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Lansoprazole

In the Treatment of Gastro-oesophageal Reflux Disease in Children and Adolescents

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Contents

Abstract

▲ Lansoprazole is a proton pump inhibitor that inactivates the H^+/K^+-ATPase pump in parietal cells, thus inhibiting gastric acid secretion and increasing intragastric pH.

▲ In an open-label, uncontrolled trial in children aged 1–11 years with gastro-oesophageal reflux disease (GORD), treatment with lansoprazole 15 or 30mg (depending on weight) once daily for 8–12 weeks improved symptoms compared with baseline in 76% of patients (47 of 62) based on patient diaries and healed erosive oesophagitis (confirmed endoscopically) in all 27 children who had it at baseline.

▲ In adolescents aged 12–17 years with GORD, 8 weeks' treatment with lansoprazole 15mg (in 64 patients with nonerosive disease) or 30mg (in 23 patients with erosive oesophagitis) once daily reduced the frequency and severity of symptoms by 63% and 69% compared with baseline, based on patient diaries. In this open-label, uncontrolled trial, 96% of evaluable patients with erosive disease (21 of 22) had mucosal healing by week 8, as confirmed by endoscopy; mucosal healing did not occur after an additional 4 weeks' treatment in one patient.

▲ Lansoprazole was generally well tolerated in children and adolescents, with the most common treatment-related adverse events being gastrointestinal events and headache.

Features and properties of lansoprazole (Prevacid®)	
Therapeutic use	
Short-term treatment of symptomatic gastro-oesophageal reflux disease (GORD) and erosive oesophagitis in paediatric patients aged 1–17 years	
Mechanism of action	
Proton pump inhibitor	Inactivates parietal cell H^+/K^+-ATPase pump, inhibiting gastric acid secretion
Dosage and administration	
Children aged 1–11 years	15mg (if weight ≤30kg) or 30mg (if weight >30kg)
Adolescents aged 12–17 years	15mg (nonerosive GORD) or 30mg (erosive oesophagitis)
Route of administration	Oral
Frequency of administration	Once daily for up to 8 weeks in adolescents or up to 12 weeks in children aged 1–11 years
Pharmacokinetic profile (oral administration of 15 or 30mg once daily for 5 days in children/adolescents aged 1–17 years)	
Peak plasma concentration	Aged 1–11 years: 791 μg/L (15mg) and 899 μg/L (30mg). Aged 12–17 years: 415 μg/L (15mg) and 1005 μg/L (30mg)
Time to peak plasma concentration	1.5–1.7h
Area under the plasma concentration-time curve	Aged 1–11 years: 1707 μg • h/L (15mg) and 1883 μg • h/L (30mg). Aged 12–17 years: 1017 μg • h/L (15mg) and 2490 μg • h/L (30mg)
Elimination half-life	0.68–0.95h
Adverse events	
Most frequent	Headache, constipation, abdominal pain

The prevalence of gastro-oesophageal reflux disease (GORD) in children is not well defined, but community-based studies suggest that symptoms may be present in 1.8–22% of children aged 3–18 years.[1] Very young children with GORD may present with vomiting or dysphagia, while older children tend to have symptoms similar to those experienced by adults, such as heartburn, regurgitation and abdominal pain.[2] Treatment is primarily aimed at alleviating symptoms and healing oesophageal inflammation.[2]

Amongst pharmacological treatment options, proton pump inhibitors, such as lansoprazole and omeprazole, are more effective than histamine H_2-receptor antagonists at suppressing gastric acid secretion, and are currently the drugs of choice for adult patients with GORD.[3] Current guidelines from the North American Society for Pediatric Gastroenterology and Nutrition (published in 2001) recommend short-term therapy with a proton pump inhibitor or histamine H_2-receptor antagonist in children and adolescents with symptomatic GORD with or without oesophagitis.[2]

The properties of lansoprazole (Prevacid®)[1] in adults with GORD have been reviewed previously.[4-7] This profile summarises the pharmacological properties of oral lansoprazole and reviews its use at US-approved dosages in the treatment of GORD and erosive oesophagitis in children and adolescents aged 1–17 years. It should be noted that in the US, approval for use in the paediatric population is based on data from trials in adults with additional pharmacokinetic, pharmacodynamic and clinical data from trials in paediatric patients.[8] Discussion of its use in children with other acid-related disorders is beyond the scope of this article.

