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Review Article

Clinical Pharmacology of Lansoprazole in Infants and Children

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- Lansoprazole
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- Metabolism
- Pharmacokinetics
- Treatment
- Drug-interaction
- Infants
- Children

Abstract

Lansoprazole is a proton pump inhibitor and is a prodrug. After absorption into the systemic circulation, the prodrug diffuses into the parietal cells of the stomach and accumulates in the acidic secretory canaliculi. Here, it is activated by proton-catalysed formation of a tetracyclic sulfenamide trapping the drug so that it cannot diffuse back across the canalicular membrane. The activated form then binds covalently with sulfhydryl groups of cysteine in the H+, K+-ATPase irreversibly inactivating the pump molecule. Acid secretion resumes only after new pump molecules are synthesized and inserted into the luminal membrane, providing a prodrug (up to 24 to 48 hours) suppression of acid secretion, despite the much shorter plasma elimination half-life of about 0.5 to 3 hours of the parent compound. Lansoprazole is used to promote healing of gastric and duodenal ulcers, and to treat gastroesophageal reflux disease, including erosive esophagitis. In newborns, the oral lansoprazole is 0.2 to 0.3 mg/kg once-daily, and in children, lansoprazole dose varies with the child body-weight. Lansoprazole has been found efficacy and safe in infants and children. Lansoprazole is converted into hydroxy lansoprazole by CYP2C19 and into lansoprazole sulfone by CYP3A4. The elimination half-life is less than 1 hour in infants and children. The treatment of infants and children with lansoprazole has been extensively studied and lansoprazole interacts with drugs. The aim of this study is to review lansoprazole dosing, efficacy and safety, pharmacokinetics, and the treatment in infants and children, and lansoprazole metabolism and interaction with drugs.

INTRODUCTION

Proton pump inhibitors (PPIs)

The most potent suppressors of gastric acid secretion are inhibitors of the gastric H^+, K^+-ATPase or proton pump. These drugs diminish the daily production of acid (basal and stimulated) by 80 to 95% [1].

Mechanism of action and pharmacology of PPIs

Six PPIs are available for clinical use: omeprazole, its S-isomer esomeprazole, dexlansoprazole, rabeprazole, prazole, lansoprazole and its R-enantiomer, dexlansoprazole, rabeprazole, and pantoprazole. All PPIs have equivalent efficacy at comparable doses. PPIs are prodrugs that require activation in acid environments. After absorption into the systemic circulation, the prodrug diffuses into the parietal cells of the stomach and accumulates in the acidic secretory canaliculi. Here, it is activated by proton-catalysed formation of a tetracyclic sulfenamide trapping the drug so that it cannot diffuse back across the canalicular membrane. The activated form then binds covalently with sulfhydryl groups of cysteine in the H^+, K^+-ATPase irreversibly inactivating the pump molecule. Acid secretion resumes only after new pump molecules are synthesized and inserted into the luminal membrane, providing a prolonged (up to 24 to 48 hours) suppression of acid secretion, despite the much shorter plasma elimination half-life of about 0.5 to 3 hours of the parent compounds. Because they block the final step in acid production, the PPIs effectively suppress stimulated acid production, regardless of the physiological stimulus, as well as basal acid production. The amount of H^+, K^+-ATPase increases after fasting; therefore PPIs should be given before the first meal of the day. In most individuals, one-daily dosing is sufficient to achieve an effective level of acid inhibition, and a second dose, which is occasionally necessary, can be administered before an evening meal. Rebound acid hypersecretion occurs following prolonged treatment with PPIs, and clinical studies suggest that rebound after ceasing treatment can provoke symptoms such as dyspepsia. To prevent degradation of PPIs by acid in the gastric lumen and improve oral bioavailability the oral dosage forms are supplied in different formulations: (1) enteric-coated pellets with gelatin capsules (omeprazole, dexlansoprazole, esomeprazole, lansoprazole, and rabeprazole), (2) delayed-release tablets (omeprazole formulations), (3) delayed release capsules (dexlansoprazole, esomeprazole formulations), (4) enteric-coated microgranules in orally disintegrated tablets (lansoprazole), (5) enteric-coated tablets (pantoprazole, rabeprazole, and omeprazole), (6) powered omeprazole combined with sodium bicarbonate (capsules and oral suspension). The delayed release and enteric-coated tablets dissolve only at alkaline pH, whereas mixture of omeprazole with sodium bicarbonate simply neutralizes stomach acid; both strategies substantially improve the oral bioavailability of these acid-labile drugs. Patients for

