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What is the long term acid inhibitor treatment in gastroesophageal reflux disease? What are the potential problems related to long term acid inhibitor treatment in gastroesophageal reflux disease? How should these cases be followed?

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ABSTRACT

The meta-analyses of observational studies (OBS) showed the risk of any fracture and hip fracture slightly increased with proton pump inhibitor (PPI) treatment depending on the dose and regardless of time. This was not observed with histamine-2 receptor antagonists (H2RA). The risk of bacterial overgrowth and spontaneous bacterial peritonitis were increased with PPI therapy, but not with H2RA. In meta-analyses of OBS, a slight increase was observed in the risk of community-acquired pneumonia (CAP) in the early stages (<1 month) of PPI use and particularly at high doses. In a five-year LOTUS study, no difference was found in vitamin B12, folic acid, vitamin D, and calcium values in terms of the initial and end of follow-up levels. No increase in the risk of premalignant gastric lesions was observed in the meta-analysis of RCTs in which PPI treatment (≥6 months) was given to *Helicobacter pylori* negative patients. The risk of hypomagnesemia with PPI use was increased in patients having GFR<60, using diuretics, and over 65 years of age. Quasi-experimental studies showed a reduced zinc absorption with PPI use. In the meta-analysis of OBS, long-term (>1 year) PPI use increased the risk of fundic polyps, but no risk was found in shorter use. The meta-analyses of RCTS showed no difference between PPI and surgery or placebo arms and between the arms of H2RA and placebo in terms of all side effects. No difference was found between the PPI and H2RA arms both in all and serious adverse effects.

Keywords: Gastroesophageal reflux, proton pump inhibitors, histamine H2 antagonists, adverse effects, drug-related side effects and adverse reactions

Decreased acid secretion is thought to adversely affect the absorption of calcium and increase the risk of fracture by causing a decrease in bone density. The meta-analyses of observational studies conducted with heterogeneous populations showed that the risk of any fracture (OR: 1.29, 95% CI: 1.18-1.41) and hip fracture (OR: 1.23, 95% CI: 1.11-1.36) slightly increased with PPI depending on the dose and regardless of duration; but no risk increase was detected with H2RA use (1,2).

There are meta-analyses with different methodologies reporting that high gastric pH values developing due to acid inhibition increases *Clostridium difficile* infections by altering the intestinal microflora and in observational studies conducted with different patient populations. This risk has been reported to be higher in PPI treatment (OR: 2.15, 95% CI: 1.81-2.55) compared to H2RA (OR: 1.44, 95% CI: 1.22-1.70) (3,4).

It was reported in the meta-analysis published in 2013 that bacterial overgrowth increased with the use of PPI (OR: 2.26, 95% CI: 1.24-4.2) (5). Spontaneous bacterial peritonitis that develops due to the translocation of enteric pathogens is a significant cause of mortality for cirrhotic patients. The hypothesis that the risk of spontaneous bacterial peritonitis may increase due to easy proliferation of intestinal bacteria with decreased stomach acid has been confirmed in the meta-analysis of observational studies in which the relationship with PPI was investigated (OR: 3.15, 95% CI: 2.09-4.74). On the

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other hand, no risk increase was found with H2RA use (OR: 1.71, 95% CI: 0.97-3.01) (6).

Community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) are other problems that are associated with the treatment of acid inhibition. In the meta-analysis of observational studies, a slight increase in the risk of CAP was observed with the use of PPI in early stages (<1 month) and especially with high doses (OR: 1.38, 95% CI: 1.1-1.76). In the long-term use of PPI therapy, risk increase was found to be non-significant for CAP (OR: 1.1, 95% CI: 0.9-1.2) or HAP (OR: 1.04, 95% CI: 0.58-1.88). It was shown that neither of the two drug groups differed for HAP in hospitalized patients (RR: 1.06, 95% CI: 0.73-1.52) in the meta-analysis of randomized controlled trials (7-9).

Though it was reported that the inhibition of gastric acid negatively affected the absorption of vitamin B12, folic acid, vitamin D, and calcium, no difference was found between the initial and end of follow-up levels in a five-year LOTUS study in which PPI and surgical arms were compared (10).

No increase in the risk of premalignant gastric lesions was observed in the meta-analysis of randomized controlled trials in which PPI treatment was given to *H. pylori* negative patients for more than 6 months (11).

The relationship between hypomagnesaemia and acid inhibitor therapy was considered to be an idiosyncratic situation. In the cross-sectional and case-controlled studies, in which the presence of hypomagnesaemia-related disease and the use of medication are taken as exclusion criteria, no relationship was found between magnesium deficiency and PPI (12,13). However, in two cross-sectional studies that were conducted recently, it was noted that the risk increased with the use of PPI in patients using diuretics ($p<0.001$), having GFR<60, and over 65 years of age ($p=0.03$) (14,15).

