Over 30 Years of Omeprazole

Praveen Sharma*

Received: 08 May 2023; Accepted: 29 June 2023

ABSTRACT

Background: In the last 3 decades, omeprazole has proved its mettle in managing acid peptic diseases (APDs). It has established itself as the first line of therapy for duodenal and gastric ulcers, gastroesophageal reflux disease (GERD), ulcers due to nonsteroidal anti-inflammatory drugs (NSAIDs), and Zollinger-Ellison syndrome (ZES). The superiority of PPIs over other drugs is due to their 15–20 hours a day. Additionally, they are longer-acting than the placebo.6 Similarly, a systematic review comparing PPIs, H2RAs, potassium-competitive acid blockers, and alginates in a pooled analysis of RCTs and 45,964 patients that compared the efficacy of 40 mg omeprazole once daily (OD), 80 mg pantoprazole OD, and 80 mg famotidine OD found that omeprazole had the best performance in both symptom relief and drug tolerance. Omeprazole (20 mg) was 10 times more effective in healing and four times more effective in symptom relief than a placebo in patients with GERD; patients also had a 39% greater tolerance to the drug than the placebo.5 Similarly, a systematic review comparing PPIs, H2RAs, potassium-competitive acid blockers, and alginates in treating reflux disease demonstrated that omeprazole (20 mg OD; taken for 2–4 weeks) ranks first in complete symptom relief.7 Omeprazole strongly inhibits gastric acid secretion without serious adverse effects. A study evaluating the effectiveness of quadruple therapy for 2 weeks with bismuth subcitrate, antibiotics, and omeprazole (20 mg) indicated that the regimen could effectively eradicate Helicobacter pylori (H. pylori) and that the treated individuals tolerated this regimen well.8 In a systematic review of the safety and effectiveness of omeprazole and lansoprazole in managing GERD, four studies demonstrated that omeprazole (40 mg) was significantly more effective than lansoprazole (30 mg) in raising gastric pH (p < 0.05) and that the effects of omeprazole lasted for a longer time than those of lansoprazole.4 Omeprazole was also observed to be more effective than H2RAs in healing ulcers in patients with diabetes, with an established safety profile in these patients.11 This review aims to explore the aspects of omeprazole that make it unique; these include its effectiveness in preventing nocturnal breakthroughs, rapid action, and antioxidant effects. In addition, this review also aims to evaluate the use of omeprazole in treating patients with comorbidities. Omeprazole was first discovered 30 years ago.9 Servier, a pharmaceutical company from France, reported the antisecretory activities of CMN 131, a thioacetamide derivative; however, most thioacetamide derivatives showed acute toxicity in animals. Later, scientists in Häsle, Sweden, investigated other structural analogs of these molecules that showed no toxicity. These scientists hypothesized that the thioamide group in the molecules was responsible for toxicity and added a

INTRODUCTION, BACKGROUND, AND HISTORY

Acid peptic disease (APD) is a group of conditions where the impaired gastric mucosa has been damaged by gastric acid. Gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD) belong to this group of conditions. Individuals with APD have an impaired quality of life (QoL) along with significant morbidity and mortality.1

Gastric acid secretion is a complex process coordinated by various stimuli. Histamine, gastrin, and postganglionic muscarinic acetylcholine regulate this process. Although anticholinergics and histamine 2 receptor antagonists (H2RAs) are used to manage gastric hypersecretion, proton pump inhibitors (PPIs) are more effective as they block the acid pump response to all types of parietal cell stimulation. They are longer-acting than H2RA and can maintain a pH of >4 for 15–20 hours a day. Additionally, they are effective against a postprandial and nocturnal rise in gastric acid. Therefore, PPIs are pivotal in managing a plethora of gastric conditions, such as esophagitis, PUD, nonerosive reflux disease (NERD), ulcers caused by nonsteroidal anti-inflammatory drugs (NSAIDs), functional dyspepsia, and Zollinger-Ellison syndrome (ZES).9 A meta-analysis of 19 trials in NERD patients has shown that PPIs are superior to prokinetics and H2RAs against heartburn.3 The superiority of PPIs over other drugs in acid suppression, healing of ulcers, and symptom relief makes them the mainstay of APD management.1

