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Review Article

A Review on Complications of the Prolonged Use of Proton Pump Inhibitors (PPIs) and Presenting a Case of Barrett's Esophagus

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Abstract

Background: Gastroesophageal reflux disease (GERD) is the most common among gastric disorders and treated by antacids especially proton pump inhibitors (PPIs). Though symptoms are reported to be controlled by PPIs, however the complications like barrettes esophagus, Cancers at GE junction are not studied and reported extensively. In view of symptomatic relief, the long, non-supervised, over the counter medication use has increased. Safety of such long-term has been attempted with the review of available evidence and presentation of a case.

Aim: To update available literature on the long-term use of PPIs and possible mechanisms behind adverse events.

Materials and Methods: A case of Barrette's esophagus was presented, with long-term use of PPIs. Detailed history taking of the case was done and another evidence synthesis was done on the effects of the long and short-term use of PPIs. The literature search using Medline, Scopus, Scholar on adverse effects of the use of PPIs was done which were language and date unrestricted.

Results: Studies report many adverse effects on short-term (up to 5 years of use, namely: clostridium associated diarrhea, bacterial peritonitis, cholecystitis, pyogenic liver, liver cirrhosis, pneumonia, esophageal inflammations, nocturnal breakthrough acid reflux, interstitial nephritis, drug interaction and nutritional deficiencies mainly of Vitamin B 12 and iron) and long-term use, namely: Concomitant dyspepsia, Barrettes esophagus, osteoporosis, dementia, hypomagnesia, cancers at GE junction.

Conclusion: The health care providers and community should be made cautious, larger cohort observational studies are also recommended for more evidence.

Keywords: Barrette's esophagus, GERD, Proton Pump Inhibitors

Background

Estimated Prevalence of Gastroesophageal Reflux Disease (GERD) is 18.1 to 27.8% in North-America, 8.8 to 25.9% in Europe, 2.5 to 7.8% in East Asia, 8.7 to 33.1% in the Middle East, 11.6% in Australia, and 23.0% in South America.[1] The proton pump inhibitors market is expected to register a compound annual growth rate (CAGR) of 5% during the forecast period of 2018-2023.[2] In India, there is lack of

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figures on use of antacids specially Proton Pump Inhibitors (PPIs), yet it is estimated as 2nd top-grossing medicine prescribed as well as consumed as over the counter medicine. PPIs with a total market share of 15.4 percent of prescriptions in the United States costing more than $10 billion US dollars. In India PPIs have been among the top 10 bestselling medicines for several years.[3]

How Long the Use of PPI is safe?

Cochrane reviews have reportedly found PPIs safe for short term use in hospital settings.[4-6] One study finds PPIs more efficacious in Asians as compared to Europe and America.[7] However, these reports have not followed observational cohort studies which are considered one of the best methods to study adverse effects of medications used in real-world settings.[8-10] The case reported in this paper prompted us to explore and review the issue of safety with prolonged PPIs use. It was observed that there is dearth of literature with proper study designs. So, this article also highlights need of meta-analyses of existing studies and further studies to fill the gap in literature.

The publications reporting that PPIs are safe in long term use, define long term up to 12 months. It is accepted even in papers advocating PPIs safety that very long term use up to 3 years is with side effects like vitamin B12 deficiency.[151] Though some papers report PPIs as gastro protective in management of GERD, there are strong evidences of it causing gastric atrophy and changing organism colonisation in stomach.[152] The side effects become more evident with increasing period of use of PPI beyond one year. After emergence of evidence from field level experiences, nowadays it has become concern, "safety of duration of use of PPIs" which was earlier not thought of. PPIs were being considered as harmless no matter how long one consumes it.

We are presenting herein a case to narrate it further with compilation of evidences of potentially serious side effects (table 1 and 2) with prolonged use of PPIs. In view of plenty of evidences of adverse events like gastric atrophy beyond one year use, vitamin B12 deficiency beyond 3 years of use, some complications within 6 months of use, further studies in the form of long-term cohort observation, meta-analysis on specific conditions with review of available literature is recommended.[145] Despite vast variety of opinion[146], rational use of PPI is surely warranted.[10, 147-150]

Case Description

This case is about 34 years old, vegetarian, nonalcoholic, nonsmoking male, who was healthy before 12 years when he first presented with hematemasis and pain in upper abdomen in the year 2006. First endoscopy revealed multi oesophageal ulcers with bleeding. There was no abnormal growth visible anywhere. Test for H. Pylori was positive. No significant family history of illness was present. He was treated with regimen of antibiotic, antacid-PPI, multivitamins and advised to continue with these medications for 5 more days on discharge.

