ORIGINAL ARTICLE

Gut and Liver, Vol. 5, No. 3, September 2011, pp. 302-307

A Multicenter, Randomized, Comparative Study to Determine the Appropriate Dose of Lansoprazole for Use in the Diagnostic Test for Gastroesophageal Reflux Disease

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Background/Aims: The diagnostic proton pump inhibitor test (PPI test) is a method used in diagnosing gastroesophageal reflux disease (GERD). This study aimed to determine the appropriate dose of lansoprazole for use in the diagnostic test for GERD. **Methods:** This study was a randomized, controlled, multicenter trial in the Daegu-Gyeongbuk area. Patients with typical reflux symptoms such as regurgitation and heartburn for at least three months were enrolled in this study. Patients were divided into two groups, the erosive reflux disease (ERD) group and the non-erosive reflux disease (NERD) group, and randomized to 14 days of treatment with lansoprazole at a dose of 15 mg, 30 mg or 60 mg once daily. The PPI test was considered positive if the patient's symptoms improved by more than 50%. **Results:** A total of 218 patients were enrolled, and analysis was performed on the 188 patients who completed the study. The PPI test was positive in 93.2% of the ERD group and 87.2% of the NERD group. A positive PPI test was observed in 91.7%, 89.4%, and 87.2% of the 15 mg, 30 mg, and 60 mg groups, respectively. Significant symptom score changes were observed starting on day 8 for the 15 mg, 30 mg, and 60 mg groups. **Conclusions:** In this multicenter, randomized study of Korean patients, the standard dose of lansoprazole was as effective as a high dose of lansoprazole in relieving the symptoms of GERD, regardless of the presence of ERD, by day 14 of treatment. **(Gut Liver 2011;5:302-307)**

Key Words: Diagnosis; Lansoprazole; Gastroesophageal reflux disease; Dose

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition that develops when reflux of the stomach contents causes symptoms and/or complications based on the Montreal definition and classification.[1] The most common symptoms associated with GERD are heartburn and regurgitation.

The prevalence of GERD in Western countries is higher than in Eastern countries at about 10-20%.[2] However, the prevalence of GERD depends on the diagnostic tools for establishing the diagnosis of GERD.

The available diagnostic tests for GERD include upper endoscopy, ambulatory 24-hour esophageal pH monitoring, barium esophagogram, and multichannel intraluminal impedance with a pH sensor. Endoscopy allows assessment esophageal mucosal injury. However, endoscopy is invasive, expensive (in some Western countries) and technically demanding, and the sensitivity for diagnosing GERD is low, about 50%. Also, ambulatory 24-hour pH monitoring also is time-consuming and an invasive method and has a low sensitivity in cases with mild or non-erosive reflux disease. In addition, pH monitoring has inter-observer and intra-procedure variation. The proton pump inhibitor (PPI) test is a simple and noninvasive method for diagnosing GERD and sensitivity of the PPI test ranges from 27% to 89% and the specificity from 35% to 73%.[3-8] But, proper dose and duration of PPI for PPI test has not been fully evaluated.

This study was performed to evaluate the proper dose and duration of PPI test according to erosive esophagitis in Korean patients.

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Received on July 12, 2010. Accepted on January 20, 2011.
pISSN 1976-2283 eISSN 2005-1212 http://dx.doi.org/10.5009/gnl.2011.5.3.302

MATERIALS AND METHODS

This study was a randomized, controlled, multicenter trial from January 2007 to December 2007. The study was carried out at five tertiary referral centers in the Daegu and Gyeongbuk areas of Korea after Institutional Review Board (IRB) approval of the study. We enrolled 218 patients with typical reflux symptoms such as regurgitation and heartburn for at least three months and that had the symptoms for two or more days during a seven-day interval preceding commencement of the study (Fig. 1). Patients were eligible for the study if they were between 19 and 75 years of age. All patients provided written consent to participate in the study. The exclusion criteria were: patients that declined study enrollment; a pregnancy or breast-feeding; patients that could not undergo esophagogastroduodenoscopy; active gastric ulcer or duodenal ulcer; complications of GERD such as an esophageal stricture or Barrett's esophagus; LA classification D GERD; warning signs such as anemia, weight loss, or severe dysphagia; severe allergy history for a drug; history of gastric or esophageal surgery; impaired hepatic or renal function; uncontrolled diabetes mellitus or hypertension; severe concomitant cardiovascular, hepatic, renal, pulmonary, malignant or hematological disease; recent (within 1 week) treatment with a proton pump inhibitor, H2 blockers, prokinetics, sulcrafate, steroid, antibiotics, non-steroid anti-inflammstory drugs, antihistamine, angiotensin-converting enzyme inhibitor or warfarin; alcohol or drug abuse.

