Oral proton-pump inhibitors and step-down therapy for nonulcer dyspepsia: is this the right approach?

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Introduction

Dyspepsia is a condition with symptoms thought to originate in the upper gastrointestinal tract including epigastric pain or discomfort, heartburn, acid regurgitation and nausea. Such symptoms may be caused by peptic ulcer disease, gastroesophageal reflux disease (GERD), gastric cancer, or may be the result of none of these conditions, without any objective findings, which is known as nonulcer dyspepsia (NUD). To exclude peptic ulcer, gastric cancer and reflux esophagitis, an upper gastrointestinal endoscopy has to be performed before NUD is diagnosed. Moreover, since peptic ulcer disease shows a cyclic course [Myren, 1983], *Helicobacter pylori* (HP), the main cause of peptic ulcer disease [Marshall and Warren, 1984], has to be excluded either by biopsies taken during the endoscopy or by serology, at least if the endoscopy is performed in an asymptomatic phase. Furthermore, since HP is also an important factor in gastric carcinogenesis [Parsonnet *et al.* 1991], it is wise to test the patients for this infection, particularly if an upper gastrointestinal endoscopy is not performed. In the first period of endoscopy most patients with dyspepsia were examined with an upper gastrointestinal endoscopy. Owing to high cost of endoscopy, particularly in North America, this strategy has been changed to eradicate HP in those positive (test and treat) or often to treat just using an inhibitor of acid secretion, which in recent years have mostly been proton-pump inhibitors (PPIs). These two strategies seem to give similar results with respect both to cost and effect on symptoms [Ford *et al.* 2008].

As only a portion of those with GERD also have esophagitis at endoscopy [Schindlbeck *et al.* 1987], ideally a 24-h monitoring of esophageal pH should also be carried out before making the exclusion diagnosis of NUD. Alternatively, those

with typical reflux symptoms such as heartburn and acid regurgitation should be excluded, leaving the remaining patients with so-called functional dyspepsia characterized by just epigastric pain or discomfort [Drossman, 2006]. When evaluating the effect of treatment trials with inhibitors of acid secretion in patients with NUD, it is essential that those with reflux disease have been excluded, since acid reflux is the cornerstone in the pathogenesis of GERD. Nevertheless, there is an overlap between GERD and NUD with respect to symptoms [Carlsson *et al.* 1998], which may explain the positive effect of gastric acid inhibition in some patients with NUD [Farup *et al.* 1995].

Nonulcer dyspepsia and proton-pump inhibitors

NUD, a condition with dyspepsia with normal upper gastrointestinal endoscopy, negative HP status and without symptoms or signs (normal 24-h esophageal monitoring) of GERD, is without known cause and pathogenesis. Previously chronic gastritis was thought to give symptoms but this is no longer accepted [Katelaris *et al.* 1992], although acute gastritis is symptomatic [Ramsey *et al.* 1979]. Naturally, HP infection causing gastritis and peptic ulcer disease [Marshall and Warren, 1984] could also be suspected to cause NUD. However, the correlation between HP infection and dyspepsia is at best weak [Bernersen *et al.* 1992; Katelaris *et al.* 1992], and HP eradication has been reported not to improve NUD [Talley *et al.* 1999]. Nevertheless, in a Cochrane analysis of randomized controlled trials, a slight beneficial effect of HP eradication was found [Moayyedi *et al.* 2006].

Since the symptoms in NUD have some resemblance to those of peptic ulcer disease, an accepted acid-related disease, it was natural also to try inhibitors of acid secretion in patients with

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NUD. However, there is no indication of any difference in acid secretion between patients with NUD and normal healthy people [Nyren, 1991]. Trials with PPIs in the treatment of NUD have given variable and marginal results [Bolling-Sternevald *et al.* 2002; Wong *et al.* 2002; Talley *et al.* 1998]. Nevertheless, a therapeutic test starting with a high per-oral dose of PPI, which is subsequently tapered down, has been used in the evaluation of the role of acid in the pathogenesis of NUD in the individual patient [Talley *et al.* 2007]. This will necessarily lead to an overuse of PPI since those with a placebo effect [Talley *et al.* 2006] will, erroneously, be thought to respond to the active drug.