whom the oral route of administration is not available can be treated parenterally with omeprazole sodium or pantoprazole [1].

Therapeutic uses of PPIs

Prescriptions PPIs are primarily used to promote healing of gastric and duodenal ulcers and to treat gastroesophageal reflux disease, including erosive esophagitis, which is either complicated or unresponsive to treatment with H^2 receptor antagonists. They are also used in conjunction with antibiotics for the eradication of pathological hyper-secretory conditions, including the Zollinger-Ellison syndrome. Lansoprazole, pantoprazole, and esomeprazole are approved for treatment and prevention or recurrence of nonsteroidal anti-inflammatory drugs-associated gastric ulcers in patients who continue nonsteroidal anti-inflammatory drugs use. It is not clear if PPIs affect the susceptibility of nonsteroidal anti-inflammatory drug-induced damage and blending in the small and large intestine. All PPIs are approved for reducing the risk of duodenal ulcer recurrence associated with Helicobacter pylori infection. Over-the-counter omeprazole, esomeprazole, and lansoprazole are approved for the self-treatment of acid reflux [1].

Therapeutic use of lansoprazole in infants and children

Whether gastroesophageal reflux causes apnoea in premature infants has long been a controversial issue. Medications to reduce acid production (and thus reflux), nonetheless, are frequently prescribed both in the neonatal intensive care unit and at discharge. Use of the proton pump inhibitors lansoprazole, omeprazole, and esomeprazole has been reported in newborns and older infants but they are widely and somewhat indiscriminately prescribed. Lansoprazole, approved for marketing in 1995, is a racemic mixture of enantiomers dexlansoprazole and levolansoprazole. It is used to suppress gastric acid secretion when endoscopically-proven oesophagitis or peptic ulceration persists despite treatment with H^2-receptor antagonists. Use is not of benefit in most young children with simple gastroesophageal reflux [2]. Lansoprazole is used to treat reflux oesophagitis. Lansoprazole inhibits gastric acid secretion by inhibiting of H^+, K^+ ATPase the enzyme responsible for the final step in the secretion of hydrochloric acid by the gastric parietal cell ("proton pump"). Lansoprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4. Onset of lansoprazole action is within one hour of administration maximal effect is approximately 1.5 hours. The average elimination half-life is 1.5 hours in infants and young children. The inhibition of acid secretion is about 50% of maximum at 24 hours and the duration of action is approximately 72 hours. The absorption of weakly acid drugs such as digoxin and furosemide is enhanced and the absorption of weakly basic drugs such as ketoconazole is inhibited [3] (Figure 1).

LITERATURE SEARCH

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "lansoprazole dosing infants, children", lansoprazole efficacy safety infants, children", "lansoprazole metabolism", "lansoprazole pharmacokinetics infants, children", "lansoprazole treatment infants, children", and "lansoprazole drug interactions". In addition, the books: The Pharmacological Basis of Therapeutics [1], Neonatal Formulary [2], NEOFAX® by Young and Mangum [3], and The British National Formulary for Children [4], have been consulted.

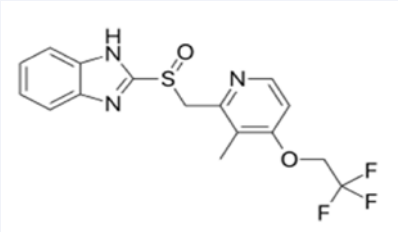

Figure 1 Lansoprazole molecular structure (molecular weight = 369.363 grams/mole).

