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THE BENEFITS AND RISKS OF PROTON PUMP INHIBITORS (PPI) ON LONG-TERM USE

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A B S T R A C T

Proton pump inhibitors (PPIs) initially known for the inhibition of gastric acid secretion are widely used in the treatment of various acid-related diseases including primary prevention of GERD (gastrointestinal reflux disease) and secondary prevention of aspirin / NSAIDs induced ulcers. Although most of the PPIs class of drugs cause adverse effects which are not majorly examined during or after administration of them. In most cases, the only side of PPI beneficial and safety is considered but the other side of the risks and adverse effects are not considered. Several PPI-related adverse effects have been reported, but their clinical relevance is not yet clear and the evidence reported in many studies is not at enough level. Hence, this article reviews the findings of most research studies on the benefits and risks of proton pump inhibitors on long-term use.

1. INTRODUCTION

Due to its reversible blockage of the hydrogen/potassium pump in the gastric parietal cells, proton pump inhibitors (PPIs) are regarded as an efficient medication for stomach acid suppression. They are frequently prescribed, and it is deemed safe to use them over-the-counter. Histamine H2 receptor antagonists (H2RAs), which were created in the late 1970s, can replace PPI (proton pump inhibitor) medications, which were used in the early stages of this treatment. In particular, during the post-prandial phase, this H2RA promotes the effects of gastrin and acetylcholine, which effectively controls gastric acid release.

- **Benefits of proton pump inhibitors on long-term Use:**

PPIs are often used during the daytime hours after a single daily morning dose that reduces stomach acid output. PPIs are recognized as the most successful initial maintenance therapy and recurrence prevention in the treatment of GERD. Since gastroesophageal refluxes usually happen after meals, patients with GERD typically complain of reflux symptoms after meals. Since a single morning dose's acid-suppressing effects are said to be useful in preventing the recurrence of reflux symptoms. Therefore, recurrence of GERD within 1 year without maintenance medication is projected to be greater than 50%, but recurrence within 1 year with maintenance therapy is reported to be less than 15%. [1,2]

- **Risks involved in Proton Pump Inhibitors on long-term Use:**

There are two categories of risks: those connected to acid inhibition and those unconnected. When using proton pump inhibitors for a long time, individuals have clinically documented these side effects. Pneumonia, gastrointestinal infection, gastric carcinoid tumor, gastric fundic mucosal hypertrophy, changes in the gut microbiome, and small intestine bacterial overgrowth are some of the negative side effects. Bone fracture, a lack of vitamin B12, a lack of iron Hepatic encephalopathy, colon cancer, gastric fundic gland polyps, hypomagnesemia, gastric cancer, and spontaneous bacterial peritonitis Included in drug interactions and unrelated side effects are sensitivity to a drug's chemical, Chronic kidney disease, acute interstitial nephritis, collagenous colitis dementia, drug interactions, Ischemic disorders of the heart and the brain. [6,7,8]

2. ADVERSE EVENTS UNRELATED TO ACID INHIBITION

(i) **Collagenous Colitis**: Patients receiving PPI therapy frequently have diarrhoea. Collagenous colitis, which is characterized by diarrhoea and histological identification of thick collagen bands beneath the intestinal epithelium, may aggravate diarrhoea brought on by PPIs. Patients who take lansoprazole frequently can attest to this. As a result, patients complaining of diarrhoea are assessed for the possibility of collagenous colitis.

(ii) Acute Interstitial Nephritis and Chronic Kidney Disease: Interstitial nephritis has been noted to develop in people on PPIs, presumably as a result of an allergic reaction to the medication, however the exact process is unclear. When the renal functions were assessed by the blood

creatinine levels or estimated glomerular filtration rate, long-term PPI use was linked to chronic kidney disease. Therefore, patients must be monitored often if renal failure occurs even when it is not specifically noted. [7,8]

(iii) **Drug Interaction During Activation and Degradation Phase in Liver**: The hepatic drug-metabolizing enzyme CYP2C19 at least degrades medicines like PPIs, diazepam, phenytoin, and warfarin. [9] PPI dosing may have a variety of pharmacological effects by reducing the rate of medication breakdown for various substances. A lack of PPI-induced increase in major cardiac events was suggested by three prospective randomised controlled studies, including the well-known COGENT research (the Clopidogrel and the Optimization of Gastrointestinal Events Trial).