However, patient continued the use of PPIs for more than 10 years almost continuously (Pantoprazole 40 mg once a day), as he felt relieved from symptoms.

During last 2 years he developed progressive dysphasia. He again underwent endoscopy in July 2018 and was found having stricturing growth adjacent to lumen at gastroesophageal (GE) junction. The histopathology of this exophytic growth (figure 1) was reported as Barrett's esophagus with low grade dysplasia. It was observed that endoscope was negotiable with maneuvering through irregular mass at GE junction with narrowing of lumen. Mucosa of fundus, body antrum, pylorus of stomach and duodenum was reported as normal.

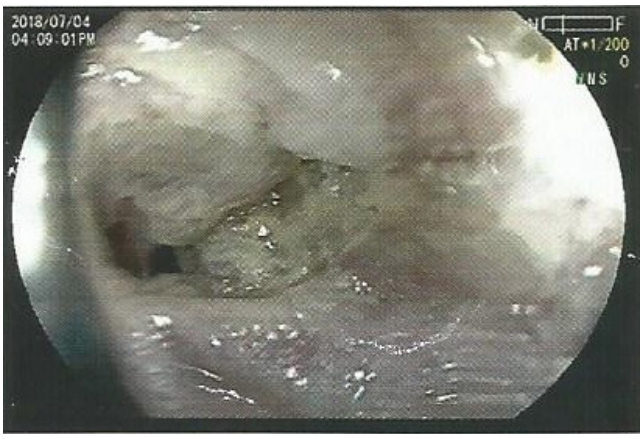

Figure 1.Stricturing growth at GE junction after 10 years use of PPI

Histopathological examination from biopsy of growth showed fragments of squamous epithelium with severe koilocytosis and neovascularization. Accompanying tissue showed gastric glands with acute on chronic inflammations and slough formation. Focal severe dysplasia was noted in glandular epithelium. Positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with computed tomography (^{18}F-FDG-PET/CT) showed mild prostatomegaly and raised FDG uptake at mucosal thickening involving GE junction with luminal narrowing along with diffuse increased uptake in bilateral adrenal gland with no obvious glandular lesion corresponding to plain CT image. Enhanced reactive inflammatory rise in uptake in mediastinal lymph nodes was also there. There was no other significant change seen in other organs.

This type of case is being reported first time, with so prolonged use of PPI in GERD for more than 10 years (occasionally discontinued for short durations but almost consistently during last 10 years). Patient was in follow-up for last 10 years from Government as well as Private Hospitals in Delhi, but both gave no warning or comment on his continued use of PPI for so long.

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The use of PPIs was first debated when it was reportedly found affecting anti-platelet function of clopidogrel in genotype CYPZC19.[11] Thereafter many studies reported various adverse events. Table 1 and 2 are summarizing commonest side effects and other published experimental, observational case control studies, cohort, meta-analysis, case reports and reviews available on pub-med registered journals, scholar, using key words of "short term use of proton pump inhibitors/PPIs", long term use of proton pump inhibitors/PPIs, side effects and adverse effects of proton pump inhibitors/PPIs. Reports of adverse reactions with up to 5 years use are given in Table 1 and longer than 5 years are in Table 2.

Table 1.Short term use of PPI: adverse effect reported with/after up to 5 year's use

