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Lansoprazole: A Brief Review of Chemistry, Pharmacology, Clinical Efficacy, and Safety

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Abstract

Lansoprazole is one of the most prescribed drugs of choice for the disorders related to acid secretion and ulceration caused therein. The current review presents brief details on its chemistry, pharmacology, clinical efficacy, and safety. The present literature on the drug is vast including several clinical studies that have nearly discussed all possible aspects of the drug. An attempt has been made to put forward the key ideas of the clinical studies results and the outcomes in the real-world setting. This shall help researchers and health care professionals to appreciate the various treatment and prevention options available aiding increased patient compliance and relief. The literature review was undertaken by looking for the keywords associated with lansoprazole, the disorders, the regulatory label and the guidelines available.

Keywords: *Lansoprazole, Peptic Ulcer, Gastro-esophageal Reflux disease, NSAID Ulcer, Safety Profile*

1. Introduction

The drug, lansoprazole, belongs to the Proton Pump Inhibitors (PPIs) category, and their capacity to bind covalently to their targets, PPIs can offer long-term suppression of acid secretion. PPIs are acid-activated prodrugs that convert to sulfenic acids or sulfenamides that bind to one or more cysteines on the ATPase's luminal surface. They have a significantly longer inhibitory impact than their plasma half-life due to covalent bonding. They are weak bases made up of two moieties: a substituted pyridine with a primary pKa of approximately 4.0, which allows for selective accumulation in the parietal cell's secretory canaliculus, and a benzimidazole with a secondary pKa of around 1.0. All PPIs help to repair peptic ulcers and treat reflux esophagitis effectively. Helicobacter pylori are killed by PPIs coupled with antibiotics.[1]

Lansoprazole is an antacid that is authorized for the short-term treatment of active gastric ulcers, active duodenal ulcers, erosive reflux esophagitis, symptomatic gastroesophageal reflux disease, and NSAID-induced gastric and duodenal ulcers.[2]–[4] It decrease the amount of acid produced thus treating and/or preventing stomach and intestinal ulcers and other related mentioned conditions. It is available with the brand names Prevacid, Prevacid Solu tab, Prevacid 24HR in both capsule and orally disintegrating tablet dosage form in 15mg and 30 mg. It may be used to maintain and treat a variety of stomach disorders, such as duodenal ulcers, NSAID-related gastric ulcers, and erosive esophagitis. In individuals with a documented history of stomach ulcers who also use NSAIDs regularly, lansoprazole helps to avoid recurrence. It's also helpful in the treatment of hypersecretory diseases like Zollinger-Ellison syndrome. It has also been used in combination therapies. For instance, When combined with amoxicillin and clarithromycin (triple treatment) or taken alone, lansoprazole is successful at eliminating H. pylori (dual therapy). [4].

2. Chemistry

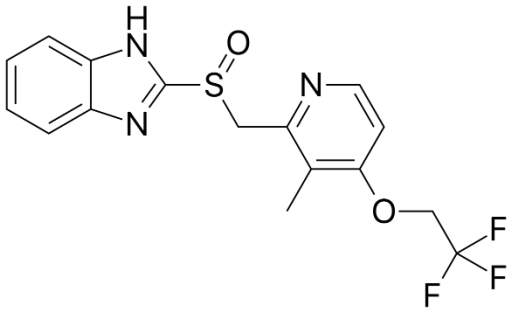


Fig. 1 Chemical structure of Lansoprazole: 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methylsulfinyl]-1H-benzimidazole

Structurally, Lansoprazole is a benzimidazole, a member of pyridines and a sulfoxide consisting of an asymmetric atom in structure and is clinically administered as a racemic mixture of (R) and (S)-enantiomers, R one is called dexlansoprazole [5] Its empirical formula is $C_{16}H_{14}F_3N_3O_2S$ and it has a molecular weight of 369.37. It is soluble in dimethylformamide, ethyl acetate, dichloromethane, and acetonitrile; it is very little soluble in ether, and it is completely insoluble in hexane and water. Decomposition causes it to melt at around 166 degrees Celsius. In an aqueous solution, lansoprazole degrades at a rate that is inversely proportional to pH. It has a half-life of 0.5 hours at pH 5.0 and 18 hours at pH 7.0 at 25 degrees Celsius. When exposed to light for up to two months, lansoprazole remains stable. [3]

3. Pharmacodynamic Properties

Lansoprazole appears to be at least as effective as omeprazole at inhibiting stomach acid secretion in vitro tests. It is less powerful than the H2-receptor antagonists' ranitidine and famotidine but as efficacious as omeprazole in several in vivo animal models. It reduced stomach acid production more effectively when given intravenously rather than orally in animal models, and it was efficacious independent of the initial stimulation.