(iv) **Dementia**: According to retrospective investigations using a German database, the increased risk of dementia is primarily observed in elderly people. There is no discernible risk of dementia, according to retrospective investigations on databases in the USA and Europe. As a result, one meta-analysis contends that there is no statistical evidence linking PPI usage to an increased risk of dementia or AD. [12,13]

(v) **Possible allergic reactions to drug chemicals**: A minority of people on PPIs may experience anaphylaxis, pancytopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, acute liver damage, Lyell syndrome, Stevens-Johnson syndrome, interstitial nephritis, and rhabdomyolysis. Patients are advised to contact their doctor right away if they experience any unexplained skin eruptions, fever, or general malaise after beginning a PPI administration.

3. ACID INHIBITION RELATED ADVERSE EVENTS

(i) **Increased Gastrointestinal Infection:** There are two types of bacteria that can cause gastrointestinal infections: acid-resistant and acid-labile. When gastric acid output is reduced by a PPI, acid-labile bacteria like Salmonella, Campylobacter, and the vegetative form of Clostridium difficile may have a higher likelihood of infecting and growing in the digestive tract. While some cohort studies have failed to demonstrate such increased infection in PPI-treated cases, many retrospective investigations have revealed increased infection rates during the administration of PPIs with regard to Salmonella and Campylobacter. It is challenging to determine if PPIs raise the risk of Salmonella and/or Campylobacter infection due to the inconsistent study findings.

PPI use has been linked to a higher risk of gastrointestinal infections, particularly those caused by Clostridium difficile. Due to the rising number of strains of Clostridium difficile (C. difficile) that are resistant to antibiotics, both the incidence and severity of CDI have been on the rise globally over the past 20 years.

(ii) **Pneumonia**: The minimal risk of pneumonia associated with PPI therapy that was only seen in the short term may not actually be a clinically significant danger for the long-term management of GERD. [17]

There may be a connection between the use of PPIs and the emergence of community-acquired pneumonia, according to retrospective observational studies and their meta-analyses. PPI use was linked to a 27 percent higher risk of either hospital- or community-acquired pneumonia, according to a meta-analysis that included eight observational studies.

No elevated risk for pneumonia was seen in a more recent systematic evaluation of trials involving just individuals who were given PPI medication for newly-onset NSAID usage. The authors of this study contend that the previously found link may have been somewhat influenced by protopathic bias as a result of the inclusion of GERD patients (a risk factor for pneumonia) or the incorrect diagnosis of early pneumonia symptoms mistaken for GERD. [18]

(iii) **Gastric Neuroendocrine Tumor**: PPI treatment significantly raises intragastric pH, which raises plasma gastrin concentration. PPIs have regularly been found to increase the number of ECL cells in the gastric fundic mucosa because gastrin encourages the proliferation of gastric enterochromaffin-like (ECL) cells with numerous gastrin receptors.[20]

Three incidences of gastric neuroendocrine tumours (g-NETs) in patients receiving long-term proton pump inhibitors were documented in recent clinical research (PPIs). These tumours cannot be classified using the accepted standards. g-NETs are currently divided into three forms: type 1, normogastrinemic and more aggressive; types 1 and 2, associated with hypergastrinemia caused by chronic atrophic gastritis and Zollinger-Ellison syndrome, respectively. Only a few examples have been recorded thus far, despite the biological plausibility of the g-NETs emergence in PPI-using patients.[21]

(iv) **Changes in Gut Microbiome and Small Intestinal Bacterial Overgrowth**: According to reports, PPIs alter the gut microbiome and boost the population of Streptococcus bacteria, which are known to heavily populate the mouth cavity. Additionally, using PPIs makes the jejunum and duodenum bacteria denser. PPI medication is therefore viewed as a SIBO risk factor (small intestinal bacterial overgrowth). [24]

According to these findings, PPIs boost Streptococcus levels in the gut microbiome and small intestine while decreasing stomach acid output and the bactericidal impact of the gastric juice. Additionally, it has been proposed that PPIs may be labile when given to individuals who have trans-oral infections with other pathogenetic bacteria, though the clinical significance of that has not been shown. The clinical significance of a modified microbiome in PPI-treated individuals is unclear at this time.

