication treatment [34]. Therefore, *H. pylori* eradication greatly reduces or abolishes risk of further hemorrhage in patients known to have ulcer disease. Curiously, *H. pylori* is less commonly present in patients with complicated ulcer than in the majority
who present with dyspepsia and pain, so the benefits of successful treatment would be expected only in those who harbor the organism [35-38].

The impact of H. pylori treatment: the reality

Continuing peptic ulcer complications: Peptic ulcer complications tend to occur much more commonly in the elderly. The problem is that many such patients present for the first time with complications, either having had symptoms earlier that were not identified as ulcer-related or, equally common, never having had symptoms before. For example, 14 percent of young patients (age 34 or below) seen here between 1979 to 1983 presented with complications, 11 percent in 1984 to 1988 and 10 percent in 1989 to 1993. In contrast, complications were more common in patients aged 65 or more, the proportions presenting in the three periods being 25 percent, 42 percent and 38 percent DU, respectively. Half of the patients aged over 75 years presented for the first time with complications. Thus, in patients known to have a DU, hemorrhage and perforation will be reduced by successful anti-H. pylori treatment, but when these complications are the first manifestation of the problem, they cannot be forestalled.

The development of gastroesophageal reflux

The benefits of ulcer cure are to some extent offset by having to treat a proportion of such patients with anti-secretory drugs again, this time for reflux. A recent large study of 203 DU patients, followed up for one to five years after successful H. pylori eradication, confirmed very low DU recurrence (n = 5, of which four were associated with aspirin or non-steroidal anti-inflammatory drugs [NSAID]). But, surprisingly, 10 percent of the patients developed GERD, all with erosive changes [31].

A similar trend was seen in a large community program, where 706 patients were treated. A subset of 163 was followed for a mean of eight months (three months to two and a half years). Intermittent heartburn, the cardinal symptom of reflux disease, continued in 55 percent of those with persistent infection but also in 39 percent of patients with confirmed eradication. Furthermore, after anti-H. pylori therapy, 67 percent with persistent infection had further anti-ulcer treatment from their doctor, as might be expected, but so did 19 percent following successful therapy [39].

We have also identified in this center that GERD develops on a background of DU. For example, we have identified 1,364 patients with both DU and GERD (representing 12 percent of 11,613 patients, of whom 5,049 had pure DU and 5200 GERD alone). In half, the two conditions were found together at presentation; and in three-quarters of the remainder, GERD developed on follow-up after the patient had presented with DU, necessitating an increase in the dose of H2RA maintenance treatment or a change over to PPB maintenance therapy. Thus, the DU may be cured but further anti-secretory therapy may still be needed if GERD develops.

The impact of anti-H. pylori therapy in the community

It is reasonably extrapolated from clinical trial results that curing DU in the community will be followed by marked clinical and economic benefits, the latter through reduced long-term drug costs. Indeed, various government bodies are encouraging this treatment approach. The efficacy of this policy has been assessed recently, perhaps for the first time. The results are not quite so encouraging but they do indicate what might be expected in practice, in contrast to research studies.

A major program in Suffolk (UK), covering a population of 650,000, offered anti-H. pylori treatment through general practitioners of patients with "proven" duodenal or gastric ulcer currently on long-term anti-secretory therapy. Such patients were identified from their doctors' computer records. The serology for H. pylori was tested in 1,897 patients:
duodenal ulcer, \( n = 923 \); gastric ulcer, \( n = 214 \); but also non-ulcer dyspepsia, \( n = 778 \). Treatment (omeprazole, amoxycillin and metronidazole for one week) had a 92 percent eradication efficacy rate in a subset examined by breath test. It was projected, therefore, that around 1000 patients treated would have had their infection eradicated. Surveillance of further anti-ulcer drug prescription showed a fall of 55 percent in patients with earlier positive serology and by only three percent of those serologically negative. These savings, however, were far exceeded by increased community expenditure on omeprazole used to treat the increasing number of patients with GERD [40]. The savings on anti-secretory treatment are not as large as one might have expected, and it is difficult to know why such drugs were continued. But the surprise was the rising total drug budget of PPB for the community as a whole.