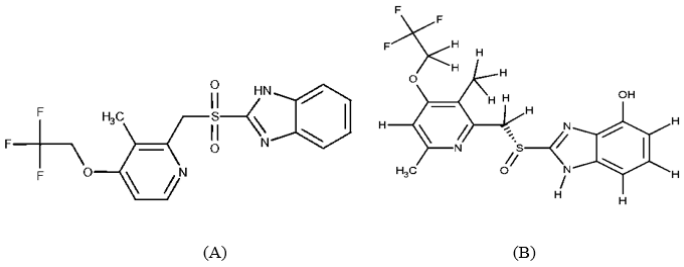
Lansoprazole works by inhibiting H+K+-ATPase, an enzyme in parietal cells that catalysis the final step in the acid secretion route. Unlike H2-receptor antagonists, it suppresses both daytime and nocturnal acid production regardless of when it is taken, making it convenient to take it at any time of day. As a consequence, lansoprazole is helpful in the treatment of duodenal ulcers, the reduction of ulcer-related discomfort, and the alleviation of heartburn symptoms. It also inhibits pepsin production, making it an effective therapy for diseases like Zollinger-Ellison syndrome.[5] It is a prodrug that must be activated by protonation in an acidic environment. It may react with cysteine residues on parietal H+K+-ATPase, especially Cys813 and Cys321, to form persistent disulfides once protonated. [6], [7]

In humans, lansoprazole induces dose-proportional suppression of acid secretion when taken orally in doses ranging from 15 to 60 mg. After a first 30mg dosage, inhibition is about 80%, and after 7 days of therapy with a once-daily 30mg dose, it's around 90%. Lansoprazole also lowers stomach acid secretion volume and inhibits pepsin secretion and activity. In short-term clinical investigations, lansoprazole 30 mg/day for two months produces a near-doubling of serum gastrin levels in individuals with peptic ulcers, although these levels revert to normal within a few days to four weeks after stopping treatment. Lansoprazole 60mg daily significantly raises serum gastrin levels, according to 12-month research. Stomach acid suppression, whether done pharmacologically or surgically, results in increased serum gastrin levels, which do not appear to be related to any substantial alterations in gastric mucosal morphology in people. The formation of enterochromaffin-like cell carcinoids in rats has been linked to the long-term use of various acid-suppressing medications at high dosages.

4. Pharmacokinetic Properties

Lansoprazole is given in an enteric-coated formulation because it is unstable in acidic environments. In some literature, it is mentioned that eating at the same time slows absorption and reduces bioavailability. It has an oral bioavailability of 80-90 per cent [1], and the peak plasma concentration (Cmax) is reached around 1.7 hours after oral administration.[4] Because

food affects lansoprazole absorption (both Cmax and AUC are decreased by 50-70%), patients should be told to take lansoprazole before meals.[4] It has an apparent volume of distribution of 0.4 L/kg. [6] Lansoprazole is linked to plasma proteins in 97 per cent of cases.[4] CYP3A4 and CYP2C19 are the enzymes that break down lansoprazole in the liver. 5-hydroxy lansoprazole and the lansoprazole sulfone derivative are the two main metabolites that arise. [4], [6]



(A) (B)

Fig. 2 Metabolites of Lansoprazole (A) Lansoprazole sulfone derivative (B) Hydroxylansoprazole

The half-life of lansoprazole is reported to be 0.9 - 1.6 hours [1] by one source, and 0.9 - 2.1 hours by another. [6] Lansoprazole has a short half-life of around 2 hours or less, according to most sources. These figures may be deceptive since they imply that lansoprazole has a limited duration of action while, in fact, according to its mode of action, it can effectively suppress acid production for up to 24 hours. [4] In the urine, 14-23% of lansoprazole is reported to be excreted, with this range comprising both conjugated and unconjugated hydroxylated metabolites. The clearance rate is found out to be 400-650 mL/min

5. Clinical Efficacy

Lansoprazole's clinical efficacy has been investigated in the treatment of active duodenal ulcers, maintenance of healed duodenal ulcers, active benign gastric ulcers, short-term treatment of erosive reflux esophagitis, maintenance healing of erosive esophagitis, NSAID-induced gastric and duodenal ulcers, hypersecretory conditions such as Zollinger-Ellison syndrome. Lansoprazole has also been studied in individuals with non-erosive esophagitis for the treatment of heartburn [8] and GERD in pediatric patients.[9]

