Optimal use of proton pump inhibitors for treating acid peptic diseases in primary care

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Abstract

Heartburn, reflux and epigastric pain are frequently encountered symptoms in primary care medicine. Acid peptic diseases such as peptic ulcer and gastrointestinal reflux disease have a high prevalence, can have important impact on patient quality of life and represent a considerable health care cost. Proton pump inhibitors (PPIs) are the most potent pharmacological inhibitors of gastric acid secretion currently available and are the mainstay medical therapy for acid peptic diseases.

This review summarizes current evidence on treatment of acid-peptic diseases with proton pump inhibitors and provides primary care clinicians with best practice guidelines for optimal use of these drugs. (Acta gastroenterol. belg., **2013**, 76, **393-402**).

Key words : Proton pump inhibitors, acid peptic diseases, best practices, review.

Introduction

Heartburn, reflux and epigastric pain are frequently encountered symptoms in primary care medicine. Acid peptic diseases such as peptic ulcer and gastrointestinal reflux disease (GERD) have a high prevalence, can have a major impact on patient quality of life and are responsible for a considerable health care cost. Proton pump inhibitors (PPIs) are the most potent pharmacological inhibitors of gastric acid secretion currently available and are the mainstay medical therapy for presumed acid peptic diseases.

PPIs inhibit gastric acid secretion by inhibiting the H^+-K^+-adenosine triphosphatase enzyme in the parietal cells of the gastric mucosa. Since the introduction of omeprazole in 1988, several other molecules from the same drug class have become available, including lansoprazole (1995), pantoprazole (1997), rabeprazole (1999), esomeprazole (2001) and dexlansoprazole (2009). PPIs are superior to Histamine-2(H2)-receptor antagonists for treatment of peptic ulcer and reflux disease and have a good safety profile.

In this article, we provide evidence-based best practice guidelines for the management of acid peptic disease in primary care settings, comprising : optimal PPI use, combination of PPI treatment with lifestyle changes, correct administration of PPIs, considerations for long-term use, dose escalation and down-titration schemes.

Current PPI prescription recommendations

PPIs currently on the market in Belgium are omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole. Except for rabeprazole, all PPIs are also available as generics. In Belgium, only pantoprazole is available as over-the-counter drug.

The 2010 revision of the guidelines for good use of PPIs from the healthcare reimbursement authority, the Rijksinstituut voor Ziekte- en Invaliditeitsverzekering/ Institut national d'assurance maladie-invalidité (RIZIV/ INAMI), enumerates four indications for which the use of PPIs is recommended : (1) gastroesophageal reflux disease and reflux esophagitis, (2) NSAID-induced ulcers or their prevention in high-risk patients treated with non-steroidal anti-inflammatory drugs (NSAIDs), (3) gastroduodenal ulcers and eradication of H. pylori, and (4) Zollinger-Ellison syndrome. RIZIV/INAMI currently does not recommend PPIs for treatment of functional dyspepsia (FD) (1).

NSAID-treated patients with high-risk for developing NSAID-induced gastroduodenal ulcers, for whom PPI prophylaxis is recommended, are either above 65 years of age, suffer from extensive comorbidity, have a history of peptic ulcer, gastrointestinal bleeding or perforation, or are treated with NSAIDs in combination with corticosteroids, acetylsalicylic acid, antiplatelet or anticoagulant drugs.

Zollinger-Ellison syndrome is characterized by gastric acid hypersecretion due to a gastrin-secreting tumor (gastrinoma), resulting in refractory peptic ulcer disease. Since Zollinger-Ellison syndrome is a rare disease requiring specialist care, the use of PPI for this indication is beyond the scope of this article and will not be discussed further.

