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A Systematic Review On Pharmacokinetic, Pharmacodynamic, Interaction with Other Drugs, Toxicity and Clinical Effectiveness of Proton Pump Inhibitors (PPI)

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Abstract: *The most effective category of medicines for treating acid-related intestinal conditions are proton pump inhibitors, or PPIs. The mechanism of action, pharmacokinetics, pharmacodynamics, drug interactions, toxicity, and clinical efficacy of two commonly given PPIs—omeprazole and pantoprazole—are the main topics of this review. The final stage of gastric acid production is blocked by both medications' irreversible inhibition of the H^+/K^+-ATPase enzyme on the stomach parietal cells, which results in a long-lasting reduction of both baseline and enhanced acid output. Pantoprazole has more bioavailability and fewer clinically relevant medication interactions than omeprazole, which is highly binding to proteins and extensively processed by hepatic cytochrome P450 enzymes. Whenever it comes to managing GERD, peptic ulcer disease, Zollinger-Ellison syndrome, NSAID-induced ulcers, and Helicobacter pylori eradication therapy, both PPIs are effective.Prolonged therapy may result in adverse effects such as vitamin B12, calcium, magnesium, and iron deficiencies, increased fracture risk, kidney damage, and increased susceptibility to infections, even though it is generally safe for short-term use. Pantoprazole has a lower probability for interaction and an unusually favorable safety profile.*

Keywords: Proton Pump Inhibitors, Omeprazole, Pantoprazole, Gastric Acid Suppression, GERD, Peptic Ulcer Disease, Pharmacodynamics, Pharmacokinetics, Drug Interactions, Long-term Safety

I. INTRODUCTION

Digestion and defense against viruses depend greatly on gastric acid. However, various gastrointestinal conditions, especially erosive esophagitis, peptic ulcers, gastroesophageal reflux disease (GERD), and hypersecretory disorders, including Zollinger-Ellison syndrome, are caused by excessive gastric acid secretion. These illnesses have a significant adverse effect on quality of life and, if mismanaged, can cause serious effects.Antacids and H_2-receptor blockers were once often used to treat acid-related diseases, even though they only partially reduced acid. Because they can provide strong and long-lasting control of gastric acid output, the discovery of proton pump inhibitors (PPIs) altered the treatment of acid-related illnesses.Pantoprazole, a more recent generation of PPI, and omeprazole, the first PPI to be used in medical conditions, are currently given frequently throughout the world.The two drugs inhibit both basal and generated acid secretion by concentrating on the proton pump in gastric parietal cells. They are widely used to prevent NSAID-induced ulcers, treat GERD and peptic ulcer disease, kill H. pylori, and prevent stress ulcers in hospitalized patients.

II. OMEPRAZOLE

Omeprazole is a commonly used medication classified as a Proton Pump Inhibitor (PPI) that works by reducing the amount of acid produced in the stomach. It is widely prescribed for conditions such as acidity, heartburn, gastroesophageal reflux disease (GERD), and peptic ulcer disease. Omeprazole is also used in combination with antibiotics to treat Helicobacter pylori infection and to prevent ulcers caused by long-term use of NSAIDs. It acts by

