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REVIEW ARTICLE

Proton pump inhibitors and stomach neoplasm

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Abstract

This study aimed to explore the relationship between proton pump inhibitors (PPIs) and gastric tumors and determine the reasons behind these connections. We reviewed studies on PPIs and stomach tumors. We explored the relationship between PPIs and different types of gastric neoplasms according to the classification of gastric neoplasms. Long-term use of PPIs is associated with stomach infection, high gastrin levels, and rebound acid hypersecretion, which are directly or indirectly related to the development of gastric neoplasms. PPIs can increase the risk of gastric fundal polyps. Further evidence is needed to prove that it can increase the risk of gastric cancer.

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Gastric tumor is a tumor that develops in the gastric mucosa and gastric mucous membrane below the lymphatic tissue, including gastric benign and malignant tumors. Gastric cancer (GC) is the most common gastric malignancy [1]. In China, GC has the second highest incidence rate, after lung cancer, and has second highest mortality rate among all cancers [2]. A proton pump inhibitor (PPI) is widely used in the treatment of gastric acid-related diseases and considered a relatively safe drug. It is often used to treat peptic ulcer, offset gastroesophageal reflux, and *Helicobacter pylori* (HP) infection and prevent primary or recurrent peptic ulcer [3–4]. Moreover, peptic ulcer and HP infection are high-risk factors for gastric tumors. Therefore, PPIs have an inhibitory effect on the development of gastric tumors [5]. However, recently, researchers have found that there is an increased risk of gastric tumors among PPI users [6–7]. Therefore, we have reviewed relevant literature and summarized the relevant information in this study.

Adverse reactions of the gastrointestinal tract in the clinical use of PPIs

PPIs, introduced in the 1980s, are effective stomach acid inhibitors that reduce stomach acid by inhibiting H±k ±atpase (proton pump) [8]. After absorption in the blood, PPIs diffuse into the gastric parietal cells and irreverently bind with H±k± at pase in the parietal cells of the gastric mucosa, deactivating the proton pump. Gastric acid secretion resumes only when a new proton pump is formed. Therefore, PPIs are effective in inhibiting gastric acid secretion; they are widely used in diseases related to increased gastric acid secretion. A PPI has been regarded as a relatively safe drug with few adverse reactions since its inception. However, the adverse reactions of PPIs in the digestive, immune, endocrine, urinary, and nervous systems and other aspects have attracted the attention of many domestic and overseas scholars [9–10].

The adverse reactions related to gastrointestinal diseases have been summarized below.

Infection

Long-term use of PPIs leads to non-HP infection in the stomach. Eusebi proposed that long-term acid inhibition would lead to an increase in gastric pH, reducing the bactericidal and bacteriostatic effect of gastric acid and causing microbial infection[11]. Additionally, according to Leonard and Bavishi, PPIs induces sodium hypochlorite damage, a natural defense mechanism of the human body against ingestion of bacteria, leading to bacterial colonization, gastrointestinal flora change, and increase in the risk of gastrointestinal infection. The relationship

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between PPIs and gastrointestinal bacterial infection has also been confirmed in various studies [12–13].

Increased blood gastrin levels

Several studies have found that long-term use of PPIs can increase serum gastrin levels, which is caused by a stress response of G cells in the gastric antrum to lower gastric acid concentration [7, 10]. Gastrin has a proliferative effect on cell growth, especially gastrin hyperemia, and nutritional effect on enterochromaffin-like (ECL) cells. Long-term increase in gastrin levels will lead to gastric hyperplasia, further increasing the risk of gastric tumor [13–14].

Rebound acid hypersecretion

When PPls are abruptly discontinued, stomach acid production will be higher than that before PPI use, a phenomenon known as "rebound acid hypersecretion," which causes rebound of gastrointestinal symptoms. This adverse reaction is more common in patients with poor compliance [15].

PPIs and benign gastric tumor

PPIs and gastric polyps

Gastric polyp refers to the papillary tissue developing on the surface of the gastric mucosa, which is a type of benign gastric tumor and related to a variety of risk factors [16]. PPI-related polyps are mainly fundic gland polyps.

A meta-analysis of 12 studies on the association between PPI use and gastric polyps by Tran-Duy found that the risk of gastric polyps was significantly increased in individuals who had been using a PPI for > 1 year, but the clinical significance of this increased risk was unclear [17]. Lundell integrated 16 studies and found that the blood gastrin level of individuals who had been using a PPI for > 3 years was 1 times higher than the upper limit of the normal range (≤ 100 pg/mL) [7]. This increase was not associated with the presence or absence of HP infection, and the ECL cell density increased over time in PPI users during the treatment. However, Lundell believes there is insufficient evidence to link these changes. Further, a 5-year follow-up study by Fiocca showed that elevated gastrin levels in PPI users had a sustained drive to proliferate endocrine cell populations in the fundus gland [18]. This drive significantly increases the risk of polyps in the fundus glands, while PPI use increases the risk of non-HP infections in the stomach; inflammatory stimuli also increase the risk of polyps.

In combination with the abovementioned views, the risk of gastric polyps will be increased in individuals who have been using a PPI for a long time, which is mainly attributed to the fact that long-term PPI use can lead to gastrointestinal adverse reactions such as increased blood gastrin levels and non-HP infection in the stomach [19].

PPIs and other benign gastric tumors

Except for gastric polyps, there was no significant association between PPI use and other benign gastric tumors. Ezekwudo found the development of neuroendocrine tumors in patients treated with PPls for a long time, but the cause of this phenomenon is unknown as it rarely occurs. Only a few cases have been reported; hence, these findings may be coincidental, and more cases are needed to confirm these results [19].