(v) **Hypomagnesemia**: Magnesium is an essential cation that is implicated in several physiological processes in the body. Fifty to 60% of total magnesium is stored in bones, about 40% is intracellular (mainly in muscles) and only 1% is found in extracellular fluid. Magnesium balance is tightly regulated through intestinal and renal absorption and excretion as well as exchange with bone. Approximately one-third of

the average daily magnesium intake (about 360 mg; 15 mmol) is absorbed in the small intestine through both a saturable transport system and passive diffusion and excreted through urine. Magnesium plays an important role in neuromuscular activities. Therefore, chronic diarrhea is a risk factor for hypomagnesemia, and affected patients may experience convulsions, muscle cramps, seizures, or anorexia.

Hypomagnesemia has been linked to long-term PPI usage, probably as a result of diminished magnesium absorption in the small intestine. As a result, the other reports do not support the hypothesis that PPI treatment causes hypomagnesemia. Although the nature of the relationship between PPI treatment and hypomagnesemia is unclear, a systematic review and meta-analysis of observational data was published. [25]

(vi) **Gastric Neuroendocrine Tumor**: PPI treatment significantly raises intragastric pH, which raises plasma gastrin concentration. PPIs have regularly been found to increase the number of ECL cells in the gastric fundic mucosa because gastrin encourages the proliferation of gastric enterochromaffin-like (ECL) cells with numerous gastrin receptors. [23]

Three incidences of gastric neuroendocrine tumours (g-NETs) in patients receiving long-term proton pump inhibitors were documented in recent forms: type 1, normogastrinemic and more aggressive; types 1 and 2, connected to hypergastrinemia due to chronic atrophic gastritis and Zollinger-Ellison syndrome, respectively. Only a small number of cases have been documented thus far, despite the biological plausibility of the g-NETs emergence in PPI-using patients.

(vii) **Decreased Absorption of Other Nutrients**: PPIs have been linked to a higher risk of nutritional deficiencies, which can affect the metabolism of calcium, iron, magnesium, vitamin C, vitamin B12, and vitamin B12. Long-term PPI use may reduce gastric acid secretion, particularly in the postprandial hours of the day, which could reduce levels of iron, calcium, and vitamin B12 absorption and possibly lead to a pathological condition brought on by a deficiency in those nutrients.

Gastric acid may be a key factor in calcium absorption. Although it hasn't been conclusively shown, there has been some evidence of decreased absorption of insoluble calcium during acid suppression, such as calcium carbonate. Although a study did not confirm the idea that PPI medication affects calcium absorption, such decreased absorption from the diet, if caused by PPI administration, may produce calcium shortage, which can result in osteoporosis and an increased risk of bone breakage.[28]

(viii) **Gastric Cancers**: One of the most deadly tumours, especially in East Asia, is stomach cancer, which continues to be one of the most common. Because it causes stomach inflammation and subsequent neoplastic development, Helicobacter pylori infection is largely responsible for noncardiac gastric malignancies. The risk of getting stomach cancer after the removal of H. pylori can be diminished but not completely eliminated. Although there are currently no randomised clinical trials to prove a link between long-term PPI usage and stomach cancer, evidence-based observational research suggest PPIs are linked to an elevated risk of the disease. According to a recent study, PPI use increased the incidence of stomach cancer up to a hazard ratio value of 4.29, even after H. pylori had been successfully eradicated. Therefore, PPIs increase the risk of stomach cancer in both individuals with H. pylori infection and those who have undergone complete eradication. [35]

(ix) **Spontaneous Bacterial Peritonitis**: A potentially fatal bacterial infection of the abdominal cavity known as spontaneous bacterial peritonitis has been reported in cases of ascites brought on by liver cirrhosis. Due to the cirrhosis-related increased permeability of the intestinal mucosa, gut bacteria may pass through the intestinal wall and multiply in the ascites fluid without causing macroscopic intestinal damage. Despite significant discrepancies in the study findings, it has been consistently reported that using PPIs increases the risk of spontaneous bacterial peritonitis by a hazard ratio of 1.4 to 5.0. Therefore, when doctors give PPIs to patients with liver cirrhosis, the benefit and risk of PPI treatment should always be balanced. [38]

(x) **Hepatic encephalopathy**: Alterations in the gut flora and bacterial translocation may be responsible for the effect of PPIs on the emergence of HE. A close connection between PPI use and SIBO has been shown in other research (small intestinal bacterial outgrowth). In addition, recent research revealed that PPI usage was linked to a less healthy gut microbiota, reduced microbial diversity, and a higher incidence of Streptococcaceae. The emergence of HE has been linked to changes in gut flora, according to research. However, PPI use may increase bacterial proliferation and impair gastrointestinal motility, which might put patients at risk for bacterial infections. As a result, PPIs could raise the production and absorption of nitrogenous chemicals, raising the risk of HE.