5.1 Peptic Ulcer Disease

H2-receptor antagonists are less efficient than lansoprazole for healing stomach ulcers. At 2, 4, and 8 weeks, lansoprazole 30 mg daily cured gastric ulcers in 23, 64, and 93 per cent of Japanese subjects, respectively, compared to 9, 38, and 83 per cent of patients who received famotidine 20 mg b.i.d. Another study found that lansoprazole had a better healing rate than ranitidine for treating stomach ulcers. [10] At 4 weeks, the healing rates for lansoprazole 30 mg and 60 mg daily against ranitidine (300 mg) at bedtime were 78, 84, and 61 per cent, respectively. For the treatment of stomach ulcers, lansoprazole outperforms other PPIs. Based on an intention to treat the study, lansoprazole 30 mg daily had a higher healing rate for stomach ulcers at 8 weeks than omeprazole 20 mg daily. When comparing lansoprazole to omeprazole, the study found that lansoprazole took less time to relieve symptoms that is 6.6 days and 11 days.

PPIs are more successful than H2-receptor antagonists in treating duodenal ulcers as a group. Furthermore, PPIs relieve symptoms faster than H2-receptor antagonists.[11] In a study comparing lansoprazole 30 mg and 60 mg daily vs ranitidine 300 mg at bedtime for the treatment of duodenal ulcers, healing rates at 2 weeks were 78, 80, and 60% for lansoprazole 30 mg and 60 mg daily over ranitidine 300 mg at bedtime, respectively. At four weeks, the comparable rates were 93, 97, and 81 per cent. [12] Several trials comparing lansoprazole to omeprazole in the treatment of duodenal ulcers show similar results, despite lansoprazole's better healing rates compared to H2- receptor antagonists.[13]–[16] In two trials, however, the healing rate with lansoprazole (30 mg/day) was higher than with omeprazole (20 mg/day) after two weeks of treatment. In the treatment of duodenal ulcers, one research found a tendency toward better pain reduction with lansoprazole compared to omeprazole after 4 weeks, similar to studies in the treatment of gastric ulcers indicating more immediate alleviation of symptoms with lansoprazole.

In addition to its effectiveness in treating acute duodenal ulcers, lansoprazole was found to be beneficial as a maintenance medication in avoiding duodenal ulcer relapse in a dose-dependent way. At one month, lansoprazole (15 mg/day) decreased ulcer recurrence to 13% of cases, compared to 27% in the placebo group. Duodenal ulcers were cured in 70% of individuals treated with lansoprazole 15 mg daily after a year of treatment. Treatment with lansoprazole (30 mg/day) resulted in an ulcer healing rate of 85 per cent. In another research, individuals with peptic ulcers resistant to ranitidine were given maintenance treatment for up to three years. Endoscopy showed that lansoprazole (30-60 mg/day) for 1–3 years prevented ulcer recurrence in all patients. [17]

5.2 *Helicobacter Pylori*

Due to the importance of Helicobacter pylori in the etiopathogenesis of peptic ulcers, treatment methods aiming at sustaining long-term remission have turned away from controlling intragastric pH and toward targeting H. pylori. According to worldwide recommendations, a combination therapy consisting of an anti-secretory medication (proton pump inhibitor or ranitidine) and two antibacterial drugs is the best way to achieve the therapeutic goals of fast ulcer healing and recurrence prevention (preferable amoxicillin, clarithromycin or metronidazole). Pharmacokinetic considerations may assist to enhance H. pylori eradication rates, which should be above 85 to 90 per cent on an intention-to-treat basis when using such combination regimens, due to potential synergy between the medications. [18]

5.3 NSAID-Related Ulcers

The development of a stomach ulcer is one of the most serious side effects of NSAIDs. In the treatment of benign stomach ulcers caused by NSAID usage, lansoprazole was found to be more effective than ranitidine. After 8 weeks, stomach ulcer healing rates for 150 mg b.i.d., lansoprazole 15 mg daily, and 30 mg daily were 53, 69, and 73 per cent, respectively, for 150 mg b.i.d., lansoprazole 15 mg daily, and 30 mg daily, respectively. Healing rates were comparable whether or not H. pylori infection was present. [19]

5.4 Zollinger-Ellison syndrome

Gastrinomas, which generally occur in the pancreas or duodenum, produce Zollinger-Ellison syndrome. Increased blood gastrin concentrations cause an increase in the number of parietal cells in the stomach, gastric mucosal hypertrophy, and basal gastric acid production in individuals with this disease. Peptic ulcer illness, oesophagitis, and diarrhoea are all symptoms of acid hypersecretion. Pharmacotherapy to reduce acid hypersecretion and/or surgical excision of the gastrinoma is used to treat this condition. Lansoprazole was shown to be beneficial in the treatment of Zollinger-Ellison syndrome in 26 individuals. Following a 60 mg/day start, the lansoprazole dosage was modified to restrict baseline acid production to less than 5 mmol/h in patients with intact stomachs and less than 1 mmol/h in patients with gastrectomy or oesophagitis. Within a few weeks of starting lansoprazole medication, ulcer healing and resolution were accomplished, and the results were maintained for a median of 28 months. [20], [21]