We divided the patients into two groups, erosive reflux disease and non-erosive reflux disease group after esophagogastroduodenoscopy (EGD). Patients took lasoprazole 15 mg or one 30 mg or 60 mg once daily before breakfast for 14 days, according to the randomization schedule based on sequential patient numbers.

The severity of symptom was evaluated before the study, based on the information in a symptom diary, by the patient. The patients were asked to keep a diary in which they recorded the severity of symptoms associated GERD throughout the study. The symptoms scale in the diary included 2 variables, regurgitation and heartburn. The symptom severity was graded by the patient as none=0, mild=1 (symptom did not last long and was easily tolerated), moderate=2 (symptom caused discomfort but not interrupted usual activities), severe=3 (symptoms caused interference of usual activities) and disabling symptom=4 (disabling symptom caused significant interference of usual activities). The maximum score was 8 (regurgitation 4+heartburn 4). Patients that did not take their medication of keep their diary at a frequency of at least 75% (protocol violations) were excluded from the study. The PPI test was considered positive if the patient's symptoms improved by more than 50%.

All adverse symptoms were evaluated and classified as mild (transient and easily tolerated), moderate (caused considerable interference with usual activity) or severe (caused considerable interference with usual activity and may have been incapacitating or life-threatening). All efficacy variables were analyzed according to the per-protocol approach.

RESULTS

A total of 218 patients entered this study, and 188 patients were eligible for analysis. A total of 30 patients were excluded

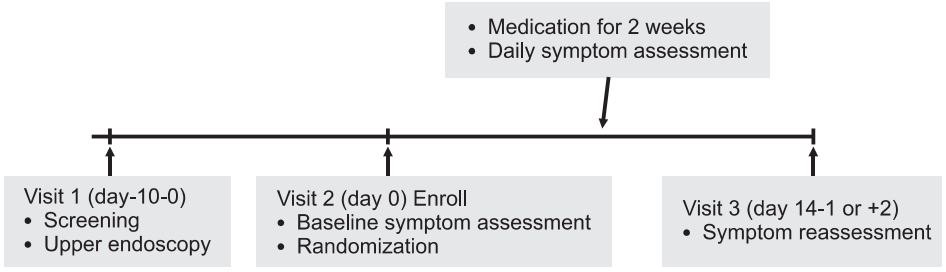

Fig. 1. A schematic diagram of study design.

Table 1. Clinical Characteristics by Daily Dosage of Lansoprazole

Characteristic	15 mg	30 mg	60 mg	p-value
Female, n (%)	34 (58.6)	40 (58.8)	36 (58.1)	0.996
Age, mean±SD, yr	50.7±10.7	49.1±12.5	50.0±11.9	0.742
BMI, mean±SD, kg/m^2	23.2±2.9	23.7±2.9	22.9±2.6	0.197
Alcohol: yes, n (%)	16 (27.6)	21 (30.9)	20 (32.3)	0.850
Current smoker, n (%)	12 (20.7)	10 (14.7)	11 (17.7)	0.678
Total symptom score, mean±SD	7.5±5.7	7.5±5.3	7.6±5.6	0.987
Compliance, mean±SD, %	97.4±9.2	98.1±5.5	97.0±7.3	0.695

SD, standard deviation; BMI, body mass index.

from the analysis because of protocol violations. There were no patients who stopped taking the medication because of adverse events.

The mean age of the 188 patients was 49.9±11.8 years. Male to female ratio was 78:110. Heartburn and regurgitation was observed in 171 (91%) and 151 (80.3%) of patients, respectively.

