ADVERSE RISKS ASSOCIATED WITH PROTON PUMP INHIBITORS: REVIEW

Suresh.p¹, Mounika.r¹, Venkatesh.j¹, Satyanarayana.v², J.N.Suresh kumar³

1. V Pharm.D Students, Narasaraopeta Institute of Pharmaceutical Sciences, Narasaraopet, Guntur (Dt), Andhra Pradesh, India-522601.
2. Assistant Professor, Department of Pharmacy Practice, Narasaraopeta Institute of Pharmaceutical Sciences, Narasaraopet, Guntur (Dt), Andhra Pradesh, India-522601.
3. Principal, Department of Pharmaceutics, Narasaraopeta Institute of Pharmaceutical Sciences, Narasaraopet, Guntur (Dt), Andhra Pradesh, India-522601.

ABSTRACT

Proton pump inhibitors (PPIs) are among the most commonly utilized agents for treatment of symptomatic disorders of the upper gastrointestinal tract, accounting for a significant proportion of sales of both over-the-counter and prescription formulations. A systematic review of the literature was conducted via MEDLINE to evaluate the most rigorous studies linking the potential risk of PPI therapy with adverse events. Emerging data illustrate the potential risks associated with both short- and long-term PPI therapy including clostridium difficile-associated diarrhea, community-acquired pneumonia, osteoporotic fracture, vitamin B12 deficiency, and inhibition of antiplatelet therapy. Due to these associations, it is recommended that clinicians assess the continuing need for PPI therapy and use the lowest possible dose to achieve the desired therapeutic goals.

key words: Proton pump inhibitors, osteoporotic fracture, vitamin B12 deficiency, clostridium difficile-associated diarrhea.

Corresponding Author:
Mr.V. Satyanarayana,M.Pharm(Ph.D)
Assistant Professor, Department of Pharmacy Practice,
Narasaraopeta Institute of Pharmaceutical Sciences,
Narasaraopet, Guntur(Dt), A.P. India-522601.

PROTON PUMP INHIBITORS:

Proton pump inhibitors are a group of drugs whose main action is a pronounced and long-lasting reduction of gastric acid production. within the class of medications, there is no clear evidence that one agent works better than other [1]

MECHANISM OF ACTION:

Proton pump inhibitors act by irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system(the H+/K+ATPase or more commonly the gastric proton pump)of the gastric parietal cells [2]

Available proton pump inhibitors:
Omeprazole
Lansoprazole
Dexlansoprazole
Rabeprazole
Pantoprazole
Esomeprazole
**THERAPEUTIC USES OF PPIs:**
These drugs are used in the treatment of many conditions, such as:

1. **Dyspepsia**[^3]
2. Peptic ulcer disease including after endoscopic treatment for bleeding[^4]
3. As part of helicobacter pylori eradication therapy[^5]
4. Gastro esophageal reflux disease (GERD or GORD) including symptomatic endoscopic negative reflux disease[^6] and associated laryngopharyngeal reflux causing laryngitis[^7] and chronic cough[^8]
5. Barrett's esophagus[^9]
6. Esophagitis[^10]
8. Gastrinomas and other conditions that cause hyper secretory of acid including Zollinger–Ellison Syndrome (often 2-3x the regular dose is required)^[^12]

**MANAGEMENT:**

1. **Erosive esophagitis associated with GERD:**
   - Maximum duration of therapy up to 8 weeks per oral once in a day. Iv route 7 to 10 days[^13]
2. Gastrinomas and other conditions that cause hyper secretory of acid including Zollinger–Ellison Syndrome[^14]

**Oral:** Short-term (up to 8 week) treatment and maintenance of heeling of erosive esophagitis associated with GERD; reduction and relapse rates of day time and night time heart burn symptoms in GERD hyper secretory disorders associated with Zollinger–Ellison syndrome or other GI hyper secretory disorders.

**I.V:** Short term treatment (7 to 10 days) of patients with GERD and a history of erosive esophagitis; hyper secretory disorders associated with Zollinger–Ellison syndrome or other GI hyper secretory disorders.

3. **Helicobacter pylori eradication therapy:**[^15]

   **Non penicillin allergy:** 40 mg twice daily administrated with amoxicillin 1000 mg and clarithromycin 500 mg twice daily for 10-14 days

   **Penicillin allergy:** 40 mg twice daily administered with clarithromycin 500 mg and metronidazole 500 mg twice daily for 10-14 days or 40 mg once or twice daily administered with bismuth subsalicylate 525 mg and metronidazole 250 mg plus tetracycline 500 mg 4 times daily for 10-14 days.