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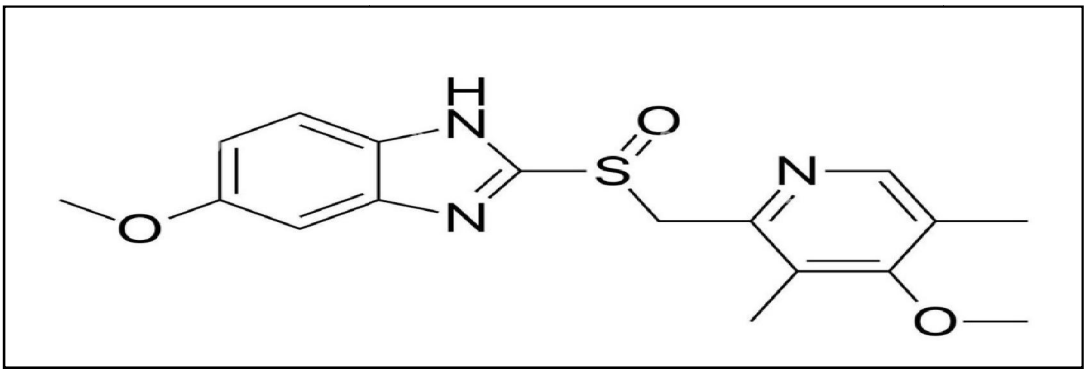
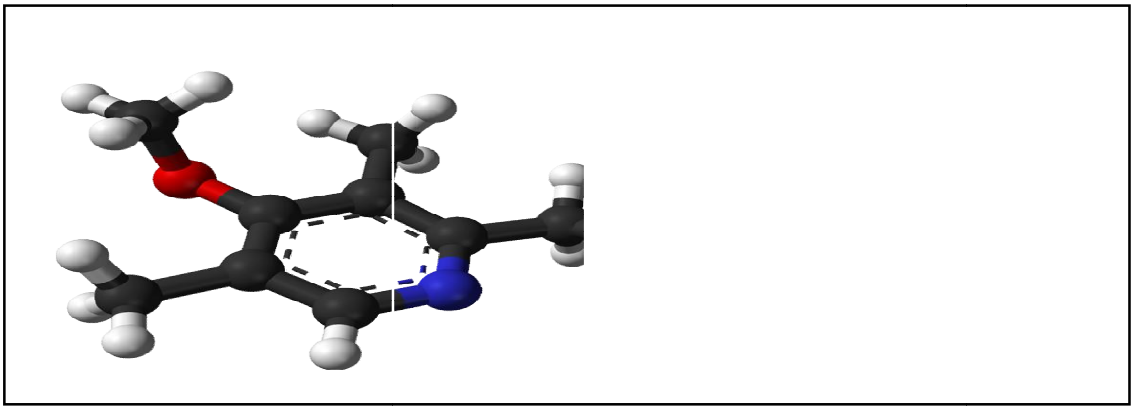
blocking the H^+/K^+ ATPase enzyme (proton pump) in the stomach lining, which is responsible for the final step of acid secretion. The drug is available in various forms, including delayed-release capsules, tablets, and oral suspensions. Although generally safe, it may cause mild side effects like headache, nausea, abdominal discomfort, or diarrhea, and long-term use may lead to vitamin or mineral deficiencies or increased risk of infections. Overall, Omeprazole is an effective and widely used therapy for managing acid-related gastrointestinal disorders and improving patient comfort and healing.



(Str.no.1) Structure of Omeprazole



(Str. no.1.1) 3D Structure of Omeprazole

MECHANISM OF ACTION

Omeprazole is a proton pump inhibitor. It is a substituted benzimidazole that belongs to the antisecretory class of compounds. It inhibits the parietal cell H+/K+ adenosinetriphosphate pump, the final step of acid production. In turn, omeprazole suppresses gastric basal and stimulates acid secretion. The inhibitory effects of omeprazole occur rapidly within 1 hour of administration, with the maximum effect occurring in 2 hours. The inhibitory effects last for approximately 72 hours after administration, followed by a return to baseline activity in 3 to 5 days. The effects will plateau on the fourth day with daily use of the medication. Omeprazole is extensively metabolized by the hepatic cytochrome P450 (CYP) enzyme system, mainly via CYP2C19 and CYP3A4 isozymes. Urinary excretion is a primary route for the excretion of omeprazole metabolites. Omeprazole has a short half-life of a half-hour to an hour in healthy subjects and about 3 hours half-life for patients with hepatic impairment. However, the pharmacological effect of omeprazole lasts much longer as the drug preferentially concentrates in parietal cells, where it forms a covalent linkage with H+/K+ adenosine triphosphatase, which it irreversibly inhibits.

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PHARMACOKINETIC

Omeprazole exhibits characteristic pharmacokinetic properties due to its prodrug nature. It is rapidly absorbed after oral administration, but its absolute bioavailability is initially about 30–40%, increasing with repeated dosing due to reduced first-pass metabolism. Omeprazole is lipid-soluble and enters systemic circulation, becoming concentrated in the acidic canaliculi of gastric parietal cells, where it is converted to its active sulfenamide form.The drug is highly protein-bound (≈95%) and undergoes extensive hepatic metabolism primarily via cytochrome P450 enzymes (CYP2C19 and CYP3A4). Genetic polymorphism of CYP2C19 may alter plasma levels, making metabolism slower in poor metabolizers. The metabolites are inactive and primarily excreted through the kidneys (≈80%), with a smaller portion eliminated via bile. Although the plasma half-life is short (0.5–1 hour), its pharmacodynamic effect lasts up to 24 hours due to irreversible inhibition of the proton pump. Peak plasma concentration occurs within 0.5–3 hours after ingestion, and therapeutic effects are usually observed after a few days of regular dosing.