1. Pharmacodynamic Properties

The pharmacodynamic properties of lansoprazole in adults have been reviewed in detail previously.[4,5,7]

- Lansoprazole inhibits basal and stimulated gastric acid secretion, causing an increase in intragastric pH.[4] This is achieved by the active sulphenamide metabolites of lansoprazole inactivating the H^+/K^+-ATPase pump in gastric parietal cells, thus blocking the final step in gastric acid secretion.[4,7]

- In children aged 1–11 years (n = 52)[9] and adolescents aged 12–17 years (n = 19)[10] with GORD, mean 24-hour intragastric pH and the percentage of time that pH was >3 or >4 increased significantly from baseline after treatment with lansoprazole 15 or 30mg once daily for 5 days. For example, in adolescents mean intragastric pH increased from 2.7 to 3.8 ($p = 0.013$) and from 2.8 to 3.9 ($p = 0.026$) in the 15 and 30mg groups.[10] The percentage of time that pH was >3 or >4 increased from 27% to 59% and from 20% to 47% in the 15mg group (both $p \leq 0.009$); increases in the higher dosage group were similar (from 29% to 60% and from 20% to 49% [both $p \leq 0.013$]).[11]

- In children aged 1–11 years with GORD (n = 22), treatment with lansoprazole improved intraoesophageal pH (presented as an abstract/poster).[12] Patients had an abnormal intraoesophageal pH test at baseline (defined as pH <4 for >6% of a 24-hour period). Compared with baseline, the median percentage of time that intraoesophageal pH was <4 decreased significantly by day 5 (from 11.4% to 3.6%; $p < 0.001$).[12] The proportion of patients with a normal intraoesophageal pH test on day 5 was 87.5% (7 of 8) for those with erosive oesophagitis and 64.3% (9 of 14) for those with nonerosive disease. Lansoprazole dosages were 15mg for children weighing ≤30kg or 30mg for those weighing >30kg, both once daily.[12]

- As reviewed previously,[4] in adult healthy volunteers, inhibition of gastric acid secretion by lansoprazole was dose-related over the range 15–60mg, with a single dose of 30mg reducing secretion by 81–97%.

- Also in adult healthy volunteers, control of intragastric acidity was achieved more quickly with lansoprazole 30mg than omeprazole 20 or 40mg, rabeprazole 20mg or pantoprazole 40mg.[7] In

1 The use of trade names is for product identification purposes only and does not imply endorsement.

healthy volunteers or patients with GORD, a pH >4 was maintained with lansoprazole 30 mg/day for a similar or longer duration than with omeprazole 20 mg/day or rabeprazole 20 mg/day and for longer than with pantoprazole 40 mg/day or ranitidine 600 mg/day, although not for as long as with esomeprazole 40 mg/day.[7,13] Differences in effects on intragastric pH amongst proton pump inhibitors do not necessarily correlate with clinically relevant differences in GORD clinical outcomes.[14]

- Lansoprazole increases serum gastrin levels.[5,7] See section 4 for a discussion of gastrin levels in children during clinical trials.
- In adults with GORD, treatment with lansoprazole 15 or 30 mg/day for 12 months led to hypertrophy of gastric parietal cells, an effect that was reversible on stopping treatment.[15] At the same dosage and duration of treatment, lansoprazole reduced hyperplasia of the basal cell layer and elongation of papillae of the oesophageal mucosa.[16] In both studies, these effects were similar to those seen with omeprazole 20 mg/day.[15,16]

2. Pharmacokinetic Properties

The pharmacokinetics of oral lansoprazole in adults have been reviewed previously.[4,5,7] Pharmacokinetic data from paediatric patients are available from several studies;[9,10,12,17,18] where possible this section focuses on data from children (aged 1–11 years; n = 59)[9] and adolescents (12–17 years; n = 59)[10] with GORD who received multiple doses of lansoprazole 15 or 30mg. In the case of children aged 1–11 years, those weighing ≤30kg received 15mg and those weighing >30kg received 30mg once daily.[9] Pharmacokinetic data from children were similar to those observed in adult healthy volunteer studies.[9,10]

Several formulations of lansoprazole are available (e.g. capsule, oral suspension and a new orally disintegrating tablet [ODT]).[8] Lansoprazole capsules can be swallowed intact or opened and the contents mixed with soft food (e.g. apple sauce) or fruit juice, with no significant change in pharmacokinetic parameters.[6] Both methods were used in paediatric studies. ODTs are bioequivalent to intact capsules when both are administered orally at the same dose,[19] and the ODT dispersed in water and administered by oral syringe is bioequivalent to the intact ODT.[20]

