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Lansoprazole in the treatment of gastro-oesophageal reflux disease in childhood

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Background. *Acid suppressive therapy is the mainstay of pharmacologic treatment of gastro-oesophageal reflux disease. Use of proton pump inhibitors in children is still limited and has only included omeprazole in a few controlled studies.*

Aim. *To determine efficacy of lansoprazole, a relatively new proton pump inhibitor, on symptoms and oesophagitis in a group of children with gastro-oesophageal reflux disease refractory to H_2 receptor antagonists. The required dose of the drug for inhibiting gastric acidity was also determined.*

Patients and Methods. *A series of 35 children (median age: 7.6 years, range: 3-15) with oesophagitis refractory to H_2 receptor antagonists received a 12-week therapeutic course with lansoprazole. Prior to the study, children underwent symptomatic and endoscopic assessment, oesophageal manometry and 24-hour intragastric and intra-oesophageal pH test. The latter was repeated after one week of therapy while patients were on treatment in order to monitor the degree of acid suppression and adjust the dose of the drug. Symptomatic assessment and endoscopy were repeated at the end of the trial.*

Results and Conclusions. *In 12 patients (group A), the initial dose of the drug was efficacious (1.3 to 1.5 mg/kg/day), whereas in 23 (group B) the initial dose (0.8 to 1.0 mg/kg/day) was increased by half because of insufficient inhibition of intragastric acidity (i.e., when the intra-gastric pH remained below 4.0 for more than 50% of the recording time). Nine patients in group A (75%) and 8 in group B (53.5%) healed (χ^2: 3.6, $p<0.05$); 1 patient in group A (8.3%) and 7 in group B (30.5%) remained unchanged (χ^2: 6.9, $p<0.01$); 2 patients in group A and 8 in group B improved and underwent a further month of therapy. The two groups did not differ as far as concerns baseline pH, endoscopic and clinical variables. In both groups, those patients failing to respond at the end of the trial showed a more impaired oesophageal motility than improved or healed patients. The drug was well tolerated and no significant laboratory abnormalities occurred. In children with gastro-oesophageal reflux disease refractory to H_2 receptor antagonists, a 12-week course of lansoprazole is effective both in healing oesophagitis and improving symptoms. An initial dose of 1.5 mg/kg/day of the drug is suggested. However, if during treatment, patients remain symptomatic the dose should be increased and a prolonged intra-gastric and intra-oesophageal pH test performed to evaluate the acid suppression efficacy of the adjusted dose. A short course of lansoprazole appears to be safe and well tolerated in paediatric age.*

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Submitted June 6, 2000.
Revised August 12, 2000.
Accepted September 19, 2000.

Digest Liver Dis 2000;32:660-6

Key words: gastro-oesophageal reflux; intra-gastric acidity; lansoprazole; oesophagitis

Digestive and Liver Disease. 2000 Vol. 32 No. 8 P. 660-666

Introduction

Although motor abnormalities involving the lower oesophageal sphincter (LOS) as well as oesophageal body peristalsis and delayed gastric emptying are the main pathogenetic mechanisms of gastro-oesophageal reflux (GOR) disease, healing of oesophagitis requires optimal suppression of intra-gastric acidity [1,2]. For many years, histamine-2 receptor antagonists (H_2RAs) have been the most commonly used antisecretory drugs in children with GOR disease [3,4]. However, a new class of drugs inducing marked suppression of gastric acid secretion, the parietal cell proton pump (H^+K^+ATPase) inhibitors (PPIs), have been found to be more effective than H_2RAs both in healing oesophagitis of moderate to severe degree and in controlling symptoms in adults with GOR disease [5,6]. However, the use of PPIs in childhood is still limited and usually includes omeprazole which is the first of this new class of drugs [7-10].

Recent investigations have established dose regimens, efficacy and safety for the use of omeprazole in children, whereas there is little experience with the newer PPIs, such as lansoprazole [11].