RESULTS

Administration schedules to infants and children

Administration to infants [2].

Newborns. Give: 0.2 to 0.3 mg/kg once-daily orally.

Infants beyond the neonatal period: In younger infants start with 0.5 to 1 mg/kg given orally once-daily. Older infants, aged > 10 weeks, may be treated with 1 to 2 mg/kg once-daily (subject to a maximum dose of 15 mg daily). While once-daily will reduce oesophageal acid exposure and gastric acidity in most subjects, it appears to have little impact on many symptoms and signs traditionally associated with neonatal and infant reflux in the absence of gastroesophageal reflux disease complicated by erosive oesophagitis.

Administration to children [4].

Oral treatment of benign gastric ulcer

Children with body-weight up to 30 kg. Give: 0.5 to 1 mg/kg once-daily to be taken in the morning.

Children with body-weight of 30 kg and above. Give: 15 to 30 mg once-daily, the dose should be taken in the morning.

Oral treatment of duodenal ulcer

Children with body-weight up to 30 kg. Give: 0.5 to 1 mg/kg once-daily (maximum per dose = 15 mg once-daily), the dose should be taken in the morning.

Children with body-weight of 30 kg or above. Give: 15 to 30 mg once-daily, the dose should be taken in the morning.

Oral treatment of nonsteroidal anti-inflammatory drugs-associated with duodenal ulcer. Nonsteroidal anti-inflammatory drug-associated with gastric ulcer

Children with body-weight up to 30 kg. Give: 0.5 to 1 mg/kg once-daily (maximum per dose = 15 mg once-daily), the dose should be taken in the morning.

Children with body-weight of 30 kg or above. Give: 15 to 30 mg once-daily, the dose should be taken in the morning.

Oral treatment of gastroesophageal reflux disease

Children with body-weight up to 30 kg. Give: 0.5 to 1 mg once-daily (maximum per dose = 15 mg once-daily), the dose should be taken in the morning.

Children with body-weight of 30 kg or above. Give: 15 to 30 kg once-daily, the dose should be taken in the morning.

Oral treatment of acid-related dyspepsia

Children with body-weight up to 30 kg. Give: 0.5 to 1 mg/kg once-daily (maximum per dose = 15 mg once-daily), the dose should be taken in the morning.

Children with body-weight of 30 kg or above. Give: 15 to 30 mg once-daily, the dose should be taken in the morning.

Oral treatment of fat malabsorption despite pancreatic enzyme replacement therapy in cystic-fibrosis

Children with body-weight up to 30 kg. Give: 0.5 to 1 mg/kg once-daily (maximum per doe = 15 mg once-daily), the dose should be taken in the morning.

Children with body-weight of 30 kg or above. Give: 15 to 30 mg once-daily, the dose should be taken in the morning.

Efficacy and safety of lansoprazole in infants and children

The treatment of gastroesophageal reflux disease is significantly higher with lansoprazole plus metoclopramide than with ranitidine plus metoclopramide in infants [5]. Lansoprazole, omeprazole, and esomeprazole effectively treat gastroesophageal reflux disease in infants [6]. Lansoprazole given at a dose of 15 mg or 30 mg once-daily reduces symptoms of gastroesophageal reflux and erosive esophagitis in adolescents [7]. Lansoprazole is efficacious in healing erosive esophagitis and in relieving gastroesophageal reflux disease-related symptoms in children [8]. A 12-week course of lansoprazole, administered at a dose of 1.5 mg/kg once-daily, is effective both in healing oesophagitis and improving gastroesophageal reflux disease symptoms in children [9]. Lansoprazole is effective and safe in children with gastroesophageal reflux disease and the optimal starting dosage is 30 mg/m^2 or 1.4 mg/kg once-daily [10]. Lansoprazole, given at a dose of 15 mg or 30 mg once-daily for 5 days, produces significant increases in intragastric pH and effectively relieves symptoms of gastroesophageal reflux disease in adolescents [11].

