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A Comprehensive Review on Omeprazole: Pharmacological Effects and Its Adverse Effects

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ABSTRACT

Omeprazole, a widely used proton pump inhibitor (PPI), has become a cornerstone in the treatment of various acid-related gastrointestinal disorders such as gastroesophageal reflux disease (GERD), peptic ulcers, and Zollinger-Ellison syndrome. By inhibiting the proton pump in parietal cells, omeprazole effectively reduces gastric acid secretion, thereby promoting healing and alleviating symptoms associated with hyperacidity. This review aims to provide a comprehensive overview of the pharmacological actions, therapeutic uses, and potential adverse effects of omeprazole. The drug's mechanism of action, pharmacokinetics, and clinical applications in both acute and chronic conditions are discussed in detail. Additionally, attention is given to the adverse effects associated with its prolonged use, including but not limited to gastrointestinal disturbances, nutrient deficiencies, renal complications, and an increased risk of infections. The balance between its therapeutic benefits and associated risks is explored, with a focus on the clinical decision-making process in prescribing omeprazole. The review also highlights the potential for drug interactions, particularly with medications that alter gastric pH or are metabolized via the cytochrome P450 enzyme system. Overall, while omeprazole remains a highly effective therapeutic agent, its adverse effects necessitate careful consideration, particularly in long-term use or in vulnerable patient populations.

Keywords- Proton Pump inhibitors, Git, pH, Clinical.

I. INTRODUCTION

Proton-pump inhibitors (PPIs) represent a class of drugs most prominently known for their use in acid-related disorders. Omeprazole, a drug belonging to this class, is among the top 10 most prescribed drugs in the United States. PPIs are derivatives of the heterocyclic organic molecule benzimidazole. They are often the first-line agents amongst gastroenterologists. Omeprazole is a widely used medication belonging to the class of proton pump inhibitors (PPIs). It is primarily prescribed for the treatment of gastrointestinal disorders such as gastroesophageal reflux disease (GERD), peptic ulcers, and Zollinger-Ellison syndrome. By reducing stomach acid production, it helps alleviate symptoms and promotes healing in conditions related to excess acid. Proton Pump Inhibitors (PPIs) are antisecretory agents that are used widely to diminish acid secretion. PPIs are prescribed commonly to manage gastric acid-related conditions such as gastroesophageal reflex disease (GERD), gastritis, esophagitis, Barrett esophagus, Zollinger-Ellison syndrome, peptic ulcer disease, nonsteroidal anti-inflammatory drug-associated ulcers, and *Helicobacter pylori* (*H.pylori*) eradication, around the globe[1,2]. Current PPIs may include omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole and rabeprazole.[3,4] PPIs diminish acid secretion by

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binding covalently to sulfhydryl groups of cysteines of proton pump in parietal cells of stomach, thereby inactivating H^+/K^+-ATPase (Proton pump)[5,6].

The most common side effects of PPIs may include headache, constipation, diarrhea, nausea and vomiting[7,8]. In addition, long-term use of PPIs found to be associated with some serious and rare adverse effects including kidney diseases (acute kidney injury, acute interstitial nephritis, chronic kidney disease, end stage renal disease), cardiovascular disease (myocardial infarction, stroke), liver disease (hepatocellular carcinoma), fractures, infections (*Clostridioides difficile* infection, Community-acquired pneumonia, COVID-19), micronutrient deficiencies (hypomagnesemia, anemia, vitamin B12 deficiency, hypocalcemia), dementia, and gastric cancer[9,10].

Inappropriate use (overuse or misuse) of PPIs enhances the healthcare cost as well as the risk of polypharmacy and numerous PPI-associated adverse effects. The use of PPIs is increased exponentially in recent decades. Approximately half of the PPI prescriptions found to be with inappropriate indications[11,12] PPIs are the most widely used drugs around the globe and they are considered one of the top ten most used drugs. Generally, PPIs are misused to prevent gastro-duodenal ulcers in patients without risk factors, overtreatment to manage functional dyspepsia, treatment with antiplatelets or anticoagulants without the risk of gastric injury, stress ulcer prophylaxis in patients not admitted in intensive care units, and steroid alone therapy[13].

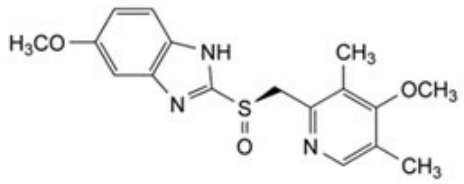

Fig: 1 Structure of Omeprazole

As per previous studies, PPIs are prescribed for up to 70% of cases without any clear indication. According to a prospective observational cross-sectional study conducted in the emergency department, almost one-third of PPI prescriptions were determined to be inappropriate.9 Similar findings were made by another prospective observational cross-sectional investigation of PPI-using hospitalized patients, which found that almost half of the patients had received their prescriptions for erroneous conditions.[14,15] The GI symptoms could be managed non-pharmacologically by various measures including avoidance of meals within 2-3 hours of bedtime, elevation of head of bed, weight loss, cessation of smoking or tobacco products, and avoidance of dietary triggers.[16,17].