In this report, we describe a population of children with severe GOR disease, refractory to earlier treatment with H_2RAs and receiving a 12-week therapeutic course with lansoprazole. The effect of this drug on symptoms and endoscopic lesions as well as the efficacious dose for inhibiting gastric acidity were studied.

Patients and methods

The patient population comprised 35 children (18 males) (median age: 7.6 years, range: 3-15). All had oesophagitis documented endoscopically and were refractory to H_2RAs (ranitidine, 8-10 mg/kg/day for 12 weeks). Prior to the study, patients underwent symptomatic assessment, 24-hour intra-oesophageal and intra-gastric pH measurement, oesophageal manometry and upper gastrointestinal endoscopy. Systemic and neurologic disorders as well as structural abnormalities of the gut were excluded in all. The starting daily dose of lansoprazole (manufactured as 15 mg and 30 mg capsules) was given in the morning, 30 minutes before breakfast for 12 weeks. The initial doses were given according to different weight ranges: 30 mg for children weighing ≥30 kg, 22.5 mg (the content of one capsule and half) for those weighing ≥20 <30 kg, 15 mg for those with a weight of <20 ≥10 kg and 7.5 mg for those weighing <10 kg. In accordance with the manufacturer's instructions, most of the patients were receiving the granular content of the capsule in a few milliliters of an acid vehicle such as grapefruit or orange juice. The 24-hour double site pH study was repeated in all patients after one week of therapy and the daily dose was increased by half if "lansoprazole failure" occurred, i.e., when the intra-gastric pH remained below 4.0 for more than 50% of the recording time [12]. The increased dose was then given for 12 weeks. The additional dose was given in the evening, 30 minutes before dinner. At the end of the trial, symptomatic assessment and endoscopy were repeated. During the therapeutic course, the patients were evaluated on a clinical basis, 6 weeks after starting therapy, and parents were instructed to record, on a diary card, frequency and severity of GOR symptoms and to keep off other anti-reflux drugs. Symptom grading was done at baseline and at the end of the trial according to a scale 0→6 (Table I), and related to the 4 weeks preceding the beginning of the study and to the last 4 weeks of the trial, respectively. Blood and urine samples were collected upon entry and at the end of the trial. Haematological and biochemical analysis included complete blood cell count, erythrocyte sedimentation rate, serum creatinine, bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, serum electrolytes, and urinalysis. Fasting serum gastrin concentration was determined at around week 8 of the trial.

The 24-hour combined intra-oesophageal and intra-gastric pH test was performed using two antimony electrodes located on the same flexible catheter (Medtronic, Milan, Italy) (Ø 1.2 mm). Catheters with

Table I. Clinical score for children with gastro-oesophageal reflux disease.

Symptoms and signs	Frequency	Score
Emesis	0	0
regurgitation and/or vomiting	1-3	2
episodes/week	>3-6	4
	> 6	6
Chest pain, dysphagia, irritability	0	0
episodes/month	1	2
	>1-3	4
	>3	6
Epigastric or mesogastric pain,		
epigastric distress, bloating	0	0
episodes/week	1-3	2
	>3-6	4
	>6	6
Nocturnal cough (paroxysmal attacks),	0	0
asthma, post-feeding cough	1	2
episodes/month	>1-3	4
	>3	6