PHARMACODYNAMIC

Omeprazole is a proton pump inhibitor that exerts its action by irreversibly inhibiting the H^+/K^+-ATPase enzyme located on the parietal cell membrane of the stomach. After oral administration, it reaches the acidic environment of the parietal cell canaliculi, where it is converted to its active metabolite, a sulfenamide form, which covalently binds to sulfhydryl groups of the proton pump. This prevents the final step of gastric acid secretion, leading to a significant reduction in both basal and stimulated acid production. Because the inhibition is irreversible, acid-secreting ability is restored only after new proton pumps are synthesized, which explains why the pharmacological effect lasts much longer than its plasma half-life. Omeprazole also increases gastric pH, reduces pepsin activity, and promotes healing of acid-related disorders such as GERD, peptic ulcers, and Zollinger–Ellison syndrome.

DRUG INTERACTION WITH OTHER DRUGS

Omeprazole interacts with several drugs mainly due to its effect on gastric pH and inhibition of hepatic CYP enzymes (especially CYP2C19 and CYP3A4). By increasing gastric pH, it may reduce the absorption of drugs that require an acidic environment, such as ketoconazole, itraconazole, and iron salts. As a CYP2C19 inhibitor, omeprazole can increase plasma levels and enhance toxicity of drugs metabolized by this pathway, including diazepam, phenytoin, and warfarin, requiring dose adjustments and monitoring. A clinically significant interaction occurs with clopidogrel, as omeprazole reduces its activation, diminishing its antiplatelet effect and increasing the risk of thrombosis. Conversely, drugs like rifampin and St. John's Wort, which induce CYP enzymes, may decrease omeprazole levels and reduce its effectiveness. Additionally, combined use with other agents causing hypomagnesemia (e.g., diuretics) may potentiate electrolyte imbalance.

TOXICITY

Omeprazole, a commonly prescribed proton pump inhibitor (PPI), is generally safe when used short-term and at recommended therapeutic doses. However, long-term use or overdose may lead to significant toxicity. Chronic use can reduce gastric acid secretion to extremely low levels, causing decreased absorption of essential nutrients such as vitamin B12, magnesium, calcium, and iron, potentially leading to anemia, hypomagnesemia, muscle cramps, and osteoporosis-related fractures. Long-term therapy is also linked to increased risk of Clostridioides difficile infection, pneumonia, and altered gut microbiota due to reduced natural acid defense. Renal complications such as acute interstitial nephritis and chronic kidney disease have also been reported. Rarely, hepatotoxicity, headache, dizziness, and rebound acid hypersecretion may occur after sudden discontinuation. Toxicity risk increases with duration of therapy, high doses, elderly patients, and drug interactions. Therefore, omeprazole should be used cautiously, at the lowest effective dose and for the shortest duration necessary, under medical supervision.

CLINICAL EFFECTIVENESS

Omeprazole, a commonly prescribed proton pump inhibitor (PPI), is generally safe when used short-term and at recommended therapeutic doses. However, long-term use or overdose may lead to significant toxicity. Chronic use can

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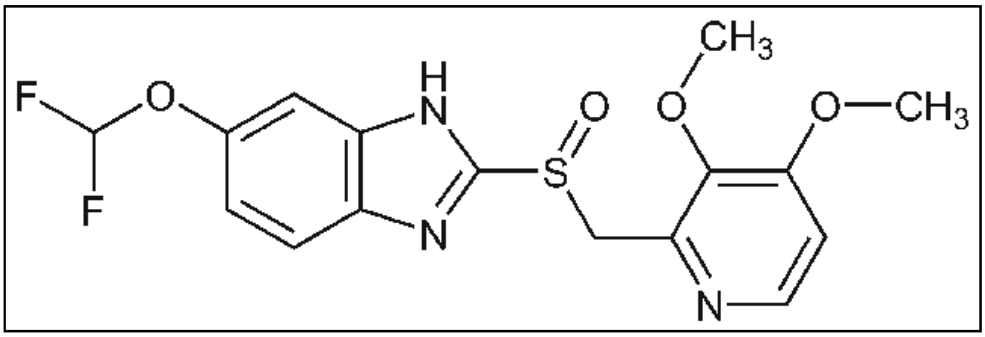
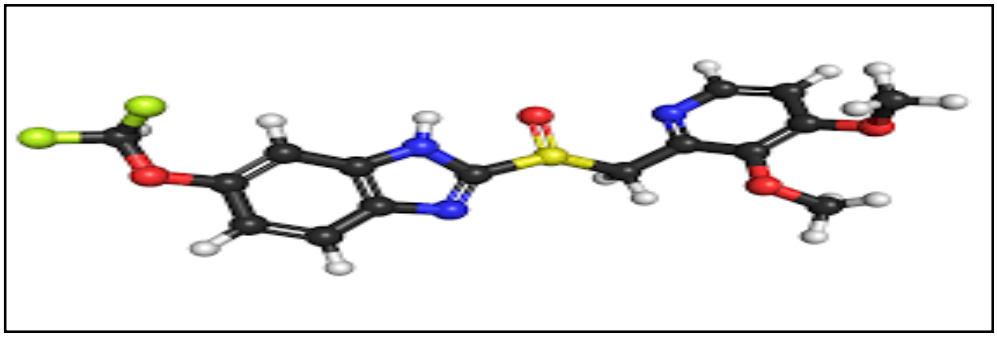
III. PANTOPRAZOLE