The number of patients in ERD and NERD group was 70 (37.2%) and 118 (62.8%) patients. The erosive esophagitis by LA classification in ERD group consisted of LA-A in 51 patients, LA-B in 16 patients, and LA-C in 3 patients.

Clinical characteristics between ERD and NERD group were well matched at baseline for age, body mass index, and total symptom score. However, female was predominant in NERD group and alcohol consumption and current smoking status was more frequently observed in ERD group. The three groups based on the dose of PPI were well matched at baseline (Table 1).

A positive PPI test was observed 93.2% of the ERD group and 87.2% of the NERD group during 2 weeks treatment (Table 2). There was no difference between two groups (p>0.05).

The baseline mean symptom score by heartburn and regurgitation in ERD group and NERD group was 8.0±6.3 and 7.3±5.0, respectively (Table 3). The day to significant symptom score change from baseline was 6th day in ERD group and 11th day in NERD group (Table 3, Fig. 2).

A positive PPI test by dosage of lansoprazole was noted

Table 2. Cumulative Improvement over 50% of the Initial Symptom Score by Erosion during a 2 Week Treatment

Day	ERD (n=70)		NERD (n=118)	
	No.	Cumulative %	No.	Cumulative %
2	35	50.0	55	46.6
3	42	60.0	60	51.3
4	50	71.4	69	58.5
5	48	68.6	75	63.6
6	55	78.6	79	66.9
7	51	73.9	78	66.1
8	53	76.8	86	73.5
9	62	88.6	86	73.5
10	60	85.7	91	77.8
11	63	90.0	91	79.8
12	62	88.6	92	81.4
13	61	89.7	91	82.0
14	55	**93.2**	82	**87.2**

ERD, erosive reflux disease; NERD, non-erosive reflux disease.

Table 3. Daily Change in the Mean Symptom Score by Erosion

Day	ERD (n=70)		NERD (n=118)	
	Mean±SD	p-value	Mean±SD	p-value
Baseline	8.0±6.3	-	7.3±5.0	-
2	4.6±4.5	-	4.8±4.8	-
3	3.9±3.9	0.395	4.6±5.1	-
4	3.1±3.7	0.054	4.2±4.6	-
5	3.1±4.1	0.056	4.0±4.8	-
6	**2.6±3.6**	**0.005**	3.7±4.6	-
7	2.5±3.6	0.000	3.6±4.5	0.490
8	2.4±3.1	0.000	2.9±3.6	0.010
9	2.0±2.8	0.000	3.1±4.2	0.058
10	1.8±2.6	0.000	2.9±4.4	0.036
11	1.6±2.5	0.000	2.6±4.1	**0.002**
12	1.5±2.6	0.000	2.7±4.0	0.003
13	1.5±2.2	0.000	2.3±3.6	0.000
14	1.3±2.0	0.000	2.0±3.3	0.000

ERD, erosive reflux disease; NERD, non-erosive reflux disease; SD, standard deviation.

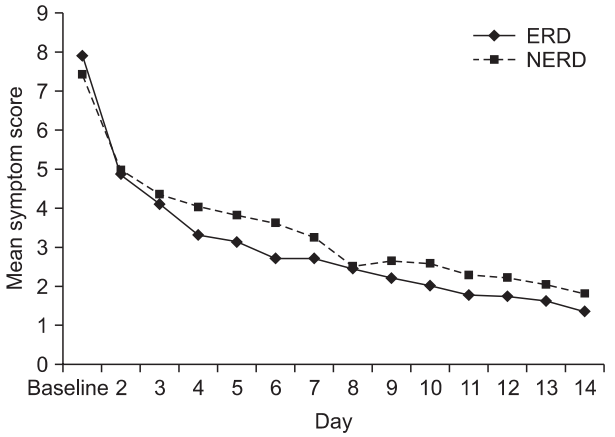

Fig. 2. Daily change in the mean symptom score for all subjects: erosive reflux disease (ERD) *vs.* non-erosive reflux disease (NERD). The X axis shows medication day from baseline (visit 2), and the Y axis shows the mean symptom score for each day.

