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Review Article

Influence of Long-Term Use of Proton Pump Inhibitors on Esophageal and Gastrointestinal Precancerous Lesions or Carcinoma

Abstract

Patients with GERD and Barrett's oesophagus should be encouraged to continue long term use of PPI therapy as a preventive measures for oesophageal adenocarcinoma. However, the conclusions, whether long-term use of PPI may casuse FGPs and gastric carcinoma development, remain inconsistent. Now, individual reports showed that long-term treatment with PPI might cause gastric neuroendocrine tumors (g-NETs) and the development of ECL cell carcinoids. Presently enormous study's conclusion supported that long-term use of PPI does not increase in risk of colorectal cancer. Hence, clinical physicians must weigh potential risks of long-term use of PPI against gastrointestinal precancerous lesions or carcinoma.

Introduction

Previously the substantial data on long-term treatment of humans with proton pump inhibitors (PPI) has not revealed any definite risks [1] and prolonged gastric acid suppression with PPI rarely produced adverse event [2]. Hence, Proton pump inhibitors have an excellent safety profile [3], supporting the short-and long-term safety of PPI [4]. They have been become a commonly prescribed class of drugs worldwide [3,5], long-term use of PPI is becoming more prevalent [6]. However, current evidences have demonstrated that long-term use of PPI might generate certain adverse events [3]. Thus, the viewpoints of adverse events for long-term use of proton pump inhibitors in human remain inconsistent. Moreover, studies have shown that chronic acid suppression by proton pump inhibitor therapy might lead to hypergastrinemia [7-9] and increasing enterochromaffin-like cell dysplasia and risk of gastric.

NET development, and progression of carcinogenesis in a certain predisposed subset of Barrett's esophagus patients [9]. However, a contradictory conclusion did not support gastrin dependence of adenocarcinoma of the stomach or the colon and considering that it might be explained by the presence of gastrin receptors of tumour cells and the role of gastrin as an autocrine growth factor in some of these tumours [10]. Additionally, a study suggestd that prolonged hypochlorhydria predisposed to gastric carcinoma by an increase in the production of carcinogenic N-nitroso compounds [11].

However, accumulated evidence [12], has shown that gastrin likely does not promote-and may even suppress-distal antral gastric cancer. Hence, these hypotheses have led to concerns about the safety of long-term PPI administration [11,13]. Particularly, whether long-term use of proton pump inhibitors in human might result in esophageal and gastrointestinal precancerous lesions or carcinoma causes the extensive concern in the clinical.

1. The associations between long-term uses of proton pump inhibitors and Barrett's esophagus, esophageal cancerGastroesophageal reflux disease (GERD) is a risk factor for the development of Barrett's esophagus and esophageal adenocarcinoma. Current evidences have confirmed that long-term use of PPI seems to be a safe and efficient treatment for GERD [14,15] and Barrett's oesophagus [16]. Long-term acid suppression reduced proliferation in Barrett's esophagus samples [17] and may reduce esophageal adenocarcinoma (EAC) by a minimum of 19% [18]. Use of ongoing PPI therapy appeared beneficial in the prevention of dysplasia and adenocarcinoma in patients with Barrett's oesophagus [19]. Although PPI treatment over 1-13 years did not shorten the Barrett's oesophagus segment but squamous islands appeared in many patients, and, the incidence of oesophageal adenocarcinoma received proton pump inhibitor-treated patients was low [20]. Hence, PPI use was associated with a decreased incidence of neoplasia in Barrett's esophagus [21], supporting a cancer-protective role for PPI in patients with Barrett's esophagus

[22]. However, an opposite study result revealed that PPI did not present the cancer-protective effects [23]. We summarize the above results, reconsidering that patients with GERD and Barrett's oesophagus should be encouraged to continue long term use of PPI therapy as a preventive measures for oesophageal adenocarcinoma.

2. The association between long-term uses of proton pump inhibitors and polyps, gastric carcinoma, gastric neuroendocrine tumors

Gland Polyps (FGPs) is an important precancerous lesions of gastric carcinoma. Whether long-term use of PPI might increase or decrease the a incidence of denoma remains no consistent conclusion .Studies have revealed that long-term use of PPI was a particularly strong risk factor [24,25]. Among them, PPI have been linked to gastric fundal polyposis and not antral gland polyposis [26]. Another report originating from an Asian country showed that fundal Gland Polyps (FGPs) in the corpus of stomach were significantly higher than the fundus in a patient of long-term PPI therapy [27]. There was a possible causal relation between the use of omeprazole and the development of fundic gland polyps in patients without H. pylori gastritis [28].