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Submission date : 12/06/2013
Acceptance date : 24/06/2013

Table 1. — **Daily dosage regimens for proton pump inhibitor use for different indications. Recommendations in the 2010 RIZIV/INAMI guidelines**

Indication	Duration	PPI daily dose (mg)				
		Omeprazole	esomeprazole	lansoprazole	pantoprazole	rabeprazole
Therapeutic trial in suspected reflux	4 weeks	10-20	20	15-30	20	10
GERD with esophagitis	4-8 weeks	20-40	40	30	20-40-80	20
Maintenance treatment after esophagitis	Periodical for symptom control	10-20	20	15-30	20-40	10-20
NSAID-related gastroduodenal ulcer	Prevention : during NSAID treatment Acute ulcer treatment : 4-8 weeks	20	20	30	20	not registered for this indication
Gastric ulcer	4-8 weeks	20	not registered for this indication	30	40	20
Duodenal ulcer	4 weeks	20	not registered for this indication	30	40	20
In an HP eradication scheme with antibiotics	1 week	2 × 20	2 × 20	2 × 30	2 × 40	2 × 20
Ulcer prevention (HP negative ulcers or after failed HP eradication	long-term	10-20	not registered for this indication	not registered for this indication	not registered for this indication	not registered for this indication

Recommendations published in the Moniteur belge on August 20, 2010 and in effect since September 1, 2010 [1].

The different PPI molecules are considered equally effective (1). The recommended doses and treatment durations for the approved indications are summarized in Table 1.

Optimal use of proton pump inhibitors in clinical practice

Proton pump inhibitor therapy in peptic ulcer disease

A peptic ulcer is a localized lesion of the mucosa down to the muscularis mucosa. Ulcers can occur in the stomach or duodenum ; they are mainly caused by Helicobacter pylori infection or NSAID use and usually lead to symptoms of abdominal pain and dyspepsia, but may also cause serious complications such as gastrointestinal bleeding and perforation.

PPIs have been shown to be superior to H2-receptor antagonists for healing gastroduodenal ulcers. The recommended doses and treatment durations for ulcer treatment are summarized in Table 1. For duodenal ulcers, PPI therapy should be continued for 4 weeks, whereas for healing of gastric ulcers, PPI therapy must be continued for up to 8 weeks. Reported ulcer healing rates are generally high (> 85%) and comparable for the different PPI molecules. PPIs are also superior to H2-receptor antagonists for healing NSAID-associated ulcers (2). For the prevention of NSAID associated ulcers, however, the efficacy of PPIs is not superior to misoprostol, a prostaglandin E_1 analogue, but PPIs are generally better tolerated (3). Twice daily PPI administration is also part of short-term H. pylori eradication schemes, in combination with antibiotics (4,5). H. pylori eradication generally prevents development of complications and ulcer relapse (6). Long-term maintenance treatment with PPIs is indicated in case of ulcer recurrence in H. pylori negative patients or after failed H. pylori eradication (7).

Proton pump inhibitor therapy in gastroesophageal reflux disease

Gastroesophageal reflux disease is characterized by intermittent and recurrent symptoms of heartburn and regurgitation. Heartburn is a retrosternal burning sensation or discomfort that may radiate from the epigastric region towards the neck. Heartburn symptoms mostly occur after a meal, during exercise or when lying down. Regurgitation is the sensation of bitter or acid tasting gastric content rising up to the level of the throat.

Therapeutic trial with PPIs

For patients younger than 50 years, with typical reflux symptoms and without alarm symptoms, an empirical therapeutic trial with a PPI inhibitor is advocated as the best therapeutic option for a period of 4 weeks (Table 2).

Patients consulting their physician for reflux symptoms often will have tried self-medication with over-the-counter medications such as antacids, H2-receptor antagonists or even PPIs. It is important to bear in mind that failure of previous self-medication with a PPI inhibitor does not preclude treatment success of a therapeutic trial with PPIs, because correct intake and dosage of PPIs is

Table 2. — **Standard single doses for all currently available PPIs**

PPI	Standard dose
omeprazole	20 mg
esomeprazole	40 mg
lansoprazole	30 mg
pantoprazole	40 mg
rabeprazole	20 mg

necessary for optimal effectiveness. Moreover, PPIs are generally more effective in continuous treatment than in an 'on demand' schedule where they are taken only when symptoms occur. According to the guideline, patients with first onset of reflux symptoms over 50 years of age, or presenting with alarm symptoms such as dysphagia, odynophagia, weight loss, anemia or gastrointestinal (GI) bleeding should be referred for endoscopic evaluation. Patients who do not respond to empirical PPI therapy should also be referred for endoscopic examination.