different distances between the two electrodes (5, 10 and 15 cm apart) were selected according to the size and the age of the patients so that the pH was monitored in the distal oesophagus and in the gastric body. The tip of the oesophageal electrode was located at a point 87% of the distance between nares and the LOS as determined by manometry. A silver/silver chloride reference electrode was attached to the chest skin. The measuring electrodes were calibrated at the beginning and at the end of each study using commercially available standard buffer solutions (pH 7.01 and pH 1.07, Medtronic, Milan, Italy). In all recording sessions, drifts of the electrodes did not exceed 0.2 pH units. The electrodes were connected to a portable battery operated recorder (Proxima Light, Medtronic, Milan, Italy) and the recorded data were transferred to a Personal Computer for analysis with the appropriate software (Esophogram 5.4, Medtronic). Gastro-oesophageal reflux was defined whenever the distal oesophageal pH dropped to less than 4.0 for at least 20 seconds. The following oesophageal and gastric pH variables were measured: 1) oesophageal acid exposure time, i.e., time the oesophageal pH was <4.0 (% of GOR); 2) intra-gastric median pH; 3) percentage of intra-gastric time with pH <4.0. During the pH sessions, patients were given standardized meals according to age and no food was allowed during intervals between meals. All pH studies started at 8.00 a.m. after an overnight fast and all patients were requested to stop drugs affecting intestinal motility or reducing gastric acid secretion for at least one week before the pH study.

Oesophageal manometry was performed, after a 4-hour fasting period, with a flexible catheter introduced through the nose and perfused with distilled water through a pneumohydraulic system (Arndorfer, Med. Spec. Greendale, WI, USA) (flow rate: 0.3 ml/min). The catheter was an assembly of 4 small probes (Ø 0.6 mm) with distal side holes. There was a pressure rise >200 mmHg at the occlusion of the perfused holes. The latter were 3 cm apart in the catheter used in children aged less than 6 years and were 5 cm apart in catheters for patients over 6 years of age. The basal LOS pressure (LOSP) (mmHg) was measured with a stationary pull-through technique: the probe was located with all orifices in the stomach and then moved at 0.5 cm intervals through the oesophagus. The mid-respiratory values of the LOSP were calculated at the level of the four recording holes with the mean intra-gastric pressure reference equal to zero. The pull-through was done three times giving twelve readings and a final mean value was calculated. Oesophageal body peristalsis was evaluated with the most distal side hole located immediately above the LOS. To assess peristalsis, only waves induced by wet swallows (2 to 5 ml of 5% dextrose) preceded by at least 20 seconds of absent motor activity in the oesophageal body were measured. Amplitude of peristalsis was measured from the mean resting oesophageal pressure to the peak of the wave, giving a mean value for the four recording holes. Contractions in the oesophageal body were defined as oesophageal pressure increase of at least 15 mmHg. Non-specific oesophageal motor defects (NOMD) were identified as simultaneous waves or double and triple peaked waves and as broad-based or irregularly shaped waves; prevalence of NOMD was given as percentage of the motor activity elicited by swallowing. At least 10 peristalsis sequences were measured in each patient.

All patients underwent upper intestinal endoscopy using a paediatric videoendoscope (Olympus, Turin, Italy) with a 2.2 mm diameter biopsy channel, after sedation with intravenous (iv) meperidine (1-2 mg/kg) and midazolam (0.1 mg/kg). Biopsy specimens were examined for basal zone thickness, elongation of papillae, presence of intraepithelial neutrophils and/or eosinophils, and for mucosal slough or ulcerations. Histological evidence of oesophagitis was required when only non-specific endoscopic findings such as hyperaemia, friability and/or granularity were present. Severity and extent of oesophagitis were assessed according to an endoscopic classification [8] in which grade 0: no mucosal abnormalities, grade 1 = no macroscopic erosions, but mucosal erythema, friability or granularity; grade 2 = superficial erosions involving <10% of the surface of the last 3-5 cm of the distal oesophageal mucosa; grade 3 = superficial erosions or ulcerations involving 10-50% of the surface of the last 3-5 cm of the distal oesophageal mucosa; grade 4 = deep ulcerations localized anywhere in the oesophagus or confluent erosions of >50% of the surface of the last 3-5 cm of the distal oesophagus.

At the end of the trial, patients were classified as healed if the endoscopic and clinical scores decreased by >75% compared to baseline values; as improved, if changes both in endoscopic and clinical scores were ≤75% and >50%, respectively, compared to baseline; if clinical and endoscopic scores did not change or showed a decrease of less than 50% of the baseline values, patients were judged as unchanged.

