Medical Therapy of Gastroesophageal Reflux Disease in Secondary and Tertiary Care Settings

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Gastroesophageal reflux disease (GERD) is common. Many patients with recurring or troublesome symptoms are referred for endoscopic examination. Patients seen in secondary care usually have failed OTC or primary care anti-reflux therapy. Acid suppression is the mainstay of healing and maintenance therapy. Increasingly proton pump inhibitors (PPIs) are preferred above H₂ receptor antagonists (H₂RAs), not only for the more severe end of the GERD spectrum but also for patients with mild degrees of esophagitis. Not all patients respond symptomatically to acid suppression, not even with high dose PPI. Prokinetics are mainly useful in the milder degrees of GERD. It is still not clear whether a particular symptom cluster can be recognized for which prokinetics are especially useful. The concept of “step-up versus step-down” approach remains in need for proper validation. Switching from PPIs to cisapride for “step-down” maintenance appears inadequate in practice. All current therapies have shortcomings; H₂RAs insufficiently block meal-stimulated acid secretion; long-term strong acid suppression worsens Helicobacter pylori-associated inflammation in the corpus and may accelerate development of atrophy; PPI-potency is substantially weaker in non-H. pylori infected individuals. Optimization of individualized therapy will require more potent and more precisely targeted motility modulating drugs and superior acid/peptic inhibiting pharmaceuticals.

INTRODUCTION

This overview focuses on the current medical possibilities and shortcomings to heal and maintain remission in patients with gastroesophageal reflux disease (GERD) in secondary and tertiary care settings.

The clinical presentation of GERD covers a wide spectrum of abnormalities, including postprandial heartburn and acid regurgitation. Recurrent or troublesome or recalcitrant symptoms are the main reason for specialist referral for endoscopic examination. Indeed, physicians often use endoscopic results to tailor medical therapy in patients with reflux symptomatology [1].

GERD is in essence a motility disorder. Meticulous studies have shown that transient relaxations of the lower esophageal sphincter and of the crural diaphragm are to be considered as the dominant mechanism allowing reflux to

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Abbreviations: GERD, gastroesophageal reflux disease; H₂RA, H₂ receptor antagonist.
occur especially in patients exhibiting the milder end of the reflux spectrum [2]. So-called spontaneous or stress-induced reflux becomes more readily demonstrable in patients with more severe GERD and more severe impairment of sphincter function. Particularly the studies of Mittal [3, 4] have emphasized the double component to the lower esophageal barrier mechanism: the smooth muscle of the lower esophageal sphincter proper and the striated muscle of the crural diaphragm. Sphincteric function of the crural diaphragm is particularly impaired in patients with a hiatal hernia.

For many patients, GERD is a chronic relapsing problem. This becomes readily apparent when confronted with the very rapid and almost universal symptomatic and/or endoscopic relapse after prior healing of reflux-induced damage with acid suppressant drugs [5]. The main explanation for this chronic relapsing nature is the failure to correct the underlying motor abnormality responsible for GERD. As no medical therapy is capable of providing a permanent correction of the motor disorder, it is logically to be expected that reflux will recur as soon as therapy is stopped.

**PHARMACEUTICAL POSSIBILITIES TO HEAL REFLUX ESOPHAGITIS**

Traditionally, antireflux therapy starts with general life style advice. To what extent life style modifications (weight reduction, avoiding of straining at stool, avoiding gastric overdistension, etc.) can control the reflux diathesis in the absence of drug therapy is insufficiently known at the present time. The widespread consumption of drugs (OTC and prescription drugs) would indicate that life-style changes as sole therapeutic measure often fail to control the disease.

There are essentially two pharmacological avenues, used in clinical practice, to induce clinical and/or endoscopic
remission in GERD. Prokinetics aim at improving the motor abnormalities, through increasing basal lower esophageal sphincter pressure, improving peristaltic quality and clearing efficacy and through accelerating gastric emptying when delayed [6]. Acid suppressants, be it H₂-receptor antagonists (H₂RAs) or proton pump inhibitors (PPIs), aim at decreasing the volume and acidity of the refluxate available for reflux [7, 8].

Amalgamation of the world literature of drug efficacy to induce remission or healing is schematically shown in Figure 1. As can be seen, PPIs are substantially superior in inducing healing compared to H₂RAs and prokinetics. It should be stressed that this difference in efficacy is more marked in patients with more severe mucosal damage. This difference is much less clear for milder degrees of damage. Many studies have shown that esophagitis of greater severity is more difficult to heal with H₂RAs than lesser grades of esophagitis. Based upon these data, it is readily understandable that it is often said that acid suppression is the best option for initial therapy in patients with troublesome symptoms as this therapy is most likely to succeed. Cost-effectiveness analyses also suggest that PPIs are the best initial option in patients with all degrees of esophagitis as a prompt and predictable response to reflux disease results in lower total utilization of health care resources as well as a reassured and comfortable patient.