PPI treatment in erosive versus non-erosive reflux disease

When endoscopy reveals erosions in the mucosa of the esophagus, the diagnosis of erosive reflux disease is confirmed, whereas non-erosive reflux disease refers to the combination of a negative endoscopy with evidence of ongoing reflux, as demonstrated by esophageal pH monitoring or by typical symptoms that respond to acid suppressive therapy, although the latter criterion is often not rigorously applied. PPIs are highly effective in healing esophageal erosions, with a number needed to treat of 1.7 (95% CI 1.5-2.1) (8). Most studies indicate a lower symptomatic response rate in non-erosive reflux disease compared to erosive disease (9). Failure to respond to PPIs in non-erosive patients has been attributed to a higher number of reflux episodes and increased sensitivity to esophageal acid or non-acid reflux in these patients (10). Data on non-erosive disease are sometimes confounded by different definitions, as a number of studies cover all patients with presumed reflux symptoms and negative endoscopy, a patient group which often also includes a subset of patients with functional heartburn and/or functional dyspepsia (11). This is supported by a recent meta-analysis, which confirmed the lower response rate in non-erosive reflux disease defined by negative endoscopy, but found that PPI treatment is equally effective in erosive and non-erosive reflux disease if the latter were selected on the basis of pathological pH monitoring (12).

Incorrect intake of PPIs (see below) and inadequate compliance are two important factors to consider in heartburn patients with an incomplete response to PPI therapy (2,13). In addition, incomplete response to PPI therapy can also be associated with atypical symptoms thought to be induced by GERD, female gender, polymedication, or severity of initial disease (esophageal ulcer or Barrett's esophagus) (14).

The use of proton pump inhibitors in functional dyspepsia

Functional dyspepsia (FD) is defined as the presence of symptoms thought to originate in the gastroduodenal region in the absence of any organic, systemic, or metabolic disease that readily explains the complaints (15). In clinical practice, FD is characterized by the presence of postprandial fullness, early satiation or epigastric pain or bloating in the absence of endoscopic lesions. Although overlap exists between functional dyspepsia and endoscopy-negative reflux disease (16,17), the symptom pattern of FD differs considerably from heartburn and regurgitation, and treatment recommendations for FD are substantially different from those for non-erosive reflux disease. A number of studies reported that PPI treatment may have significant benefit over placebo in FD (number needed to treat : 9 ; 95% CI 5-25) (18), but these studies were probably confounded by co-inclusion of GERD patients, and the response of FD patients to PPI treatment is weaker than in non-erosive reflux and the use of PPIs for this indication remains controversial. Moreover, no dose-response effect was found with PPI's in FD, indicating that dose escalation is unlikely to improve disappointing symptom benefit at standard doses (18).

Response to PPI treatment was shown to be good and sustained in the category of patients with overlapping FD and GERD symptoms (19). PPI administration in these patients decreased heartburn and acid regurgitation but did not decrease other dyspeptic symptoms such as postprandial abdominal fullness, early satiation, and belching or food regurgitation. Moreover, esophageal acid exposure could not predict the response to PPI treatment in FD patients (20,21). Evidence to date thus indicates that PPIs are not the first choice for treating FD, but in case reflux-like symptoms are present, a PPI test treatment may be useful. In FD patients, long-term PPI treatment without GI investigation cannot be recommended.

PPI maintenance therapy

Reflux symptomatology frequently reappears after treatment is stopped and relapse of erosive disease occurs in up to 80% of patients, especially in those with more severe esophagitis grades. Current evidence indicates that treatment with a maintenance therapy dose is adequate for the majority of patients. However, higher response rates for adequate symptomatic relief and keeping patients erosion free occur with a full standard dose regimen in a maintenance treatment setting (2,22). In successfully treated patients, maintenance therapy should be limited in time and a step-down approach or downtitration (see below) is recommended to try and stop treatment. When symptoms reoccur, treatment is to be resumed at the lowest effective dose.

A number of studies have indicated that 'on-demand' PPI treatment for GERD relapse, i.e. PPI intake only when symptoms reoccur, may be an efficacious and cost-effective alternative to continuous maintenance therapy (23,24).

