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Lansoprazole Oro-Dispersible Tablet

Pharmacokinetics and Therapeutic Use in Acid-Related Disorders

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Contents

Abstract

Lansoprazole is an H^+, K^+-adenosine triphosphatase proton pump inhibitor (PPI) used for management of acid-related disorders. Lansoprazole has been reformulated as an oro-dispersible tablet (LODT) that quickly dissolves in the mouth without water. In healthy adults the safety and bioavailability of LODT 15–30mg, taken without water or dispersed in water, were found to be comparable with those of lansoprazole 15–30mg capsules. Moreover, the bioavailability of LODT administered without water has been found to be similar to that of water-dispersed LODT given via a nasogastric tube. In a clinical study, the vast majority of patients found the mouth feel of LODT acceptable and almost all found it easy to take. A comparison of LODT with esomeprazole in a small group of patients with non-erosive reflux disease showed similar decreases in symptoms from baseline and no significant difference between groups.

In conclusion, LODT is effective, bioequivalent to the capsule formulation and acceptable to patients. LODT offers an alternative dose administration method to all patients requiring a PPI, especially those who have difficulty swallowing, and may increase patient convenience and compliance.

Acid-related disorders comprise upper gastrointestinal symptoms and/or mucosal lesions that are causally linked to the hydrochloric acid produced by the stomach. They can range from occasional heartburn or acid reflux to severe oesophagitis and gastric or duodenal peptic ulcers. Acid-related disorders contribute substantially to the direct costs of medical care.[1] Lifetime prevalence of reflux symptoms is estimated to be >40% in the US population[2] and heartburn symptoms are experienced by 7–10% of Western populations each day.[3]

The most effective suppressors of gastric acid secretion are undoubtedly the gastric H^+, K^+-adenosine triphosphatase proton pump inhibitors (PPIs). Consequently, these agents have found worldwide popularity over the past decade as therapy for acid-related disorders. Currently, there are several different PPIs available for clinical use: omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole.

Lansoprazole has the most consistently high bioavailability of any PPI after the first dose (80–91%).[4-9] Accordingly, acid production is rapidly inhibited following lansoprazole administration[6] and extensive clinical experience has shown it to be an effective and well tolerated treatment option in the management of acid-related disorders.[10] In addition, lansoprazole is effective in the treatment or prevention of gastroduodenal lesions induced by NSAIDs or Zollinger-Ellison disease, and in *Helicobacter pylori* eradication when used in combination regimens including antibacterials.[11,12] Lansoprazole has recently been reformulated as a fast-acting, oro-dispersible tablet (lansoprazole orodispersible tablet [LODT]), thus providing an alternative formulation for many patients who find earlier formulations inconvenient or difficult to take. This article reviews pharmacokinetic and clinical data from LODT studies.

1. Pharmacokinetics and Oral Proton Pump Inhibitor Formulations

PPI agents enter parietal cells from the blood and, because of their weak basic nature, accumulate in the acid secretory canaliculi, where they are activated by a proton-catalysed process that results in the formation of a thiophilic sulphenamide or sulphenic acid.

PPIs are unstable at a low pH. Delayed-release oral dosage forms are supplied as enteric-coated granules encapsulated in a gelatine shell (e.g. omeprazole capsules and lansoprazole capsules) or as enteric-coated tablets (e.g. pantoprazole tablets, rabeprazole tablets and omeprazole multiple unit pellet system [MUPS]). The granules dissolve only at an alkaline pH, thus preventing degradation of these drugs by acid in the stomach. PPIs are rapidly absorbed, highly protein-bound and extensively metabolised in the liver by the cytochrome P450 (CYP) system (particularly CYP2C19 and CYP3A4); their sulfated metabolites are excreted in the urine and faeces. The plasma half-lives of PPIs are all about 1–2 hours but their durations of action are much longer.[13,14]

Most PPI tablets (e.g. rabeprazole) are formulated as an enteric-coated, single-unit system, that is, a tablet with a gastric acid-resistant layer only on its outer surface. There is a risk that the enteric coat of such tablets can become damaged during gastric emptying. As PPIs are acid labile, a small crack or damage to a single-unit system may, therefore, affect the entire dose. Multiple unit systems have been developed to overcome this problem.[15] Common formulations of multiple unit systems include both capsules and tables containing enteric-coated granules. The very small size and multiple coatings of these granules means that they are less likely to be damaged during gastric emptying,[16] and so absorption issues are minimised. If a granule is damaged and a crack develops on the surface, only a small portion of active substance is likely to be affected.