The critical pH to be reached in GERD is 4. Intraesophageal pH must be maintained above 4 for at least 16 hr a day and preferably longer to achieve mucosal healing [9]. Meta-analysis has indeed shown a correlation between acid suppression and healing of esophagitis, the healing proportion being directly related to the degree and duration of acid suppression. As a consequence PPIs show higher and more effective healing compared to H₂RAs [10]. Meta-analysis predicts healing in approximately 90 percent of patients with erosive esophagitis within eight weeks if intragastric acidity is maintained above pH 4.0 for between 20 and 22 hours per day [9]. Clinical differences between the various PPIs (omeprazole, lansoprazole, pantoprazole), if any, may be explained, at least in part, by differences in oral bioavailability and the velocity to reach the peak antisecretory effect [11]. Lanzoprazole seems to have an earlier onset of action than omeprazole, ascribed to higher bioavailability during the first days of treatment [12].

Numerous clinical trials have assessed the healing rates at arbitrary time intervals. Results of healing do not reflect a true rate but rather represent the proportion of patients healed. The speed at which healing occurs may be substantially different. This healing rate can be determined by the slope of the healing/time curve. The rate of symptom relief can be determined in a similar fashion. Calculation of speed of healing and speed of symptoms relief has been made by Chiba et al. [8]. PPIs show a significantly faster healing rate (approximately 12 percent/week) versus H₂RAs (approximately 6 percent/week) and provide faster and more complete heartburn relief (approximately 12 percent/week versus 6 percent/week). Thus healing and symptom relief occur nearly twice as fast with PPIs.

"STEP-UP" VERSUS "STEP-DOWN" APPROACH?

Most patients with mild symptoms can be successfully managed by lifestyle modification plus antacids/alginites, supplemented when necessary by courses of H₂RAs or prokinetics (cisapride). For moderate to severe symptoms and for moderate to severe esophagitis, PPIs are increasingly favored as first line therapy. Responses are also likely in patients who have failed to improve on H₂RA treatment.

Yet the controversy regarding the "step-up" and "step-down" approach continues. The "step-up" approach follows the principle of applying the minimum pharmacological force necessary to achieve a
stated therapeutic objective. This approach targets more powerful and costly therapy towards patients with proven therapeutic need for more intensive treatment. In contrast, in the “step-down” approach, the patients are initially treated with the maximally effective (PPI) therapy, only being “stepped-down” to less intensive interventions in strictly defined circumstances. The principal problem inherent in this approach is the universal application of powerful and costly drugs in patients in whom less intensive interventions may have been adequate but have not previously been proven to be ineffective.

PHARMACEUTICAL POSSIBILITIES TO MAINTAIN REMISSION

Once healing is achieved and treatment is stopped, recurrence is common, particularly in patients with erosive esophagitis. Maintenance therapy is, therefore, necessary in a large number of such patients.

Amalgamation of the world literature for remission rates during 12 months maintenance therapy is schematically shown in Figure 2. As can be seen, roughly 60 percent of the patients can be maintained in remission with H$_2$RAs and prokinetics (cisapride). With PPIs, remission can be maintained in roughly 90 percent. These data are obtained when prokinetics or acid suppressants are used in standard dosage. Occasionally higher doses are necessary to maintain remission [13-15]. A meta-analysis of long-term trials with PPIs has shown that the latter are superior to all other regimens with acid suppressants in maintaining remission [16].

Carlsson et al. [16] conducted a meta-analysis of long-term omeprazole

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**Figure 2.** Remission rates during maintenance therapy: amalgamation of the literature.
trials in order to detect prognostic factors influencing relapse of esophagitis. Data from 1154 patients, included in five independent randomized trials, were pooled for this meta-analysis. Omeprazole 20 mg/d maintained 82 percent of patients in endoscopic remission over a six-month period compared to 72 percent for omeprazole 10 mg, 52 percent for ranitidine 150 mg twice daily, and 11 percent for placebo. Four factors were associated with a higher relapse rate: pre-treatment severity of esophagitis, young age, non-smoking and moderate/severe regurgitation before entry into the trials. Permanent symptom relief was highly predictive for maintenance of healing. Patients over 65 years old were less likely to relapse, probably due to decreased metabolic clearance of omeprazole, which would be expected to result in greater bioavailability. The authors argue that a low PPI dose should be the appropriate initial maintenance dose in the elderly.

Subsequent management needs to acknowledge that long-term therapy is needed in most patients and that acid suppression is one of the major options. Available information suggests that adequate symptom relief is possible provided PPI dosage is adjusted upwards if the response is incomplete. In patients who respond completely to initial acid suppressant therapy, this should be made as cost-effective as possible by “step-down” of the dose to the lowest cost option that controls symptoms and esophagitis adequately. Symptom control is a relatively sensitive surrogate for adequate control of esophagitis.

