Proton Pump Inhibitors in the Management of Gastroesophageal Reflux Disease

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The primary treatment goals in patients with gastroesophageal reflux disease (GERD) are relief of symptoms, prevention of symptom relapse, healing of erosive esophagitis and prevention of complications. The severity of GERD is directly correlated with the degree and duration of oesophageal acid exposure and is highly pH dependent. Healing of reflux esophagitis is directly correlated with the intragastric pH > 3.5. In patients with GERD, treatment is directed at acid suppression through the use of lifestyle modifications (e.g., elevating the head of the bed, modifying the size and composition of meals) and pharmacologic agents (a histamine H2-receptor antagonist [H2RA] or a proton pump inhibitor [PPI]). The relief of symptoms and the long-term control of the disease are the primary aims of therapy for the majority of patients. The efficacy of antisecretory drugs in healing GERD depends on the strength and duration of acid suppression within a 24 h period, and the duration of the treatment. PPIs are more effective for acid-related symptoms and higher endoscopic healing rates in comparison with H2-RAs. Most PPIs (except pantoprazole) inhibit the bioactivation of clopidogrel to its active metabolite as they are associated with the loss of the beneficial effects of clopidogrel as well as an increased risk of reinfarction. Some clinicians reported their experiences that the generic has sometimes shown less effective than the corresponding branded PPIs. We conducted the overview of the effectiveness of PPIs in the treatment of patients with both categories of GERD; nonerosive reflux disease (NERD) and erosive reflux disease (ERD). We also report about interactions between PPIs and other drugs and differences between generic and branded PPIs. Key Words: Gastro-oesophageal reflux disease, Proton pump inhibitor, Interaction with clopidogrel, Branded and generic PPIs.

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1. INTRODUCTION

Gastro-oesophageal reflux disease (GERD) is a spectrum disease ranging from non-erosive to erosive or complicated forms, in which each stage may progress to the next more severe in the absence of adequate therapy (1). Gastroesophageal reflux may be defined as the backward passage of stomach contents through the lower esophageal sphincter. Reflux in itself is not necessarily pathologic. Normal reflux usually occurs after meals, when the person is upright; the episodes are short lived and asymptomatic. Pathologic reflux is more frequent, more often occurs when the person is horizontal and lasts longer; heartburn and regurgitation are frequent (2, 3). The goals of GERD treatment are: control of symptoms, healing of oesophagitis and the prevention of complications (stricture, Barrett’s oesophagus and oesophageal adenocarcinoma) (4-7). The efficacy of antisecretory drugs in healing reflux esophagitis depends on the strength and duration of acid suppression within a 24 h period, and the duration of the treatment. Symptomatic (or endoscopic) relapse is very frequent and most patients therefore need long-term antisecretory therapy. The two most popular non-continuous strategies are intermittent and on-demand therapy. In the intermittent approach, patients take medication for a certain period (for example, 7 or 28 days) after relapse of symptoms, whereas patients adopt the on-demand approach initiate therapy only when symptoms occur; each time waiting for a symptom relapse to take next medication. Proton pump inhibitors (PPIs) therapy are proving more effective for acid-related symptoms compared to H2-receptor antagonists (H2-RAs), and are commonly used also in the long-term management of GERD, in both erosive oesophagitis and non-erosive reflux disease, the more prevalent condition. Randomized-controlled clinical trials in either form of GERD have shown that PPIs were superior to placebo and H2-RAs for controlling symptoms, whereas
in erosive esophagitis, PPIs are also the most effective agents for healing erosions and for maintenance of healing. Most proton pump inhibitors inhibit the bioactivation of clopidogrel to its active metabolite. Among the patients who have received clopidogrel following acute myocardial infarction, concomitant therapy with proton pump inhibitors other than pantoprazole was associated with the loss of the beneficial effects of clopidogrel and an increased risk of reinfarction. Some clinicians have reported that the generic were sometimes less effective than the corresponding branded drugs. We conducted the overview of the effectiveness of proton pump inhibitors in the treatment of the patients with both categories of GERD; nonerosive reflux disease (NERD) and erosive reflux disease (ERD). We also report about interactions between PPIs and other drugs and differences between generic and branded PPIs.