A further problem is created because demand for diagnostic endoscopy exceeds supply. *H. pylori* serology testing is, therefore, being used in young dyspeptics (aged less than 45 years) to aid selection for the procedure. Those with negative serology are treated symptomatically (anti-secretory drugs, etc.) while those positive (and/or are on NSAID) are gastroscopied and treated according to the findings [41-44]. A further development is growing commercial pressure to treat serologically positive dyspeptics with anti-*H. pylori* therapy without any endoscopy at all. As reflux disease becomes more recognized and ulcer disease less common, particularly in the young, the number of patients helped in the long-term by anti-*H. pylori* therapy applied thus is likely to diminish and not bring about the cost-benefits hoped for [45].

Antibiotic resistance

The increasing use of anti-*H. pylori* therapy raises concerns of anti-microbial resistance. Such resistance is common in developing countries, reaching up to 90 percent; but it is also fairly common in the West. For example, nitroimidazole resistance (either primary or secondary) in the European multi-center study ranged from seven to 49 percent (mean 28 percent) [46]. In the recent large UK national study, the mean (range) proportion of strains found resistant was to: metronidazole, 32 percent (11 to 68 percent); tinidazole, 28 percent (17 to 43 percent); clarithromycin, four percent (3 to 10 percent). Resistance to amoxycillin was rare, less than one percent (0 to three percent) [47]. Other centers in the West have reported similar patterns [48]. However, though resistance to nitroimidazoles reduces the efficacy of therapies containing metronidazole or tinidazole, on the whole such treatment remains fairly effective [49].

Possibly of greater concern is the emergence of resistance to the powerful new antibiotic, clarithromycin, which now is increasingly used in anti-*H. pylori* therapy. In this center, for example, 10 of 70 patients whose *H. pylori* was not eradicated on pantoprazole + tinidazole + clarithromycin, given for 10 days, had developed resistance to the macrolide, having been sensitive at the start. Such resistance is thought to result from a mutation in the ribosomal RNA of the 23S subunit. The change in antibiotic target renders the drug less efficient and allows survival of mutant clones [50]. Fortunately the resistance is not through plasmids, otherwise the risk of spread of this phenomenon among strains of *H. pylori* would be greater.

Because of tremendous patient demand for anti-*H. pylori* treatment, fuelled in part by mass media coverage, general practitioners are under pressure to treat. Increasingly, patients are given treatment without any investigation, not even serology, in the belief "it won’t harm and may do good"! Such indiscriminate use may well make antibiotic resistance a bigger problem.
THE "CONQUEST" OF DUODENAL ULCER

Effective treatment or natural history?

With powerful anti-secretory treatment, and now anti-\textit{H. pylori} therapy, one might have expected DU to be conquered. Yet a good deal remains to be achieved. An example is provided from the statistics from our own health region (Trent Regional Health Authority, population 4.6 million). Elective surgery, a marker of severe ulcer disease, has declined dramatically in recent years (as it has elsewhere) and supports this contention. Yet this decline started long before the introduction of modern medical treatment; furthermore, the rate of decline, year upon year, has not changed. This suggests changing natural history plays a significant part in the altered pattern seen. In contrast, hemorrhage and perforation are unchanged, indeed rising in the over 65-year-old population despite a more than three-fold increase in H\textsubscript{2}RA use [51]. Further evidence of the influence of natural history can be seen in the prevalence of H\textsubscript{2}RA-refractory DU in our center (defined as failure to heal within three months on H\textsubscript{2}RA given at standard dose or greater dose). Here the H\textsubscript{2}RA, principally cimetidine, was (and remains) the main anti-ulcer drug used. The incidence of refractoriness was: 1976 to 1978, 127/397 (32 percent); 1979 to 1983, 406/1272 (32 percent); 1984 to 1988, 200/1308 (15 percent); 1989 to 1993, 79/1120 (7 percent). These changes precede the use of PPB in this center [52]. Thus, the decline of DU is perhaps as much due to a changing natural history as to powerful medical treatment.

COMMENTS

1. In the West, nature has reduced the number of patients with new DU. Those who come to medical attention can now be swiftly treated medically and probably be cured. However, a higher proportion of patients are now older. For many, the first sign of ulcer disease is hemorrhage or perforation: these complications cannot be prevented (though treatment of the underlying disease should be able to reduce or prevent recurrence).