Below is a detailed review of the pharmacological effects and the potential adverse effects of omeprazole[18].

II. PHARMACOLOGICAL EFFECTS OF OMEPRAZOLE

Animal to human Trails

Proton pump inhibitors (PPIs) are effective when appropriately used for treating gastrointestinal acid-related disorders in human and veterinary medicine. However, multiple studies have identified patterns of inappropriate prescription characterized by the overuse of PPIs [19,20,21,22]. This study confirms that dogs chronically administered omeprazole develop hypergastrinemia but do not exhibit abnormalities in serum cobalamin concentrations. The use of PPIs is not recommended except for specific disease processes outlined in the ACVIM consensus statement, such as reflux or erosive esophagitis, gastrointestinal bleeding, acute abdomen secondary to gastroduodenal ulceration and erosion, gastric or duodenal perforation, prophylaxis of mast cell tumor or gastrinoma, and toxicosis associated with non-steroidal anti-inflammatory drugs (NSAIDs) [23,24,25].

The secretion of gastric acid is a normal physiological mechanism that contributes to the proper digestion of proteins, the release of cobalamin, the absorption of inorganic iron [26,27,28] and calcium [29,30] and the regulation of the intestinal microbiome by suppressing excessive bacterial growth [31,32]. The stomach has natural protective mechanisms to prevent gastric erosion and ulceration as a result of gastric acid secretion, and therefore, acid suppression is generally not recommended in the absence of erosive or infiltrative disease [33,34,35,36]. Routine administration of PPIs appears to occur frequently in the hospital setting, even for the treatment of nausea, vomiting, or both, despite there being no pharmacological evidence of an antiemetic effect or control of nausea [37,38]. It is also important to emphasize the side effects detected with their use, primarily detected when used long-term [39,40,41,42]. In this study, long-term administration of omeprazole was associated with increased serum gastrin levels. This finding is consistent with previous research indicating that omeprazole treatment leads to an increase in gastric pH by inhibiting the H^+/K^+ ATPase pump, resulting in reduced gastric acid production [43,44]. Gastrin increases because of the lack of negative feedback due to the pharmacological suppression of gastric acid [45,46]. Hypergastrinemia can potentially induce hyperplasia of enterochromaffin cells, which secrete histamine, stimulating gastric acid release from parietal cells [47,48,49,50].

In human medicine, hypergastrinemia related to the use of PPIs occurs in 80–100% of the cases [51] and may be a pathogenic factor in the development of gastric carcinoma [52,53]. Animal model studies on gastric hypoacidity and hypergastrinemia have yielded evidence suggesting hypergastrinemia as a common causative factor across various gastric pathologies. In species where sufficient hypoacidity and hypergastrinemia have

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been induced, a subset of animals develops malignant lesions in the gastric oxyntic mucosa [54]. Long-term administration of the proton pump inhibitor omeprazole in rats has been linked to hyperplasia of the oxyntic mucosa and carcinoids. Similarly, short-term omeprazole administration (400 μmol/kg) to rats led to a 15-fold increase in plasma gastrin levels, along with oxyntic mucosa hyperplasia [55,56,57,58]. Gastrin receptors in the oxyntic mucosa are predominantly found in enterochromaffin-like cells, which play a functional role in mucosal growth regulation [59]. Further investigations are warranted to elucidate the potential relationship between the long-term administration of PPIs and mucosa hyperplasia or gastric cancer in dogs and cats.[60]

A study involving 231 dogs with chronic enteropathy receiving antisecretory therapy demonstrated higher levels of serum gastrin in dogs treated with omeprazole. However, serum gastrin levels in these dogs did not exceed 3 times the upper reference limit (URL), excluding the diagnosis of gastrinoma [61]. Notably, the omeprazole group in the present study exhibited mean gastrin levels four times higher than the control group. This could be due to the variability between laboratories, or variability between the different times in which the samples were analyzed. Nonetheless, gastric histological samples were not evaluated in this study.[62,63,64]

A study involving six cats showed that long-term PPI use resulted in increased serum gastrin levels in 83.33% of the sample after 30 days and in 100% of the sample after 60 days [65]. In this study, 100% of dogs exhibited increased serum gastrin levels after 30 days of treatment, with 87.7% showing increased levels after 60 days. This outcome is consistent with the more pronounced hypergastrinemia observed in the initial phase in other studies involving dogs treated with famotidine, where a notable increase in gastrin levels shortly after treatment initiation was detected, followed by a gradual decrease in serum gastrin levels from the second week of treatment onwards [66,67,68,69].