The various PPIs that are currently available are omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole, of which omeprazole and lansoprazole have been in use for the longest time.4 It is essential for health professionals to possess a thorough knowledge of the indications and dosages of these drugs. Omeprazole is the most used and the most cost-effective of all.3 A meta-analysis of 98 randomized controlled trials (RCTs) and 45,964 patients that compared the efficacy of 40 mg omeprazole once daily (OD), 80 mg pantoprazole OD, and 80 mg famotidine OD found that omeprazole had the best performance in both symptom relief and drug tolerance. Omeprazole (20 mg) was 10 times more effective in healing and four times more effective in symptom relief than a placebo in patients with GERD; patients also had a 39% greater tolerance to the drug than the placebo.5 Similarly, a systematic review comparing PPIs, H2RAs, potassium-competitive acid blockers, and alginates in treating reflux disease demonstrated that omeprazole (20 mg OD; taken for 2–4 weeks) ranks first in complete symptom relief.7 Omeprazole strongly inhibits gastric acid secretion without serious adverse effects. A study evaluating the effectiveness of quadruple therapy for 2 weeks with bismuth subcitrate, antibiotics, and omeprazole (20 mg) indicated that the regimen could effectively eradicate Helicobacter pylori (H. pylori) and that the treated individuals tolerated this regimen well.8 In a systematic review of the safety and effectiveness of omeprazole and lansoprazole in managing GERD, four studies demonstrated that omeprazole (40 mg) was significantly more effective than lansoprazole (30 mg) in raising gastric pH (p < 0.05) and that the effects of omeprazole lasted for a longer time than those of lansoprazole.4 Omeprazole was also observed to be more effective than H2RAs in healing ulcers in a pooled analysis of RCTs. When used for maintenance therapy, no relapses occurred, and tolerance to omeprazole was good. In addition, omeprazole was found to be effective in patients refractory to H2RAs, with individuals experiencing relief from the very first day of treatment.7

Omeprazole can be used to treat various conditions such as GERD, duodenal, and gastric ulcers, ulcers infected with H. pylori, ulcers due to NSAIDs, and ZES.9 However, apart from these conventional uses, omeprazole has also been repurposed for use in treating coronavirus disease 2019 (COVID-19) as it is hypothesized to inhibit viral replication.10 In addition, when patients with diabetes were given hypoglycemic agents along with omeprazole, better glycemic control was achieved than when the hypoglycemic agents were taken alone. There seems to be some potential for the use of omeprazole in patients with diabetes, with an established safety profile in these patients.11 This review aims to explore the aspects of omeprazole that make it unique; these include its effectiveness in preventing nocturnal breakthroughs, rapid action, and antioxidant effects. In addition, this review also aims to evaluate the use of omeprazole in treating individuals with comorbidities.

Omeprazole was first discovered 30 years ago.9 Servier, a pharmaceutical company from France, reported the antisecretory activities of CMN 131, a thioacetamide derivative; however, most thioacetamide derivatives showed acute toxicity in animals. Later, scientists in Häsle, Sweden, investigated other structural analogs of these molecules that showed no toxicity. These scientists hypothesized that the thioamide group in the molecules was responsible for toxicity and added a
A Review of Omeprazole

The introduction of omeprazole as a drug to treat APDs was followed by the invention of six other PPIs varying slightly in their structures and having similar efficacies as omeprazole in controlling heartburn, healing erosive esophagitis, and reducing relapses of erosive esophagitis. Despite the introduction of newer PPIs, omeprazole has remained relevant and the most studied drug in the clinical management of APD.

Currently, India exports omeprazole to >158 countries. Between April 2020 and November 2022, India exported 163.88 million USD worth of omeprazole. This is equivalent to roughly 4,323,030 tablets, demonstrating the extensive use of and demand for omeprazole.

Mechanism of Action
Omeprazole inhibits the parietal cell H⁺K⁺-ATPase, which leads to the suppression of acid secretion. The inhibitory effects set in rapidly, within 1–2 hours of administration, and continue for approximately 72 hours; once the administration of omeprazole is stopped, the baseline activity of the H⁺K⁺-ATP pump returns to normal within 5 days (Fig. 2). Intake of food delays the absorption of omeprazole (as the area under the plasmic curve [AUC] is reduced), increases absorption variability, and decreases the maximum concentration of the drug in the stomach; therefore, administration under fasting conditions is recommended.

As PPIs are prodrugs, they need to be activated in the secretory canaliculi of parietal cells to inhibit the H⁺K⁺-ATP pump. Since food affects omeprazole bioavailability, the drug is administered 30 minutes to one hour before a meal.

Omeprazole is metabolized by the hepatic cytochrome P₄₅₀ (CYP) enzyme and is excreted in the urine. It has a half-life of 30 minutes to one hour in healthy individuals and 3 hours in those who are hepatically impaired. Nevertheless, the pharmacological effects of omeprazole last much longer as it is preferentially accumulated in the parietal cells and binds covalently with H⁺K⁺-ATPase.

Omeprazole was found to increase the gastric pH to a greater extent in CYP2C19-poor metabolizers (PMs) than in early metabolizers (EMs). In PM, the phenotype is common in the Chinese population; therefore, omeprazole was found to be more effective in reducing bleeding in peptic ulcers in the Chinese population.

In contrast, the Clinical Pharmacogenetics Implementation Consortium guidelines for PPI dosing and CYP2C19 mention that PPIs were less effective in normal metabolizers in the Asian population, who, thus, require higher doses of the drug. A study in Tamil Nadu, India, phenotypically classified individuals as EMs, heterozygous EMs, PMs, heterozygous ultra-metabolizers, and ultra-metabolizers.