Table I. Formulations of proton pump inhibitors in European countries (availability of formulations differs between European countries)

Omeprazole	Lansoprazole	Pantoprazole	Rabeprazole	Esomeprazole
MUPS tablet: 10, 20, 40mg Capsule: 10, 20, 40mg IV injection and infusion: 40mg OTC: 10mg capsule	Delayed-release capsule: 15, 30mg Oro-dispersible tablet: 15, 30mg Suspension: 30mg	Delayed-release tablet: 20, 40mg IV (as sodium): 40mg for injection/ infusion	Delayed-release tablet: 10, 20mg	MUPS tablet: 20, 40mg IV: 40mg powder for solution for injection/ infusion

IV = intravenous; **MUPS** = multiple unit pellet system; **OTC** = over-the-counter.

The lansoprazole capsule and omeprazole MUPS are examples of multiple unit systems. While enteric coating of oral formulations is beneficial for ensuring that PPI agents are effectively delivered, it does mean that the individual dose administration unit, be it a tablet or a granule-containing capsule, is relatively large. This poses a challenge to the routine use of oral PPIs in critically ill patients or in patients unable to swallow adequately. Table I summarises the currently available formulations of PPIs in European countries.

The LODT is a new formulation, containing much smaller microgranules than lansoprazole capsules (330 vs 1100μg). The tablet disintegrates rapidly (within 30 seconds) in the mouth without water. Unlike the granules in lansoprazole capsules, which have a core, a lansoprazole layer and a gastroresistant enteric coating, each LODT microgranule comprises seven layers.[17] The active lansoprazole layer surrounds an inert core, followed by an inert undercoating layer that improves stability in high humidity. Three enteric-coating layers prevent dissolution in the stomach, improve stability, reduce damage during compression and neutralise the taste of the microgranule. An outer layer increases the hardness of the tablet.[17]

1.1 Bioavailability of Lansoprazole Oro-Dispersible Tablet

When LODT disintegrates in the mouth the microgranules are swallowed with the patient's saliva. The enteric-coated microgranules dissolve in the neutral condition of the small intestine and lansoprazole is absorbed into the bloodstream. In two studies reported by Freston et al.,[18] the safety and bioavailability of LODT taken without water were compared with those of lansoprazole capsules taken in a single dose of 15 or 30mg. Each study enrolled 60 healthy adults and utilised a randomised, open-label, single-centre, two-period, crossover design with a 7-day washout interval. The mean plasma concentration profiles were comparable for LODT and lansoprazole capsules at both 15 and 30mg doses. The 90% confidence intervals for maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) were within the 0.80–1.25 range, indicating that LODT was bioequivalent to capsules at both doses.

Since LODT can be taken with or without water, a study was performed to assess the bioavailability of lansoprazole following the administration of LODT dispersed in water, compared with that following administration of LODT placed directly on the tongue.[19] Forty healthy adults received two single 15mg LODT doses in a randomised, crossover design. Doses were separated by 3 days, one administered directly onto the tongue without water and one dispersed in 4mL of water and administered orally via a syringe. Serial blood samples, for the determination of lansoprazole plasma concentrations, were drawn from 0 to 12 hours after each dose. Both dose administration options resulted in similar mean lansoprazole plasma concentration profiles and overall extent (AUC) and rates (C_{max}) of lansoprazole absorption that were statistically indistinguishable from each other. Similar results were obtained in 36 healthy volunteers aged between 18 and 44 years in an open, single-dose, two-