Metabolism of lansoprazole

The formation of hydroxy lansoprazole is catalysed by CYP2C19 and the formation of lansoprazole sulfone is catalysed by CYP3A4. Lansoprazole is a racemate and the intrinsic clearance of formation of both hydroxy lansoprazole and lansoprazole sulfone from S-lansoprazole is 4.9 and 2.4-fold higher than those from the R-lansoprazole [12] (Figure 2, 3, 4).

Pharmacokinetics of lansoprazole in infants: Ward and Kearns [13] studied the pharmacokinetics of lansoprazole in 12 infants with postnatal age of 4.3 weeks (range, 1 to 19) and lansoprazole was administered orally at a dose of 1.4+0.19 once-daily. Infants were suffering from gastroesophageal reflux disease (Table 1).

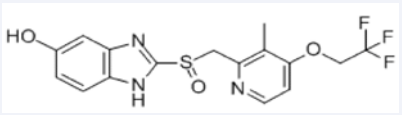

Figure 2 5-Hydroxy lansoprazole molecular structure (molecular weight = 385.36 grams/mole).

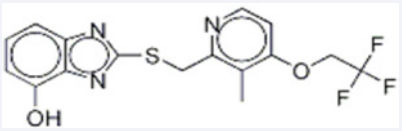

Figure 3 4-hydroxy lansoprazole molecular structure (molecular weight = 385.36 grams/mole).

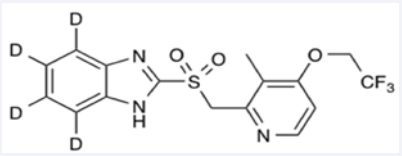

Figure 4 Lansoprazole sulfone molecular structure (molecular weight = 385.4 grams/mole).

Pharmacokinetics of lansoprazole in children: Faure et al. [14], investigated the pharmacokinetics of lansoprazole in 23 children, aged 3.5 years (range, 3 months to 13 years), with gastroesophageal reflux disease. Table 2 reports the child age and lansoprazole dose and table 3 summarizes the pharmacokinetic parameters of lansoprazole.

This Table 3 shows that AUC values are greater in children of group A than in children of group B and C, the total body clearance is greater in children of group B than in children of groups A and C, and the elimination half-life is similar to that obtained in infants (for comparison with infants see table 1).

Treatment of infants and children with lansoprazole: After 5 days of administration, lansoprazole is well tolerated and increases intragastric pH in paediatric subjects aged < 1 year [15]. Lansoprazole treats children with gastroesophageal reflux disease [16]. Lansoprazole treats gastroesophageal reflux disease in children [17]. Omeprazole and lansoprazole are safe and effective medications in children with gastroesophageal reflux disease [18]. Treatment with lansoprazole improves gastroesophageal reflux disease symptoms in children [19]. Lansoprazole treatment may be considered in early management of gastroesophageal reflux disease in children [20]. Omeprazole, lansoprazole, and esomeprazole treat gastroesophageal reflux disease in children [21]. Lansoprazole, omeprazole, and esomeprazole maintain high level of pharmacologic efficacy in the treatment of children with gastroesophageal reflux disease [22]. Lansoprazole is a useful and well tolerated agent in the management of acid-related disorders in children [23]. In children, lansoprazole dosage range used for the management of gastroesophageal reflux disease and related disorders is 0.73 to 1.66 mg/kg once-daily (maximum 30 mg once-daily) [24]. Oral lansoprazole, given at a dose of 30 mg on the night before surgery

Table 1: Pharmacokinetic parameters of lansoprazole which are obtained in 12 infants. Figures are the mean±SD, by Ward and Kearns [13].

Parameter	Value
$AUC_{0\text{-}24h}$ (nmol*h/ml)	1,901±770
Tmax (h)	1.4±0.9
Peak concentration (ng/ml)	894±345
Elimination half-life (h)	0.66±0.30
This table shows that lansoprazole is rapidly absorbed as Tmax is 1.4 hours and lansoprazole is rapidly eliminated as the elimination half-life is 0.66 hours.	

Table 2: Child age and lansoprazole dosing schedules. Figures are the mean±SD, by Faure et al. [14].