Pharmacokinetics of Omeprazole
The bioavailability of omeprazole (20–40 mg OD) is 30–40%. Omeprazole attains peak plasma concentrations in 0.5–3.5 hours which increases proportionally up to a dose of 40 mg. Doses >40 mg show a nonlinear increase in peak plasma concentration and AUC due to the saturation of the first-pass effect above 40 mg. Despite the nonlinear relationship between AUC and the inhibition of gastric acid release at doses >40 mg, the AUC leads to the suppression of acid secretion.

Evolution of omeprazole

In 1960, Hinsle in Malmö, Sweden, conducted experiments on local anesthesia that could be taken orally and exhibit its action on gastric cells. Experiments were performed on local anesthesia that could be taken orally and exhibit its action on gastric cells.

The double bounded sulfur and it severely toxic.

The sulfur atom of the thioamide group was masked by incorporating it into a ring system, creating H116/05 and H116/15.

Thymus and thymus toxicity of five structures led to development of picoprazole.

Thymus and thymus toxicity of five structures led to development of picoprazole.

It was the most powerful inhibitor of gastric acid secretion without adversely affecting thyroid, thymus, or any other toxicity.

Picoprazole and E. Omeprazole

A. Picoprazole and E. Omeprazole

Fig. 1: Evolution of omeprazole

Journal of the Association of Physicians of India, Volume 71 Issue 8 (August 2023)
Omeprazole is as effective as pantoprazole and lansoprazole and superior to cisapride, cimetidine, or ranitidine in promoting healing in patients with acute GERD with esophagitis. Patients are treated with 20 mg omeprazole (OD) for 4–8 weeks.

Pathological hypersecretory conditions such as ZES: Though surgical excision of the neuroendocrine tumor remains the mainstay in patients with ZES, medical management of acid peptic complications in these patients is necessary as they experience a constitutive release of gastrin. Gastric hypersecretion can be managed by the use of PPIs. A longitudinal study demonstrated the safety and effectiveness of omeprazole when administered for a period of up to 4 years in patients with ZES. Patients are treated with 60 mg omeprazole (OD); however, dosage and duration vary based on the clinical situation and patient response.

Maintenance of acid-mediated GERD-led erosive esophagitis: Omeprazole alone or combined with cisapride as maintenance therapy for 12 months was significantly more effective in maintaining endoscopic remission than cisapride alone (p = 0.003), ranitidine alone (p < 0.001) or ranitidine and cisapride combined (p = 0.003) after a year of maintenance therapy. Patients are prescribed 20 mg omeprazole (OD) for 4–8 weeks.

Heliocobacter pylori (H. pylori) eradication: It has been established that H. pylori is one of the etiological factors associated with gastroduodenal ulcer disease. A high level of evidence supports the use of PPIs along with antibiotics to effectively eradicate H. pylori. Omeprazole eradicates H. pylori by a urease-independent mechanism by inhibiting the growth of the organism at a low pH. Studies have demonstrated that omeprazole as triple therapy (with two antibiotics) is more effective against H. pylori than lansoprazole, ranitidine, or bismuth. The therapy aims to reduce the risk of recurrence of duodenal ulcers. Omeprazole is prescribed concomitantly with antibiotics as dual therapy (40 mg omeprazole (OD) with clarithromycin (500 mg) thrice a day for 10 days) or triple therapy (20 mg omeprazole with amoxicillin (1000 mg) and clarithromycin (500 mg), all prescribed three times a day for 10 days).

Symptomatic GERD: Damage to the esophageal mucosa is noticed in GERD due to the reflux of the gastric contents into the esophagus. The prevalence of GERD in Indian patients is around 7.6%. Omeprazole has shown rapid and better symptom relief than cisapride, ranitidine, and placebo in symptomatic GERD. Omeprazole (20 mg OD) is prescribed for up to 4 weeks to reduce pain, inflammation, and heartburn.

Active duodenal ulcers: Omeprazole has shown greater healing of duodenal and gastric ulcers over 2 weeks as compared to cimetidine and ranitidine. Omeprazole (20 mg OD) is prescribed for 4 weeks, and if found refractory, the same dosage is continued for another 4 weeks.

Active benign gastric ulcers: Patients with PUD refractory to high-dose, 450 mg, ranitidine OD have demonstrated healing of ulcers with the administration of 40 mg omeprazole (OD) for a period of 2–8 weeks. Bleeding of the upper gastrointestinal tract from PUD results in significant mortality, morbidity, and healthcare expenses. Early administration of PPIs has been associated with a reduction in the proportion of patients with rebleeding ulcers and the need for surgery. Patients are treated with 40 mg omeprazole (OD) for 4–8 weeks.

Acid-mediated GERD-led erosive esophagitis: More rapid healing and symptom resolution is observed in patients with esophagitis who were administered PPIs when compared to those on H2RA or prokinetics. Omeprazole is as effective as pantoprazole and lansoprazole and superior to cisapride, cimetidine, or ranitidine in promoting healing in patients with acute GERD with esophagitis. Patients are treated with 20 mg omeprazole (OD) for 4–8 weeks.