Very few data are available in the literature to support the value of the “step-down” concept. Two recent studies looked at the capability of maintaining remission when switching to cisapride therapy after prior healing with proton pump inhibitors [17, 18]. In both studies, cisapride was no better than placebo in maintaining the remission. It remains puzzling why prior healing with a PPI apparently jeopardizes the efficacy of prokinetics, a phenomenon that was already seen in the earlier large scale “Scanedcis” study [19]. Whether the same holds true for H₂RAs is unknown at the present time as no systematic studies of “PPI-H₂RA step-down” have been published so far. Clinical experience teaches that it is difficult in practice to switch from PPIs to H₂RAs for maintenance. The alternative would be to decrease the dose of the PPI. However several studies have now shown that PPIs, at half the usual dose, are inferior to full dose therapy in relieving GERD symptomatology as summarized in Table 1. The same is true for maintaining endoscopic healing. Although, for example, both 10 and 20 mg daily doses of omeprazole can maintain remission, significantly fewer patients maintained remission after six months with the 10 mg dose than with the 20 mg dosage (35 percent versus 59 percent) [20].

Despite the above considerations, clinical practice also teaches that many patients gradually reduce the PPI dose and

### Table 1. GERD: Complete symptom relief

|                | Cisapride | Ranitidine | Omeprazole | Lansoprazole | Omeprazole | Placebo |
|----------------|-----------|------------|------------|--------------|------------|---------|
|                | 4w/994    | 29%        | 40%        | 49%          | 61%        |         |
| Venables [26]  |           |            |            |              |            |         |
| Galmiche [27]  | 4w/426    | 29%        | 49%        | 60%          | 60%        |         |
| Bardhan [28]   | 2w/448    | 26%        | 40%        | 55%          | 55%        |         |
| Jones [29]     | 4w/609    | 31%        | 49%        | 60%          | 60%        |         |
| Lind [30]      | 4w/509    | 31%        | 49%        | 60%          | 60%        |         |
some are even able to stop those drugs and continue only with antacids taken intermittently for instantaneous relief of heartburn. Proper guidelines on how to conduct long-term acid suppressant therapy (dose? duration?) are lacking yet urgently needed. The Practice Parameters Committee of the American College of Gastroenterology has published guidelines for the diagnosis and treatment of gastroesophageal reflux disease [21]. The guidelines cite the PPIs as the most effective medical therapy to control symptoms of GERD and heal esophagitis and suggest that PPIs may be used as initial therapy in some cases.

**SHORTCOMINGS OF PHARMACOLOGICAL MAINTENANCE THERAPY**

Effective control of the 24-hr esophageal acid exposure is the most effective medical therapy for healing and maintenance in patients with reflux esophagitis.

A major shortcoming of all trials in reflux disease is the lack of specification of the symptom patterns present in the patients selected for the trials. GERD symptomatology may vary substantially in practice. Acid suppressants may well control heartburn but up to 20 percent of the patients continue to complain of regurgitation, nocturnal cough and retrosternal pain.

Prokinetics as monotherapy are mainly indicated for the milder end of the spectrum of reflux disease. Whether there are patients with a specific symptom pattern (e.g., associated dysmotility like dyspepsia?) who preferentially benefit from cisapride is unknown at the present time. Combination of cisapride and acid suppressants in patients with more intractable disease has been insufficiently evaluated, although not infrequently done in practice. PPIs are undoubtedly superior to H2RAs for symptom relief and endoscopic healing. H2RAs insufficiently suppress food stimulated acid production. Moreover tachyphylaxis and acid rebound is possible [12, 22]. Boosting the H2RAs rarely produces the required effect. For more severe reflux disease BID dosing of a proton pump inhibitor is often necessary. Occasionally acid rebound is also demonstrable after stopping PPI therapy [23, 24].

**FUTURE PROSPECTS**

We have witnessed major progress in medical therapy of GERD over the last few years, through the development of more powerful prokinetics (cisapride) and especially through the development of PPIs for prolonged suppression of intragastric acidity and intragastric volume available for reflux. Yet the optimal goals have still not been reached and areas of improvement can be envisaged. The basic disturbances causing transient sphincter relaxation need further unraveling. Some very recent studies would indicate that it may well be possible to interfere with transient relaxations, for example through antagonism of the cholecystokinin A receptor [25]. Other modalities to regulate sphincter function are currently being explored.

Long-term modulation of intragastric acidity may also improve through further refinement of blockade of the acid pumps or through combination therapy. Also further improvement of surgical possibilities is to be expected, in parallel with the pharmacological improvement. Whether simultaneous prevention of intestinal metaplasia in the cardia or in the distal esophagus in patients with GERD is a reachable aim with pharmacological or surgical therapy will require carefully conducted long-term evaluations.

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