2. To abolish peptic ulcer requires treatment not only of proven cases but also of those at risk, namely, people infected with \textit{H. pylori}, most of whom are asymptomatic. Modern anti-\textit{H. pylori} treatment is effective (one-week therapy: greater than 90 percent eradication) but still carries side-effects sufficiently often to make it unattractive for mass treatment of the asymptomatic as part of a "public health campaign." Equally important, the present treatment, though affordable in the West, is beyond the financial means of many in developing countries where ulcer disease is rife.

3. Vaccination may be the future approach. Experimental work shows it prevents infection and, intriguingly, can cure it [53-55]. However, it will be some years before this strategy is available for mass use. Despite spectacular advances in treatment, duodenal ulcer and its complications will be with us for a long time to come.

GASTROESOPHAGEAL REFLUX DISEASE

The superiority of PPB over H\textsubscript{2}RA

The achievements: PPB is markedly superior to H\textsubscript{2}RA in treating erosive esophagitis. After eight weeks of therapy, the approximate healing rates in clinical trials are: PPB in standard doses (20 mg omeprazole, 30 mg lansoprazole, 40 mg pantoprazole), 80 to 90 percent; H\textsubscript{2}RA (300 mg ranitidine, 1.6 g cimetidine), 50 to 60 percent [56, 57]. Symptom relief is more rapid, the proportions free of heartburn at four weeks being about 75 to 80 percent on PPB compared with 45 to 50 percent on H\textsubscript{2}RA. After healing, maintenance therapy with PPB gives markedly better results than with H\textsubscript{2}RA. Relapse at one year, after 300 mg ranitidine, ranges from 55 to 79 percent whereas on 20 mg omeprazole it is only 12 to 28 percent. Ten mg omeprazole is less effective than the higher dose but superior to
ranitidine, with relapse rates of 37 to 50 percent. A similar pattern is seen with 30 mg lansoprazole (relapse, 10 to 20 percent) and 15 mg lansoprazole (13 to 31 percent) [58-66]. Treatment with PPB is also more cost-effective. Using a model derived from clinical trials and common clinical practice, the drug cost for treating 100 patients over a year (covering healing, relapse, re-healing and maintenance therapy) was $62,272.50 for ranitidine and $47,125 for omeprazole, a reduction of 32 percent [67]. As lansoprazole is a little less expensive than omeprazole, the saving would be even greater. Thus, on grounds of efficacy (in healing, relieving symptoms and preventing relapse by maintenance therapy) and cost-effectiveness, the case for routine use of PPB in GERD is overwhelming. But is this the full story? I suggest not. Some of the issues are discussed below.

THE TREATMENT OF GERD: AREAS TO BE EXPLORED

Symptomatic gastroesophageal reflux in patients with normal endoscopy

Virtually every trial comparing the PPB against H2RA has been done in patients with erosive esophagitis. This is understandable, for healing of the breached mucosa is clearly recognizable and healing rates, therefore, measurable. In patients with symptomatic gastroesophageal reflux but with normal mucosa, however, symptom improvement is the only quantifiable parameter, and being subjective is less accurate. Yet in reflux disease about half the patients investigated in hospital have normal endoscopy and the proportion in general practice is higher still [68-70]. For example, in this center only 42 percent of 2,786 patients seen between 1989 to 1993 had erosive changes.

It remains to be proven if the margin of superiority of PPB over H2RA in such patients is great enough to make it cost-effective. Results from an important study of patients with erosive esophagitis give some indication what might be expected in less severe disease. In this investigation omeprazole proved superior to ranitidine, as expected. The cost-benefit of omeprazole was greatest in patients with severe erosive changes, when symptoms were very troublesome and index of life-satisfaction low. There was little difference, however, in mild disease; indeed, when the index of life-satisfaction was only slightly reduced, ranitidine proved marginally more cost-effective [71].