Pathological hypersecretory conditions such as ZES: Though surgical excision of the neuroendocrine tumor remains the mainstay in patients with ZES, medical management of acid peptic complications in these patients is necessary as they experience a constitutive release of gastrin. Gastric hypersecretion can be managed by the use of PPIs. A longitudinal study demonstrated the safety and effectiveness of omeprazole when administered for a period of up to 4 years in patients with ZES. Patients are treated with 60 mg omeprazole (OD); however, dosage and duration vary based on the clinical situation and patient response.

Heliocobacter pylori (H. pylori) eradication: It has been established that H. pylori is one of the etiological factors associated with gastroduodenal ulcer disease. A high level of evidence supports the use of PPIs along with antibiotics to effectively eradicate H. pylori. Omeprazole eradicates H. pylori by a urease-independent mechanism by inhibiting the growth of the organism at a low pH. Studies have demonstrated that omeprazole as triple therapy (with two antibiotics) is more effective against H. pylori than lansoprazole, ranitidine, or bismuth. The therapy aims to reduce the risk of recurrence of duodenal ulcers. Omeprazole is prescribed concomitantly with antibiotics as dual therapy (40 mg omeprazole (OD) with clarithromycin (500 mg) thrice a day for 10 days) or triple therapy (20 mg omeprazole with amoxicillin (1000 mg) and clarithromycin (500 mg), all prescribed three times a day for 10 days).
to those of incretin. A trial reported that the addition of omeprazole to metformin treatment significantly improved fasting blood glucose and glycated hemoglobin levels in 3 months. A retrospective study of almost 400,000 individuals with data over 5 years demonstrated a statistically significant (p < 0.001) dose-dependent decrease in the risk of diabetes development in individuals being treated with PPIs to manage an upper gastrointestinal disease. A retrospective cohort study, 505 cirrhotic patients with high-risk esophageal varices who underwent primary prophylactic EVL were evaluated, and it was found that bleeding after prophylactic EVL was associated with coexisting gastric varices and the nonadministration of PPIs. Another retrospective cross-sectional study of 46 cirrhotic patients with bleeding gastroesophageal varices (GEV) who underwent EVL demonstrated that PPIs lower the occurrence of early bleeding and adverse events after EVL. The study also reported that nonprescription of PPIs and the presence of GEVs were significantly associated with a higher risk of bleeding.

Role of Omeprazole in the Management of COVID-19

The COVID-19 pandemic has followed an unpredictable course in its effects on human health, with most people having mild-to-moderate symptoms and recovering rapidly, but others developing grave symptoms. A multidisciplinary approach has been employed in the management of COVID-19, including the use of antisecretory agents. Omeprazole can inhibit the replication of the virus by interfering with the acidification of lysosomes. At concentrations much higher than the therapeutic concentrations currently being used, omeprazole impairs the formation of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A synergistic action was observed when the antiviral agent remdesivir was used with aprotinin (a protease inhibitor) and therapeutic concentrations of a PPI. The antiviral efficacies of PPIs are also related to their antioxidative and antiinflammatory actions. Omeprazole reduces the symptoms of COVID-19 by decreasing oxidative stress in endothelial and gastric epithelial cells and reducing the production of cytokines in duodenal epithelial cells.

Other Uses

Role of Omeprazole in NSAID-associated Gastrointestinal Effects

The mainstay therapies for the management of arthritis, visceral pain, headache, postoperative pain, and musculoskeletal disorders are NSAIDs. However, they can cause significant adverse reactions, such as gastrointestinal complications, hypertension, renal injury, and cardiovascular disease. A meta-analysis demonstrated that treatment with NSAIDs and PPIs lowered the risk of developing dyspepsia by 66% as compared to that when treatment consists of NSAIDs alone. A systematic review demonstrated that PPIs are significantly more effective than H2RAs and antacids in managing nonspecific dyspepsia. Antacids provided only symptomatic relief and did not reduce the risk of peptic ulcers and their complications. Omeprazole, however, also reduced the risk of bleeding caused by low-dose aspirin usage in managing cardiovascular disease.

Role of Omeprazole in Diabetes Mellitus

Diabetes mellitus is a growing health concern, particularly in developing countries. Although various hypoglycemic agents have been used to manage diabetes, a combination of therapies has been recommended to avoid long-term complications of the disease. It has been suggested that PPIs increase the mass of islet cells, decrease the speed of gastric emptying, and reduce glucagon secretion. This is because PPIs increase the secretion of gastrin, which, due to its resemblance to incretin, may stimulate the pancreatic cells to secrete insulin and mediate other metabolic effects similar
in the use of omeprazole, following North America and Europe.39

