Mistakes in the use of PPIs and how to avoid them

Roos E. Pouw and Albert J. Bredenoord

Proton pump inhibitors (PPIs) inhibit gastric acid secretion by blocking the gastric hydrogen potassium ATPase (H-K-ATPase). When omeprazole, the first PPI, became available in 1988, it soon appeared to be more effective than H_2 antagonists, and PPIs rapidly became one of the most prescribed drug classes worldwide.[1]

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PPIs have proven highly efficient for the management of gastro-oesophageal reflux disease (GORD), gastroduodenal ulcers and in the treatment of *Helicobacter pylori* infections. PPIs are, however, also commonly prescribed for chronic complaints of dyspepsia and upper abdominal discomfort, for which there is no proof that gastric acid is an underlying patho-physiological factor. Lately, the safety of long-term PPI use has been the subject of debate, because chronic use of PPIs has been linked to several complications, such as vitamin and mineral malabsorption, pneumonia, gastrointestinal infections and dementia.[2]

For anyone working in gastroenterology, having knowledge of one of the most prescribed drugs in this field is fundamental. As such, we address nine frequently made mistakes when it comes to the use of PPIs, and also hope to disprove some of the misconceptions about PPI use.

Mistake 1 Prescribing a PPI without providing adequate instructions for their use

Excretion of acid from parietal cells into the gastric lumen by the H-K-ATPase–the proton pump–is the final step of gastric acid secretion. PPIs accumulate in the secretory canaliculus of the parietal cell, where they are catalyzed to thiophilic sulfonamide, which irreversibly inhibits the H-K-ATPase, resulting in a specific and long-lasting impairment of gastric acid secretion. PPIs are thus most effective when the concentration of H-K-ATPase in the parietal cells is highest, which is after a prolonged fast c.q. before breakfast. In addition, only activated H-K-ATPase can be inhibited, and activation is stimulated by food intake. For these reasons, it is pivotal to instruct patients to take their PPI at least 30 minutes before breakfast, to ensure there is an adequate concentration of the drug in the parietal cells before the H-K-ATPase is activated.[3] This is also the case when there are symptoms predominantly in the evening, as the effect lasts for longer than 24 hours.

Not all parietal cells are activated during a meal, and not all H-K-ATPase is blocked after one dose of PPI. After 5 days of taking a PPI once a day, the maximal acid output is inhibited by about 66%.[3,4] With this in mind, the often proposed idea of taking a PPI 'on demand' for occasional reflux complaints is, in our opinion, neither very logical nor effective.

Mistake 2 Increasing the PPI dose for persistent heartburn when there is no evidence of GORD

Patients who have complaints that fit with acid reflux disease (e.g. heartburn, acid regurgitation, chest pain) are often prescribed a 2–4 week trial course of a PPI once daily, which is often prolonged if symptoms decrease. In about 40% of patients, however, symptoms respond only partially or not at all. While moving to a PPI twice daily is reasonable, further increases should not be done automatically, and other diagnoses should be considered.

In patients who have reflux symptoms, but who do not respond, or only partially respond, to a course of PPIs once or twice daily, it is better to evaluate whether the complaints are indeed reflux related; many of them will not suffer from GORD and hence, acid inhibition will not be effective at any dose. In patients who do have reflux disease, upper endoscopy may reveal reflux oesophagitis or Barrett's oesophagus. However, patients with GORD may have a normal upper endoscopy, defined as non-erosive reflux disease (NERD). Therefore, also in the absence of endoscopic abnormalities, 24h pH or pH-impedance monitoring should be performed to evaluate whether symptoms are indeed related to (pathologic) acid reflux. Preferably, the patient will undergo oesophageal manometry prior to pH monitoring. These examinations allow the identification of patients who have functional heartburn, achalasia, oesophageal spasm, functional chest pain and dyspepsia.[5] According to the Rome IV criteria for functional gastrointestinal disorders, the diagnosis of functional heartburn is made when there are no indications that reflux is the cause of the patient's heartburn: no erosions during endoscopy, no response to acid suppression, normal acid exposure and absence of a temporal relationship between reflux and symptoms during pH monitoring. This category of patients will not benefit from PPI treatment at any dose, and require a different management approach.

Mistake 3 Considering the PPI test to be perfectly accurate for the diagnosis of GORD

The PPI test is often used in the primary care setting as a 'diagnostic' test to evaluate whether upper gastrointestinal symptoms are related to reflux of gastric acid. For the PPI test, patients are prescribed a standard dose of PPI once daily for 2 weeks. If symptoms decrease by 50%, the test result is considered positive. However, it is important to realize that a positive PPI test result is not specific for GORD, as complaints caused by gastroduodenal ulcer disease will also improve with PPI

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Roos E. Pouw and Albert J. Bredenoord are at the Department of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, the Netherlands.