PPIs have a steep concentration–response curve and a variable bio-availability [Sharma *et al.* 1984]. Thus, to examine the effect of acid on symptoms, it is necessary to start with a high dose in order to obtain hypo-acidity in the majority of the patients. Reducing the dose will result in some patients losing all effect whereas others retain the full effect. PPIs are accordingly not suited to tapering of the dose. On the other hand, the side effects of PPIs are mainly connected to their biological effect, which is inhibition of gastric acid secretion resulting in gastric hypo-acidity and secondary hypergastrinemia. It is strange that so few studies have been concerned with possible side effects related to the inhibition of gastric acid secretion. After all, secretion of acid in the upper gastrointestinal tract is a function that is highly preserved during phylogenesis and individually through feedback mechanisms mainly involving gastrin [Steen *et al.* 1980]. The reason for the belief that gastric hypo-acidity does not cause any harm is most probably due to experience with patients with atrophic gastritis and particularly pernicious anemia. However, this is a condition that starts in the middle or later part of life [Villako *et al.* 1976]. Therefore, diseases secondary to anacidity and with a long latency will not have sufficient time to manifest themselves in these patients. It is well known that patients with pernicious anemia have an increased risk of developing gastric neoplasms, both gastric enterochromaffin-like carcinoids (ECLomas) [Sjoblom *et al.* 1988], as well as gastric carcinomas [Zamcheck *et al.* 1955], the latter being diagnosed as adenocarcinomas, but possibly neuro-endocrine carcinomas of ECL cell origin [Qvigstad *et al.* 2002]. Furthermore, reduced gastric acidity may predispose to infections

[Martinsen *et al.* 2005], and concerns related to long-term safety of PPIs, not only to infectious diseases, but also to nutritional deficiencies, have been raised [Ali *et al.* 2009]. Recently, it has also been shown that PPI withdrawal after 8 weeks dosing of PPI may induce dyspeptic symptoms [Reimer *et al.* 2009], due to rebound acid hypersecretion [Waldum *et al.* 1996]. To understand the mechanisms behind rebound acid hypersecretion after PPI, it is necessary to comprehend the physiological and clinical consequences of the localization of the gastrin receptor to the ECL cell and not the parietal cell [Bakke *et al.* 2001; Athmann *et al.* 2000]. The rebound acid hypersecretion is mainly due to increased histamine release secondary to the stimulation of ECL cell function and proliferation caused by hypergastrinemia as a consequence of gastric hypo-acidity [Waldum *et al.* 1991a]. Gastrin stimulates acid secretion indirectly by stimulating the ECL cell [Waldum *et al.* 1991b], and maximal histamine-stimulated acid secretion exceeds that of gastrin [Kleveland *et al.* 1987]. Therefore, gastrin-stimulated histamine release, which depends on the ECL cell mass [Waldum *et al.* 1991a], will restrict gastrin-stimulated acid secretion. The PPI-induced hypo-acidity leads to hypergastrinemia, which stimulates the proliferation of the ECL cell and thus increases the ECL cell mass. In the long term, the general trophic effect of hypergastrinemia on the oxyntic mucosa, including the parietal cell [Bakke *et al.* 2000; Crean *et al.* 1969], which may be a direct or an indirect effect via mediators from the ECL cell, will also lead to acid hypersecretion. However, the relatively short period of rebound acid hypersecretion (2–3 months) [Fossmark *et al.* 2005] suggests that the ECL cell mass is quantitatively most important in rebound acid hypersecretion after PPI since the ECL cell has a shorter life span than the long-living parietal cell. Rebound acid hypersecretion after PPI causes dyspeptic symptoms [Reimer *et al.* 2009] and probably also acid-related diseases such as duodenal ulcer and reflux esophagitis similar to those seen in patients with gastrinoma [Saeed *et al.* 1991; Miller *et al.* 1990]. Accordingly, any PPI treatment test, if used, should not last more than a couple of weeks to avoid post-treatment dyspepsia. In fact, discontinuation of PPI treatment has been reported to be a problem [Bjornsson *et al.* 2006]. Accordingly, any use of PPI for more than a few weeks will increase the population of patients dependent on these drugs. There are, therefore, important side effects of PPIs that

indicate that their use should be restricted to cases and conditions where there are no other alternatives. NUD is a condition without known etiology and pathogenesis, and which carries an excellent prognosis, although it may have some impact on quality of life. The principle of treatment should be to disturb normal physiology as little as possible. A thorough initial examination may reduce the possible psychological component in the pathogenesis. With similar symptoms to those in patients with peptic ulcer, it may be logical to try to reduce gastric acidity in patients with NUD. Owing to their immediate effect and lack of important side effects, it is natural to start with antacids. Alternatively, histamine-2 blockers may be tried. PPIs have no place in the treatment of NUD since the condition itself is not serious, and the drugs have important side effects. In the very recent DIAMOND study a step-up approach starting with antacids and progressing to histamine-2 blocker to PPI was compared with a step-down regimen starting with PPI and gradually reducing the efficacy of acid reduction [Van Marrewijk *et al.* 2009]. Symptomatic effects in the two regimens were similar, but the cost was lower for the step-up strategy.

Summary

Patients with chronic dyspepsia ought to be diagnosed as completely as possible before treatment is given. In addition to upper gastrointestinal endoscopy and determination of HP status, GERD should be excluded. When the outcome of the diagnostic procedures is negative, the diagnosis of NUD may be made. These patients should be given symptomatic treatment resulting in as little disturbance of normal physiology as possible. Owing to the problems related to PPI use, which until now have been underestimated, antacids or histamine-2 blockers should be the first choices. In the long term, this approach, which is correct from a clinical point of view, will also be less expensive.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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