PPIs and malignant gastric tumor

PPIs and GC

GC is a multifactorial disease, which is affected by several factors during its development. After discovering that PPI use leads to elevated blood gastrin levels and increased risk of gastric polyps, many scholars have started exploring the relationship between PPI use and GC.

PPIs can cause stomach cancer

In a 2018 Hong Kong-wide retrospective cohort study by Cheung [20] on 63 397 patients who underwent radical treatment for HP infection, the incidence of GC in those who had been using a PPI for > 1 year was significantly higher than that in the control group, and the difference was more significant with longer period of PPI use. The risk of GC was also higher among individuals using PPIs than among those using H2 receptor blockers.

Moreover, in a cohort study based on the Swedish national population, Brusselaers found that among 797 067 patients who received PPI treatment for at least 180 days [3], the standardized incidence ratio for GC was 3.38 and that the risk of GC increased, regardless of whether there were any signs of GC (e.g., chronic gastritis and HP infection). Meanwhile, the study also compared PPI users and H2 receptor blocker users and found that the incidence of GC did not significantly increase in H2 receptor blockers users. The study revealed that long-term use of PPIs is a risk factor for GC, although factors, such as reverse causality, can skew the results. Moreover, there were several scholars who agree with this point [21–22], Shichijo summarized the characteristics of GC in patients with HP eradication and reported that long-term PPI use in patients with HP eradication may be one of the causes of GC development [23]. Additionally, many researchers attempted to explain this phenomenon using the mechanism of action of PPIs that leads to GC.

(1) Hypergastrinemia theory. PPI use will increase the blood gastrin level, leading to the development of GC. Lundell found that PPI use can increase serum gastrin levels [7]. Moreover, a study by Smith on the relationship

between gastrin and GC showed that gastrin may activate the intracellular signal transduction pathway through the cholecystokinin B receptor-mediated pathway and its own characteristics, such as angiogenesis and anti-apoptotic effects, resulting in the development of malignant tumors and GC [24] Meanwhile, GC precancerous status was also observed after injection of gastrin into animal models [25]. Therefore, long-term use of PPIs may cause hypergastrinemia and further lead to the development of GC.

(2) Infection. PPI use leads to non-HP infection in the stomach, which causes GC. Long-term PPI use can cause gastrointestinal flora imbalance [8, 26] and increase the risk of non-HP infection. Such nonspecific infection will also cause inflammatory hyperplasia of the gastric mucosa. In the long-term development of gastric mucosa, atrophy, intestinal adenosis, polyp formation, and other precancerous lesions will develop, leading to GC [3]. Additionally, some studies have also shown that PPI treatment may promote the process of HP-inducing GC, inducing further malignant transformation of gastric glands [19, 27–28]. This hypothesis seems to explain the results of the previous study by Cheung [21].

PPIs causing stomach cancer needs more evidence

Although these hypotheses attempt to justify the long-term PPI use for GC, there are still many objections.

Some of these hypotheses have not been well explained. H2 receptor blockers mentioned in the Swedish national cohort study did not increase the risk of GC, but H2 receptor blockers can reduce acidity in the stomach, cause the reaction of G cells in the gastric antrum, and weaken the gastric defense mechanism, leading to infection. However, this phenomenon is explained by the author; they stated that H2 receptor blockers are not as effective as PPIs in inhibiting acid secretion. This explanation involves blood concentration, dose, medication use duration and body sensitivity to drugs which still to be confirmed by experiment [3], and many scholars have proposed that, although long-term PPI use is associated with precancerous lesions (e.g., gastric polyps and gastric mucosal hyperplasia), it cannot be regarded as an independent risk factor for GC [29–30]. In a meta-analysis of 11 studies, Ahn came to a conclusion contradictory to that reported in the Swedish national cohort study, suggesting that H2 receptor blockers increase the risk of GC, while PPIs are not significantly associated with the risk of GC [31]. This contrary conclusion suggests that more studies are needed to confirm the association between long-term PPI use and GC risk. Similarly, in the study by Brusselaers, it was clearly stated that patients who had been using a PPI for a long time, regardless of the presence of HP infection, had an increased risk of GC [3]. This suggests that PPI use promotes GC development by inducing HP infections also needs to be extensively investigated.

PPIs and gastric malignant lymphoma

Gastric malignant lymphoma is the most common cancer, excluding GC [32]. Recently, many studies have found that gastric malignant lymphoma is associated with HP infection and that HP eradication plays an important role in the prevention and treatment of gastric malignant lymphoma. Therefore, several individuals regard HP eradication as the first treatment for gastric malignant lymphoma[33]. In HP eradication therapy, PPI use has not been associated with gastric malignant lymphoma.

PPIs and other malignant gastric tumors

Gastric malignancies also include gastric malignant stromal and gastric carcinoid tumors. However, studies on the relationship between PPI use and gastric malignancies are extremely rare, and the relationship between PPI use and these cancers has not been explored.

Conclusion

A PPI is an effective acid-inhibiting drug, which is widely used in clinical practice. Concurrently, PPI use and adverse reactions of the digestive tract have been paid more attention. PPI use can increase the risk of glandular polyps of the fundus, which is associated with hypergastrinemia and non-HP infection in the stomach. Meanwhile, PPI use can increase the risk of GC, which may be related to the development of gastric polyps, hypergastrinemia and infection. However, there are still speculations against this view; hence, more studies are needed to prove or overturn this view.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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