Medical Therapy of Gastroesophageal Reflux Disease Beyond Proton Pump Inhibitors: Where Are We Heading?

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Summary

Proton pump inhibitors (PPI) have greatly improved the treatment of gastroesophageal reflux disease. However, recent investigations have revealed that reflux symptoms persist in a substantial number of patients. Therefore, treatment strategies beyond PPI are urgently required. One such strategy may involve more reliable acid suppression, e.g., with new acid inhibitory drugs. Furthermore, the rapid appearance of an acidic compartment in the proximal stomach after a meal, which is largely responsible for postprandial heartburn, requires a specific kind of therapy in addition to PPI which still needs to be established. Pharmacological augmentation of the lower esophageal sphincter may represent another approach to diminish reflux, but the clinical efficacy of compounds tested so far is limited. Altered esophageal perception represents a major component involved in the generation of reflux symptoms, particularly in non-erosive reflux disease, but effective pharmacological intervention is largely lacking. Presumed reflux-induced respiratory symptoms (cough, laryngitis, etc.) in the absence of typical esophageal symptoms (e.g., heartburn) remain a hot topic, but recent research points towards a hypersensitivity syndrome and only a minor role of gastroesophageal reflux. Treatment options for this condition are still pending.

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Introduction

There is no question that proton pump inhibitors (PPI) have revolutionized the conservative (medical) treatment of gastroesophageal reflux disease (GERD) since the 1990s, and PPI therapy has evolved as the treatment of choice for this disease [1]. Healing of reflux esophagitis can be achieved in the vast majority of cases, and this is paralleled by symptomatic improvement (though in a slightly smaller number of patients). However, it has become evident in recent years that symptoms attributed to reflux of gastric content persist despite ongoing PPI treatment in up to 40% of patients in primary care [2, 3], and doubling the PPI dose is effective in only a small proportion of these cases. In addition, an effective therapy of (presumed) extraesophageal manifestations of reflux disease in the absence of heartburn and regurgitation is still lacking [4]. Thus, a broader concept is required for the non-surgical management of gastroesophageal reflux disease which includes treatment strategies beyond PPI.

Role of Acid Inhibition

Potassium-competitive acid blockers (P-CABs) as the novel class of acid suppressants have been recently developed which inhibit proton pump function by a different mechanism compared to PPI: P-CABs reversibly inhibit the proton pump by competing binding at the potassium-binding site of the H^+/K^+ -ATPase. In contrast to PPI, P-CABs do not require activation in the acidic compartment of the parietal cell (i.e., formation of the active tetracyclic sulfonamide); thus they can be administered independent of the ingestion of a meal. Since P-CABs are rapidly absorbed, the onset of action is claimed to be faster compared to PPI. Among several P-CABs, vonoprazan has evolved as the most intensively studied compound. Depending on the dose administered, more profound acid inhibition and longer duration can be achieved [5] which is also reflected by exaggerated gastrin increases compared to PPI [6, 7]. In rand-

Fig. 1. Schematic representation of the interaction of noxious gastric content refluxing into the esophagus and esophageal sensitivity in different subtypes of gastroesophageal reflux disease (modified from Weijenberg and Bredenoort [15]).

omized studies, vonoprazan was equally effective both in terms of healing of erosive esophagitis and improvement of symptoms [8], and in patients with PPI-refractory GERD vonoprazan demonstrated efficacy in a substantial number of cases [6, 9].

The future role of P-CABs in the management of GERD remains to be established. It is well accepted that the degree of acid inhibition is closely correlated with healing of reflux esophagitis [10]. Since – at least some – PPI show marked interindividual variability in acid suppression [11], more consistent acid suppression with P-CABs should result in fewer treatment failures. Thus, this drug class may have a role in PPI-resistant GERD, and CYP 2C19 extensive metabolizers may also profit from these compounds [7]. Meal independency and rapid onset of acid inhibition may turn out to be a further advantage, particularly in the setting of on-demand therapy. However, further studies have to confirm these expectations for P-CABs in the management of reflux disease.