Although India exports medicines globally, the affordability of these drugs to the local population is limited by the prices of the drugs, which remain highly variable, and the use of such drugs adds to the out-of-pocket expenses borne by patients. An Indian study has demonstrated that the tablet rabeprazole (20 mg) has the highest cost ratio (9.15) and percentage cost variation (815.78) in India. A single vial of injectable omeprazole (40 mg) has the lowest cost ratio (1.47) and percentage cost variation (47.95). In a country like India, where 80% of health-related costs are borne by the patient, physicians have an important role in prescribing cost-effective drugs.40 Another study from India has shown that 20 and 40 mg of omeprazole are the most cost-effective drugs in both injectable and oral forms, whereas 10 mg of ilaprazole is the most expensive oral PPI, and 40 mg of rabeprazole is the most expensive injectable PPI. This information is important as PPIs are commonly prescribed drugs, and the prescription of expensive drugs affects the patient’s health-seeking behavior and healthcare expenses.41

Recent Research on Omeprazole

Details on the systematic reviews, RCTs, and observational studies on omeprazole included in this review are provided in Table 2.4,6–8,42

Table 2: Recent research data on omeprazole4,6–8,42

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design and setting</th>
<th>Sample size</th>
<th>Exposure</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barberio et al., 2022</td>
<td>A systematic review and meta-analysis</td>
<td>23 RCTs with 10,735 subjects</td>
<td>Efficacy and safety of PPIs, H2RA, potassium-competitive acid blockers, and alginates in reflux disease.</td>
<td>Omeprazole 20 mg, taken OD, ranked first in complete symptom relief between 2–4 weeks.</td>
</tr>
<tr>
<td>Javed et al., 2020</td>
<td>A systematic review using PRISMA guidelines</td>
<td>9 studies with 418 participants</td>
<td>Medline, Embase, and CENTRAL were searched for studies on the effectiveness and safety of omeprazole and lansoprazole in the management of GERD.</td>
<td>Omeprazole lowered gastric pH faster, and the effects lasted for a longer time than with lansoprazole.</td>
</tr>
<tr>
<td>Zhang et al., 2017</td>
<td>A network meta-analysis and GRADE system</td>
<td>9 RCTs with 45,964 participants</td>
<td>Effectiveness and tolerability of different recommended doses of PPIs and H2RAs in GERD.</td>
<td>Omeprazole 40 mg/day ranked first in both symptom relief and drug tolerance.</td>
</tr>
<tr>
<td>Salmanroghani, Mirvakili, Baghbanian, et al., 2018</td>
<td>Randomized, open-label clinical trial</td>
<td>228 participants</td>
<td>To evaluate the effectiveness of quadruple therapy with bismuth subsitrate, antibiotics, and omeprazole for 2 weeks on eradication of H. pylori and patient compliance with treatment.</td>
<td>The results of the study indicated effective eradication of H. pylori and good tolerance of the regimen among the individuals treated.</td>
</tr>
<tr>
<td>Lazebnik et al., 2021</td>
<td>Multicountry, multicenter, observational study</td>
<td>18,724 participants</td>
<td>Patient-reported outcomes to 40 mg and 20 mg omeprazole on measures of heartburn due to varying etiologies.</td>
<td>Better patient-reported outcomes were found with omeprazole 40 mg compared to 20 mg omeprazole.</td>
</tr>
</tbody>
</table>

CENTRAL, Cochrane central register of controlled trials; GERD, gastroesophageal reflux disease; GRADE, Grading of recommendations, assessment, development and evaluations; H. pylori, Helicobacter pylori; H2RA, histamine 2 receptor antagonist; PPI, proton pump inhibitors; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial

Comparing the Relative Effectiveness of Omeprazole, Lansoprazole, and Pantoprazole

Omeprazole exhibits dual action in protecting the gastric mucosa by suppressing acid secretion and by acting as a potent antioxidant. Its ability to scavenge free radicals was far superior to pantoprazole and lansoprazole and at par with esomeprazole.43

A systematic review comparing the efficacies of 20 mg omeprazole and 30 mg lansoprazole found that omeprazole was consistently better at reducing gastric acidity and increasing gastric pH. Omeprazole was also more effective in controlling nocturnal gastric pH and reducing nocturnal acid breakthroughs. Four studies demonstrated that omeprazole (40 mg) lowered gastric pH significantly more than lansoprazole (30 mg) (p < 0.05) in both healthy individuals and patients with GERD.4

A single-center, three-way crossover, open-label study compared the effectiveness of immediate-release omeprazole (20 mg)/sodium bicarbonate (1100 mg) with delayed-release lansoprazole (15 mg). Omeprazole was significantly better at decreasing the median intragastric pH level as compared to lansoprazole on the 7th day of administration; omeprazole exerted this effect as early as 10–15 minutes after the dose was administered and showed sustained effects up to 115–120 minutes after administration. Even on day 1, omeprazole was able to decrease intragastric acidity more rapidly than lansoprazole. Furthermore, omeprazole maintained a pH of >4 for a significantly longer duration than lansoprazole over 24 hours on the 7th day (p < 0.007). Thus, the study demonstrated that omeprazole had significantly better acid suppression effects and faster onset of action than lansoprazole.44