Treatment of mild gastroesophageal reflux: A recent large study of patients with reflux seen in family practice showed ranitidine was significantly superior to placebo for relieving symptoms and improving the quality of life [72]. Similarly, omeprazole was clearly superior to placebo in the two studies done so far on the treatment of symptomatic reflux in patients with normal endoscopy [73,74]. Three interesting additional findings emerged from these studies. First, the co-existence of irritable bowel syndrome was associated with a poorer outcome [73]. Second, the diagnostic accuracy of gastroesophageal reflux when judged against the gold standard of esophageal pHmetry varied from 22 to 85 percent across the 16 participating centers [74]. Third, the greater the reflux, the greater was the benefit produced by omeprazole [74]. Irritable bowel syndrome is commonly present in patients with symptomatic gastroesophageal reflux but with normal endoscopy, and reflux itself may be mild despite symptoms. Although the advantage of PPB over placebo in such patients is clear, it cannot necessarily be assumed it will be superior over the H2RA to an extent as to make it cost-effective.

This area was investigated recently in a large study of 994 patients with heartburn seen in general practice, one-third of whom had mild erosive changes. Twenty mg omeprazole, 10 mg omeprazole and 150 mg ranitidine twice daily relieved heartburn in 61 percent, 49 percent and 40 percent of patients, respectively; the cost per treatment success being $87.00, $61.50 and $97.50, respectively. In the subgroup with erosive esophagitis, symptom relief was still higher on 20 mg omeprazole, 79 percent compared with 48 percent on the 10 mg dose and 33 percent on ranitidine; the corresponding cost of treatment success
was $67.50, $63.00 and $118.50, respectively. This important study, probably the first of its type, clearly shows that PPB is superior [75].

The natural history of GERD: Based on clinical trials, relapse off therapy is generally thought to occur in 50 to 80 percent of patients with erosive esophagitis within six to 12 months. However, this is not always the case. For example, in a major study of 1030 patients with erosive disease healed on omeprazole or H2RA, the relapse rate at six months was only 25 percent [76]. A similar low relapse rate on placebo was observed in some of the early maintenance studies investigating H2RA [77].

A recent report described the outcome of a large group of reflux patients followed for up to six years [78]. At the end of the follow-up, one-third of patients were asymptomatic or controlled their symptoms adequately with occasional doses (22 percent) or courses (16 percent) of antacids. A further 17 percent needed antacids frequently, 19 percent were on maintenance H2RA (including eight percent on high dose) and 26 percent had had surgery. This study was started before PPB were available, and today the proportions on acid suppression would be different. But, importantly, the study emphasizes the benign nature of reflux in many patients, reflected by the fact that one-third controlled their symptoms with infrequent use of antacids alone.

The aim of treatment

There is no “medical cure” of reflux; the disease is only controlled. There is no evidence that short-term vigorous treatment early on (e.g., with high-dose PPB) in patients with mild disease improves long-term outcome. Consequently, except in clinical trials, symptom relief is the principal aim of treatment. In clinical practice few have repeat endoscopy to confirm healing, unless disease was severe to start with.

Alternative therapeutic approaches

Intermittent treatment: Long-term treatment can be tailored according to the severity of symptoms. Theoretically, patients with mild, infrequent relapses could be treated for short periods and therapy repeated as needed, i.e., intermittent treatment (as has been used in duodenal ulcer). Such an approach is commonly used in general practice, but no study has reported on the outcome of such a policy. However, ranitidine given intermittently has recently proved almost as effective as when given by daily maintenance therapy (unpublished data: personal communication). Intuitively, younger, fitter patients with mild intermittent symptoms and with normal endoscopy, or at most with mild erosive changes, would be selected for such an approach.

Is there still a place for the H2RA? H2RA is more effective than placebo in healing erosive esophagitis (60 percent vs. 30 percent at six to eight weeks) [79] (although not nearly so dramatic as in duodenal ulcer disease, when greater than 80 percent healing would be expected). Low-dose maintenance therapy is generally ineffective in preventing relapse [56]. These observations, together with the superior results achieved with proton pump blockers, created the general impression that H2RA have little or no place in the management of GERD [80]. I believe this conclusion premature for the following reasons:

1. Personal experience: Between 1976 to 1988, 1200 patients in this center were treated satisfactorily with H2RA, principally 1.6 to 2 g cimetidine (or 0.45 to 0.6 g ranitidine), both in the short- and long-term. The majority, 85 percent, continued with little or no symptom recurrence. In half of the remaining 15 percent, control was achieved by doubling the dose. The remainder needed omeprazole. Today, many more people are treated with PPB, but in almost two-thirds, H2RA suffices.