Lifestyle changes

Lifestyle changes are not indicated as sole first-line treatment of reflux symptoms, but can contribute to enhanced symptom control in PPI treated patients (25). Useful lifestyle advice includes : smoking cessation, body weight reduction (25), small meal size, avoiding the recumbent position after a meal (26) and elevation of the bed head in patients with nocturnal reflux (27). While there is no hard evidence that avoidance of carbonated beverages or specific foods would have an impact on reflux symptoms (28,29), clinical experience learns that reflux symptoms in individual patients are susceptible to the intake of certain foods.

In a case series of 23 patients with reflux symptoms receiving lifestyle counseling when consulting a dietetic practice, improvement of GERD symptoms after implementation of lifestyle changes was reported by 22 patients, with 11/18 patients on GERD medication being able to reduce their medication (30). Such observations indicate that, in spite of the absence of hard evidence from randomized controlled trials, primary care physicians should take the time to inform and counsel patients with reflux on lifestyle measures. Physicians may choose to refer patients to one of numerous websites providing information and counseling for GERD patients (e.g. Lifestyle Changes to Manage Heartburn on www.webmd.com ; 8 top lifestyle changes to manage heartburn on www.everydayhealth.com ; lifestyle changes that can prevent heartburn on www.heartburn.about.com ; www.maagzuur.net ; etc.). Recently, a number of web-based devices and handheld applications have been developed, aimed at individualizing lifestyle adjustment recommendations for GERD patients. Examples include the Heartburn Log on www.webmed.com, Reflux Coach on www.refluxcoach.be ; diet4gerd on iTunes ; and many others. Studies are needed to evaluate whether these personalized approaches lead to better control of GERD symptoms.

Correct intake of PPIs

To ensure optimal suppression of gastric acid production, correct intake of PPIs is of crucial importance. In a once-daily regimen PPI therapy should be administered 30 to 60 minutes before breakfast, in a twice-daily regimen 30-60 minutes before breakfast and before the last meal of the day.

These recommendations follow directly from the pharmacological properties of the PPI molecules. All PPIs are administered as prodrugs and require acid to become protonated and be converted to their active forms. Absorbed, unprotonated PPIs are delivered by the circulation to the parietal cells of the gastric mucosa, where they diffuse into the acidic secretory canaliculus. There, PPIs become protonated and will bind covalently with the H^+-K^+-adenosine triphosphatase enzyme, the so-called proton pump. This binding irreversibly inhibits this enzyme, which exchanges H^+ for K^+ as the final step in gastric acid secretion. Because PPIs need protonation to become active, they can only inhibit active proton pumps ; and since a greater number of proton pumps are activated with a meal after a prolonged period of fasting, PPIs are best taken before breakfast. The timing of the PPI dose is crucial because all PPIs currently available have a relatively short half-life, ranging from 0.5 to 2 hours (2).

Criteria for selecting a PPI

Proton pump inhibitor efficacy

Studies comparing the relative efficacies of different PPIs have shown that all PPIs are more or less equally effective for the treatment of peptic ulcer or GERD (1,31), although differences exist in their effects on gastric pH (32). PPIs control reflux symptomatology better than other drug classes ; they generally provide better control of heartburn than of regurgitation symptoms (33). Existing differences in symptom control between PPIs are small and probably without major clinical importance. These small differences do not seem to justify systematic preference of one PPI molecule over another (2).

Differences in bioavailability or formulation may be related to different onset of symptom relief and explain some patients' preference of one compound over another. Because of this, symptom control may show modest changes when switching to another PPI (34).

PPI metabolization and interactions with other medications

All PPIs undergo a first pass effect in the liver. The bioavailability of omeprazole, esomeprazole and lansoprazole is decreased and delayed by food intake. PPIs are predominantly metabolized via the cytochrome P450 system (CYP2C19) and therefore may show interaction with other drugs metabolized through this pathway such as diazepam, phenytoin, carbamazepine, digoxin and warfarin. Pantoprazole and rabeprazole are less dependent on the CYP pathway for their metabolization, as they can also be metabolized by an alternative pathway (35). PPIs do not require dose adjustment in elderly patients, or patients with hepatic or renal insufficiency (2).