Additionally, PPI medication has been linked to hepatic encephalopathy in cirrhotic patients, according to reports. Hepatic encephalopathy is thought to be linked to PPI-induced alterations in gut microbes, hypomagnesemia, and vitamin B12 insufficiency, but the mechanism is yet unclear.

(xi) **(Drug Interactions in the Gastrointestinal Tract**: Gastric acid secretion affects the absorption of a variety of medications, including digitalis, which is broken down by gastric acid in the stomach. As a result, when PPIs are administered, the pharmacological action of digitalis and other drugs may be increased.

Additionally, because PPIs have low solubility at neutral pH, several medications, including itraconazole and atazanavir, are difficult to absorb well.

4. CONCLUSION

Although the majority of the data for these concerns is insufficient or insufficient to draw a strong conclusion, clinical practices should take the risk of long-term PPI medication into consideration.

REFERENCES

[1] Murakami K, Sakurai Y, Shiino M, Funao N, Nishimura A, Asaka M. Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for Helicobacter pylori eradication: a phase III, randomised, double-blind study. Gut. 2016;65:1439–1446.

[2] Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut. 1999;45:172–180.

[3] Singh S, Garg SK, Singh PP, Iyer PG, El-Serag HB. Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis. Gut. 2014;63:1229–1237.

[4] Hawkey CJ, Karrasch JA, Szczepañski L, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. Omeprazole versus misoprostol for NSAID-induced ulcer management (OMNIUM) study group. N Engl J Med. 1998;338:727–734.

[5] Choi SW, Han JM, Bae YJ, et al. Lessons from two cases of anaphylaxis to proton pump inhibitors. J Clin Pharm Ther. 2012;37:614–616.

[6] Berney-Meyer L, Hung N, Slatter T, Schollum JB, Kitching AR, Walker RJ. Omeprazole-induced acute interstitial nephritis: a possible Th1–Th17-mediated injury? Nephrology (Carlton) 2014;19:359–365.

[7] Lazarus B, Chen Y, Wilson FP, et al. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Intern Med. 2016;176:238–246.

[8] Arora P, Gupta A, Golzy M, Patel N, Carter RL, Jalal K, Lohr JW. Proton pump inhibitors are associated with increased risk of development of chronic kidney disease. BMC Nephrol 2016;17:112.

[9] Chen J, Chen S, Lian J, Zeng X, Luo T. Pharmacodynamic impacts of proton pump inhibitors on the efficacy of clopidogrel in vivo-a systematic review. Clin Cardiol 2013;36:184-189.

[10] Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA 2009;301:937-944.

[11] 11.Serbin MA, Guzauskas GF, Veenstra DL. Clopidogrel-proton pump inhibitor drug-drug interaction and risk of adverse clinical outcomes among PCI-treated ACS patients: a meta-analysis. J Manag Care Spec Pharm 2016;22:939-947.

[12] Haenisch B, von Holt K, Wiese B, et al. Risk of dementia in elderly patients with the use of proton pump inhibitors. Eur Arch Psychiatry Clin Neurosci 2015;265:419-428.

[13] Gomm W, von Holt K, Thomé F, et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. JAMA Neurol 2016;73:410-416.

[14] Gray SL, Walker RL, Dublin S, et al. Proton pump inhibitor use and dementia risk: prospective population-based study. J Am Geriatr Soc 2017;66:247-253.

[15] Wang YF, Chen YT, Luo JC, Chen TJ, Wu JC, Wang SJ. Proton-pump inhibitor use and the risk of first-time ischemic stroke in the general population: a nationwide population-based study. Am J Gastroenterol 2017;112:1084-1093.

[16] Vaezi MF, Yang YX, Howden CW. Complications of proton pump inhibitor therapy. Gastroenterology 2017;153:35-48.

[17] Sarkar M, Hennessy S, Yang YX. Proton-pump inhibitor use and the risk for community-acquired pneumonia. Ann Intern Med 2008;149:391-398.

[18] Johnstone J, Nerenberg K, Loeb M. Meta-analysis: proton pump inhibitor use and the risk of community-acquired pneumonia. Aliment Pharmacol Ther 2010;31:1165-1177.