2. H2RA: rapid response: Many patients with reflux have symptoms at specific times, for example, after their main meal. A moderate degree of acid suppression for a short period with appropriately-timed treatment suffices. This is feasible with the
H$_2$RA, particularly the effervescent preparations [81-84], whereas the PPB lacks such flexibility.

3. Cost-benefit: PPB will remain expensive for several years more, whereas the price of H$_2$RA has fallen markedly. Earlier cost-benefit studies therefore need reassessing. In groups where the clinical advantage of PPB is slight, it may now be more cost-effective to use H$_2$RA.

The rising prevalence of GERD

It is common experience that reflux disease is now seen more frequently. Figure 1 shows the number of new patients seen in this center each year from 1976 to 1994 with GERD (erosive and non-erosive disease), duodenal and gastric ulcer. The rising numbers of patients with GERD is striking. As this was not a formal epidemiological study, conclusions on changing prevalence have to be tentative and limited. The annual number of endoscopies since 1980 has not changed, so the rise cannot be entirely explained by increasing use of diagnostic methods. Greater awareness of GERD, particularly of non-erosive disease, presumably contributes. However, it is difficult to avoid the possibility that at least a part of the rising numbers results from a true increase in prevalence.

The “middle ground”

Is there a need for a new molecule? PPB will dominate the treatment of more severe disease; antacid-alginate preparations are perhaps all that are needed in very mild cases, and H$_2$RA, and prokinetics suffice for those with troublesome symptoms. It is the large group in between these two ends where treatment strategies need to be re-examined, and the number of patients in this group is steadily increasing as reflux disease is more frequently diagnosed. Such patients have moderately troublesome symptoms that recur in short relapses followed by longer remissions. The irreversible PPB (omeprazole, lansoprazole, pantoprazole) takes three to four days to reach peak effect, so is more suited for patients who need continuous long-term treatment (although recent evidence suggests

![UGI Endoscopy: Rotherham 1976-1994](image)

Figure 1. The number of patients newly diagnosed each year (1976-1994) in Rotherham Hospital with DU, GU or GERD.
lansoprazole may have a reasonable "first-day" effect and suppresses acid more quickly than omeprazole) [85]. H₂RA acts rapidly, particularly the effervescent preparations, but do not sustain pH above 4 for long enough [81-84].

A new type of drug, therefore, needs to be considered: Ideally it should: raise the pH above 4 rapidly; sustain this pH level for eight to 10 hours, thus requiring no more than twice daily dosing (and once daily would suffice if symptoms occur only at certain times); have no attenuation of effect in the short-term (say up to four weeks of daily use). The new generation of reversible-PPB approaches this [86]. If the early encouraging results from pharmacological studies are confirmed, these drugs would allow treatment to be tailored more accurately to individual patients' needs. For example, patients with symptoms confined to the daytime need take only a morning dose; and if relapses are short-lived, the drug would be suitable for intermittent therapy. If more frequent and longer periods of treatment become necessary, the patients would have selected themselves for long-term treatment with irreversible PPB.

**Preliminary anti- H. pylori therapy?**

A recent report cautioned on the development of corpus gastritis within eight weeks of omeprazole treatment in patients with *H. pylori* despite unchanged degree of colonization. This phenomenon was absent in patients who did not harbor the organism. As PPB is often needed for long periods, the investigators recommended eradicating *H. pylori* first [87]. If this report is confirmed, a new consideration enters the treatment of GERD.

**CONCLUSIONS**

1. In severe disease, or where relapse is rapid and frequent, treatment with irreversible PPB is needed, permanent in most. Surgery is the alternative but only in some patients; the proportion may rise if good results from laparoscopic fundoplication become more widely available.
2. H₂RA is under-valued. It is useful in patients with mild symptoms.
3. Intermittent treatment as a strategy needs to be investigated. Theoretically it seems suitable for patients with mild or moderately troublesome disease with infrequent relapses.
4. There is a place for a new molecule specifically for patients needing intermittent treatment for whom H₂RA is not powerful enough and the irreversible PPB excessive. The reversible PPB may prove to have the appropriate properties.
5. There is a suggestion eradicating *H. pylori* first may prevent or reduce the development of corpus gastritis in patients needing long-term PPB.

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