Pantoprazole is a proton pump inhibitor (PPI) used to decrease the secretion of gastric acid in the stomach. It works by irreversibly inhibiting the H^+/K^+ ATPase enzyme (also called the gastric proton pump) present on the parietal cells of the stomach. This enzyme is responsible for the final step in the production of gastric acid, so blocking it effectively reduces both basal and stimulated acid secretion.



(Str. no.2) Structure of Pantoprazole



(Str. no.2.1) 3D Structure of Pantoprazole

MECHANISM OF ACTION :

1. Absorption and Activation

Pantoprazole is administered as an enteric-coated form to prevent degradation by stomach acid.After absorption into the bloodstream, it reaches the parietal cells of the stomach.

2. Conversion to Active Form

In the acidic environment of the parietal cell canaliculus, pantoprazole is protonated and converted to its active form: sulfenamide (or sulfenic acid derivative).

3. Binding to Proton Pump

The active sulfenamide binds covalently (irreversibly) to cysteine residues on the H^+/K^+ ATPase enzyme, also known as the proton pump.

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4. Inhibition of Acid Secretion

Once bound, the enzyme becomes nonfunctional, resulting in:

Basal acid secretion

Meal-stimulated acid secretion

Nocturnal acid secretion

5. Duration of Action

The inhibition lasts until new proton pumps are synthesized, which takes 24–48 hours, even though the drug's plasma half-life is short (~1 hr).

PHARMACOKINETICS:

1. Absorption

Pantoprazole is well absorbed after oral administration.

Bioavailability: ~77% (not affected by food).

It is an enteric-coated tablet → prevents degradation by gastric acid.

Time to peak plasma concentration (Tmax): 2–3 hours.

2. Distribution

Protein binding: ~98% (mainly to albumin).

Volume of distribution (Vd): ~0.15 L/kg.

Crosses into breast milk in small amounts.

3. Metabolism

Extensively metabolized in the liver.

Primary pathway: CYP2C19.

Minor pathway: CYP3A4.

Major metabolite: Desmethyl-pantoprazole (inactive).

4. Elimination / Excretion

Half-life: ~1 hour

(effect lasts much longer—24 hours—because it irreversibly inhibits the proton pump).

Eliminated mainly as metabolites:

Kidneys: ~80%

Feaces: ~20%

PHARMACODYNAMICS

Pantoprazole exerts its pharmacodynamic effect by selectively and irreversibly inhibiting the H^+/K^+ ATPase proton pump located on the luminal surface of gastric parietal cells, which is responsible for the final step of gastric acid secretion. After being absorbed and converted into its active sulphonamide form in the acidic environment of the secretory canaliculi, pantoprazole binds covalently to cysteine residues of the proton pump, leading to prolonged suppression of both basal and stimulated gastric acid secretion. This inhibition results in an increase in gastric pH, promoting healing of acid-related conditions such as GERD, peptic ulcers, and erosive esophagitis. Despite having a short plasma half-life, pantoprazole's therapeutic effect lasts up to 24–48 hours due to irreversible pump inhibition, requiring synthesis of new pumps for acid restoration. The drug shows high selectivity for activated proton pumps, particularly after food-induced stimulation, which enhances its therapeutic effectiveness when taken before meals.

DRUG INTERACTIONWITHOTHR DRUGS:

Pantoprazole has fewer drug interactions compared to other proton pump inhibitors because it has a lower dependency on CYP2C19 metabolism. However, certain interactions still occur due to its effect on gastric pH and hepatic metabolism.

1. Drugs Affected by Increased Gastric pH

Pantoprazole increases stomach pH, which may reduce the absorption of drugs requiring an acidic environment.