[19] Williams C, McColl KE. Review article: proton pump inhibitors and bacterial overgrowth. Aliment Pharmacol Ther 2006;23:3-10.

[20] Delle Fave G, Capurso G, Annibale B, Panzuto F. Gastric neuroendocrine tumors. Neuroendocrinology 2004;80(suppl 1):16-19.

[21] Yu JY, Wang LP, Meng YH, Hu M, Wang JL, Bordi C. Classification of gastric neuroendocrine tumors and its clinicopathologic significance. World J Gastroenterol 1998;4:158-161.

[22] Haga Y, Nakatsura T, Shibata Y, et al. Human gastric carcinoid detected during long-term antiulcer therapy of H2 receptor antagonist and proton pump inhibitor. Dig Dis Sci 1998;43:253-257.

[23] Kinoshita Y, Ishihara S, Kadowaki Y, Fukui H, Chiba T. Reg protein is a unique growth factor of gastric mucosal cells. J Gastroenterol 2004;39:507-513.

[24] Jackson MA, Goodrich JK, Maxan ME, et al. Proton pump inhibitors alter the composition of the gut microbiota. Gut 2016;65:749-756.

[25] Hoorn EJ, van der Hoek J, de Man RA, Kuipers EJ, Bolwerk C, Zietse R. A case series of proton pump inhibitor-induced hypomagnesemia. Am J Kidney Dis 2010;56:112-116.

[26] Biyik M, Solak Y, Ucar R, et al. Hypomagnesemia among outpatient long-term proton pump inhibitor users. Am J Ther 2017;24:e52-e55.

[27] Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, et al. Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of observational studies. Ren Fail 2015;37:1237-1241.

[28] Wood RJ, Serfaty-Lacrosniere C. Gastric acidity, atrophic gastritis, and calcium absorption. Nutr Rev 1992;50:33-40.

[29] Ngamruengphong S, Leontiadis GI, Radhi S, Dentino A, Nugent K. Proton pump inhibitors and risk of fracture: a systematic review and meta-analysis of observational studies. Am J Gastroenterol 2011;106:1209-1218.

[30] Gray SL, LaCroix AZ, Larson J, et al. Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative. Arch Intern Med 2010;170:765-771.

[31] Targownik LE, Lix LM, Leung S, Leslie WD. Proton-pump inhibitor use is not associated with osteoporosis or accelerated bone mineral density loss. Gastroenterology 2010;138:896-904.

[32] Ally MR, Veerappan GR, Maydonovitch CL, et al. Chronic proton pump inhibitor therapy associated with increased development of fundic gland polyps. Dig Dis Sci 2009;54:2617-2622.

[33] Choudhry U, Boyce HW, Coppola D. Proton pump inhibitor-associated gastric polyps: a retrospective analysis of their frequency, and endoscopic, histologic, and ultrastructural characteristics. Am J Clin Pathol 1998;110:615-621.

[34] Brunner G, Athmann C, Schneider A. Long-term, open-label trial: safety and efficacy of continuous maintenance treatment with pantoprazole for up to 15 years in severe acid-peptic disease. Aliment Pharmacol Ther 2012;36:37-47.

[35] Wennerström ECM, Simonsen J, Camargo MC, Rabkin CS. Acid-suppressing therapies and subsite-specific risk of stomach cancer. Br J Cancer 2017;116:1234-1238.

[36] KS, Chan EW, Wong AYS, Chen L, Wong ICK, Leung WK. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study. Gut 2018;67:28-35.

[37] Yu T, Tang Y, Jiang L, Zheng Y, Xiong W, Lin L. Proton pump inhibitor therapy and its association with spontaneous bacterial peritonitis incidence and mortality: a meta-analysis. Dig Liver Dis 2016;48:353-359.

[38] Khan MA, Kamal S, Khan S, Lee WM, Howden CW. Systematic review and meta-analysis of the possible association between pharmacological gastric acid suppression and spontaneous bacterial peritonitis. Eur J Gastroenterol Hepatol 2015;27:1327-1336.

[39] Tadayuki Oshima and Hiroto Miwa. Potent Potassium-competitive Acid Blockers: A New Era for the Treatment of Acid-related Diseases.J Neurogastroenterol Motil. 2018 Jul; 24(3): 334–344. Published online 2018 Jul 12