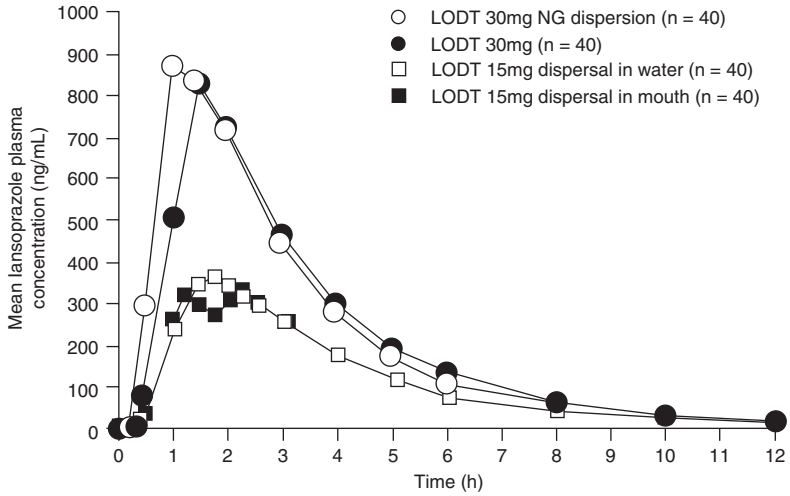

Fig. 1. Mean lansoprazole plasma concentrations after a single dose of lansoprazole oro-dispersible tablet (LODT) 15mg or 30mg dispersed in the mouth, 15mg dispersed in water before swallowing, and 30mg dispersed in water and administered via a nasogastric (NG) tube.[20,21]

period crossover study. The patients received LODT 15mg dispersed in the mouth and LODT 15mg dispersed in 40mL of water.[20] Dispersal of LODT in water prior to administration was found to be bioequivalent to dispersal of the tablet in the mouth (see figure 1).

The greater flexibility of the LODT formulation was tested in a more recent study[21] undertaken to assess whether the administration of LODT dispersed in water through a nasogastric (NG) tube had an effect on the pharmacokinetic profile of lansoprazole. Forty healthy adults were enrolled in this study. Each patient received 30mg doses of lansoprazole in a randomised crossover fashion, with each dose separated by at least 3 days. The intact LODT was administered directly onto the tongue, without water, and the LODT dispersed in 10mL of water was administered via an NG feeding tube. Blood samples for determination of lansoprazole plasma concentrations were drawn serially over the first 12 hours after drug administration. Mean lansoprazole plasma concentration profiles were similar following administration of both dose administration regimens (see figure 1). Both the intact LODT and the LODT NG dispersion showed rapid absorption, reaching C_{max} within 1–2 hours of dose administration, and producing equivalent overall lansoprazole plasma exposure (AUC). As expected, time to C_{max} (t_{max}) for the LODT NG dispersion occurred slightly earlier and C_{max} values for lansoprazole were 20.9% greater than corresponding values for the intact LODT. However, this increase is not considered clinically significant.[22] This study demonstrates that, when dispersed in water, LODT provides an alternative dose administration method for patients with severe swallowing difficulties, including those with NG or gastric tubes.

In a recent study examining LODT in extensive metabolisers,[23] orally administered LODT 15 and 30mg were shown to be bioequivalent to lansoprazole 15 and 30mg capsules.

2. Clinical Experience

2.1 Patient Acceptability

Lansoprazole is indicated for all patients with acid-related disorders. LODT offers an alternative formulation for patients requiring a PPI, particularly those who find conventional oral dosage forms in-

convenient or difficult to swallow. A study was carried out to establish how, given the choice, patients chose to take LODT, and the acceptability of the tablet following their preferred mode of administration.[24] General practitioners (GPs) in the UK recruited 156 patients who were already taking lansoprazole 30mg capsules daily. After taking one LODT 30mg each day for 4 days (2 days dispersed in the mouth and 2 days swallowed whole with water in a random order), the patients were given the choice of how to take the tablet for the rest of the week (3 days). Patients completed a daily diary of questions relating to taste, ease of administration and preference. Eighty-six patients (55%) chose to take the tablet dispersed in the mouth on ≥1 days and 94% of them considered the 'mouth feel' acceptable. Practically all patients found the tablet easy or very easy to take and a higher proportion (70%) of patients who dispersed the tablet preferred it to the capsule formulation.

