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Review Article

Long-Term Use of Proton Pump Inhibitors and Risk for Benign and Malignant Gastric Changes

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1. Abstract

Proton Pump Inhibitors (PPIs) have been in use for about three decades. The large number of indications, safety profile, and over-the-counter availability make the drug group one of the most widely sold medications. Some of the patients are treated with PPIs for long periods, and several adverse effects are known. In the present review we focused on the benign and malignant stomach changes among long-term PPIs users, including gastrin levels, carcinoid tumor, Fundic Gland Polyps (FGPs), gastric atrophy, intestinal metaplasia, and gastric carcinoma.

The hypoacidity causes increase of the gastrin, which affects the different cells, including hyperplasia of enterochromaffin cells; however only few case reports were published regarding the association between long-term PPI use and carcinoid tumor development. PPI users have an increased risk for FGPs, with OR of 1.43-5.32 in different studies. Gastric atrophy and intestinal metaplasia are increased among long-term PPI users along with an increasing cancer risk.

The association between chronic treatment with PPIs and gastric cancer is an unresolved issue; however, recently, several reports showed an increased risk for gastric cancer among long-term PPI users without evidence of causality and with different bias.

PPIs always should be stopped, and only in cases with high benefit and low risk should the long-term treatment be considered.

3. Introduction

Proton Pump Inhibitors (PPIs) suppress gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. Fellenius et al. [1] in 1983 were the first to report regarding this effect and in the last three decades six different proton pump inhibitors were approved for treatment. Omeprazole was the first PPI approved and marketed for clinical use in Europe in 1988 and the United States in 1989.The high efficacy, low cost, low rate of side effects, and over-the-counter availability are the most important factors for the high frequent use of PPIs.

There are some disparities of the different PPIs in terms of pharmacokinetics, pharmacodynamics, efficacy, side effects, and drug-drug interactions. Proton pump inhibitors are indicated in management of acid-related disease, the most common indications are: heartburn and Gastroesophageal Reflux Disease (GERD), erosive esophagitis, peptic disease, Helicobacter pylori infection, acute gastrointestinal bleeding, prevention of GI bleeding after acute myocardial infarction, prevention of stress ulcers, eosinophilic esophagitis, and Zollinger-Ellison syndrome.

After about three decades of PPI use, our knowledge regarding adverse effects is increasing. Some simple side effects are common among more than 1% of the patients, the most common are headache, diarrhea, nausea, flatulence, abdominal pain, dry mouth, and constipation [Thomson et al. [2]]. Moreover, there are more serious and chronic adverse drug interactions found in relationship with PPI use: Clostridium difficile infection, bone fractures, interstitial nephritis, elevation of blood gastrin level, Vitamin B12 deficiency and hypomagnesaemia [Thomson et al. [2]].

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The aim of the present review is to summarize the most important chronic benign, premalignant, and malignant stomach changes among chronic PPI users.

Several different adverse effects of PPI in the stomach are known, and recently studies were published regarding the possibility of increasing stomach neoplasm. In the present review the important gastric adverse effects will be summarized, including hypergastrinemia, carcinoid tumors, fundic gland polyps (FGPs), gastric atrophy, intestinal metaplasia, and gastric cancer.

3.1. Hypergastrinemia

Increase of the gastrin level is a homeostatic reaction by the G cells of the gastric antrum to the reduced acidity of the gastric juice.

Enterochromaffin-like (ECL) cell hyperplasia was observed due to the hypergastrinemic state. During long-term PPI therapy, mean gastrin levels rose one to three times above the upper limit of the normal range and an increased prevalence of ECL cell hyperplasia and cell density was observed. Some reports showed correlation between the prevalence of ECL cell hyperplasia and serum gastrin [Lundell et al. [3]].

Another important player is chromogranin A; during long-term gastric acid inhibition, serum chromogranin A levels reflect the presence and severity of fundic enterochromaffin-like cell hyperplasia. In patients on long-term acid inhibition, serum chromogranin A was equally sensitive but more specific than serum gastrin for the detection of ECL cell hyperplasia [Sanduleanu et al. [4]].