Side/adverse effect with short term use	Reference
Rise in clostridium difficile associated diarrhea	Am J Gastroenterology 2008[12], Am Journal of Gastroenterology 2012[13], Gut Liver 2016[14], Clin Infect Dis. 2015[15], Am J Gastroenterol 2012[16], Curr Opin Gastroenterol. 2012[17]
Enhanced spontaneous bacterial peritonitis (SBP) and complications of cirrhosis in PPI users	Gut 2016[18], Aliment Pharmacol Ther 2012[19], Eur J Intern Med 2016[20]
Small intestinal bacteria overgrowth during PPI therapy	Clinical Gastroenterology and Hepatology, 2010[21], Clin Gastroenterol Hepatol 2007[22], Eur J Clin Invest 2011[23], Am J Gastroenterol 2015[24]
Increased risk of cholecystitis	Gut 2018[25]
Liver abscess-cryptogenic liver abscess and pyogenic liver abscess, hepatitis	Aliment Pharmacol Ther 2015[26], Gastroenterology 2017[27]
Liver cirrhosis among PPI users	Eur J Clin Pharmacol 2017[28]
Pneumonia cases, more with PPI users	PLoS One, 2017[29], Annals of Neurology 2014[30], Ann Intern Med 2008[31], Medicine (Baltimore) 2015[32], JAMA 2004[33]
Esophageal inflammation, eosinophilia	Clin Infect Dis 2017[34], Aliment Pharmacol Ther 2012[35], JAMA Intern Med 2014[36], Respir Med 2015[37]
Nocturnal breakthrough acid reflux	Aliment Pharmacol Ther 2000[38]
Interstitial Nephritis, Chronic Kidney disease	Canadian Medical Association Journal 2009[39], Aliment Pharmacol Ther. 2007[40], CMAJ Open 2015[41], JAMA Intern Med. 2016[42], J Am Soc Nephrol. 2016[43], Dig Dis Sci. 2017[44], JAMA Intern Med. 2016[45, 46]
Drug interactions	European Journal of Gastroenterology and Hepatology 1996[47], Aliment Pharmacol Ther. 2010[48], Clin Ther., 2016[49], Int J Cancer 2018[50], J Gastroenterol. 2013[51], JAMA Oncol. 2017[52], Case Rep Gastrointest Med. 2018[53, 54]
Nutritional Deficiencies- B12, Iron.	JAMA 2013[55], Gastroenterology 2017[56], Intern Med. 2018[57], Curr Ther Res Clin Exp. 2017[58], Geriatr Gerontol Int. 2017[59], Ned Tijdschr Geneeskd. 2016[60], Circ J. 2015[61], Intern Med. 2014[62], Expert Rev Clin Pharmacol. 2013[63], Ther Adv Drug Saf. 2013[64], Dig Dis Sci. 2011[65], Am J Ther. 2012[66], Pain Physician 2009[67], Rev Prat. 2008[68, 69], Dig Dis Sci. 2002[70], Adv Nutr. 2018[71], Gut, 2017[72], Eur Rev Med Pharmacol Sci., 2015[73], Intern Med J. 2015[74], JAMA 2013[75], Georgian Med News 2012[76], Diabetes Care 2012[77], J Nutr Elder. 2010[78], Aliment Pharmacol Ther. 2008[79], J Am Med Dir Assoc. 2008[80], J Clin Epidemiol. 2004[81], Ann Pharmacother. 2002[82], Aliment Pharmacol Ther. 1999[83], Aliment Pharmacol Ther. 1999[84], J Intern Med. 1996[85], J Am Coll Nutr. 1994[86], Ann Intern Med. 1994[87]
Headache, visual disturbances	Cephalalgia 2015[88]

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Table 2.Long term adverse effect reported with 10 year's use of PPI

Side/adverse effects of long-term PPI use	References
Concomitant dyspepsia, stroke, suppression of acid reflux leading to Barrett's, ulcer deaths reduced but non-ulcer deaths increased.	Neurogastroenterol Motil. 2011[89], Digestion 2017[90], Am J Gastroenterol. 2017[91]
Osteoporosis, hip/bone fracture	JAMA 2006[92], Calcify Tissue Int. 2014[93], www.fda.gov 2015[100], Osteoporos Int. 2015[94], Bone 2011[95], Pharmacoepidemiol Drug Saf. 2010[96], Gastroenterology 2010[97]
Dementia	JAMA Neurol. 2016[98], J Am Geriatr Soc. 2017[99]
Hypomagnesia	www.fda.gov. 2015[100], Aliment Pharmacol Ther. 2012[101], Am J Kidney Dis. 2015[102], Mol Pharm. 2012[103], PLoS One 2015[104], Am J Kidney Dis. 2010[105], Am J Kidney Dis. 2015[106], PLoS Med. 2014[107]
Gastro esophageal cancer/other cancers	JAMA 2017[108], Eur J Gastroenterol Hepatol. 2005[109], Aliment Pharmacol Ther. 2004[110], Br J Cancer 2009[111], Aliment Pharmacol Ther. 2018[112], Am J Gastroenterol. 2008[113], Front Pharmacol. 2018[114], Gut 2018[115], Aliment Pharmacol Ther. 2018[116], Pharmacoepidemiol Drug Saf. 2009[117], Int J Cancer 2016[118, 119]