Informed written consent was obtained from all parents. The diagnostic protocol had been approved by the Ethics Committee of the Faculty.

The Mann-Whitney U test was used for comparison between data from different groups of patients and Wilcoxon signed rank test was used to analyse paired data. A p value <0.05 was regarded as statistically significant.

Results

In 12 patients (group A) (age: 7.8±3.5 years; median: 9.0), the initial dose of the drug was found to be efficacious (1.3 to 1.5 mg/kg/day), according to the second double site pH metry. In 23 patients (group B) (age: 8.7±4.3 years; median: 7.0), the second pH test revealed a "lansoprazole failure" and the initial dose of the drug (0.8-1.0 mg/kg/day) was increased by 50%. The two groups did not differ as far as concerns baseline pH, endoscopic and clinical scores, whereas group B patients had a higher prevalence of NOMD than group A patients. The LOSP and peristalsis amplitude were lower in patients who needed an increased dose of lansoprazole compared to those with an efficacious initial dose of the drug, however, the difference was not statistically significant. Baseline values of pH, endoscopic and manometric variables as well as clinical score for the two groups of patients are shown in Table II. Changes in intra-gastric and intra-oesophageal pH variables following the first week of treatment are shown in Table III. At the 6-week clinical evaluation, 2 patients in group A and 9 in group B were still symptomatic and the lansoprazole dose was further increased by 50%.

Healing at the end of the trial was obtained in 9 patients in group A (75%) and 8 in group B (53.5%) (χ^2: 3.6, $p<0.05$). Two patients in group A and 8 in group B improved and underwent a further month of therapy.

Table III. Changes in oesophageal and gastric pH metric variables after one week of therapy in patients with effective (group A) and ineffective (group B) initial dose of lansoprazole*.

Variables	Basal	One week	p
Oesophageal acid exposure time (% of GOR)			
Group A	9.86±2.5	3.12±2.1	<0.01
Group B	11.75±4.9	6.57±3.04	ns
% of time with intra-gastric pH <4.0			
Group A	81.6±6.5	36.3±10.04	<0.01
Group B	85.13±7.24	66.4±8.91	ns
Median intragastric pH			
Group A	1.27±0.16	2.74±0.81	<0.01
Group B	1.25±0.22	1.70±0.30	ns

**data: mean±SD*

One patient in group A (8.3%) and 7 in group B (30.5%) were judged as unchanged (χ^2: 6.9, $p<0.01$). The effective dose of lansoprazole in group A ranged from 1.3 to 1.5 mg/kg/day, whereas the initial dose of the drug in group B ranged from 0.5 to 1.0 mg/kg/day. Table IV shows clinical, endoscopic, motility and pH metry data from patients in groups A and B that improved or healed at the end of the trial compared to

Table II. Clinical, endoscopic, pH metric and motility variables at beginning of study in patients with effective (group A) and ineffective (group B) initial dose of lansoprazole*

Variables	Group A	Group B	p
Age (years)	7.8±3.5	8.7±4.4	ns
Clinical score	10.5±1.0	11.26±1.13	ns
Endoscopic score	2.91±0.66	3.21±0.79	ns
Oesophageal acid exposure time (% of GOR)	9.86±2.5	11.75±4.9	ns
% of time with intra-gastric pH <4.0	81.6±6.5	85.13±7.24	ns
Median intra-gastric pH	1.27±0.16	1.25±0.22	ns
Lower oesophageal sphincter pressure (mmHg)	14.5±3.31	10.04±5.01	ns
Amplitude of oesophageal peristalsis (mmHg)	59.5±9.89	46.43±14.06	ns
Non-specific oesophageal motor defects (%)	5.0±3.95	10.08±5.93	<0.05

** data: mean±SD; ns: not significant.*

Table IV. Baseline clinical, endoscopic, pH metric and motility variables in patients improved or healed and in patients unchanged at end of trial*.