6. Safety Profile of Lansoprazole

Abdominal discomfort, constipation, diarrhoea, and nausea are the most often reported side effects among lansoprazole-treated patients when compared to placebo.[4] A case of toxic epidermal necrolysis (TEN), an uncommon but dangerous cutaneous response induced by lansoprazole, has been reported. 15 days after initiating lansoprazole to treat peptic illness, the previously healthy patient developed TEN symptoms. Although PPI usage is seldom linked to TEN, causality should be explored if a patient develops TEN after using a PPI for the first time.[22] A patient took 600 mg of lansoprazole and had no side effects or overdose symptoms, according to a single case report. Lansoprazole is generally well tolerated, with few side effects. [4]

Pregnancy Category B applies to lansoprazole. Although animal research shows that lansoprazole is safe for the foetus, there is currently a lack of human evidence. As a result, lansoprazole should only be given to pregnant women after all other alternatives with more data have been exhausted. Lansoprazole is not known to be excreted in human breast milk. It's worth noting that lansoprazole has been safely used in babies, so it's probably safe to use when nursing. [23]

7. Drug Interaction

Diazepam, phenytoin, prednisone, warfarin, and oral contraceptives do not appear to be significantly inhibited by lansoprazole.[24]–[27] Lansoprazole appears to have some induction potential based on tests with human hepatocytes in primary culture [28] and research using antipyrine.[27] Several interaction studies have been conducted using theophylline as a CYP1A2 probe. Initially, lansoprazole 30mg once a day for 11 days reduced t1⁄2β, by 12 per cent ($p < 0.05$), but neither AUC nor CL/F indicated a meaningful change.[29] When theophylline 200mg 4 times a day was coadministered, lansoprazole 60mg once daily reduced the AUC modestly (6%) but considerably ($p = 0.02$) during an administration interval. [30]

In contrast, lansoprazole 30 mg twice daily for seven days did not affect theophylline clearance in five Caucasian EMs, six Korean EMs, or even seven CY2C19 PMs. [31] When bioequivalence criteria were used, lansoprazole 60 mg/day did not influence the oral bioavailability of theophylline 350 mg twice daily for 3 days at steady-state conditions.[32] Caffeine metabolism is frequently used to assess in vivo CYP1A2 activity. Once-daily coadministration of omeprazole 20 mg or lansoprazole 30 mg did not affect the EM or PM metabolic ratios of caffeine. [33], [34]

In a study of the delayed MTX elimination group, co-administration of a PPI (omeprazole, lansoprazole, or rabeprazole) was more common than in the regular MTX elimination group. PPI co-administration was found to be a significant risk factor for delayed plasma MTX elimination in a multiple logistic regression analysis with adjustment for relevant variables. The therapeutic unbound concentration in the plasma was considerably greater than the half-maximal inhibitory concentration of each PPI in suppressing BCRP function, suggesting that co-administration of PPIs is a risk factor for delayed elimination. [35]

8. Conclusion

Lansoprazole is one of five proton pump inhibitors (PPIs) that are widely used in most countries. When compared to other PPIs, lansoprazole had a similar rate of erosive oesophagitis and duodenal ulcer healing (omeprazole, rabeprazole, pantoprazole and esomeprazole). Lansoprazole tends to relieve symptoms of reflux oesophagitis or duodenal ulcer sooner than other PPIs. The absence of commercially accessible liquid formulations of PPIs is one of their major drawbacks. The relative instability of PPIs in oral solution precludes the development of a liquid formulation with a long enough shelf life to be commercially viable. Locally, the encapsulated PPIs lansoprazole can be converted into an oral suspension. Patients who cannot swallow capsules, such as babies, children, and the elderly, benefit from this formulation. The oral suspension can also be given to individuals who have gastrostomy tubes. Lansoprazole has a longer history of usage in children than other PPIs. The usage of these drugs during pregnancy is unknown. PPIs were a big step forward in the treatment of acid-peptic diseases. Patients' demand for treatment of heartburn, oesophagitis, and peptic ulcer has grown as a result of these medicines' greater effectiveness compared to H2-receptor antagonists and direct to consumer advertising. These medicines are more expensive than H2-receptor antagonists, putting additional financial strain on healthcare delivery systems, but they provide better effectiveness in the management of acid-peptic illness in individuals with these diseases.

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