Discussion

Possible cause of the reaction seen in the case presented here was explored and found published mechanism which says that the changes in GE Mucosa after prolong use of PPIs can happen as result from the removal of the low pH barrier between upper GI tract bacteria and the lower gut leading to bile salts acting as constant irritant to GE junction.[120] Various bile acids (BA) may cause intestinal metaplasia, which is yet to be elucidated for more detailed mechanism. In vitro evidence suggests that the secondary BA, deoxycholic acid, and lithocholic acid, are more potent inducers of intestinal metaplasia. Secondary BA is formed by intestinal microbiota in the terminal ileum and the anaerobic bacteria in the colon, which are distal to the foregut and require a neutral pH environment. Secondary BA has poor solubility, and their inability to ionize at the gastric pH, largely prevents them from reaching the esophagus in sufficient quantities to induce metaplasia.[121]

The effectiveness of PPIs in controlling acid-related symptoms has resulted in their widespread use. However, in such an environment, the majority of bile salts, most likely glycoconjugates, potentially, may ionize and mobilize upstream into the esophagus.[122] Thus, patients on long-term PPI treatment, and with a dysfunctional lower esophageal sphincter, may be at increased risk for Barrett's esophagus and esophageal adenocarcinoma.[121]

Possible cause and role of hyper intake at Adrenal gland in the presented case should be subjected to further research and review as there is no precedent report observing increased uptake of FDG-18 by adrenal gland. However, adrenal gland is the choice of seat for metastasis from adenocarcinoma but it may be reactive hyperactive adrenal gland too, so needs to be regularly followed-up in such cases.[122]

As antacids, oral PPIs are reported with greater efficacy than histamine H_2-receptor antagonists for the initial and maintenance treatment of GERD.[36] In addition, PPIs has been shown to improve the quality of life of patients with GERD and is associated with high levels of patient satisfaction with therapy.[36] The Food and Drug Administration (FDA) approved indications for PPI uses are: duodenal ulcer, erosive esophagitis, GERD, and gastric ulcer. For duration, maximum 2 weeks use in one time (though may repeat after 4 months) is the recommended-on duration of use by FD[10], but overuse is quite rampant as is evident from the side effects reporting studies with long term use of PPIs. Controlled studies have provided only 12 months use data to FDA.[123] But now post marketing data from various studies is also available as listed in Table 1 and 2.

The treatment of GERD with PPIs is reported to improve symptoms and health-related quality of life outcomes.[124] GERD patients are reported developing histopathological changes such as Barrett's esophagus[125], significant risk for esophageal adenocarcinoma[126] however, treatment information with PPIs use are not taken in to account in these reporting's. The incidence of GERD has progressively increased in Western industrialized nations; incidence of esophageal adenocarcinoma is also rising. Adenocarcinoma was reported among 26 per 100,000 person-years among patients with previously diagnosed erosive esophagitis against quite lower - 2.79 per 100,000 person-years in the general population in a Danish study.[138] PPIs came in use for management of erosive esophagitis since it proved to be better in comparisons with ranitidine[36], patients receiving pantoprazole 40 mg daily were significantly more likely to remain in remission (after 12 month's use) than patients receiving ranitidine daily.[36] On the duration for use there are few studies showing quite good safety too with prolonged use of PPIs. For example, two trials are there, reporting

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data for treatment with oral Pantoprazole for up to 3 years which reported only 4 of 111 patients having adverse events which were definitely related to Pantoprazole.[19, 128] The another 10-years study (long term), in which maintenance therapy with Pantoprazole 40 mg to 160 mg daily was found well tolerated in patients with healed peptic ulcers or erosive Esophagitis.[144, 146] These studies report that there were no increases in signs associated with an enhanced risk of gastric cancer, although fasting serum gastrin levels increased slightly after the second year of treatment. Of 536 patients originally enrolled in one long-term study, 99 patients were treated with Pantoprazole for at least 5 years, and 25 reported completing 10 years of treatment with no adverse event.[127]