Variables	Healed or improved	Unchanged	p
Age (years)	7.72±3.69	10.73±4.5	< 0.01
Clinical score	10.85±0.98	11.5±1.5	ns
Endoscopic score	2.96±0.75	3.6±0.46	< 0.05
Oesophageal exposure acid time (% of GOR)	10.2±3.5	11.5±5.7	ns
% of time with intra-gastric pH <4.0	83.85±7.3	84.25±6.9	ns
Median intra-gastric pH	1.3±0.3	1.25±0.23	ns
Lower oesophageal sphincter pressure (mmHg)	13.3±4.21	5.7±1.6	< 0.01
Amplitude of oesophageal peristalsis (mmHg)	55.7±12.17	34.5±4.2	< 0.01
Non-specific oesophageal motor defects (%)	6.3±4.8	15.12±3.13	< 0.05

** data: mean±SD*

findings in patients who remained unchanged. The two populations did not differ as far as concerns clinical, endoscopic and pH metry variables, whereas modifications in the oesophageal motor variables were significantly more marked in the unchanged patients than in the improved or healed patients.
Eight patients presented hypergastrinaemia (upper limit of normal: 120 ng/l) during the trial with levels ranging from 200 to 400 ng/l. No serious adverse events to require discontinuing drug were observed: two patients had transient episodes of diarrhoea and one had transient headache. No significant abnormalities in the laboratory data were recorded.
Of those patients healed or improved, 18 subsequently relapsed and were considered for a long-term course with lansoprazole. Patients, unchanged at the end of the trial, underwent surgery.

Discussion

Over the last twenty years, the better understanding of the pathogenetic mechanisms underlying GOR disease has shown that oesophageal and gastric motility defects are critical in promoting GOR [1]. Nevertheless, clinical sequelae of GOR and oesophageal mucosa damage are due to the noxious quality of the refluxate, i.e., the hydrochloridric acid and pepsin content [13]. The recently developed PPIs selectively inhibit the proton pump H^+, K^+ ATPase in the parietal cell membrane and suppress gastric acid secretion in response to all stimulatory agents [14]. These drugs have dramatically changed the therapeutic strategy of GOR disease by providing a more rapid symptomatic relief and a better healing rate of oesophagitis than H_2RAs; furthermore, they have led to a healing rate of 80%-97% of oesophagitis in adults refractory to H_2RAs [2]. However, consensus guidelines on the treatment of GOR disease in childhood suggest a step-up approach including conservative therapy and prokinetics for mild disease and H_2RAs in severe disease; if the latter are unsuccessful the step-up approach progresses to PPIs [15].
Children in the present study had persisting symptoms and oesophagitis in spite of previous courses with H_2RAs; therefore, these patients were candidates for a trial with lansoprazole. This is a potent PPI similar to omeprazole, but with a greater bioavailability after oral administration, and, like omeprazole, formulated in capsules containing enteric-coated granules [16 17]. In children unable to swallow capsules or in those requiring less than a full capsule, granules are mixed with an acidic substance in order to preserve the enteric coating and allowing granules to remain intact until the small intestine is reached.