An additional mechanism through which PPI use can interfere with the absorption of other drugs is directly due to their acid suppressive effect. Thus, PPIs will increase absorption of drugs which are sensitive to breakdown in an acid environment, e.g. some antibiotics. On the other hand, drugs requiring an acid medium for their absorption, such as the antifungal agents ketoconazole and itraconazole, will be absorbed to a lesser degree

when combined with PPI treatment, with the possible risk of therapeutic failure. Clarithromycin is known to decrease CYP3A4-mediated metabolization of lansoprazole, thereby increasing lansoprazole plasma concentrations (2,36).

Although PPIs may interfere with the activation of the anti-platelet agent clopidogrel to a certain extent via the CYP219 enzyme, the clinical impact of this interaction remains questionable (37-40). Co-prescription of clopidogrel and PPIs has no demonstrated impact on cardiovascular mortality, but has proven effectiveness in preventing GI bleeding in patients on dual anti-platelet therapy with aspirin and clopidogrel (37). Proposed recommendations to reduce this interaction include avoidance of omeprazole, the PPI with the strongest negative effect on clopidogrel activation (37,41).

PPI dose escalation in clinical practice

It has been estimated that 10 to 40% of GERD patients inadequately responds to standard, single-dose PPI treatment. In patients failing to respond adequately to standard single dose PPI therapy, proper dosing time and compliance should be reviewed, as these factors are responsible for a considerable fraction of treatment failures. Subsequently, another PPI at standard single dose can be tried for 2 months (42).

When therapy failure persists with a second PPI at single dose, patients should receive PPI treatment at double the standard dose, preferably in a twice-daily administration regimen (43). This recommendation is partially based on indirect evidence, including pH monitoring data in patients with incomplete PPI response showing better acid control in those on twice daily PPIs (44,45). Further support is obtained from a limited number of studies indicating that double dose PPI treatment is more effective than standard single dose treatment in patients with refractory GERD symptoms (42,46-48). One recent study indicated that dividing the standard single dose over two administrations may also increase its effectiveness (48), although two daily administrations may have a negative effect on patient compliance. As mentioned above, PPI dose escalation has no beneficial effect in the treatment of FD symptoms (18).

The optimal management of patients who do not respond to two months of treatment at double PPI dose has not been established. It has been proposed that these patients should be referred for further diagnostic evaluation by endoscopy (if not performed recently), pH, impedance and motility testing. However, there is no consensus as to whether these patients should be studied off or on PPI, and whether pH/impedance monitoring allows to select those who should be referred for surgery (49).

In case of occasional loss of symptom control, an H2-receptor antagonist may be added at bedtime. This addition should only occur intermittently, as chronic H2 blocker therapy leads to rapid desensitization and loss of efficacy (50,51).

PPI down-titration in clinical practice

The recurring character of heartburn or regurgitation symptoms and the rebound acid hypersecretion after stopping PPI administration both contribute to long-term use of these drugs. In some instances, long-term use occurs, sometimes beyond the recommended treatment period, without periodical re-evaluation of the indications (52), or despite either the absence of an established indication or an advice to stop the treatment (53).

One of the proposed mechanisms underlying difficulties to stop PPI therapy in some patients is the rebound acid hypersecretion that occurs after long-term suppression of gastric acid secretion is stopped. Long-term inhibition of gastric acid secretion is accompanied by increased gastrin levels and increases in enterochromaffin-like and parietal cell masses ; these phenomena are responsible for an increased gastric acid secretory capacity, which is revealed upon withdrawal of gastric acid suppressing drugs (54,55). Rebound acid hypersecretion thus has the potential to create 'physical dependency' on PPI treatment, as symptoms tend to reoccur upon withdrawal of treatment.