Role of Perception (Esophageal Sensitivity)

As early as 60 years ago, there was an interest in the role of perception when gastric content refluxes into the esophagus: Lyonel Bernstein [12] established an acid perfusion test (called accordingly ‘Bernstein test’) to study esophageal sensitivity by recording symptoms in response to perfusion of the esophageal lumen with saline and hydrochloride acid which are applied separately. The wide range of symptomatic responses to this standardized acid perfusion clearly demonstrated the profound differences in individual esophageal perception. Although the Bernstein test is obsolete nowadays in clinical routine due to its low therapeutic relevance, it represents one of the first experimental attempts to study the phenomenon of esophageal sensitivity.

The development of pH recording techniques has further increased our knowledge of esophageal perception. It is quite obvious that there is poor correlation between the amount of gastric juice refluxing into the esophagus and the severity of symptoms: more acid exposure to the esophagus is found in patients with Barrett’s esophagus and erosive reflux disease (ERD) compared to non-erosive reflux disease (NERD), and NERD patients as a group have more reflux compared to controls while there are no differences with respect to non-acid reflux [13]. However, these differences are not reflected by the intensity of symptoms since ERD and NERD patients have about the same symptom burden [14]. Therefore, in addition to the amount of refluxed gastric content, esophageal sensitivity plays a significant role in symptom generation [15]: within the subsets of patients with reflux disease from severe esophagitis down to patients with NERD or a hypersensitive esophagus, the role of the refluxate is becoming less important while altered perception in the esophagus is becoming progressively more dominant (fig. 1).

It is of particular interest that stress increases the perception during intraesophageal acid perfusion in patients with reflux disease but not in healthy controls [16], and disorders like anxiety are able to modulate esophageal sensitivity. It is therefore not surprising that particularly patients with reflux symptoms but normal results in impedance-pH recordings exhibit psychological distress [17].

Based upon these observations, the question arises of how to target altered perception by medical therapy. Such therapy would be of particular interest in NERD patients and those with a hypersensitive esophagus in whom acid reflux plays only a minor role while these patients show an overlap between GERD and functional disease. A couple of studies have been performed in which predominantly tricyclic antidepressants (e.g., amitriptyline) and selective serotonin reuptake inhibitors (SSRI) have been investigated and found to be partially effective [18]. The more the clinical picture is dominated by altered perception, the more effective is this pharmacological approach, albeit hampered by frequent side effects due to the compounds used. The German guideline for the diagnosis and treatment of GERD [1] has included this kind of medical therapy in the appropriate setting. However, much more research is required to fully understand the interaction between gastroesophageal reflux and generation of reflux symptoms.

Role of the Acid Pocket

Fletcher et al. [19] for the first time demonstrated that early in the postprandial state an unbuffered acidic compartment accumulates below the gastroesophageal junction whereas the pH in the remaining body of the stomach is still weakly acidic. It is now generally accepted that this so-called ‘acid pocket’ is predominantly responsible for postprandial heartburn which is observed in the majority of patients and which may persist during PPI therapy (fig. 2). This acid pocket becomes even more important in cases with a hiatal hernia: under these circumstances the acid pocket might extend into the hernia and thus lead to free reflux into the

esophagus [20]. PPI therapy (fig. 2) is able to reduce the acid pocket [21], but presumably very high PPI doses (which are probably not warranted) might be necessary to completely eliminate this postprandial acid accumulation. Accordingly, alternative treatment strategies need to be established.

One such possible option is the (surgical) repositioning of the hiatal hernia below the diaphragm; however, trials studying the acid pocket pre- and postoperatively have not been performed so far. Another suggested option is the administration of alginates, an anionic polysaccharide occurring naturally in brown algae, which are only slightly inferior to omeprazole in less severe forms of GERD [22]. Theoretically, the acid pocket would be an ideal target for this compound since alginates accumulate just below the esophagogastric junction creating a foam layer above the gastric content. Preliminary studies in patients with residual symptoms during once-daily PPI therapy have been promising: the alginate preparation as an add-on treatment to PPI was superior to placebo in reducing break-through symptoms [23]. More recent studies with larger numbers of patients have, however, produced conflicting results. The beneficial effect of an alginate added to the PPI in the exploratory part of the study by Coyle et al. [24] could not be reproduced in the confirmatory part of the trial. Thus, it remains to be established to what extent alginates may play a role in PPI-refractory postprandial heartburn; alternative strategies targeting the acid pocket need to be developed.