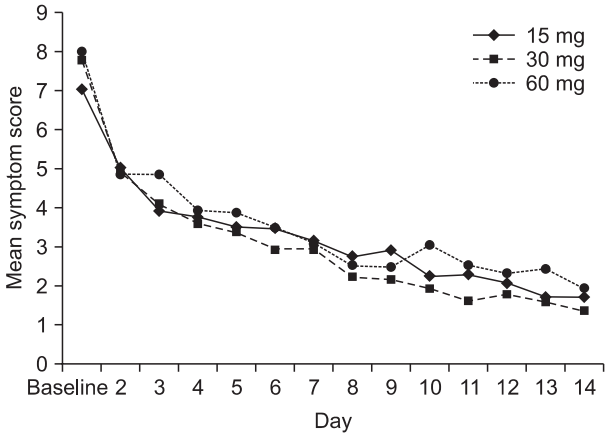

Fig. 3. Daily change in the mean symptom score for all subjects on each proton pump inhibitor (PPI) dose. The X axis shows medication day from baseline (visit 2), and the Y axis shows the mean symptom score for each day.

Table 4. Improvement over 50% of the Initial Symptom Score by Daily Dosage of Lansoprazole

Day	15 mg (n=58)		30 mg (n=68)		60 mg (n=62)	
	No.	Cumulative %	No.	Cumulative %	No.	Cumulative %
2	30	51.7	27	39.7	33	53.2
3	32	56.1	34	50.0	36	58.1
4	34	58.6	45	66.2	40	64.5
5	38	65.5	47	69.1	38	61.3
6	38	65.5	49	72.1	47	75.8
7	38	66.7	47	69.1	44	71.0
8	40	71.4	53	77.9	46	74.2
9	40	70.2	58	85.3	50	80.6
10	44	77.2	58	85.3	49	79.0
11	45	80.4	58	85.3	51	85.0
12	46	82.1	58	87.9	50	82.0
13	47	85.5	54	84.4	51	85.0
14	44	**91.7**	52	**89.7**	41	**87.2**

Table 5. Daily Change in the Mean Symptom Score by Dosage of Lansoprazole

Day	15 mg (n=58)		30 mg (n=68)		60 mg (n=62)	
	Mean±SD	p-value	Mean±SD	p-value	Mean±SD	p-value
Baseline	7.5±5.7	-	7.5±5.3	-	7.6±5.6	-
2	4.7±5.3	-	4.8±4.4	-	4.6±4.4	-
3	4.0±4.5	-	4.4±5.3	-	4.6±4.2	-
4	3.8±4.7	-	3.6±4.1	0.592	4.0±4.3	-
5	3.5±4.7	0.333	3.5±4.5	0.327	3.9±4.4	-
6	3.4±4.3	0.218	3.2±4.6	0.168	3.4±3.9	0.183
7	3.3±4.1	0.218	3.3±4.6	0.188	3.2±3.8	0.088
8	**2.9±3.8**	**0.044**	**2.5±3.2**	**0.002**	**2.9±3.5**	**0.022**
9	2.9±4.0	0.041	2.4±3.6	0.004	2.8±3.8	0.018
10	2.3±3.5	0.000	2.1±3.4	0.001	3.1±4.5	0.118
11	2.4±3.7	0.001	1.9±3.1	0.000	2.4±4.2	0.004
12	2.3±3.5	0.000	2.0±3.4	0.000	2.5±3.9	0.006
13	2.0±3.3	0.000	1.6±2.0	0.000	2.5±4.0	0.007
14	1.6±2.5	0.000	1.3±1.7	0.000	2.2±4.1	0.005

SD, standard deviation.

91.7% in 15 mg group, 89.7% in 30 mg group, and 87.2% in 60 mg of lansoprazole group (p>0.05, Table 4, Fig. 3).

The number of days to significant symptom score change was 8th day for the 15 mg, 30 mg, and 60 mg group (Table 5). Adverse symptoms observed in 6, 4, and 6 patients in the 15 mg, 30 mg, and 60 mg group, respectively. Common adverse symptoms were diarrhea and headache. However, most of adverse symptoms were mild. One moderate adverse symptom was observed in 30 mg and 60 mg group, respectively.