Absorption and Distribution

- In adult healthy volunteers, lansoprazole was rapidly and nearly completely absorbed after oral administration, displaying linear pharmacokinetics over the dose range 15–60mg.[7] When administered with food, the peak plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) decreased by ≈50%.
- Absorption of lansoprazole was also rapid in children and adolescents with GORD, with C_{max} being reached in 1.5–1.7 hours.[9,10] Dose-proportional increases in C_{max} and AUC were seen with an increase in dose from 15 to 30mg.[10] Values for C_{max} after multiple doses of 15 or 30mg (once daily for 5 days) were 791 and 899 μg/L in children aged 1–11 years[9] and 415 and 1005 μg/L in adolescents.[10] Corresponding values for AUC were 1707 and 1883 μg • h/L in children aged 1–11 years and 1017 and 2490 μg • h/L in adolescents.
- The apparent volume of distribution was 0.61 and 0.90 L/kg after single and multiple doses of lansoprazole 17 mg/m^2/day (approximately equivalent to an adult dosage of 30 mg/day) in children with gastric acid-related disorders.[18] Lansoprazole is 97% bound to plasma proteins.[7]
- Age and weight had no significant effect on C_{max} or AUC in children and adolescents with GORD.[9,10]

Metabolism and Elimination

- Within the gastric parietal cells, lansoprazole is converted to two active sulphenamide metabolites which inhibit gastric acid secretion; these metabolites are not present in plasma.[8] In the systemic circulation, lansoprazole is metabolised in the liver by the cytochrome P450 (CYP) isozymes CYP3A4/5 and CYP2C19, producing hydroxylated sulphinyl and sulphone metabolites with little or no antisecre-

tory activity.[7] It is eliminated via the bile and as metabolites in urine.

- Mean plasma elimination half-life ($t_{1/2}$) in children and adolescents aged 1–17 years with GORD who received multiple doses of lansoprazole 15 or 30 mg/day was 0.68–0.95 hours.[9,10] In adolescents there was a slight decrease in elimination rate constant with increasing age.[10]
- Mean apparent clearance was 0.71 or 1.85 L/h/kg in children with gastric acid-related disorders[18] or GORD[17] treated with multiple doses of lansoprazole 17 mg/m^2/day. Values for $t_{1/2}$ in these studies were 1.17 and 0.82 hours.
- In adults with chronic liver disease, $t_{1/2}$ more than doubled and AUC increased up to 500% compared with healthy adults; dose reductions may be necessary in patients with severe hepatic disease.[8] Based on data from adults, no dosage adjustment is needed in renal insufficiency.

Drug Interactions

- In healthy adult volunteers, no clinically significant interactions occurred between lansoprazole and most other drugs metabolised by CYP isozymes, including clarithromycin, diazepam, ibuprofen, indomethacin, phenazone, phenytoin, propranolol, prednisone or warfarin.[8] There was also no clinically relevant interaction with amoxicillin.
- When lansoprazole and theophylline were administered concomitantly in adults, the clearance of theophylline increased by 10%; while this was not considered clinically significant, it is recommended that theophylline levels are monitored when starting or stopping concomitant lansoprazole.[8]

3. Therapeutic Use

This section reviews data from clinical trials of lansoprazole in paediatric patients with GORD using dosage regimens specified in the US prescribing information. Well designed, controlled clinical trials in adults have established the efficacy of lansoprazole in patients with GORD.[7,8] Additional data on paediatric patients with symptomatic GORD (with or without erosive oesophagitis) come from two small (n = 66[21] and n = 87[11]) open-label, uncontrolled, multicentre trials of 8–12 weeks' treatment, one in children aged 1–11 years[21] and the other in adolescents aged 12–17 years.[11] Two smaller noncomparative studies in children (n ≤ 35) which evaluated dosages based on mg/m^2 or mg/kg (not US-approved dosages) are outside the scope of this review and are not discussed further.[17,22]

All patients had active symptomatic GORD, and endoscopy was performed to determine whether oesophagitis was present.[11,21] Where reported, the majority of patients had received previous medical therapy for GORD.[11,21]

In children aged 1–11 years lansoprazole was administered at a dosage of 15mg once daily to those weighing ≤30kg and 30mg once daily to those weighing >30kg; if patients remained symptomatic after at least 2 weeks' treatment the dosage could be increased up to a maximum of 30mg twice daily.[21] In the trial in adolescents, dosages were 15mg once daily for patients with nonerosive GORD and 30mg once daily for those with erosive oesophagitis.[11] In both trials, treatment was for 8 weeks, with the option to extend for an additional 4 weeks in patients with erosive oesophagitis if lesions had not healed by week 8.[11,21]

Changes in GORD symptom frequency (percentage of days with symptoms) and severity (based on a 5-point scale from none to very severe symptoms) were evaluated using patient diaries and an investigator interview assessment.[11,21] The majority of patients had mild to moderate symptoms at baseline.[11,21] Healing of erosions was evaluated by endoscopy.[11,21]

In addition to these trials, results from two randomised, single-blind studies that used a 5-point facial hedonic scale to compare the taste preferences of healthy children aged 5–11 years (n = 111)[23] or 6–11 years (n = 104)[24] when given a strawberry-flavoured lansoprazole formulation or a peppermint-flavoured ranitidine preparation are discussed.