4. **Peptic ulcer disease:**[^16]

   **Oral:** Treatment: 40 mg once daily for 2 weeks (duodenal ulcer) or 4 weeks (gastric ulcer); may extend therapy for an additional 2 or 4 weeks (based on indication) for inadequate healing

   Peptic ulcer disease (Canadian labeling): Oral: Treatment: 40 mg once daily for 2 weeks (duodenal ulcer) or 4 weeks (gastric ulcer); may extend therapy for an additional 2 or 4 weeks (based on indication) for inadequate healing

5. **Prevention of GI lesions associated with NSAID use:**[^17]

   Pantoprazole Oral: 20 mg once daily
6. Dyspepsia.\cite{18} Traditional therapies used for this diagnosis include lifestyle modifications, antacids, H2-receptor antagonists (H2-RAs), prokinetic agents, and antiflatulents. It has been noted that one of the most frustrating aspects of treating functional dyspepsia is that these traditional agents have been shown efficacy.

**ADVERSE EFFECTS OF PPIS:**

**Clostridium difficile-associated diarrhea (CDAD):**\cite{19} Use of proton pump inhibitors (PPIs) may increase risk of CDAD, especially in hospitalized patients; consider CDAD diagnosis in patients with persistent diarrhea that does not improve. Use the lowest dose and shortest duration of PPI therapy appropriate for the condition being treated.

**Fractures:**\cite{20} Increased incidence of osteoporosis-related bone fractures of the hip, spine, or wrist may occur with proton pump inhibitor (PPI) therapy. Patients on high-dose or long-term therapy (≥1 year) should be monitored. Use the lowest effective dose for the shortest duration of time, use vitamin D and calcium supplementation, and follow appropriate guidelines to reduce risk of fractures in patients at risk.

**Vitamin B12 malabsorption:**\cite{21} Prolonged treatment (typically >3 years) may lead to vitamin B12 malabsorption and subsequent deficiency.

**CONCLUSION:**

PPIs have many revolutionized for many upper gastro intestinal disorders. Appropriate utilization of these drugs for appropriate diagnosis, periodic reassessment of patients' symptoms to determine the lowest effective doses and duration of therapy, as well as close surveillance for potential adverse risks, will maximize favorable outcomes.

**Table 1.** Studies With Validated Outcomes Demonstrating Risk With Use Of PPIs.\cite{22}
<table>
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<th>STUDY DESIGN</th>
<th>POPULATION</th>
<th>OUTCOMES</th>
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| Clostridium difficile-associated diarrhea | United Kingdom; Hospitalized patients | Risk associated with PPI use within preceding 8 weeks  
Risk associated with PPI use plus antibiotics  
Risk associated with PPI use; antibiotics and chemotherapy |
| Cohort                        | Montreal, Canada: Hospitalized patients who received antibiotics | Risk associate with current PPI use  
Risk associate with receipt of 3 or more antibiotics  
Risk associate with being on a medical versus surgical ward |
| 2 population based Case control studies | United Kingdom; all cases in database and a subgroup of non hospitalized patients | Risk associated with current PPI use  
Risk associated with inflammatory bowel disease  
Risk associated with renal failure |
| Prospective case control study | United Kingdom; hospitalized patients | Risk associated with antibiotic therapy  
Risk associated with acid suppression therapy |
| Case-control                  | United States; hospitalized Patients | Risk associated with PPI use prior to or during admission |
| Case-control                  | United States; hospitalized Patients | Risk associated with PPI use  
Risk associated with renal failure |
| Systematic review             | Meta-analysis                      | Odds of taking anti-secretory therapy among patients infected with C. difficile  
Risk associated with PPI use  
Risk associated with H2RA use |
| Community-acquired pneumonia  | The Netherlands; outpatients        | Risk with any current acid-suppressive therapy  
Risk among persons currently using PPIs  
Risk among persons currently using H2RAs |
| Case-control                  | Denmark; hospitalized Patients     | Risk with current use of PPIs  
Risk with initiation of PPIs 0–7 days prior to diagnosis  
Risk when PPI was started >3 months prior to diagnosis |
| Nested case control           | United Kingdom; UK GPRD            | Risk associated with current PPI use  
Risk associated with current PPI therapy started:  
– within 2 days of diagnosis  
– within 7 days of diagnosis  
– within 14 days of diagnosis |
| Bone fracture                 | United Kingdom; UK GPRD            | Risk of hip fracture with PPI therapy >1 year  
Risk of hip fracture with >1.75 average daily-dose PPI |
| Case-control                  | Denmark; community-based           | Risk of any fracture with PPI use within last year  
Risk of hip fracture with PPI use within last year  
Risk of spine fracture with PPI use within last year |
| Retrospective matched cohort  | Manitoba, Canada; community-based | Risk of hip fracture after 5+ years of PPI use  
Risk of hip fracture after 7+ years of PPI use  
Risk of any osteoporosis-related fracture after 7+ years of PPI use |
| Vitamin B12 deficiency        | United States; university-based    | Risk associated with past use of PPI/H2RA  
Risk associated with use of PPI/H2RA for <12 months  
Risk associated with use of PPI/H2RA for ≥12 months |

GPRD=General Practice Research Database; H2RA=Histamine-2 receptor antagonist; PPIs=Proton pump inhibitor.

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