Augmentation of the Reflux Barrier

Spontaneous transient relaxation of the lower esophageal sphincter (LES) not associated with passage of food through the cardia represents one of the most important pathophysiological factors in the development of reflux disease [25]. Thus, pharmacological interventions to prevent these episodes of relaxation are an attractive therapeutic concept. Support for this hypothesis comes from another approach to strengthen the LES: recently, a device for electrical stimulation of the LES has been developed, and preliminary results using this device show promising results in terms of improvement of both reflux parameters and symptomatology [26, 27].

Among a substantial number of neurotransmitters and receptors involved in the regulation of LES function, GABA_B receptors have evolved as a pharmacological target. The prototype GABA_B antagonist is baclofen; however, since this compound crosses the blood-brain barrier, it exerts significant side effects. Therefore, several derivatives (e.g., lesogaberan, arbaclofen) have been investigated and found to be effective in reducing the number of transient LES relaxation episodes. However, when it came to investigating the clinical efficacy of these compounds in large randomized controlled studies, the therapeutic gain was small [25] and as a consequence the drug development programs were terminated. The failure to meet primary expectations may at least in part be due to the selection of the study population since the major prerequisite for study inclusion was incomplete response to PPI. This may have led

Acid reflux and acid pocket position

Fig. 2. Position of the acid pocket and acid reflux rate off and on proton pump inhibitors (PPI); adapted with kind permission of Elsevier from [21] (* $p < 0.05$).

to inclusion of a substantial proportion of patients with esophageal hypersensitivity which are unlikely to respond to augmentation of the reflux barrier.

Metabotropic glutamate receptors (mGluRs) present on vagal afferents are another target to decrease transient LES relaxation. Inhibitors of the mGluRs subtype 5 act not only peripherally but also diminish vago-vagal reflux centrally. Experiences from clinical trials are limited so far: in a double-blind, placebo-controlled, randomized study, the mGluR5 inhibitor ADX 10059 reduced reflux events and improved symptoms during a 2-week treatment phase, but therapy was associated with frequent side effects such as dizziness and vertigo [28].

In principle, inhibiting transient LES relaxation and thus strengthening the anti-reflux barrier is an attractive concept, but effective drugs need yet to be developed. On the other hand, electrical modulation of the LES tone – which can be adjusted individually – competes with pharmacological modulation of the LES and may potentially offer a more reliable therapeutic outcome due to an exclusively local mode of action.

Extraesophageal Manifestations

The Montréal classification of GERD includes the ‘established’ association of extraesophageal syndromes such as reflux cough syndrome and reflux laryngitis syndrome [29]. Especially ear/nose/throat (ENT) specialists take advantage of this classification as they refer patients with cough without overt causes to gastroenterologists assuming that gastroesophageal reflux is the underlying pathophysiological factor. There is no doubt that about one fourth of patients with heartburn and regurgitation simultaneously suffer

Fig. 3. Proposed algorithm of management of suspected extraesophageal manifestations of reflux disease (*see text).

from cough and other laryngeal symptoms. The majority of these patients will respond well to a PPI [30].

The clinical efficacy of PPI in patients with laryngeal disorders in the absence of esophageal symptoms such as heartburn is entirely different: Based upon various meta-analyses, PPI do not improve cough [31], posterior laryngitis [32], or asthma [33] when compared to placebo; furthermore, the pattern of reflux parameters (total reflux, proximal reflux, acidic and non-acidic reflux) in chronic cough is not different from healthy controls [34]; finally, only 17% of reflux episodes detected by impedance-pH monitoring are followed by a cough [35]. These findings cast serious doubt on the hypothesis that gastroesophageal reflux is frequently an essential or at least important factor in the pathophysiology of this setting.