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Decreased absorption of:
Ketoconazole,Itraconazole,Atazanavir,Rilpivirine,Iron supplements,Calcium carbonate

2. CYP Enzyme Interactions

Pantoprazole is metabolized mainly by CYP2C19 and CYP3A4, so drugs influencing these enzymes may affect its levels.
CYP2C19 inhibitors (↑ pantoprazole levels):
Fluconazole,Omeprazole,Fluvoxamine,CYP2C19inducers(↓pantoprazolelevels):,Rifampicin,Carbamazepine

3. Interaction with Clopidogrel

Clopidogrel requires CYP2C19 for conversion to its active metabolite.
Pantoprazole has minimal effect compared to omeprazole, so it is safer to use with clopidogrel.

4.Warfarin Interaction

Pantoprazole may increase prothrombin time or INR when combined with warfarin, requiring monitoring.

5. Methotrexate Interaction

High-dose methotrexate clearance may be reduced, leading to toxicity.Avoid or monitor if using pantoprazole with high-dose methotrexate therapy.

6. Digoxin

Pantoprazole may increase digoxin absorption due to altered pH, increasing the risk of toxicity—monitor in elderly and renal-impaired patients.

TOXICITY

Pantoprazole is generally well-tolerated, but prolonged use and high doses may lead to several adverse effects. Short-term side effects are usually mild and include headache, nausea, abdominal pain, diarrhea, dizziness, and rash. Long-term use may result in more significant toxicities due to reduced gastric acid production. These include vitamin B12 deficiency, iron deficiency, and hypomagnesemia because acid is required for proper absorption of these nutrients. Extended therapy may also increase the risk of bone fractures, particularly of the hip, wrist, and spine, due to impaired calcium absorption. Additionally, chronic use may predispose patients to infections such as Clostridium difficile–associated diarrhea, pneumonia, and gastrointestinal bacterial overgrowth because the normal acidic barrier is reduced.
Pantoprazole may also cause hypergastrinemia due to feedback stimulation of gastrin secretion, which in rare cases may lead to ECL cell hyperplasia or formation of benign gastric polyps. Hepatotoxicity is uncommon but may manifest as elevated liver enzymes or rare cases of hepatic impairment. Very rarely, pantoprazole may cause serious hypersensitivity reactions such as Stevens–Johnson syndrome, toxic epidermal necrolysis, or anaphylaxis. Overall, toxicity is dose- and duration-dependent, and long-term therapy should be monitored with periodic evaluation of electrolytes, vitamin levels, and bone health.

CLINICAL EFFECTIVENESS

Pantoprazole is clinically effective in treating a wide range of acid-related gastrointestinal disorders due to its strong and long-lasting suppression of gastric acid secretion. It is highly effective in the management of gastroesophageal reflux disease (GERD), where it promotes mucosal healing and reduces symptoms such as heartburn, regurgitation, and esophagitis. In cases of peptic ulcer disease, pantoprazole accelerates ulcer healing by creating a less acidic environment, allowing the gastric and duodenal mucosa to recover. When used in combination with antibiotics, it contributes significantly to the eradication of Helicobacter pylori, thereby preventing ulcer recurrence.
Pantoprazole is also effective in treating Zollinger–Ellison syndrome and other hypersecretory conditions, as it can maintain sustained acid suppression even at higher doses. In hospital settings, it is often administered intravenously to prevent stress-related mucosal injury and bleeding in critically ill patients. Compared to other PPIs, pantoprazole has fewer clinically significant drug interactions and a favorable safety profile, making it a preferred option in long-term therapy where continuous acid suppression is required. Overall, its predictable pharmacodynamics, prolonged effect, and high tolerability support its strong clinical utility across multiple acid-related disorders.

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IV. CONCLUSION

Since they provide prolonged and potent inhibition of gastric acid production, proton pump inhibitors, particularly omeprazole and pantoprazole, have changed the therapy of acid-related gastrointestinal illnesses. Both medications successfully treat conditions like GERD, peptic ulcer disease, Zollinger-Ellison syndrome, NSAID-induced ulcers, and Helicobacter pylori eradication regimens by permanently inhibiting the H^+/K^+-ATPase enzyme in stomach parietal cells. Their widespread clinical use and strong therapeutic efficacy have been confirmed by their well-established pharmacokinetic and pharmacodynamic features.

Both pantoprazole and omeprazole are typically safe for short-term use, but prolonged use is linked to major side effects such as increased risk of fracture, a lack of nutrition, kidney disease, and infection susceptibility. Pantoprazole is more appropriate for patients who require long-term therapy or are taking numerous drugs since it has some advantages over omeprazole, particularly in terms of fewer clinically relevant drug interactions and a better safety profile. To maximize therapeutic effectiveness while minimizing potential hazards, PPIs must be used logically and carefully, guided by sufficient clinical indication and regular surveillance.

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