3.2. Gastric Carcinoid

One of the results of chronic hypergastrinemia is the hyperplasia and/or dysplasia of ECL cells with risk of carcinoid development. On one hand, only a few case reports were published regarding occurrence of carcinoid tumors among long-term PPI users [Cavalcoli et al. [5], Nandy et al. [6], Jianu et al. [7], Jianu et al. [8], Lehner et al. [9], Haga et al. [10]], and on the other hand, an increase of the incidence of gastric carcinoids in two large databases was observed after the introduction and widespread use of proton pump inhibitors since the late 1980s [Hodgson et al. [11]]. Interestingly, strong evidence for association between carcinoid and gastric acid inhibition among rodents was found in the past [Havu et al. [12], Pyonter et al. [13]].

The association between long-term use of PPIs and carcinoid tumors among humans is still unclear and controversial. It is important to mention that a large part of the reported patients with carcinoid tumor and long-term use of PPIs had type 3-like carcinoid tumors.

3.3. Fundic gland polyps

Fundic gland polyps (FGPs) are benign small polyps (2-5mm) of the stomach fundus and/or body and can be found in patients with familial adenomatous polyposis. It was found that about 6% of patients who underwent esophagogastroduodenoscopy had FGP; 67.8% of them were women [Genta et al. [14]]. The chronic use of proton pump inhibitors for more than 48 months was found to be a predictor for development of FGPs [Ally et al. [15]].

An increased risk of fundic gland polyps was found in a meta-analysis among PPI users, particularly among individuals taking PPIs for at least 6 months (OR: 4.71) or 12 months (OR: 5.32) [Martin et al. [16]]. Based on another systematic review with meta-analysis, long-term use of PPIs (more than 12 months) is associated with an increased risk of FGPs with pooled odds ratios of 1.43 and 2.45 from fixed- and random-effects models, respectively [An Tran-Duy et al. [17]].Of note, a low incidence of FGPs without a clear relationship with PPIs was found in a study conducted in China [Cao et al. [18]].

3.4. Gastric Atrophy and Intestinal Metaplasia

Usually *H. pylori* colonizes the antrum; however, among PPI users the *H. pylori* colonization spreads to the stomach body. The result of the unusual *H. pylori* colonization is body-predominant gastritis with gland loss and development of atrophic gastritis.

Only several Randomized Controlled Trials (RTCs) investigated the association between the long-term use of PPIs and development of gastric atrophy and intestinal metaplasia. An increase of gastric atrophy (OR 1.5) and intestinal metaplasia (OR 1.46) were found; however, it is still no significant (p=0.39, p=0.55, respectively) [Song et al. [19]]. Several studies have not showed clear evidence of corpus gastric atrophy and intestinal metaplasia among long-term users of PPIs [Elsami et al. [20]].

3.5. Gastric Malignancy

Three decades after the development of PPIs the question regarding the association between long-term PPI use and gastric neoplasm is still an important, controversial and unresolved issue. Nowadays PPIs are one of the most marketed drugs and some of the patients need to be treated with PPI for years.

Different studies tried to find the answer and focused on the relationship between the long-term PPI use and gastric neoplasm; these are summarized in Table 1.While it is possible that after *H. pylori* infection, atrophic gastritis, intestinal metaplasia, and dysplasia can develop, but among patients without *H. pylori* infection and with hypochlorhydria due to the use of acid suppress or bacterial overgrowth with non-*H. pylori* infection can occur with

production of carcinogens and increased risk for malignancy.

In one study a 7.6-fold increase in the risk of gastric cancer was seen in patients who have Intestinal metaplasia throughout the stomach compared with patients who have no intestinal metaplasia even after *H. pylori* eradication [Shichijo et al. [21]]. The data are still scant, only few reports investigated the gastric cancer association to PPIs; however, part of these reports was conducted with a huge database and number of participants. Particularly during 2017 and 2018 there is an increase of published studies and all of these reports showed increased risk for gastric cancer among long-term PPI users.