Acid hypersecretion and the development of associated symptoms after withdrawal of PPI treatment was demonstrated convincingly in two double-blind placebo-controlled randomized trial in healthy volunteers (56,57). To prevent symptomatic relapse after stopping PPI therapy, PPI withdrawal should preferably be accompanied by life-style measures and be preceded by a gradual down titration of the administered dose (58). Over half of patients receiving more than standard dose PPI treatment can be stepped-down to single dose treatment without reoccurrence of symptoms (59). For patients treated successfully with single-dose PPIs, a step-down approach, with progressive decrease of the PPI dose, is recommended (60). During PPI dose down-titration, patients may benefit from increased adoption of lifestyle measures, such as avoiding food triggering reflux symptoms, cessation of smoking and body weight reduction. For successful downtitration, it is important that primary care physicians take time to explain the rebound acid hypersecretion phenomenon and the impact of lifestyle changes on this phenomenon to their patients. Here again, web-based devices and handheld applications could potentially be used to optimize lifestyle adjustments.

Considerations for long-term use of proton pump inhibitors

Reflux symptoms have a chronic and recurrent character, with sometimes a major impact on quality of life. In the majority of patients they can efficiently be controlled by PPI maintenance treatment. These facts, in combination with the decreased cost of PPI treatment since the advent of generic versions of these drugs, explain why an increasing number of patients receive treatment with PPIs over prolonged periods of time.

Although a number of potential risks and side effects associated with long-term PPI treatment have been described, PPIs can be considered safe medications. Most long-term risks of PPI treatment only occur in susceptible or high risk groups of patients already prone to develop a certain risk or side effect due to comorbidity or treatment with other drug classes (36). The most important long-term risks and side effects are discussed below mainly to indicate for which groups of patients extra care should be taken to limit treatment duration in view of the potential additional risks of long-term PPI treatment.

Infection risk associated with PPI therapy

Gastric acidity is part of the defense mechanisms against ingested pathogens and against colonization of the GI tract by pathogens. PPI use increases gastric pH, leading to increased microbial colonization of the stomach, GI tract and oropharynx, which in turn may expose patients under PPI therapy to an increased infection risk, mainly for respiratory and GI tract infections (61,62).

Proton pump inhibition and associated hypochlorhydria not only increase the number of bacteria in the stomach, but also influence the flora of the lower GI tract by reduced elimination of acid-sensitive ingested bacteria, by altering gastric mucus viscosity and motility and through inhibition of the migration and bactericidal activity of neutrophils (63).

A recent systematic review found a significantly increased susceptibility to enteric infections by Salmonella (Relative Risk 4.2-8.3), Campylobacter (RR 3.5-11.7) and Clostridium difficile (RR 1.2-5.0) associated with PPI treatment (63). Clinical implications of the increased susceptibility for GI infections under PPI treatment include considering chemoprophylaxis or additional vaccination for traveler's diarrhea for patients travelling to regions with high risk of GI infections (64).

The risk for C. difficile infection is less than for other intestinal pathogens, probably because C. difficile is mainly propagated by acid-resistant spores, but is nevertheless important because of the clinical implications associated with clinical C. difficile infection. A large 2012 meta-analysis found a 65% increase in the incidence of C. difficile associated diarrhea among PPI users (65). The risk of C. difficile infection shows a dose-dependent relation with the degree of gastric acid suppression (66).

The association of PPI use with increased risk for respiratory infections is less well established (62). Evidence from randomized clinical trials on the risk of respiratory infections associated with PPI use is scarce. A small meta-analysis from 2008 covering 7 trials and 16 comparisons indicated a trend towards increased risk, which failed to reach significance, however (67). A recent meta-analysis covering 9 case control and observational studies, found a significantly increased risk for community-acquired pneumonia in current PPI users, particularly if patients were treated with PPIs for less than 30 days or with high doses of PPIs, but not in patients who used PPIs for more than 180 days (68). A study investigating the pathogens responsible for pneumonia in PPI users versus controls confirmed the association of PPI therapy with community-acquired pneumonia but did not observe more gastrointestinal bacteria as causative agents for CAP in PPI-treated patients (69). More research is needed to establish the clinical importance of the risk of respiratory infections and community-acquired pneumonia under PPI treatment (61,62).