- Lansoprazole 15 and 30mg was effective at alleviating symptoms of GORD and healing erosive oesophagitis in children and adolescents aged 1–17 years, compared with pre-treatment.[11,21]

• In children aged 1–11 years, GORD symptoms resolved or improved compared with baseline in 76% of children based on patient diaries after 8–12 weeks' treatment (47 of 62 patients who had baseline diary data).[21] Among children with erosive oesophagitis who had follow-up endoscopy, lesions had healed in 78% (21 of 27) by week 8 and in the remaining six patients by week 12 (primary endpoint). Sixty-four percent of children (42 of 66) stayed on their initial dosage throughout the study (15 or 30mg once daily), while the remaining 24 patients needed a dosage increase (to a maximum of 60 mg/day).[21]

• In these children, there were significant ($p \leq 0.05$) reductions from baseline during the first 2 weeks of treatment (and during each 2-weekly interval up to 10 weeks) in the frequency and daily severity of symptoms and in the frequency and quantity of antacid used.[21] For example, during weeks 3 and 4 of treatment, symptoms were experienced on a median 50% of days (vs 100% at baseline), the mean severity score for symptoms was 0.9 (vs 1.6), antacids were used on a median 14% of days (vs 50%) and a mean 0.3 tablets/teaspoons of antacid were used per day (vs 1.0) [all $p \leq 0.001$ except $p \leq 0.5$ for days of antacid use].[21]

• In adolescents aged 12–17 years, lansoprazole 15mg once daily for 8 weeks improved GORD symptoms from baseline in those with nonerosive disease (n = 64), and lansoprazole 30mg once daily for 8–12 weeks relieved symptoms and healed oesophagitis in those with erosive disease (n = 23).[11] After 8 weeks the frequency and severity of symptoms had decreased by 63% and 69% in the overall population based on patient diaries.[8] Excluding one patient who had early endoscopy showing healed oesophagitis after 7 days, 96% (21 of 22) of patients with erosive oesophagitis had mucosal healing after 8 weeks' of lansoprazole 30mg once daily.[11] The remaining patient had persistent erosions even after 12 weeks.

• Based on patient diary entries for this trial,[11] a significant ($p < 0.001$) reduction from baseline was seen at week 8 for both the nonerosive- and erosive-disease groups in the median percentage of days on which symptoms were experienced (from 91% to 43% and from 85% to 16%) and the mean daily symptom severity score (from 1.6 to 0.6 and from 1.9 to 0.2) [primary variables; figure 1], as well as in the median percentage of days antacid was used (from 55% to 7% and from 50% to 2%) and the mean daily number of teaspoons of antacid used (from 1.3 to 0.3 and from 1.6 to 0.1). Significant (all $p < 0.001$) reductions in these parameters were apparent by week 4.[11]

• In taste test studies in healthy children, >92% of children preferred the taste of lansoprazole ODT ($p < 0.001$)[24] and >95% preferred lansoprazole oral suspension (p-value not reported),[23] both of which are strawberry-flavoured, over ranitidine pepper-

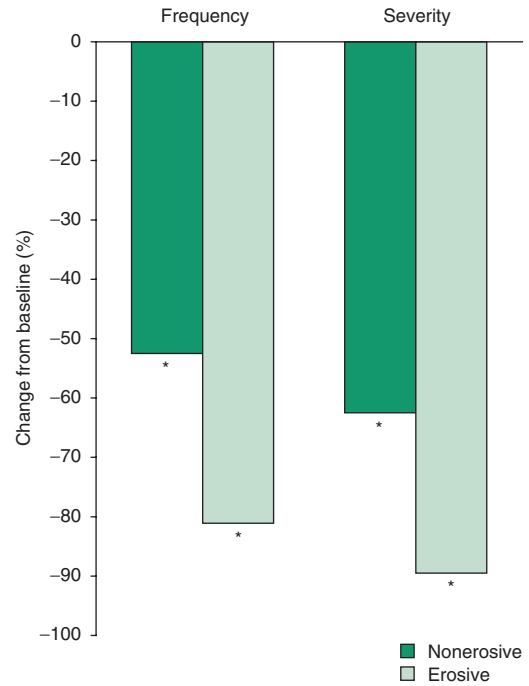

Fig. 1. Use of lansoprazole in the treatment of gastro-oesophageal reflux disease in adolescents. Data are from an open-label, uncontrolled trial in which patients aged 12–17 years received 8 weeks' treatment with lansoprazole 15mg once daily (patients with nonerosive disease; n = 64) or 30mg once daily (erosive oesophagitis; n = 23).[11] Percentage change from baseline is shown for the primary variables, symptom frequency (assessed as median percentage of days with symptoms) and mean severity (assessed using a 5-point scale where 0 = none and 4 = very severe), based on patient diaries. * $p < 0.001$ vs baseline.