Recent research points towards completely different mechanisms underlying chronic cough of unknown origin: symptoms are most likely due to a hypersensitivity syndrome. Irrespective of whether acid reflux may be acting as an initiator for this entity as proposed by Morice [36], a wide range of stimuli is involved in the activation of sensory afferent vagal neurons [37]. There are striking similarities to neuropathic pain syndromes (for details see [4, 37]). The concept of a hypersensitivity syndrome also implies that in addition to activation of peripheral receptors also central sensitization is involved.

In order to set up new therapeutic strategies, it is essential to identify receptors on vagal afferents involved in this syndrome. Clues as to potentially affected receptors are to a large extent derived from pharmacological intervention, e.g., blocking of specific receptors. The beneficial effect of gabapentin and pregabalin on cough intensity suggests that GABA receptors may play a significant role. In addition, activation of P2X3 receptors expressed on vagal afferent

neurons leads to an exaggerated cough response, whereas the antagonist to the P2X3 receptor AF-219 dramatically reduces the cough frequency [38]. Finally, also the villanoid receptor TRPV1 has to be taken into account: although the primary ligand of this receptor is capsaicin, quite a lot of other substances (e.g., heat, smoke, etc.) are also capable of activating this receptor [39].

What does all this mean for clinical practice? An algorithm based upon present knowledge is proposed in figure 3 but should be taken cautiously since this is a field very much in progress. The first key question to be answered is whether there is any evidence of other factors associated with chronic cough (e.g., smoking, ACE inhibitors, postnasal drip, etc.). Thereafter, it is essential to check whether any typical esophageal reflux symptoms (such as heartburn or regurgitation) are present in the individual patient; if so, the primary option is PPI treatment since there is a substantial chance that symptoms will resolve or at least improve in response to PPI treatment [30]. If respiratory symptoms disappear or improve, PPI therapy should be continued in doses appropriate to control symptoms.

However, there is probably a significant number of patients in whom esophageal complaints cannot be interpreted with certainty; patients may report some kind of retrosternal or upper abdominal discomfort which cannot not be convincingly attributed to GERD. In these cases, temporary PPI therapy should be initiated similar to the previous setting, using a double PPI dose in order to achieve adequate acid suppression in the vast majority of patients (since there is substantial interindividual variation in the degree of acid inhibition at standard doses of PPI [11]). If such treatment fails, PPI administration should be discontinued. Occasionally, doubt remains about a possible reflux-associated symptomatology; under

these circumstances, a sophisticated evaluation of the patient should be carried out including impedance-pH monitoring as well as manometry (to exclude abnormal peristalsis), even though the predictive value of these diagnostic procedures is not well established. If acidic reflux still remains, compliance should be critically evaluated as well as appropriate administration of the PPI. If acidic reflux is excluded, the therapeutic options are much more narrow: In these cases, no effective medical therapy is available, and a purely surgical approach is not recommended based on current experience [40] since no high-quality studies, particularly randomized trials, have been published so far [41]. It is not surprising that patients reporting concomitant typical reflux symptoms are more likely to benefit from antireflux surgery compared to those in whom typical GERD symptoms are lacking [42], placing a question mark over the surgical option (fig. 3).

Decisions about treatment in cases with complete absence of typical esophageal symptoms are the most difficult task. Primarily, PPI therapy should not be considered [40] or discontinued if started previously. From the present experience, neuromodulators (e.g., amitriptyline, imipramine, gabapentin) should be considered in this setting; treatment using these drugs will not be effective in all cases, and some patients may not tolerate the therapy due to side effects (especially tricyclics). It seems that non-pharmacologi-

cal interventions (e.g., speech pathology treatment) may have some role in the therapeutic process [37], but this interdisciplinary cooperation will require a determined ENT specialist. Surgeons should be cautious to operate on these patients. While an established and evidence-based treatment strategy for this clinical scenario is still lacking, potential new treatments are currently in development that are showing promise [37].

Conclusion

The clinical challenges discussed above show that the field of reflux therapy beyond PPI is 'work in progress' and in many aspects still in its beginning. For a long time, PPI were regarded as a drug class which can solve all problems related to GERD. However, more recent evidence increasingly demonstrates that there is a need for pharmacological interventions in GERD in addition to PPI treatment.

Disclosure Statement

The author has no disclosures or conflicts of interest to report.

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