2.2 Physician Satisfaction

In order to assess physicians' satisfaction with LODT, a study was carried out in Italy through telephone interviews with a random sample of 100 GPs, 150 gastroenterologists, 20 oncologists, 20 rheumatologists and 20 cardiologists.[25] The interviews were carried out by a team of interviewers trained on the study objectives and methodology, from 25 November to 5 December 2003, 3 months after the introduction of the new lansoprazole formulation to the market. All respondents remembered the name of the new formulation of lansoprazole. Furthermore, the majority of gastroenterologists (84%) and GPs (77%) claimed to prescribe LODT, while only 38% of the other specialists prescribed the new formulation. The indications for which LODT was prescribed were the same as for capsules: most frequently gastro-oesophageal reflux disease (GORD), oesophagitis, gastritis and protection of gastric mucosa. As expected, this latter indication represented the most frequent indication (57%) prescribed for by specialists other than gastroenterologists. LODT was prescribed for patients of all ages; on average, 84% of prescriptions were for patients receiving a PPI for the first time. The most frequently used dose of LODT was 30mg and in most cases it was prescribed once daily. Finally, when asked to describe the most interesting features of the new lansoprazole formulation, all respondents stressed its rapidity of action, good efficacy and ease of administration.

2.3 Efficacy

Lansoprazole represents an effective and well tolerated treatment option in the management of acid-related disorders. LODT retains the same pharmacological properties as the lansoprazole capsule and may potentially improve patient compliance. However, data concerning the clinical efficacy of LODT are still lacking. A preliminary study was recently performed in Italy with the aim of evaluating the effectiveness of LODT compared with esomeprazole in the relief of symptoms (pyrosis/regurgitation) and to assess patient compliance.[26] In this open-label, randomised, crossover study, 52 patients with typical reflux symptoms in the absence of oesophagitis (non-erosive reflux disease [NERD]) were assigned to one of two arms: 2 weeks LODT 30mg once daily → 2 weeks washout → 2 weeks esomeprazole 40mg once daily; or 2 weeks esomeprazole 40mg once daily → 2 weeks washout → 2 weeks LODT 30mg once daily. Patients who did not relapse during the washout period discontinued the study. Symptoms were evaluated before and after each treatment period using a 10-point visual analogue scale and a 4-point rating scale (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe). Forty-six patients completed the first treatment period and 43 completed the second treatment period. Results from each period showed a statistically significant decrease ($p < 0.01$) in symptoms with both

study drugs versus baseline; there was no significant difference between the two treatment regimens, as assessed with the equivalence test (see figure 2). Forty patients expressed a preference for one of the two drugs. Of these, 24 patients (60%) preferred LODT and 16 (40%) preferred esomeprazole. This study indicates that LODT is effective in the relief of symptoms in patients with NERD. A higher proportion of patients preferred the LODT formulation compared with esomeprazole, although the difference was not statistically significant. Additional larger studies in routine practice are necessary to confirm these preliminary results.

3. Discussion

Clinical studies during the last decade have clearly demonstrated that PPIs are the most effective drugs for the treatment of acid-related disorders, including GORD, gastric and duodenal ulcers, and NSAID-induced lesions. Oral formulations of these drugs are usually capsules or tablets containing enteric-coated granules. LODT is the most recent and innovative PPI oral formulation. LODT disintegrates rapidly in the mouth and can be swallowed with the patient's saliva without water. Pharmacokinetic studies have shown that this new formulation is bioequivalent to the lansoprazole capsule in terms of plasma concentrations reached after oral administration, so that its effect, in terms of efficacy and safety, will be the same. A clinical study carried out to assess the efficacy of LODT 30mg once daily in the relief of reflux symptoms in patients with NERD showed that it significantly reduced patients' symptoms at the end of the 2-week period of administration.[26]