Correspondence to: r.e.pouw@amc.nl
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treatment, and there may be a placebo effect on symptoms of functional dyspepsia. On the other hand, a negative PPI test result does not exclude GORD, and may be explained by lack of compliance or the presence of non-acid reflux.

A study by Bytzer et al. described 308 primary care patients who had frequent upper gastrointestinal symptoms.[6] Patients were evaluated by endoscopy, pH-metry and symptom-association monitoring, which identified 197 patients with GORD. All patients underwent the PPI test–the test result was positive in only 69% of patients with GORD and in 51% of patients without GORD. So, although the PPI test can serve as a pragmatic tool to select patients for further testing, its limitations should be kept in mind. And despite the outcomes of the PPI test, patients for whom there is a high suspicion of GORD should, in our opinion, preferably be evaluated using current standard tests, such as pH-impedance monitoring.

Mistake 4 Withholding PPI treatment because of a fear of complications

Several studies, mainly observational, have raised concerns about the safety of PPI use, mostly regarding an increased risk of osteoporosis, pneumonia and enteric infections.[2,7] However, the results from heterogeneous studies and larger studies are inconsistent, and larger studies mostly show no association between PPI use and pneumonia or osteoporosis. Furthermore, no dose-response or temporal relationship between PPI use and its alleged complications have been described.[7] Furthermore, the associations described are mostly weak (odds ratio [OR] <2) and it is worth questioning whether bias and confounding may have been of relevance.

The best evidence from several meta-analyses on the possible complications of PPI use is available for PPI use and enteric infections, especially *Clostridium difficile* infections (OR 1.74–3.33).[7] The hypothesis behind such an association is that the bactericidal effect of gastric acid is significantly decreased when the gastric pH rises above 4, and PPI use results in a changed gut microflora that predisposes patients to enteric infections. In elderly hospitalized patients who have other risk factors for enteric infection, we think it might be worth considering temporary cessation of PPI treatment to decrease the risk of *C. difficile* infection. For immunocompromised patients who are travelling to countries where enteric infections are endemic, it is our opinion that temporary cessation of PPIs may also be advisable. However, if there is a good indication the benefits of PPI treatment outweigh the potential risks, then patients should not have an effective treatment withheld.

Mistake 5 Not taking hypomagnesaemia seriously in patients who are taking a PPI

A rare (<0.01%), but relevant complication of PPI use is the occurrence of severe hypomagnesaemia (<0.5 mmol/L), which puts patients at risk of muscle weakness, dizziness, psychosis, seizures, ataxia, tetany and cardiac arrhythmia. The link between PPI use and hypomagnesaemia has been demonstrated in a number of observational studies and case reports.[8] However, the mechanism and causality of this association are not yet clear; hypotheses exist regarding decreased intestinal magnesium absorption and increased renal excretion. In true PPI-related hypomagnesaemia, the deficiency will only resolve after the PPI has been stopped, and it may recur after the PPI is restarted. Patients might benefit from switching to an H_2 antagonist if PPI use is an identifiable cause of their hypomagnesaemia. Furthermore, it is worth noting that the risk of hypomagnesaemia appears to be increased in malnourished patients and patients who are taking diuretics.[8]

Mistake 6 Stopping a PPI because of fundic gland polyposis

Fundic gland polyps are the most frequently found gastric polyps, being diagnosed in about 2% of the general population (figure 1).[9,10] Although fundic gland polyps may be associated with polyposis syndromes, most are sporadic. The risk of developing fundic gland polyps increases fourfold in patients receiving long-term PPI treatment (for at least 1 year).[10] The mechanism underlying this association is not entirely clear. One hypothesis is that mucus blocks the fundic glands as a result of decreased flow of glandular secretions. Blocking of the fundic gland, however, may also be explained by parietal cell protrusion caused by accumulation of hydrochloric acid in the parietal cells by inhibition of secretion due to the PPI.[11] The blocked fundic glands may form cysts, and eventually fundic gland polyps.[11]

Fundic gland polyps associated with PPI use have a negligible risk of malignant progression and rarely show dysplasia.[10] Routine surveillance is therefore not recommended, nor is stopping the PPI if there is a good indication for treatment. Any suspicious looking fundic gland polyps (i.e. isolated polyps >1 cm or ulcerated lesions) may be resected for histological confirmation.

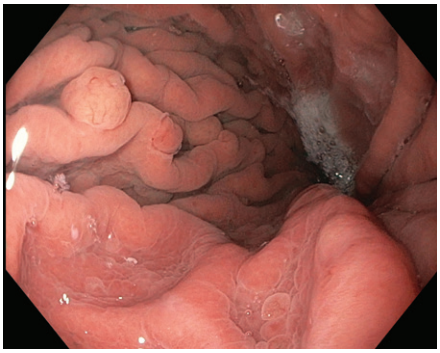

Figure 1 | Fundic gland polyposis in the gastric corpus of a patient on long-term PPI treatment because of Barrett's oesophagus. Image courtesy of R. Pouw and A.J. Bredenoord.