PPI therapy might also increase the risk of gastric cancer; the association could be biased, but the increasing number of published reports is no longer marginal and small. Furthermore, perhaps the possible confounding factors and heterogenicity of the reports contribute to the weakness and controversial nature of the issue. These include the retrospective design of a large part of the studies, lack of important data as risk factors for gastric cancer such as family history of cancer, smoking, lack data regarding the stomach histology and premalignant lesions, H. pylori status, no clear evidence of causality between PPIs and gastric cancer in the published data, and different incidences of gastric cancer in the different populations.

PPIs are an important drug group with a great benefit, but they should be used for the right patient for the right length of time and should stopped as soon as possible among high risk patients with atrophic gastritis or high risk for cancer as in pernicious anemia or patients with family history of gastric cancer.

Other studies are needed for proving the causality between long-term use of PPIs and gastric cancer.

Table 1: Studies investigating the association between long-term use of PPIs and gastric cancer.

Study	Method	Intervention	Results
GarcíaRodríguezet al. [22] UnitedKingdom	Case control study 1994-2001; 10,000 controls, H2RAs,PPIs	PPIs or H2 Blocker	Increased risk of gastric cardia and non-cardia adenocarcinoma
Tamim et al. [23] Canada	Case control study, 1995-2003	PPIs or H2 Blocker	A minor increase in the risk of gastric cancer was observed if exposure to either H2 Blocker or PPIs
Hagiwara et al. [24]	Mongoliangerbils infected with HP	Treatment with PPI	Significantly more adenocarcinomas were found in the Omeprazole +Hp (60%) than in the Hp (7%) group animals
Poulsen et al. [25] Denmark	Population-based. 1990-2003. PPIs (18,790 patients) versus histamine 2 antagonist (17,478 patients)	PPI versus Histamine 2 antagonists and non-users.	Incidence rate ratio (IRR) of gastric cancer was 9.0 among PPI users and 2.8 among H2RA users, compared with nonusers. Results of IRR after lag time (one year) analysis of gastric cancer was 1.2 among PPI users and 1.2 among H2RA users, compared with non-users.
Brusselaers et al. [26] Sweden	Population-based cohort, 2005-2012.	797,067 individuals on maintenance PPI therapy	Standardized incidence ratios (SIRs) of 3.38 for gastric cancer SIRs among PPI users younger than 40 years was 22.76
Cheung et al. [27] Hong Kong	Population-based study, 2003-2012	63,397individuals.Long-term Proton Pump Inhibitors after treatment for *H. pylori*.	PPI use was associated with an increased gastric cancer risk with HR of 2.44, even after *H. pylori* eradication therapy.
Peng et al. [28] Taiwan	Case control study. 2022 participants, 2004-2011	Treatment with PPI for gastroesophageal reflux disease.	Increased risk for gastric cancer with OR of 2.93.
Niikura et al. [29] Japan	Cohort study, 533 participants. 1998-2017	PPI after treatment of *H. pyloris*	Crude HR of 3.55
An Tray-Duy et al. [17]	Systemic review and meta-analysis	3 case control studies	The pooled risk ratio for gastric cancer was 1.43
Ahn et al. [30]	Meta-analysis	4 studies	Increased risk of gastric cancer with odds ratio of 1.39
Wan et al. [31]	Meta-analysis926,386 participants	3 case control studies and 4 cohort studies	OR of 2.1 risk for gastric cancer among long-term PPI users

4. Conclusion

Hormonal and histopathological changes are common among long-term PPI users, including hypergastrinemia, hyperplasia of ECL cells, fundic gland polyps, intestinal metaplasia, and gastric atrophy. The increased risk of gastric cancer among long-term PPI users is still controversial; however most of the recently published studies showed an increased risk. The efficacy and safety among every patient should be considered before chronic treatment with PPI.

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