2. MANAGEMENT OF GERD

The aim of effective medical treatment of esophagitis is successful reduction of acidity of the refluxate to a level outside the optimum proteolytic pH range of pepsin, i.e., greater than pH 3.5. Until the 1990s, most therapeutic trials in GERD focussed upon endoscopic lesions. It must be emphasized that there is no diagnostic gold standard for GERD. In fact the correlation between patient symptoms and both the presence and grade of esophagitis is very poor. The classical criteria for the assessment of therapeutic efficacy in GERD have therefore been revised, and there is now a consensus that the relief of symptoms and the long-term control of the disease are the primary aims of therapy for the majority of patients. Basic goals of treatment are to provide complete, or at least sufficient, control of symptoms, to maintain symptomatic remission, to heal underlying esophagitis and maintain endoscopic remission, and to treat or, ideally, prevent complications. Different drug management strategies can be divided into (i) continuous maintenance therapy and (ii) discontinuous therapy which can again be divided into two categories, intermittent and on-demand drug therapy. A case-by-case approach is recommended to determine the personal therapeutic needs and preferences of each individual. Proton pump inhibitors (PPIs) represent the mainstay of therapy for patients with non-erosive reflux disease (NERD) as well as esophagitis. There are as yet insufficient data to establish the clear superiority of one PPI over others. Symptom relief is significantly inferior in NERD than in erosive esophagitis. Although a stepwise strategy has been recommended in the past, a step-down strategy (starting with a full-dose PPI) appears to be a more cost-effective approach.

All these aspects have an important impact on the clinical management of GERD which is distinct in the initial phase and long-term care. Uncomplicated reflux disease comprises the nonerosive reflux disease (NERD) and erosive reflux disease (ERD). The objectives of the treatment are the adequate control of symptoms with restoration of quality of life, healing of lesions and prevention of relapse. Finally when making a choice between different long-term strategies both the clinician and the informed patient have to consider efficacy, safety, tolerability and cost.

3. TREATMENT OF NERD

Treatment of NERD, which consists of the administration of proton pump inhibitors (PPI) for 2–4 weeks and appropriately dosed PPI treatment, can achieve a satisfactory initial response in two-thirds of the patients. If initial treatment with 4 weeks of PPI fails to elicit adequate symptom control, increasing the PPI dose is recommended, since studies have shown that patients with acid-sensitive esophagus respond better to a high PPI dose. In nonresponders to appropriate PPI treatment, a low-dose tricyclic antidepressant is recommended at bedtime or serotonin reuptake inhibitors. The effect of other substances such as H2 blockers or prokinetic drugs is hardly better than that of placebo.

If initial treatment of NERD is successful, medication should be discontinued, since this clinical entity does not appear to necessitate measures aimed at preventing complications. Many patients with NERD or mild esophagitis do not require continuous maintenance therapy and recent studies have shown excellent results with different PPI on-demand therapy regimens. On-demand therapy means that the patient himself determines both the start and the end of treatment. Medication should be discontinued as soon as there are no further symptoms. In large scale studies, on-demand treatment with PPIs (pantoprazole, lansoprazole, rabeprazole, esomeprazole) has shown superior to continuous treatment. PPIs have proven their superiority to placebo in on-demand treatment in individual studies. Head-to-head comparisons between various PPIs are, however, lacking, so that a comparative assessment is not possible.

4. TREATMENT OF ERD

Erosive reflux esophagitis can be found in about 30–40% of GERD patients. Endoscopic classification of reflux esophagitis according to Los Angeles criterions is categorized into four degrees of severity A–D (A: mucosal breaks of ≤5 mm on the top of folds; B: mucosal breaks ≥5 mm in extent on mucosal folds; C: circumferential spreading of mucosal breaks involving less than 75% of the circumference; D: mucosal breaks involving >75% of the circumference). Therapy with a standard dose PPIs for 4–8 weeks is recommended in patients with ERD. Adequate control of symptoms is considered to have been achieved when mild reflux symptoms occur at most once a week.
elimination of symptoms after 8 weeks is predictive for healing of the esophagitis (25, 26, 27).

In the beginning of disease, treatment with a standard dose of a PPI is always recommended in patients with ERD. Mild cases (grade A/B) usually heal within 4 weeks, while severe cases (grade C/D) often require longer treatment (eight or more weeks). PPIs reduce gastric acid, and thereby reduce the bioavailability of drugs requiring intragastric acidity to maximize their absorption and bioavailability (28). Various PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole) differ in such pharmacokinetic characteristics as bioavailability and the rapidity with which effect occur. Regarding the healing rates of reflux esophagitis after 4 and 8 weeks, neither administration of the standard doses of the PPIs (omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, rabeprazole 20 mg) nor doubling of the individual dose (e.g. lansoprazole 60 mg, pantoprazole 80 mg) showed any difference in increased efficacy (29, 30).