Majority studies show complete relief of GERD-related symptoms with PPIs in the patients with erosive reflux disease ERD and non-erosive reflux disease NERD but are of only 4 to 8 weeks is the duration of study.[128]

The majority of patients with erosive esophagitis relapse when treatment is stopped (about 75 percent at one year).[128] Relapse is markedly reduced to 20 to 25 percent by daily maintenance treatment with proton pump blockers.[128] A report from Italy shows 40% Proton pump inhibitor resistance[129] and high relapse rates after cessation of treatment.[130] Mild disease relapses less often[128], so long term therapy by intermittent treatment may prove acceptable and more cost-effective than maintenance treatment. This strategy remains unexplored in trials and requires further study.[131]

About the knowledge attitude and practices regarding long term safety of PPIs among doctors in India, a study on prescription pattern on the use of PPIs reported that fifty resident doctors responded to the questionnaire. Thirty-six percent reported prescribing acid suppressive drugs for majority of their patients and 12% prescribed them to almost all patients they attended. Acute gastritis was the most common indication for prescribing PPI/H_2 blockers (50%). The majority of respondents (92%) regarded PPIs as their first choice in acid suppressive agents and 58% administered it through intravenous route. Knowledge about PPI related adverse effects was low. Similar situation is reported from their counterparts in developed countries.[132]

The rise of about 456% by 1997 with PPI use is reported since its first introduction (Omeprazole) in the late 1980s.[133] In the United Kingdom, the total number of prescriptions for PPIs in the ambulatory setting increased 10-fold between 1991 and 1995. USA Health data PPIs increased from 146 million in 2009 to 164 million in 2013 (the 8th position on the list of the top therapeutic classes by prescriptions).[134] Studies report pattern of use of PPI in different setups-on admission; 82.62%, during hospitalization; and 54.75%, at discharge; and incorrect indications for PPIs were found in 74.47%, 61.25%, and 80.24% of the cases, respectively.[134] For PPIs the 1year unjustified costs, calculated with reference to the lowest prices, were estimated to be more than 2 million United States dollars, contributing to the increasing expenditures of the health care system.[135]

There are studies reporting long term use of PPIs on barrettes however not many report developments of barrettes and histological complications during use of PPIs. Now it is considered that islands of squamous cell among barrettes mucosa, are not sign of recovery.[136, 137] Despite some new adverse event confirmed with PPI uses like a mild increased risk of vitamin B_{12} deficiency and chronic kidney disease, and a moderate increase in the risk of rebound hyper secretion, small intestinal bacterial overgrowth, and enteric infections, including Clostridium difficile. PPI's link with dementia and spontaneous bacterial peritonitis is not clear and requires further investigation.[138] PPIs are not recommended in breast-feeding mothers.[139] And caution is recommended in view of reports of asthma in children on antenatal use.[140, 141]

PPI use significantly increased the presence of Streptococcaceae and Enterococcaceae, which are risk factors for C. difficile infection, and decreased that of Faecalibacterium, a commensal anti-inflammatory microorganism.[142] Long-term PPI use has included: carcinoid formation; development of gastric adenocarcinoma (especially in patients with Helicobacter pylori infection); bacterial overgrowth; enteric infections; and malabsorption of fat, minerals, and vitamins.[143] Vitamin B12 concentration may be decreased when gastric acid is markedly suppressed for prolonged periods (e.g. Zollinger-Ellison syndrome), PPIs appear to increase susceptibility to the bacterial enteropathogens: Salmonella, Campylobacter jejuni, invasive strains of Escherichia coli, vegetative cells of Clostridium difficile, Vibrio cholerae and Listeria by PPI use, with adjusted relative risk ranges of 4.2-8.3 (two studies); 3.5-11.7 (four studies); and 1.2-5.0 (17 of 27 studies) for the three respective organisms.[144]

Conclusion

There is need to add advisory of potential harms with prolonged use of PPIs, so that its benefits are not surpassed by dangerous outcomes. There is need to generate retrospective cohort studies with various side effects reported in this paper, specially in carcinoma oesophagus cases to further define safety limits of duration of use of PPIs.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of Interest: None

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