DISCUSSION

GERD is a condition characterized by heartburn or regurgitation caused by esophageal exposure to the acidic gastric contents.[9] The most common symptoms associated with GERD are heartburn and regurgitation. However, the symptoms in Asian countries are different from western countries; atypical symptoms including hoarseness, atypical chest pain, dysphagia, and globus sensation are more common.

The prevalence of GERD in the West is higher than in Asian

countries, about 10-20%.[2,10] In Asia, the prevalence has been variably reported but is generally lower, 2.3-6.2%.[11] The prevalence of erosive esophagitis and non-erosive esophagitis in Korean has been reported to be 8% and 4%, respectively.[12] The difference of prevalence between Western and Asian countries may be due to genetic and/or environmental factors.[13] But, the prevalence of GERD may also change according to the methods used for the diagnosis of GERD, because there are several criteria/method for the diagnosis of GERD.

The PPI test has been used as an effective method for diagnosing GERD.[3,4] However, the dosage, duration, and optimal cut-off values are poorly defined. Several studies have used high dose of PPI for the inhibition of strong acid-secretion.[4,5,8] Schindlbeck *et al*.[5] reported that the sensitivity of PPI testing using 40 mg and 80 mg omeprazole was 27% and 83.3%, respectively. The definition of a positive PPI test in this study was a 75% reduction of symptoms. They concluded that GERD could be ruled out if symptoms do not improve with high dose of PPI testing. But, Fass *et al*.[4] had demonstrated that the sensitivity of omeprazole (60 mg daily, 40 mg AM+20 mg PM) test was about 80%. Thus, no definite consensus about ideal dose for PPI test has been reached.

The results of this study showed no difference between the standard dose (30 mg) and high dose (60 mg) of lansoprazole to relieve the symptoms associated with GERD. The racial difference may contribute to this phenomenon. Thus, we proposed that the dose of PPI should be modulated by the population treated, especially with regard to race.

The optimal duration of the PPI test is defined poorly. In most studies, the duration of PPI test is 7-14 days.[3-6,8,14] This duration was supported by a previous pharmacological study.[15] Previous study reported that in cases with atypical symptoms, 7 days of PPI test might be too short. Thus, 14 days in this study might be sufficient for duration of PPI test, because patients in this study had typical symptoms of GERD.

The optimal cut-off value is also important to determine the accuracy of PPI test. In a previous study, the cut-off value was a 50-75% improvement in symptoms.[8,14] In this study, a positive PPI test was defined as a 50% improvement in the symptoms during 2 weeks. In addition, relief of symptoms according to the presence of erosive esophagitis was evaluated. A positive PPI test was observed 93.2% of patients in the ERD group and 87.2% of patients in the NERD group. The duration to significant symptom resolution was 6 days in the ERD group and 11 days in the NERD group. In addition, a positive PPI test was observed 91.7% of those taking 15 mg, 89.4% of those taking 30 mg and 87.2% of those taking 60 mg of lansoprazole. The duration to significant symptom resolution was 8 days in 15 mg, 30 mg group, and 11 days in 60 mg of lansoprozole. This study showed that there was no difference in the rate of symptom resolution between ERD and NERD group. Also, the dosage of lansoprazole did not influence the rate of symptom relief in this study.

Various types of PPIs such as omeprazole, lansoprazole,[8] rabeprazole,[16] and esomeprzole[7] are used for the PPI test. The data on the PPI test using second generation medications was spare and conflicting because the majority of the PPI tests were performed using omeprazole.[3-8,14] However, the PPI test using second generation medication was as sensitive as the PPI test using omeprazole.[7,8,16]

The limitation of this study is lack of gold standard for the diagnosis of GERD and the definition of positive PPI test is determined arbitrarily.

This randomized study was performed to evaluate the proper dose and duration of PPI test according to erosive esophagitis. The results showed that standard dose PPI test using lansoprazole regardless of the presence of erosive esophagitis was as effective as high-dose PPI testing in Korean patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This study was funded by Jeil Pharmaceutical Co., Ltd., Korea.

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