Treatment with combinations of PPI and prokinetic drugs is of unproven value.

After responding well to the initial treatment, up to 90% of the patients with ERD show a tendency to relapse already within the next 6 months. Patients with mild ERD (grade A/B) often have a longer relapse-free interval than patients with severe ERD (grade C/D) (30, 31). Therefore, it is recommended that, in patients with mild ERD, therapy should first be discontinued and the further course of the disease kept under surveillance, while in severe ERD, initial successful therapy should be followed by maintenance treatment. Satisfactory control of symptoms was achieved in the vast majority of patients, but continuous therapy has proven superior in maintenance of remission of erosive ERD, although an evidenced-based recommendation is currently not possible. For the prevention of relapse in patients with healed esophagitis, PPIs have clearly shown superior to H2-receptor antagonists, prokinetic drugs and combinations of these medications (32-35).

5. INTERACTION BETWEEN PROTON PUMP INHIBITORS AND CLOPIDOGREL

PPIs may alter the intestinal first pass metabolism or the hepatic clearance of some drugs, and thereby modify their pharmacodynamics (36). PPIs have a low drug interaction through phase I/II effects (37,38), and may differ in their possibility of causing drug interactions. The metabolism of PPIs by hepatic cytochrome enzymes varies significantly between drugs. Omeprazole and lansoprazole have a high affinity for CYP2C19 and CYP3A4 but these cytochromes contribute little to rabeprazole metabolism. Pantoprazole is completely metabolized by these cytochrome enzymes, but it uniquely has no drug interactions with a wide range of drugs (36,39-41).

Therefore, PPIs have an effect in common with all acid lowering therapy to reduce the absorption of acid-dependent medications. PPIs, with the exception of pantoprazole, have been associated with reduced effectiveness of clopidogrel and a resulting 40% increased risk of coronary stent occlusions (12). This effect, which was not seen with pantoprazole therapy, presumably reflects inhibition of the metabolic bioactivation of clopidogrel. The literature suggests (12, 36-41) that, among patients taking clopidogrel following acute myocardial infarction, the concomitant use of a proton pump inhibitor that inhibits cytochrome P450 2C19 (omeprazole, lansoprazole or rabeprazole) is associated with an increased risk of recurrent myocardial infarction.

Therefore, regarding the clinical significance of drug interactions with clopidogrel, concomitant treatment with clopidogrel and proton pump inhibitors other than pantoprazole should be minimized when possible. If a proton pump inhibitor is required, pantoprazole should be used preferentially in patients who are also receiving clopidogrel.

6. WHY SOME PROTON PUMP INHIBITORS ARE MORE EQUAL THAN OTHERS

After the omeprazole patent expired in 2002, numerous generic products were introduced on the market and many patients received substitute-treatment. After the availability of generic proton pump inhibitors (PPIs) some experiences showed that the generic were sometimes less effective than the corresponding branded drugs. In some patients replacement of the brand drug by the generic PPI caused clinical consequences with rapid exacerbation of the symptoms of reflux disease. This is not a conclusive proof that the generic are inferior compared to branded drugs since factors such as increase in severity of the disease and decreased adherence can play a role.

Nevertheless, the time relationship with the substitution and recovery after resumption of the use the brand suggest that the effect of the products differ (14, 42, 43). Some authors (12, 13, 14) draw their attention to the complex situation surrounding generic and therapeutic substitution, and they give some possible explanations why PPIs effectiveness in individual cases can differ.

Otten et al. (14) suggest three possibilities to explain the inadequacy of the substitution: (a) biphasic metabolism where the raised pH in the stomach may prematurely inactivate the PPI, with an unpredictable effect, (b) differences in acid-resistant coating of the generic products, and (c) influence of multiple dosing of PPIs after several days’ use. They conclude that all three factors may contribute to the difference in absorption and therefore clinical effectiveness.

7. CONCLUSIONS

Pharmacologic treatment of reflux esophagitis and its symptoms clearly depends on the adequate suppression of gastric acidity. PPIs are more effective for acid-related symptoms and higher endoscopic healing rates in comparison with H2-RAs.

Most PPIs (except pantoprazole) inhibit the bioactivation of clopidogrel to its active metabolite and they are associated with a loss of the beneficial effects of clopidogrel and an increased risk of reinfarction. Some clinicians reported their experiences that the generic were sometimes less effective than the corresponding branded PPIs.
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