In this study, no statistical differences were found in cobalamin during the long-term administration of omeprazole compared to the control group [70]. Nevertheless, in human medicine, decreases in cobalamin levels have been reported in patients undergoing long-term PPI therapy [71,72]. Dose-dependent decreases have also been noted, with differences observed between the administration of 20 mg or 40 mg capsules [73]. Conversely, more recent studies have not found an association between long-term PPI therapy and decreased cobalamin absorption [74,75,76].

There are no previous studies that relate the use of PPIs with the decrease in cobalamin levels in dogs. In cats, one study evaluated changes in cobalamin levels during long-term omeprazole therapy and found no significant differences in cobalamin serum levels [77]. As the relationship between PPI therapy and cobalamin levels remains controversial in human medicine, and the present study did not detect any changes, it is plausible that cobalamin serum levels may remain stable with long-term omeprazole therapy in dogs. Nevertheless, further studies involving larger populations and longer durations are warranted to validate these findings[78].

In this study, 18.18% of the sample in the omeprazole group exhibited gastrointestinal signs such as diarrhea, contrasting with the control group. There was a higher median fecal score in the study group compared to the control group. This suggests that long-term administration of omeprazole could induce changes in the gastrointestinal microbiome, as described in other studies [79,80]. Diarrhea is the most common adverse effect associated with PPI administration in veterinary medicine; however, the mechanism is not fully understood. Following a 15-day treatment with omeprazole, dogs exhibited an increase in the canine fecal microbiota dysbiosis index [81,82]. It is believed that the effect of PPIs on the gastrointestinal microbiome is partly due to their impact on gastric pH [83]. Additionally, genetic factors such as variability in CYP_{450} expression could result in differences in PPI metabolism among dogs, leading to diarrhea symptoms in some animals but not in others [84].

A veterinary medicine study conducted in healthy dogs receiving omeprazole twice daily for 15 days revealed significant alterations in the gastrointestinal microbiome [85]. Although the microbiome was not a study variable in this research, it is possible that side effects such as diarrhea in 2 out of 11 dogs were due to intestinal dysbiosis. Small intestinal dysbiosis is another widely described adverse effect of chronic PPI administration in humans [86,87]. PPIs increase the survival of ingested bacteria in the upper gastrointestinal tract by reducing intestinal peristalsis, gastric emptying, altering the composition of epithelial mucus, increasing pH, and promoting bacterial translocation. Increased bacterial growth in the upper gastrointestinal tract may elevate the risk of bacterial pneumonia by aspiration [88,89,90].

The main limitations of the current study include the restricted sample size and the absence of a crossover design, which represents an advantage, especially in situations where interindividual variability can be a significant factor to consider. Changes in cobalamin levels observed in humans occurred with longer administrations than the duration of our study. Hence, a more extended administration period may be necessary to assess changes in intestinal absorption of this vitamin with long-term PPI use. Other complications observed in human medicine due to the use of this medication, such as abnormalities in serum iron, calcium, and magnesium levels, leading to alterations in patients' ossification with long-term administration, have been reported. Due to economic constraints in the present study, these parameters could not be evaluated,

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but it would be interesting to assess their implications in future research. Additionally, evaluating the microbiome and parameters of intestinal inflammation, such as calprotectin assessment, would have been beneficial to discern the degree of involvement of PPI-associated dysbiosis in our study.[91,92,93,94]

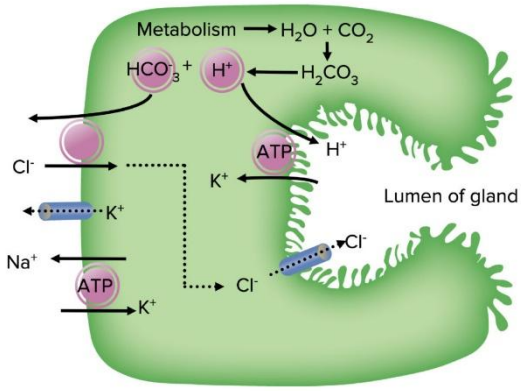

Fig: 2 Mechanism of action of Omeprazole

Therapeutic Uses:

- Gastroesophageal Reflux Disease (GERD): Omeprazole is commonly prescribed to manage GERD by controlling acid reflux and promoting the healing of esophageal mucosa[95,96].
- Peptic Ulcers: Omeprazole is used to treat peptic ulcers caused by Helicobacter pylori infection or nonsteroidal anti-inflammatory drugs (NSAIDs)[97].
- Zollinger-Ellison Syndrome: In this rare condition characterized by excessive gastric acid production, omeprazole helps control acid secretion[98].
- Prevention of NSAID-induced Ulcers: It is often used in conjunction with NSAIDs to reduce the risk of gastric ulcers[99].