Group	N	Child age (years)	Lansoprazole dose (mg/m²)*	Lansoprazole dose (mg/kg)*
Group A	9	5.0±4.1	16.9±17	0.73±0.11
Group B	6	1.3±1.6	30.3±5.0	1.44±0.17
Group C	8	5.5±4.1	32.1±4.3	1.36±0.32
*Lansoprazole was administered orally.				

Table 3: Pharmacokinetic parameters of lansoprazole, lansoprazole was given at the dose of 17 mg/m². Figures are the mean±SD, by Faure et al. [14].

Group	N	Peak conc, (ng/ml)	AUC (ng*h/ml)	TBC (L*kg/h)	§Half-life (h)
Group A	9	641±408	2,034±1,679	0.76±0.77	0.77±0.4
Group B	6	291±264	479±356*	2.94±2.38*	0.75±0.27
Group C	8	394±301	737±611*	2.26±2.80	0.93±0.64
TBC = total body clearance. §Elimination half-life. *P-value < 0.05 (Mann-Whitney test).					

or on the morning of surgery, improves gastric environment at the time of induction of anaesthesia in paediatric patients [25].

Interaction of lansoprazole with drugs: Lansoprazole has minimal effect on quizartinib pharmacokinetics indicating that quizartinib can be co-administered with lansoprazole [26]. Lansoprazole reduces the hepatic clearance of voriconazole [27]. Lansoprazole intensifies the effects of warfarin and causes bleeding events [28]. The interaction between proton pump inhibitors, such as lansoprazole, and clopidogrel causes death and myocardial infarction in 11% of patients [29]. A proton pump inhibitor, such as lansoprazole, has effect on clopidogrel's antiplatelet properties [30]. A drug-drug interaction is observed between clopidogrel and third-generation proton pump inhibitors, such as pantoprazole and lansoprazole, and causes cardiovascular events in patients with coronary syndrome [31]. Concurrent use of clopidogrel plus a proton pump inhibitory, such as lansoprazole, is associated with a significant increase in risk of adverse cardiovascular events in patients with acute coronary syndrome [32]. Oral lansoprazole causes an increase in the plasma concentration of tacrolimus in patients [33]. Lansoprazole is metabolized by CYP2C19 and CYP3A4 and inhibits these CYPs. Since tacrolimus is metabolized by CYP3A4, the plasma concentrations of tacrolimus increase in patients who were co-treated with lansoprazole [34].