Gastric polyps and nodules might be found in children receiving longterm omeprazole therapy during the mean observation period of 31 months [29]. Long-term use of proton pump inhibitors may be associated with the presence of small gastric fundic gland polyps and hyperplastic polyps [30]. But, the opposite research results showed that sporadic FGPs may not be induced by PPI therapy [31]. For instance, the prevalence of FGPs and polyps number were not link with omeprazole therapy [32]. Furthermore, longterm use of PPI did not influence the frequency, growth, or histology of adenomatous polyps [33]. Long-term use of PPI was associated with a reduction in both baseline and interval development of hyperplastic polyps [33]. Hence, whether long-term use of PPI might casue FGPs is inconsistent, it still need to further confirme that whether there are the associations between long-term use of PPI and FGPs.

Whether long-term use of PPI might result in gastric carcinoma development remains controversial. Long-term use of PPI was related to increased risk of gastric cancer [34], via stimulation of DNA-damaged cells; and, increased risk of periampullary cancers [35], via long-lasting iatrogenic hypergastrinemia induced by potent inhibitors of acid secretion. Additionally, human gastric carcinomas of diffuse type, particularly the signet-ring subtype, showed ECL cell differentiation, suggesting involvement of gastrin in the carcinogenesis [36]. However, recent study indicated no association between PPI use and the risk of gastric cancers [8]. There are tremendous reports does not support the above viewpoints, which long-term inhibition of the gastric proton pump did not increase the risk of gastric cancer because of antioxidant depletion [37]; there are no evidence that pantoprazole as a longer acting PPI conferred an excess risk of gastric cancer, other gastrointestinal cancers or all cancers compared with other shorter-acting PPI [38]. There has

even study suggested that anti-carcinogenic actions of PPI were augmented with PPI-induced hypergastrinemia [39]. But,Recently a multicenter study confirmed that elevated lesions and cobblestone-like mucosa were characteristic endoscopic features in PPI users. And ,a gender-associated difference was noted in terms of the frequency of these lesions [40]; another study results [41], pointed to a major influence of reverse causation and confounding by indication on the association between PPI use and gastric cancer incidence, the finding of increased incidence among PPI users with most prescriptions and longest follow-up warrants further investigation.In addition, PPI intake was associated with the existence and epidemiological relevance of gastric neuroendocrine tumors (g-NETs) [42,43], illustrating a patient with a poorly differentiated neuroendocrine carcinoma with ECL cell characteristics probably induced by hypergastrinemia secondary to long-term use of PPI [42]. There were reports indicating development of ECL cell carcinoids after long-term treatment with proton pump inhibitors [43] and hypergastrinemia secondary to PPI treatment might induce enterochromaffin-like cell carcinoids in man [44,45]. Additionally, based on few case reports showed although PPI-induced hypergastrinaemia has the potential to stimulate hyperplasia of enterochromaffin-like (ECL) cells,however, the role was very weak , considering Physicians have to continue PPI prescription without any fear about the occurrence of this adverse event [46]. However, Children with long-termuse of PPI did not appear to develop atrophic gastritis or carcinoid tumours [47]. In short, whether long-term use of PPI might result in gastric carcinoma development and carcinoid tumours need to be verified by large prospective studies.

3. The association between long-term uses of proton pump inhibitors and colorectal cancer,

Enormous researches have indicated no association between long-term use of PPI at a regular dose and the increase in risk of colorectal cancer [8,48-52]. However, only a previously study suggested that PPI use might be modestly associated with CRC risk [53,54]. According to the results of the present majority studies, the conclusion seem to support the opinions, which long-term use of PPI does not increase in risk of colorectal cancer. Further research should needed to confirm the lock of a risk-increasing effect of long-term us of PPI.

Conclusion

Patients with GERD and Barrett's oesophagus should be encouraged to continue long term use of PPI therapy as a preventive measures for oesophageal adenocarcinoma. However.whether long-term use of PPI may casue FGPs and gastric carcinoma development remains are inconsistent. long-term treatment with PPI might cause gastric neuroendocrine tumors (g-NETs) and the development of ECL cell carcinoids. The presently study's conclusion seem to support that long-term use of PPI does not increase in risk of colorectal cancer. Hence, Physicians must weigh potential risks of long-term use of PPI against therapeutic benefit. The continued follow-up of patients taking PPI for extended periods will provide greater experience regarding the potential gastrointestinal adverse effects of long-term acid suppression.

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