mint-flavoured syrup. In these studies, 88.5% and 79% of children 'liked' the taste of the lansoprazole ODT[24] or oral suspension[23] compared with 11.5% and 20% who 'liked' the ranitidine syrup ($p < 0.05$ for lansoprazole oral suspension vs ranitidine; not reported for lansoprazole ODT).

4. Tolerability

- Lansoprazole 15–30mg once daily was generally well tolerated in children and adolescents taking part in the clinical trials discussed in section 3.
- Fifteen percent of children aged 1–11 years (10 of 66)[25] and adolescents aged 12–17 years (13 of 87)[11] treated for 8–12 weeks experienced treatment-related adverse events (i.e. those considered possibly, probably or definitely drug-related). The majority of events were mild to moderate in severity, and were similar in incidence and nature to those reported for adults.[11,25] There were no clinically significant changes in haematological or biochemical parameters.
- Gastrointestinal events and headache were the most frequent treatment-related adverse events in 8–12 week trials.[11,25] In children aged 1–11 years, constipation occurred in 5% and headache in 3% of patients; diarrhoea, vomiting, dizziness and insomnia were experienced by one child each.[25] In adolescents, headache was experienced by 7%, abdominal pain by 5%, and nausea and dizziness each by 3% of patients.[11] Dizziness was reported by <1% of adults; the three adolescents with dizziness experienced it in conjunction with migraine, dyspnoea or vomiting.[8] Other adverse events (reported by one or two adolescents) included asthenia, diarrhoea, vomiting and anorexia; one patient with dizziness and vomiting discontinued from the study.[11]
- Among 63 adolescents treated with lansoprazole 15 or 30mg for 5 days in a pharmacokinetic/pharmacodynamic study, five patients experienced treatment-related adverse events, including one who had a mild allergic reaction which resolved on stopping treatment.[10] Diarrhoea, dizziness, rash and sensitive teeth were each reported by one patient.
- As seen in adults with GORD,[6,8] serum gastrin levels increased in children and adolescents treated with lansoprazole.[11,25] In children aged 1–11 years receiving lansoprazole 15 or 30mg, mean fasting serum gastrin level more than doubled from baseline after 8–12 weeks (from 58.0 to 121.9 pg/mL; $p \leq 0.001$ [normal range 25–111 pg/mL).[25] During the same period, median gastrin level increased by 89% (from 51 to 97 pg/mL; interquartile range [25th–75th percentile] 71–130 pg/mL), although the value remained within normal range.[8,25] A significant increase in mean gastrin level (from 58.8 to 80.1 pg/mL; $p = 0.015$) was also seen in a study in adolescents treated with the same dosages for the same duration.[11] Median gastrin level increased by 42%, from 45 to 64 pg/mL (interquartile range [25th–75th percentile] 44–88 pg/mL).[8] In adults, gastrin levels plateaued within 2 months, and within 4 weeks of discontinuing therapy they returned to pretreatment levels.[8]

5. Dosage and Administration

In the US, oral lansoprazole is approved for use in paediatric patients aged 1–17 years for the short-term treatment of symptomatic GORD and erosive oesophagitis.[8] Lansoprazole is available as a capsule, an ODT and an oral suspension.[8] It should not be crushed or chewed.

The recommended dosage in children aged 1–11 years is 15mg in those weighing ≤30kg and 30mg in those weighing >30kg, administered once daily for up to 12 weeks; the dosage was increased to 60 mg/day in some children who remained symptomatic after 2 weeks of treatment in clinical trials.[8] The recommended dosage in adolescents aged 12–17 years is 15mg for those with nonerosive GORD and 30mg in those with erosive oesophagitis, in each case administered once daily for up to 8 weeks.[8]

6. Lansoprazole: Current Status in Children and Adolescents

The effectiveness and tolerability of lansoprazole have been established in paediatric patients aged 1–17 years for short-term treatment of symptomatic GORD and erosive oesophagitis. Evidence supporting its use in this population comes from well con-

trolled trials in adults and uncontrolled trials in children and adolescents.

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