DISCUSSION

Lansoprazole is a proton pump inhibitor and is a prodrug. After absorption into the systemic circulation, the prodrug diffuses into the parietal cells of the stomach and accumulates in the acidic secretory canaliculi. Here, it is activated by proton-catalysed formation of a tetracyclic sulfenamide trapping the drug so that it cannot diffuse back across the canalicular membrane. The activated form then binds covalently with the sulfhydryl groups of cysteine in the H^+, K^+-ATPase irreversibly inactivating the pump molecule. Acid secretion resumes only after new pump molecules are synthesized and inserted into the luminal membrane, providing a prolonged (up to 24 to 48 hours) suppression of acid secretion, despite the much shorter plasma elimination half-life of about 0.5 to 3 hours of the parent compound. Lansoprazole is used to promote healing of gastric and duodenal ulcers and to treat gastroesophageal reflux disease, including erosive esophagitis, which is either complicated or unresponsive to treatment with H^2 receptor antagonists. Lansoprazole may be administered orally or intravenously and after oral administration lansoprazole is rapidly absorbed [1]. In newborns, the oral dose of lansoprazole is 0.2 to 0.3 mg/kg once-daily and in infants, aged > 10 weeks, the lansoprazole dose is 1 to 2 mg/kg once-daily [2]. In children, the dose of lansoprazole varies according to the child body-weight [4]. Lansoprazole has been found efficacy and safe in infants and children [5-11]. In infants, the treatment of gastroesophageal reflux disease is higher with lansoprazole plus metoclopramide than with ranitidine plus metoclopramide [5], lansoprazole, omeprazole, and esomeprazole effectively treat gastroesophageal reflux disease in infants [6], lansoprazole, given at a dose of 15 or 30 mg once-daily, is effective in the treatment of gastroesophageal reflux disease and erosive esophagitis in adolescents [7], lansoprazole is efficacious in the treatment of erosive esophagitis and gastroesophageal reflux disease in children [8], lansoprazole, given at a dose of 1.5 mg/kg once-daily for 12 weeks, effectively treats oesophagitis and gastroesophageal reflux disease in children [9], lansoprazole administered at a dose of 30 mg/m² or 1.4 mg/kg once-daily is effective and safe in treating childhood gastroesophageal reflux disease [10], and lansoprazole, given at a dose of 15 or 30 mg once-daily for 5 days, increased intragastric pH and effectively treats gastroesophageal reflux disease in adolescents [11]. Lansoprazole is converted into hydroxy lansoprazole by CYP2C19 and into lansoprazole sulfone by CYP3A4 [12]. The pharmacokinetics of lansoprazole have been studied in infants [13] and in children [14] and the elimination half-life of lansoprazole is < 1 hour in infants and children. The treatment of infants and children with lansoprazole has been extensively studied [15-25]. After 5 days of administration, lansoprazole is well tolerated and increases intragastric pH in young children [15], lansoprazole treats gastroesophageal reflux disease in children [16-20], omeprazole, lansoprazole, and esomeprazole treat gastroesophageal reflux disease in children [21,22], lansoprazole is a useful agent in the management of acid-related disorders in children [23], lansoprazole, given at a dose of 0.73 to 1.66 mg/kg once-daily, manages gastroesophageal reflux disease in children [24], and oral lansoprazole, given at a dose of 30 mg on the night before surgery or on the morning of surgery, improves gastric environment in paediatric patients [25]. Lansoprazole

interacts with drugs [26-34]. Lansoprazole has minimal effect on quizartinib pharmacokinetics [26], lansoprazole reduces the hepatic clearance of voriconazole [27], and lansoprazole increases warfarin effect causing bleeding events [28]. A proton pump inhibitor, such as lansoprazole, interacts with clopidogrel [29-32]. Lansoprazole combined to clopidogrel causes death and myocardial infarction in 11% of patients [29], co-administration of lansoprazole with clopidogrel affects clopidogrel's antiplatelet properties [30], and the co-administration of lansoprazole with clopidogrel increases the risk of adverse cardiovascular events in patients with acute coronary syndrome [31,32], lansoprazole increases the plasma concentration of tacrolimus [33], and lansoprazole is metabolized by CYP2C19 and CYP3A4 and inhibits these CYPs. Since tacrolimus is metabolized by CYP3A4, lansoprazole increases the plasma concentration of tacrolimus [34].

In conclusion, lansoprazole is a proton pump inhibitor and it is used to promote healing of gastric and duodenal ulcers and to treat gastroesophageal reflux disease, including erosive esophagitis, which is either complicated or unresponsive to treatment with H^2 receptor antagonists. Lansoprazole may be administered orally or intravenously and after oral dosing lansoprazole is rapidly absorbed. In newborns the oral dose of lansoprazole is 0.2 to 0.3 mg/kg once-daily, and in children aged > 10 weeks, the oral dose of lansoprazole is 1 to 2 mg/kg once-daily. In children, the lansoprazole dose varies according to the child body-weight. Lansoprazole has been found efficacy and safe in infants and children and lansoprazole is converted into hydroxy lansoprazole by CYP2C19 and into lansoprazole sulfone by CYP3A4. The pharmacokinetics of lansoprazole have been studied in infants and children and the elimination half-life of lansoprazole is < 1 hour in infants and children. The treatment of infants and children with lansoprazole has been extensively studied and lansoprazole interacts with drugs. The aim of this study is to review the clinical pharmacology of lansoprazole in infants and children.

CONFLICT OF INTERESTS

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria.

This article is a review and drugs have not been administered to men or animals.

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