Effect of long-term PPI use on vitamin and mineral levels

The well-known role of gastric pH in the absorption of nutrients, such as vitamin B12, iron, magnesium and calcium, prompts the question whether or not prolonged PPI use leads to nutritional deficiencies. Existing evidence for vitamin B12 deficiency after long-term PPI use is conflicting, but not convincing enough to justify routine monitoring of vitamin B12 levels in patients chronically taking PPIs. Impaired absorption of non-heme iron has been reported in conditions with decreased gastric acid conditions, but at present, there is no clinical proof of iron depletion after long-term PPI use. Long-term studies in Zollinger-Ellison syndrome patients did not observe iron deficiency or depletion after long-term suppression of gastric acid secretion. Routine screening for iron depletion during long-term use of PPIs is therefore not recommended (61). Retrospective data and several case reports indicate that PPI use can be accompanied by severe hypomagnesaemia. Hess *et al*. have demonstrated that hypomagnesaemia is a relatively rare drug-class effect of PPIs that has not been described for other gastric acid suppressants. Magnesaemia in affected patients recovers quickly after PPI withdrawal and reoccurs upon rechallenge. Because of the low incidence rate of PPI-induced hypomagnesaemia, follow-up of magnesium levels for all long-term PPI users is not recommended (70).

Osteoporosis and fracture risk in long-term PPI treatment

Acidic conditions increase calcium solubility and facilitate its absorption. PPI use could therefore theoretically decrease calcium absorption, which may be countered by the fact that PPIs may decrease bone resorption by inhibiting the H^+-K^+-adenosine triphosphatase enzyme in osteoclasts (61). Clinical data on the net result of these opposite effects – albeit all from observational studies – indicate that long-term PPI use is associated with a modestly increased risk for decreased bone mineral density and osteoporotic fractures, mainly in the elderly and in smokers (71-75). It remains to be established whether a true causal relationship exists. Advising patients taking long-term PPI therapy on sufficient calcium intake, and supplementing calcium if necessary, is a preventive measure that could be considered in this context (76).