Omeprazole is used as a first-line drug in eradicating H. pylori. The emergence of clarithromycin resistance has caused triple therapy to often be ineffective in eradicating H. pylori infections. Even quadruple therapy using bismuth may be ineffective as the bioavailabilities of the drugs are variable, and many patients cannot tolerate the drugs/drug combinations. Therefore, PPIs, such as omeprazole, pantoprazole, lansoprazole, rabeprazole, and esomeprazole, have been widely used as first-line acid inhibitors to treat H. pylori infections.45 A meta-analysis that evaluated the efficacy of omeprazole and lansoprazole in the management of H. pylori-associated duodenal ulcers found no significant differences between the two drugs in their ulcer healing rates; in addition, patients showed no serious adverse reactions to either drug. The two drugs also had similar efficacies in managing H. pylori-associated duodenal ulcers.46

A meta-analysis of RCTs found that new-generation PPIs and omeprazole exhibit
similar efficacies in controlling GERD, healing esophagitis, and preventing the relapse of symptoms. Though several studies claim that one PPI is more effective than another, the World Health Organization Collaborating Centre for Drug Statistics Methodology has stated that 20 mg omeprazole, 30 mg esomeprazole, 30 mg lansoprazole, 40 mg pantoprazole, 20 mg rabeprazole, and 30 mg dexlansoprazole were equally efficacious in managing GERD. Kircheiner et al reviewed 57 clinical studies and reported that the relative potencies of pantoprazole, lansoprazole, and omeprazole were 0.23, 0.90, and 1.00, respectively. Similar results were obtained by Graham and Tansel in 2018, who analyzed data from RCTs that tested the gastric pH of patients after they were administered oral doses of omeprazole, rabeprazole, esomeprazole, pantoprazole, and lansoprazole for at least 5 days. They concluded that these PPIs, based on their potencies, may be used interchangeably. Omeprazole (20 mg) and lansoprazole (30 mg) were found to be equivalent to 20 mg esomeprazole and rabeprazole.

A meta-analysis that compared the efficacies of 40 mg omeprazole OD, 80 mg pantoprazole OD, and 80 mg famotidine OD demonstrated that omeprazole ranked first in both symptom relief and drug tolerance. Additionally, omeprazole has withstood the test of time, is the most used PPI, and is also the most affordable.

**Use of Omeprazole in Special Populations**

According to the FDA, PPIs are effective and safe in children (1–17 years of age). A study has demonstrated that the administration of 1 mg/kg omeprazole in infants aged 6–12 weeks increased gastric and intraesophageal pH in cases of GERD resulting from esophageal atresia or congenital diaphragmatic hernia. The recommended dose in children from 1–16 years of age is based on their body weight (Table 3).

Data from a retrospective analysis found that the common adverse effects of omeprazole seen in children were not serious and mainly included gastrointestinal and skin manifestations. Headache, nausea, diarrhea, or constipation were seen transiently. The USDFA has approved the use of most PPIs in pediatric patients (children >1 year of age) for treating conditions like GERD and erosive esophagitis. However, pantoprazole is not suitable for use in children <5 years of age because it is currently not available in a formulation suitable for children <5 years of age; in addition, this drug is not effective in infants <1 year of age.

A systematic review of PPI usage, including omeprazole, in children showed that PPIs were superior to placebos, alginic acid, and ranitidine in the management of GERD. Observational studies have reported that in children, omeprazole in doses of 1–2 mg/kg body weight twice a day was effective in treating eosinophilic esophagitis.

An interventional study examined the response of children <16 years of age to 1 mg/kg/day of omeprazole administered in 2 doses for the management of eosinophilic esophagitis. Follow-ups for 6 months indicated that remission occurred, but only if the patients adhered strictly to the treatment. An RCT comparing the administration of omeprazole alone with omeprazole administered along with the imposition of a 4-food elimination diet to treat eosinophilic esophagitis in children found that the combination of omeprazole and diet therapy was more effective.

A study compared the triple-therapy regimens of clarithromycin, amoxicillin, and omeprazole with amoxicillin, omeprazole, and azithromycin for the eradication of *H. pylori* in children and found both treatments to be equally effective. Another similar study found that triple therapy with clarithromycin, amoxicillin, and omeprazole for 7 days was effective in eliminating *H. pylori* in children <15 years of age. Omeprazole also improved asthma control in asthmatic children (4–16 years) with GERD.

Around 40–85% of pregnant women experience GERD due to both mechanical and hormonal factors. Estrogen and progesterone have a role in the relaxation of the lower esophageal sphincter. Additionally, hormonal changes during pregnancy are believed to affect gastric motility (GM) by altering the enteric nervous system and musculature, leading to decreased GM, which may contribute to GERD. In a cohort study that included 6051 nulliparous women on PPI, PPI use during pregnancy was linked to an increased risk of overall preeclampsia; however, after 28 weeks, a protective effect against preterm preeclampsia was observed. According to a recent systematic review, there is evidence of birth defects, including cardiac defects, with PPI use during pregnancy, but there exists no evidence supporting a causal association between PPI use and these birth defects. The review also concluded that omeprazole has a low risk at doses of 20–60mg/day during the first trimester. However, due to a lack of comprehensive prospective clinical studies on its use during pregnancy, the FDA has not altered its classification of omeprazole as a category C drug.