Pharmacokinetics:

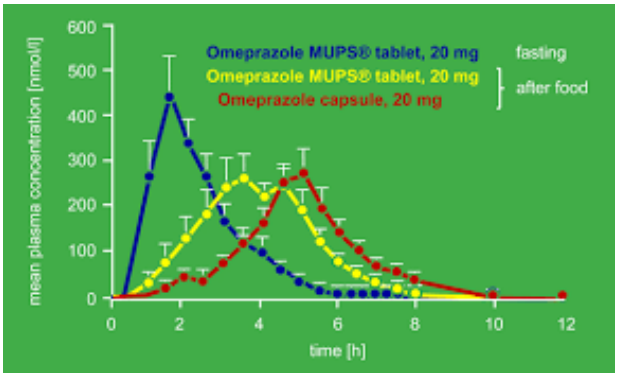

Fig: 3 Pharmacokinetics of omeprazole

- Omeprazole is rapidly absorbed in the small intestine and is highly protein-bound in the plasma[100].
- The drug undergoes extensive metabolism in the liver via the cytochrome P450 system, particularly CYP2C19 and CYP3A4[101].
- Its effects are dose-dependent, and it typically reaches peak plasma concentration within 1-2 hours after administration[102].
- Omeprazole has a half-life of around 1 hour, but its effects can last up to 24 hours due to the prolonged inhibition of the proton pump[103,104].

1. Efficacy: Omeprazole is highly effective in reducing gastric acid secretion, leading to symptom relief in conditions like GERD and peptic ulcers[105]. Long-term therapy can significantly reduce the recurrence of peptic ulcers and help in the eradication of H. pylori when used in combination with antibiotics[106,107].

III. ADVERSE EFFECTS OF OMEPRAZOLE

While omeprazole is generally well-tolerated, it is associated with several adverse effects, particularly when used for prolonged periods[108].

1. Common Adverse Effects:
   - Gastrointestinal Issues: Diarrhea, constipation, nausea, and abdominal pain are relatively common. These side effects are usually mild and transient[109].
   - Headache: This is one of the most commonly reported side effects of omeprazole, particularly during the initial phases of treatment[110].
   - Flatulence: Some individuals experience increased gas and bloating, although this effect is usually mild[111].
2. Long-term or Severe Adverse Effects:
   - Osteoporosis and Bone Fractures: Chronic use of omeprazole, especially at high doses, has been linked to an increased risk of osteoporosis and bone fractures due to reduced calcium absorption[112].
   - Hypomagnesemia: Prolonged omeprazole use may lead to low magnesium levels in the blood, which can cause muscle cramps, seizures, and abnormal heart rhythms[113].
   - Vitamin B12 Deficiency: Long-term inhibition of gastric acid can impair vitamin B12 absorption, leading to deficiencies that can result in anemia, neurological symptoms, and cognitive dysfunction[114].
   - Kidney Issues: There is evidence suggesting an increased risk of chronic kidney disease with prolonged use of PPIs, including omeprazole[115].
   - Gastric Cancer Risk: Long-term use of omeprazole has been associated with an increased risk of gastric cancer, although the association remains controversial and likely

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relates to underlying conditions like atrophic gastritis and H. pylori infection[116,117].

3. Drug Interactions:
   - Omeprazole can interfere with the absorption of drugs that require an acidic environment for optimal absorption, such as certain antifungal agents (e.g., ketoconazole) and iron supplements[118,119].
   - It may also interact with drugs metabolized by CYP2C19 and CYP3A4, leading to altered blood levels of medications like clopidogrel, warfarin, and diazepam[120].
4. Rebound Acid Hypersecretion:
   - Discontinuation of omeprazole, especially after prolonged use, can lead to rebound acid hypersecretion, where the stomach produces even more acid than before.[121]This can cause a recurrence of symptoms like GERD, making it difficult to stop the medication[122,123].
5. Clostridium difficile Infection:
   - The long-term use of proton pump inhibitors like omeprazole has been linked to an increased risk of gastrointestinal infections, particularly C. difficile[124]. The reduction in gastric acid can impair the stomach's ability to kill harmful bacteria, allowing pathogens to proliferate[125].

IV. CONCLUSION

Omeprazole is a highly effective and widely used proton pump inhibitor for managing acid-related gastrointestinal disorders. Its ability to reduce gastric acid secretion offers relief in conditions like GERD, peptic ulcers, and Zollinger-Ellison syndrome. However, while generally safe when used appropriately, long-term or excessive use of omeprazole carries potential risks, including osteoporosis, hypomagnesemia, vitamin B12 deficiency, and kidney damage. Patients on prolonged omeprazole therapy should be monitored for these adverse effects, and healthcare providers should weigh the benefits against the potential risks when prescribing this medication.

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