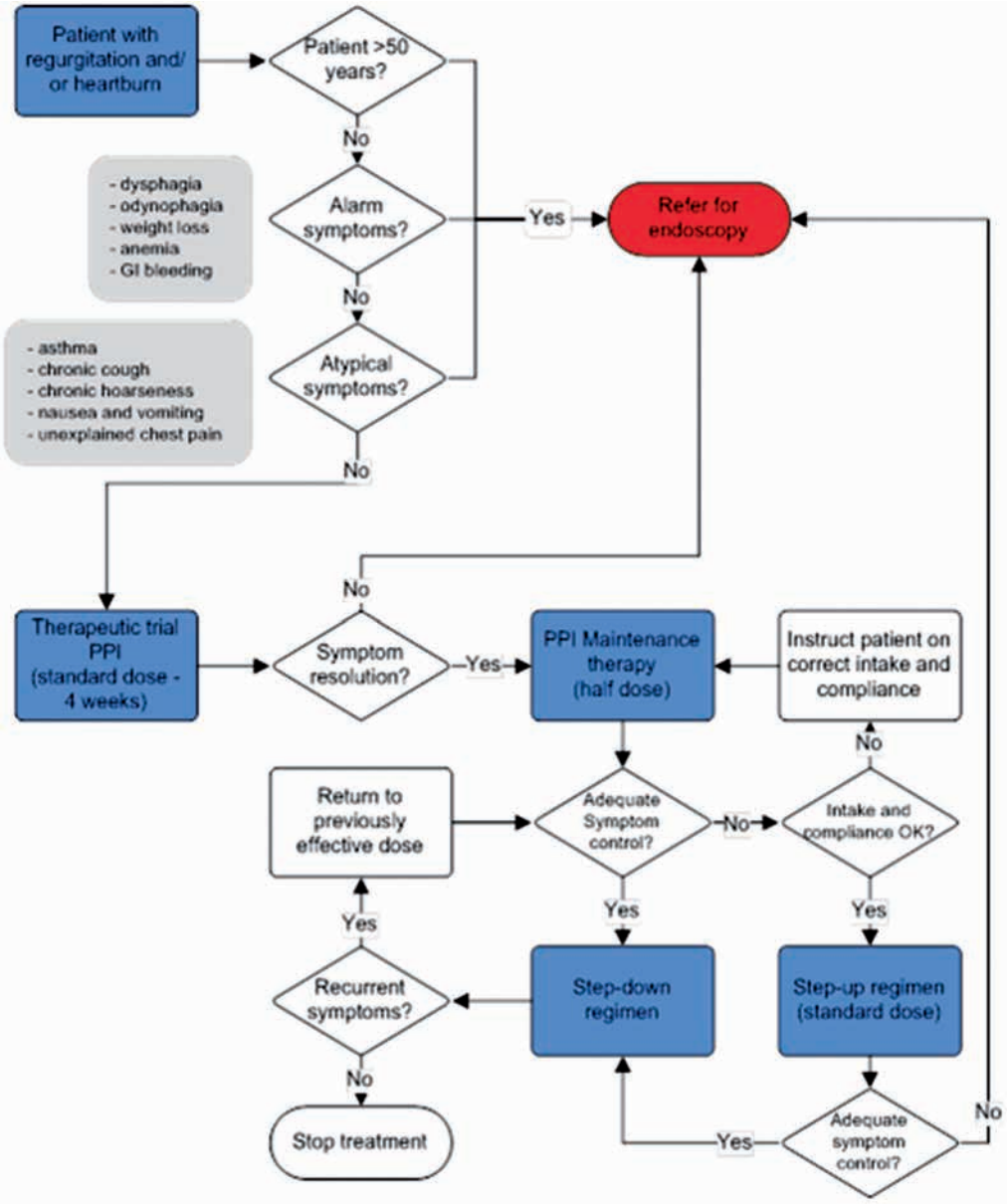

Fig. 1. — Treatment algorithm for gastroesophageal reflux in primary care

Long-term PPI use entails increased risk of gastric polyps but not of cancer

Long-term use of PPI may increase the incidence of gastric fundic gland polyps, which are considered benign lesions. No evidence indicate increased incidence of gastric or colon cancer after long-term PPI use (61).

Summary : Algorithm and best practice guidelines for optimal use of PPI in the primary care setting

Figure 1 outlines an algorithm summarizing best practice guidelines for the use of PPI inhibitors in primary care. Patients older than 50 years, with typical reflux symptoms of heartburn and regurgitation can be started on empirical therapy with a PPI at standard dose for 4 to 8 weeks. In case this provides insufficient symptom control, referral for endoscopy is recommended.

In case initial PPI therapy sufficiently controls reflux symptoms, a down titration or step-down scheme is followed and eventually attempts can be made to interrupt PPI treatment. Under Belgian reimbursement guidelines, endoscopy is mandatory prior to initiating long-term maintenance therapy. Patients with recurrence of symptoms after successful treatment are restarted on the previously effective treatment schedule. When adequate symptom control is achieved, they are switched to maintenance therapy followed by a step-down regimen (60).

Patients with atypical reflux symptoms or with alarm symptoms such as weight loss, anemia or dysphagia should immediately be referred to a gastroenterologist for further diagnostic evaluation.

It is important to instruct patients of the correct timing of PPI intake. PPI use may be supplemented with on-demand antacids or H2 receptor antagonist for occasional breakthrough reflux symptoms or nocturnal reflux. However, H2 receptor maintenance therapy leads to desensitization and loss of effect (51).

While lifestyle interventions are not advised as first or sole treatment for reflux symptoms, they can support medical treatment, especially to overcome rebound acid hypersecretion during PPI down-titration. Primary care physicians should therefore advise patients to stop smoking and treat obesity. Patients with nocturnal reflux are can benefit from bed head elevation and may achieve better symptom control with a twice daily PPI treatment scheme. Patients on PPI treatment travelling to areas with high incidence of infectious diarrhea should be warned about an increased risk of GI infections.

Because of the recurring character of gastroesophageal reflux, symptomatic relapse occurs frequently and in up to 80% of patients ; a subgroup of patients can hardly be weaned from PPI treatment and will need long-term treatment with PPIs. Routine screening for iron or vitamin B12 is not necessary for long-term PPI users, but adequate intake of calcium should be promoted to mitigate the potential increased risk of osteoporosis.

Acknowledgements

This work was supported by an unrestricted educational grant from Takeda Belgium.

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