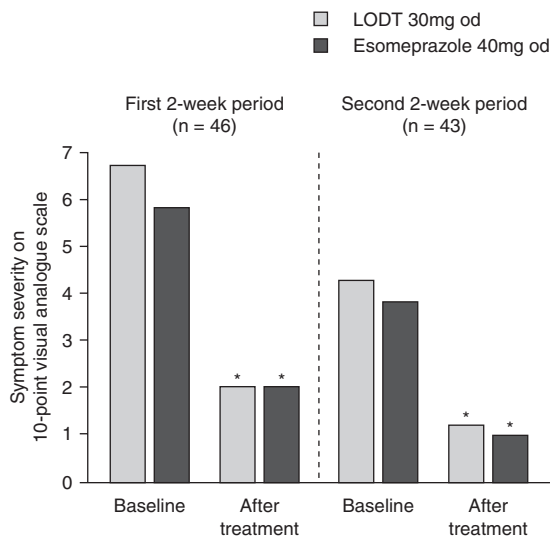

Fig. 2. Efficacy as measured by a patient-rated visual analogue scale of lansoprazole oro-dispersible tablet (LODT) and esomeprazole versus baseline from an open-label, randomised, crossover study in patients with non-erosive gastro-oesophageal reflux disease.[26] **od** = once daily.* $p < 0.01$ vs baseline.

LODT can be taken with or without water, thus offering an alternative to patients and physicians. A study performed in the UK, in which 156 patients who were already taking lansoprazole capsules were switched to take LODT, demonstrated that the majority of the patients chose to disperse the drug without water and 70% of these patients preferred LODT to the capsule formulation. The strawberry flavour of LODT may help to stimulate saliva production and is appreciated by patients of all ages.[25] The acceptability of LODT as a drug that can be taken without water clearly increases convenience for some patients since it can be taken anywhere and anytime, and this would be expected to also improve compliance.

There is no clear recommendation for the timing of PPI administration. Morning dose administration has become standard procedure with PPIs but there are few data to support this recommendation.[27-29] Studies measuring 24-hour gastric acidity after lansoprazole 30mg administration in healthy volunteers have shown no difference between dose administration in the morning and evening[28] or during the night interval.[30] More recently, a study that measured gastro-oesophageal reflux in 96 patients with oesophagitis[31] showed that after 6 months' maintenance treatment with lansoprazole (15mg once daily

or 30mg on alternate days), no significant differences were observed when comparing morning with evening administration. These results show that the timing of lansoprazole administration does not influence the clinical outcome of treatment and suggest that the time of drug administration can be symptom-driven. Therefore, as the LODT can be administered at any time, it may be particularly convenient for those patients undergoing long-term on-demand treatment.

Studies performed in healthy volunteers have clearly demonstrated that the administration of LODT dispersed in water, either orally via a syringe[19] or intragastrically via an NG tube,[18] does not affect the bioavailability of the drug. Administration via an NG tube or a gastrostomy may be useful in patients with severe dysphagia, for example those with neurological disorders. LODT via NG tube would be cost-saving compared with intravenous PPIs. The specific patient populations with most potential to benefit from LODT are those with oesophageal stricture, those with oro-pharyngeal and upper gastrointestinal malignancies, and patients in the intensive care unit.

The elderly are another large population likely to benefit from the LODT formulation as dysphagia and aspiration are very common in elderly patients, and have been reported to be present in up to 40–60% of nursing home residents.[32] Furthermore, LODT is also likely to be of benefit in the general paediatric population, where reflux symptoms may be present in up to 8% of patients.[33]

4. Conclusion

In conclusion, this new lansoprazole formulation provides flexibility for patients who need a PPI, and may also aid patient compliance. When dispersed in the mouth and swallowed with saliva it provides a convenient option for all patients, particularly the elderly and busy younger patients. When LODT is dispersed in water it provides an alternative (which is more cost saving than intravenous formulations) for patients with NG or gastric tubes in hospital or long-term care settings, thus increasing the spectrum of PPI therapy.

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