In quasi-experimental studies that were conducted with omeprazole and ranitidine, and included a small number of patients, it was indicated that the absorption and levels of zinc could be reduced (16,17).

It has been suggested that hypergastrinemia induced with PPI therapy increases the risk of fundic polyps by causing proliferation in parietal cells. In the meta-analysis of 5 observational studies that were evaluated through a systematic literature review, the use of PPI was found to increase the risk of fundic polyps (OR: 2.89, 95% CI: 1.62-5.16) (18-22). When its relationship with duration was considered, it was observed that long-term (>1 year) PPI use increased the risk of fundic polyp 6-fold, but there was no risk in shorter use (OR: 1.03, 95% CI: 0.64-1.69) (21,22).

In the meta-analysis of 17 randomized controlled trials in which reflux patients were included and PPI was compared with the arms of surgery or placebo, no difference was observed in terms of all of the adverse effects (RR: 1.04, 95% CI: 0.98-1.11) (23-39). In the meta-analysis of 6 randomized trials in which H2RA and placebo were compared, the incidence of all of the adverse effects was similar among the arms (RR: 1.13, 95% CI: 0.97-1.31) (39-44). In the meta-analysis of 8 randomized trials that compared PPI and H2RA, no difference was found between the two groups of drugs in terms of all of the adverse effects (RR: 0.94, 95% CI: 0.86-1.02) and serious adverse effects (RR: 0.93, 95% CI: 0.85-1.01) (39,45-51).

RECOMMENDATIONS

- There is a slight increase which is proportional to the dose in the risk of fracture in patients taking a PPI. Such a risk is not observed for patients using H2RA (Level of evidence: 3a). However, the presence of osteoporosis in patients with indication should not prevent PPI use. Osteoporosis should be treated independently (Level of evidence: 5).
- PPI use increases the risk of Clostridium difficile infection (Level of evidence: 3a). But PPI treatment should not be stopped in order to protect patients with indication from infection (Level of evidence: 5). H2RA use increases the risk of C. difficile infection, albeit in a lesser degree (Level of evidence: 3a).
- PPI use increases the risk of spontaneous bacterial peritonitis (Level of evidence: 3a). PPI use should not be discontinued in patients if there is an indication for its use (Level of evidence: 5).
- There is a risk of bacterial overgrowth with the use of PPI (Level of evidence: 2a). This should be considered in patients in whom the development of bacterial overgrowth may pose a risk (Level of evidence: 5).
- The risk of CAP slightly increases with especially high doses and during the first weeks of PPI use (Level of evidence: 3a). No increase in the risk of HAP is seen with the PPI use in observational studies (Level of evidence: 2a); a mild increase is observed with the use of H2RA in comparison to placebo (Level of evidence: 1a). However, the risk is similar when compared with PPI (Level of evidence: 1a). Therefore, the risk of pneumonia should be considered while deciding on the treatment selection between two agents (Level of evidence: 5). Acid inhibition should not be made unnecessarily in hospitalized patients (Level of evidence: 5).
- It has been indicated that calcium and vitamin D deficiency do not develop with PPI use (Level of evidence: 1b). Routine vitamin D and calcium screening is not recommended (Level of evidence: 5).
- It has been shown that B12 and folic acid deficiency do not develop with the use of PPI (Level of evidence: 1b). Routine B12 and folic acid screening is not recommended (Level of evidence: 5).
- No increase is observed in the risk of premalignant gastric lesion in H. pylori (-) patients with long-term

use of PPI (Level of evidence: 1a). These patients do not need the routine endoscopic screening for malignancy (Level of evidence: 5).

- There is not enough data showing the risk of hypomagnesaemia with PPI use in the general population. There is a risk of hypomagnesaemia in advanced age patients who use diuretics or have chronic renal failure and use PPI (Level of evidence: 3b).
- In quasi-experimental studies that were conducted with only omeprazole and ranitidine, and in which a small number of patients were included, it has been shown that zinc blood levels and absorption can decrease (Level of evidence: 4).
- Long-term use (over 1 year) of PPI increases the risk of fundic polyps (Level of evidence: 2a). Routine screening and follow-up through endoscopy are not recommended. The presence of fundic polyps does not interfere with PPI use in patients with indication (Level of evidence: 5).
- The use of PPIs or H2RA does not have differences in terms of the incidence of side effects when compared with a placebo (Level of evidence: 1a). However, attention should be paid in terms of fracture risk*, CAP*, spontaneous bacterial peritonitis*, C. Difficile infection*, and bacterial overgrowth** (Level of evidence: 3a*, 2a**).

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