On assessing the safety of PPIs during lactation, it was observed that pantoprazole and omeprazole are both excreted into breast milk in quantities 300–600 times lower than those administered to neonates. The excretion of PPIs into breast milk is negligible, and the acidic environment of the infant’s stomach may further break down PPIs; thus, PPIs in breast milk are unlikely to get absorbed systemically.

Another population where PPIs are increasingly being used is the elderly. In adults <40 years of age, fewer than 10% of individuals are prescribed PPIs, while in those >80 years of age, 30% of individuals are prescribed PPIs. This increase could be because PPIs decrease the risk of the development of adenocarcinomas and Barrett’s esophagus, both of which are likely to develop in old age. Bleeding from peptic ulcers is also more common in the elderly, probably because many people in this age group are also prescribed NSAIDs. The administration of PPIs can protect against bleeding peptic ulcers associated with NSAID use. These drugs have been demonstrated to be safe in the short term for the elderly.

The classification by Child-Turcotte-Pugh (CTP) for cirrhosis has been considered to guide the use of PPIs in patients with cirrhosis. It has been recommended that in patients with CTP A and B, a reduced dose of rabeprazole and omeprazole be given, and in those with CTP C, a maximum of 20 mg OD of esomeprazole may be administered. Lansoprazole and pantoprazole were unsafe due to a four to eight-fold increase in their exposure in patients with cirrhosis.

When considering the use of PPIs in patients with kidney disease, although omeprazole use has been associated with injury to the kidneys, most cases of chronic kidney disease and acute kidney injury were associated with the administration of lansoprazole and dexlansoprazole as per the FDA Adverse Event Reporting System. The American College of Gastroenterology (ACG), 2022 guidelines mention that patients with renal insufficiency can be prescribed PPIs following a nephrologist consultation along with monitored renal function.

Studies have also associated PPI use with deficiencies of vitamins, bone fractures due
to osteoporosis, and intestinal infections. However, these studies had protopathic bias as well as residual confounding and could not establish causality. High-quality evidence has demonstrated that PPIs do not pose a risk for any of these adverse events except for intestinal infections. The ACG guidelines mention that although vitamin D nor calcium intake needs to be increased in patients on PPIs without other risk factors for osteoporosis, nor does vitamin B12 intake need to be raised in patients without other risk factors for deficiency of vitamin B12. Gastroenterologists agree that the benefits of PPI outweigh the theoretical risks associated with them.

**Guidelines on Prescribing Omeprazole and Other PPIs**

According to the 2022 ACG, PPIs are recommended as the most effective treatments for GERD. In addition, the guidelines also state that the benefits of prescribing PPIs far outweigh the risk of adverse effects, as these adverse effects are mostly caused by residual confounding factors that were already present before the initiation of treatment with PPIs (protopathic bias). Confounding refers to the adverse effect being caused by the medical condition necessitating the use of the PPI and not due to the PPI per se. Protopathic bias means that the adverse effect was not due to the PPI; on the contrary, PPIs were used to manage symptoms of the already present but unrecognized condition. There are very few cases, mainly from observational studies, that show associations between PPIs and adverse effects. PPIs are superior to H2RAs in managing regurgitation and heartburn and in promoting healing. Furthermore, omeprazole is a more potent suppressor of gastric acid than pantoprazole and lansoprazole. Previously, if a patient did not respond to drugs, they were advised to undergo surgery to treat regurgitation and heartburn. However, PPIs treat heartburn and regurgitation so effectively that treatment failure is more likely to indicate a misdiagnosis of GERD. A study on individuals refractory to PPIs showed that although those who were prescribed omeprazole twice a day and given appropriate instructions on its use got relief from heartburn. A comparison of the relative acid-suppression abilities of PPIs (based on the average intragastric pH for 24 hours) to those of omeprazole is called an omeprazole equivalent (OE). Omeprazole has an OE of 1.00, pantoprazole 0.23, lansoprazole 0.90, esomeprazole 1.60, and rabeprazole 1.82.

The National Health Service (NHS), United Kingdom, recommends using 20 mg omeprazole OD as a full dose, 10 mg omeprazole OD as a low on-demand dose, and 40 mg omeprazole OD as a double dose. The NHS also recommends the use of PPIs in the following conditions:

- Suspected upper gastrointestinal bleeding.
- Peptic ulcer.
- Gastroesophageal reflux disease (GERD).
- Barrett's esophagus.
- Dyspepsia.
- Functional dyspepsia.
- Esophageal dilatation.
- For gastro-protection.
- Esophagitis.