Mistake 7 Failing to prescribe a PPI to reduce the risk of gastrointestinal bleeding in high-risk patients on anticoagulation therapy

Antiplatelet therapy is associated with an increased risk of gastrointestinal bleeding and studies have demonstrated that concomitant use of a PPI significantly reduces this risk.[12] For cost-effectiveness reasons and to avoid unnecessary prescriptions, prophylactic PPIs are recommended only in those patients taking antiplatelet therapy who have additional risk factors for gastrointestinal bleeding.[12] These risk factors are dual antiplatelet therapy, concomitant anticoagulant therapy and history of gastrointestinal bleeding or gastroduodenal ulcers.[12] If a patient has a history of ulcer disease, they should be tested for the presence of *H. pylori* and the infection eradicated if positive.[12] If these main risk factors are not present, PPI prophylaxis should be considered only if two of the following additional risk factors are present: age ≥60 years, corticosteroid use, dyspepsia or GORD symptoms.[12]

On the basis of *in vitro* studies, it has been suggested that the antiplatelet effect of clopidogrel is reduced when it is used in combination with different PPIs. However, based on the outcomes of observational studies and one randomized study, little evidence exists for any clinically relevant interaction between clopidogrel and PPIs.[12,13]

Mistake 8 Not warning the patient that rebound symptoms can occur after stopping PPIs

Rebound acid hypersecretion occurs after PPI therapy is stopped.[14] The phenomenon is characterized by a temporary increase in gastric acid secretion above pre-treatment levels and is attributable to the hypergastrinaemia

that occurs during PPI treatment. This effect is most obvious in patients who have used PPIs for at least 2 months, and a related increase of symptoms is often observed within 2 weeks of PPI treatment being withdrawn.[14] If there is not a good indication for long-term PPI use and the decision is taken to stop therapy, both the patient and physician should be aware that rebound symptoms can occur, to prevent unwarranted continuation or restarting of the PPI.[14] In our opinion, patients can be advised to take short-acting H_2 blockers or an antacid, but most important is to warn and reassure them about this phenomenon.

Mistake 9 Not stopping a PPI in time prior to certain tests

For certain tests, it is important to be aware that PPIs may influence the results. First, in patients suspected of having GORD who are scheduled for ambulatory pH-monitoring, which aims to determine the presence of abnormal oesophageal acid exposure, reflux frequency and symptom association with reflux episodes, we believe PPIs should be stopped 7 days in advance.[15] This follows from a study by Hemmink et al., in which it was shown that testing off a PPI results in a higher diagnostic yield than testing on a PPI.[15] This approach is adopted by the American College of Gastroenterology guideline on GORD, stating that as a true diagnostic test (for abnormal acid exposure) and for evaluation before considering surgery in a patient with NERD, an off therapy test is recommended.[16] In patients who have refractory reflux symptoms, testing on or off a PPI is sometimes the subject of debate. Performing pH-monitoring combined with impedance in patients who have persistent reflux symptoms and previously documented GORD on a PPI, may be useful to evaluate PPI efficacy, adherence and association of complaints with non-acidic reflux.[16]

Second, PPIs have a suppressing effect on *H. pylori*, and testing for *H. pylori* while taking a PPI can give a false-negative result. This holds for the stool antigen test, urea breath test, rapid urease test, histology and culture; with the exception of serology. For these tests, it is advised to stop PPI therapy at least 2 weeks prior to testing to allow *H. pylori* to repopulate the stomach and increase the chance of a positive test.[17]

Third, in patients suspected of having a gastrinoma, it is important to realize that PPIs may influence test results when measuring gastrin and chromografin A levels. However, since withdrawal of PPIs in patients with possible Zollinger–Ellison syndrome can lead to serious complications and stopping PPI is not always necessary, the decision to stop should be made on an individual basis.[18]

The general advice for patients on a PPI who need to stop their medication for 1 or 2 weeks, is to temporarily switch to H_2 antagonists or antacids.

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Your proton pump inhibitor briefing

UEG Week

- 'PPIs: Lifetime treatment for all?' Session at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1420&conference=109].
- 'PPI use and Clostridium difficile: Do we need to warn our healthcare systems?' presentation at UEG Week 2015 [https://www.ueg.eu/education/document/ppi-use-and-clostridium-difficile-do-we-need-to-warn-our-healthcare-systems/116536/].
- 'Start with a PPI' presentation in the 'First-line approach to dyspepsia' session at UEG Week 2015 [https://www.ueg.eu/education/document/start-with-a-ppi/116417/].

Standards and Guidelines

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- Further relevant articles can be found by navigating to the 'Oesophagus' category in the "Standards & Guidelines' repository [https://www.ueg.eu/education/standards-guidelines/].