The effectiveness of the dose of lansoprazole was evaluated by repeating the intraluminal pH test while the patients were on the drug. We identified a group of patients receiving an effective initial dose of lansoprazole and a group requiring an increase of the initial dose to suppress acid secretion. The two groups did not differ as far as concerns baseline intra-oesophageal and intra-gastric acidity. Continuous intra-gastric pH monitoring has been reported to be a reliable tool for assessing gastric secretion and, moreover, the healing rate of reflux oesophagitis correlates with the 24-hour period that gastric acidity is raised above pH 4.0 [17-19]. On the basis of this pH test, it has been shown that adults with GOR disease may require larger than usual doses of PPIs to control symptoms and heal oesophagitis and that patients with reflux oesophagitis, poorly controlled with PPIs, may present episodes of nocturnal acid breakthrough [18 20 21]. In the present study, a significantly larger number of patients receiving an effective initial dose of lansoprazole improved or healed at the end of the trial as compared to patients whose initial dose of the drug was ineffective. We did not perform additional pH tests in the latter group since this approach was thought to be invasive. Based on our results, we suggest a starting dose of lansoprazole of 1.5 mg/kg/day in children with GOR disease; furthermore, if during the therapeutic course patients are still symptomatic, the dose of lansoprazole should be increased and an intra-oesophageal and intra-gastric pH monitoring performed to determine the acid suppressive efficacy of the increased dose of the drug. Finally, if the diagnosis of GOR disease is clearly established with endoscopy and histology, the baseline pH test might be omitted [22].
It is of interest that those patients in both groups that were unchanged at the end of the trial differed from those improved or healed with regards to baseline oesophageal motility variables such as LOSP, amplitude and qualitative features of peristalsis. The significance of oesophageal dysmotility in patients with oesophagitis is still controversial [23]. There is evidence suggesting that these abnormalities are a primary disorder and a major predisposing cause of reflux [24]. Other studies, however, indicate that they are secondary to oesophagitis [25]. Whatever the nature of oesophageal dysmotility may be, motor abnormalities of the oesophagus usually indicate a severe grade of reflux disease [26]. These may contribute to the poor response to antisecretory therapy since a low LOSP would allow a large volume of refluxate to enter the oesophageal lumen and a defective oesophageal motility may prolong the duration of contact between refluxed gastric content and the oesophageal epithelium [27]. Finally, persistence of oesophageal dysmotil-

ity may determine a greater likelihood of relapse when active treatment is withdrawn. Indeed, a previous report in children with severe oesophagitis showed that omeprazole did not reverse oesophageal motor defects underlying GOR despite healing of oesophagitis [28]. This observation explains the high rate of recurrence in oesophagitis patients when active pharmacologic treatment is withdrawn [29 30]. Whether the patients in our study who did not relapse had a return to normal of the oesophageal motility disorders promoting GOR following healing of oesophagitis is not known. Interestingly, a large proportion of patients healed or improved at the end of the therapeutic course had a symptomatic relapse at the clinical follow-up. These patients were candidates for additional and prolonged courses of the drug.

Lansoprazole was well tolerated in our patients. No serious adverse clinical events thought to be treatment-related were reported. Two patients had transient diarrhoea and one headache, but reduction of the dose or withdrawal of treatment were not necessary. High serum gastrin levels were detected only in 8 patients. Some concern has been expressed regarding the effect of hypergastrinaemia on enterochromaffin-like (ECL) cells and gastric parietal cells [14 17]. However, no evaluation of endocrine cells or gastric morphology was performed in fundic or antral biopsies at the end of the trial. A growing view indicates that changes reported in endocrine cells of the stomach for up to 5 years are minimal, self-limiting and do not present dysplastic or neoplastic features [11]. Moreover, rat models, in which prolonged hypergastrinaemia has been associated with strong ECL cell hyperplasia and carcinoid tumours, may not be entirely extrapolated to man on account of a species-specific response and a very large difference in gastric ECL cell density [16 31]. In over 10 years of PPI use in humans, only ECL cell hyperplasia has been reported, but no cases of dysplastic lesions or carcinoids [11 17 32].

In conclusion, in children with GOR disease refractory to H_2RAs a short course of lansoprazole is effective both in the control of symptoms and in the healing of oesophagitis. We suggest a starting dose of 1.5 mg/kg/day; however, this dose can be increased if patients are still symptomatic and a double site intraluminal pH test should be carried out to evaluate the efficacy of the drug in controlling both reflux and gastric acidity. A short course of lansoprazole appears to be safe and well tolerated; however, it does not seem to result in prolonged symptomatic remission in most of the patients treated. Future studies should be focused on the effectiveness of prolonged courses of lansoprazole in children with relapsing GOR disease as an alternative to antireflux surgery [33].

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