The Indian recommendations on PPIs suggest prescribing PPIs for 12 weeks (long term) for GERD with peptic stricture or erosive esophagitis. In patients with GERD without complications, a short-term PPI course (<6 weeks) is prescribed. For patients demonstrating unusual symptoms of GERD (noncardiac chest pain), PPIs are prescribed on a trial basis for 2 weeks and in nonresponsive patients, further investigations are recommended to determine the etiology of the problem. Patients on NSAIDs with a high risk of ulcerative bleeding are prescribed PPIs. For patients with dyspepsia and acidity-related symptoms, such as epigastric pain syndrome, PPI therapy for a short-term is recommended. Long-term evaluation of the PPI dose is recommended periodically to ensure that the lowest dose of PPI required for effectiveness is prescribed to manage APDs.

**Comparative Pricing of Various Brands of PPI Available in India**

Details about the various PPIs available in India are provided in Table 4.

**Conclusion**

Omeprazole is the first line of treatment for APD. Omeprazole is effective in managing active and benign gastric ulcers, treating symptomatic GERD, managing active duodenal ulcers, *H. pylori* eradication, preventing ulcers due to NSAIDs, managing acid-mediated GERD-led erosive esophagitis, treating pathological hypersecretory conditions such as ZES, and the maintenance of erosive esophagitis due to acid-mediated GERD. Apart from these, omeprazole has also recently been investigated as a treatment

---

**Table 4:** Half-life, mode of metabolism, dosages, and prices of all available PPI in India (approximately)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg)</th>
<th>Half-life (hours)</th>
<th>Mode of metabolism</th>
<th>Price range (INR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>Tablet 10</td>
<td>0.6–1.5</td>
<td>Metabolized to omeprazole hydroxy sulphone by the action of CYP2C19 &amp; CYP3A4</td>
<td>24.50–39.60</td>
</tr>
<tr>
<td></td>
<td>Capsule 10–40</td>
<td></td>
<td></td>
<td>28–78.33</td>
</tr>
<tr>
<td></td>
<td>Injection 40</td>
<td></td>
<td></td>
<td>23.25–23.75</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>Tablet 20–40</td>
<td>1.1–1.6</td>
<td>Metabolized to esomeprazole sulphone by the action of CYP2C19 and CYP3A4</td>
<td>27–60</td>
</tr>
<tr>
<td></td>
<td>Injection 40</td>
<td></td>
<td></td>
<td>77–95.75</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>Capsule 15–30</td>
<td>0.9–1.6</td>
<td>Metabolized to lanoprazole sulphone by the action of CYP2C19 and CYP3A4</td>
<td>26.25–100</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>Tablet 20–40</td>
<td>0.9</td>
<td>Metabolized to pantoprazole sulphate by the action of CYP2C19 and CYP3A4</td>
<td>58–78</td>
</tr>
<tr>
<td></td>
<td>Injection 40</td>
<td></td>
<td></td>
<td>44.80–79.50</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>Tablet 20</td>
<td>1–1.1</td>
<td>Metabolized to rabeprazole sulphone by the action of CYP2C19 and CYP3A4</td>
<td>18.50–76.50</td>
</tr>
<tr>
<td></td>
<td>Injection 20</td>
<td></td>
<td></td>
<td>50–89</td>
</tr>
<tr>
<td>Drexabeprazole</td>
<td>Tablet 5–10</td>
<td>3.5</td>
<td>Metabolized by CYP450 isoenzymes in the liver.</td>
<td>18.00–120.00</td>
</tr>
<tr>
<td>Ilaprazole</td>
<td>Tablet 5–10</td>
<td>0.5–2</td>
<td>Ilaprazole is catalyzed mainly by CYP3A4 via its sulfoxide oxidation. The CYP3A4 enzyme has a prime role in ilaprazole clearance.</td>
<td>45.00–85.00</td>
</tr>
</tbody>
</table>

CYP, cytochrome; INR, Indian rupee
option for patients with both APD and diabetes to understand its effect on blood glucose levels. In addition, omeprazole was also prescribed to patients with COVID-19 who were on multiple medications that caused drug-induced acidity. The general advantages of using omeprazole are that it is effective in reducing gastric pH, acts rapidly, and is suitable for children as young as 1-month-old. Unlike in the case of H2RAs, patients prescribed omeprazole do not show tachyphylaxis. Omeprazole is well tolerated by most people, and the most common adverse effects are mild, ranging from headaches to gastrointestinal symptoms and skin rashes. Omeprazole has withstood the test of time and continues to be a clinically effective, safe, and affordable drug for managing gastric acid-related diseases. Omeprazole, therefore, remains relevant in managing APDs despite the development of newer PPIs.

FUNDING
The article processing charge is funded by Dr Reddy’s Laboratories Ltd.

ACKNOWLEDGMENTS
We would like to acknowledge Dr Ritwik Banerjee and thank BioQuest Solutions for the editorial assistance.

REFERENCES