Eradication of *Helicobacter pylori* with Lansoprazole Based Triple Therapy in Peptic Ulcer Disease

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Abstract

Lansoprazole 30 mg, amoxicillin 1000 mg, and tinidazole 500 mg were given twice daily to 39 peptic ulcer patients (26 duodenal and 13 gastric ulcer, mean age 52.4±15.01) who had *H. pylori* infection for two weeks. Additional lansoprazole 30 mg daily was given to duodenal and gastric ulcer patients for another two and six weeks respectively. Follow-up gastroduodenoscope was performed at fourth and eighth week and eighth and twelfth week for all duodenal and gastric ulcer patients, respectively. *H. pylori* status was evaluated by rapid urease test (CLO® test) and histology at first and last endoscope. The ulcers were healed at the last endoscopy in 11 (85%) gastric ulcer patients and 24 (92%) duodenal ulcers patients. *H. pylori* infection was eradicated in 31 patients (79%). Mild side effects were observed in 15 per cent. In conclusion, 2 week regimen of lansoprazole, amoxicillin, and tinidazole triple therapy resulted in a relatively high healing rate of peptic ulcer (90%) and an acceptable eradication rate of *H. pylori* infection (79%).

Key word : *H. pylori*, Lansoprazole, Triple Therapy, Peptic Ulcer

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Since first being isolated from gastric mucosa in 1983 by Warren JR and Marshall B,[1,2] *Helicobacter pylori* has been considered to be a main cause of peptic ulcer disease. In 1994 the National Institutes of Health Consensus Development Conference Panel on *H. pylori* in peptic ulcer disease recommended that all peptic ulcer patients infected with *H. pylori* receive antibiotics in addition to acid-suppressive drugs[3]. Eradication of *H. pylori* leads to dramatic reduction in duodenal and gastric ulcer recurrence from the annual relapse rate of 58 per cent and 53 per cent, respectively, in *H. pylori* positive patients to 2.6 per cent and 2 per cent in *H. pylori* negative patients[4]. Various

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combination therapies for eradication of *H. pylori* have been reported with considerable variability in effectiveness.

Classical bismuth based triple therapy has good eradication rate but this therapeutic efficacy is limited by a somewhat high incidence of side effects[5]. Proton pump inhibitor based triple therapy has been shown to have a high eradication rate of *H. pylori* when given to the patients for 1-2 weeks and has fewer side effects than classical bismuth based triple therapy.

Lansoprazole in a proton pump inhibitor that reduces gastric acid secretion and keeps gastric pH more than 4 for more than 18 hours per day. It has proved to be effective for the eradication of *H. pylori* when combined with two antibiotics (amoxicillin, clarithromycin and metronidazole or tinidazole). Amoxicillin is widely used for *H. pylori* eradication and its antibacterial activity against *H. pylori* improves when combined with a proton pump inhibitor. Resistance to amoxicillin has been observed but is rare. Tinidazole is a nitroimidazole which has antibacterial activity against *H. pylori* similar to that of metronidazole but has fewer side effects. Both amoxicillin and tinidazole are much cheaper than clarithromycin. Because Thailand is a developing country the use of tinidazole or metronidazole and amoxicillin in combination with a proton pump inhibitor will be more appropriate for Thai patients if it is proven to be effective for *H. pylori* eradication because of its cheaper cost.

In Thailand there is scant data about *H. pylori* eradication by proton pump inhibitor based regimens. This study was designed to evaluate the efficacy of a two-week regimen of lansoprazole, amoxicillin and tinidazole for eradication of *H. pylori* in Thai patients with gastric or duodenal ulcer.

MATERIAL AND METHOD

Lansoprazole (Prevacid®) 30 mg, amoxicillin 1000 mg, and tinidazole 500 mg were given orally twice daily before meals to patients who had gastric or duodenal ulcer and *H. pylori* infection. Lansoprazole 30 mg was given orally daily to gastric ulcer patients for another six weeks and to duodenal ulcer patients for another two weeks.

Esophagogastroduodenoscope was performed at entry, eighth and twelfth week after treatment in gastric ulcer patients and at entry, fourth and eighth week in duodenal ulcer patients to evaluate ulcer status, healing and *H. pylori* status.

Helicobacter pylori status was determined by rapid urease test (CLO® test, Delta West Ltd., Western Australia) and histology. Two antral and two corpus biopsies were taken for rapid urease test and histology. Giemsa stain and hemotoxylin-eosin were used for histological identification of *H. pylori*. Gastric ulcer and duodenal ulcer patients with positive CLO® test and histology were included. Patients were excluded if they were unwilling to give written informed consent, were pregnant or lactating, had an ulcer larger than 2 centimeters in diameter, had received antimicrobial or antisecretory drugs within four weeks before enrollment or had history of hypersensitivity to lansoprazole, amoxicillin, tinidazole and related drugs.

Clinical improvement, peptic symptoms, side effects and compliance were assessed by interview at second, fourth and eighth weeks after treatment for duodenal ulcer patients and at second, fourth, eighth and twelfth week for gastric ulcer patients. Peptic ulcer symptoms in terms of epigastric pain, gastric fullness, anorexia, heartburn, nausea and vomiting were scored by a gastroenterologist on a scale from 1 to 4, where 1 = no symptom; 2 = mild, symptomatic but not interfering with normal activities; 3 = moderate, symptomatic and interfering with normal activities, 4 = severe, symptomatic and unable to perform normal activities.

H. pylori eradication was defined as negative CLO® test and histology at four or more weeks after completing therapy. Ulcer healing was defined as complete reepithelialization. The *H. pylori* eradication rate was claculated as the percentage of patients whose *H. pylori* were undetectable by CLO® test and histology four or more weeks after completing treatment among those who completed the study. Ulcer healing rate was calculated as the percentage of patients whose ulcers were completely reepithelialised when they were reendoscoped. Those with duodenal ulcers were reendoscoped at fourth and eighth week, those with gastric ulcers at eighth and twelfth week.

RESULTS

Between April 1997 and August 1998, 45 patients (34 men, 11 women) were diagnosed as having an active gastric ulcer (n= 18) or duodenal ulcer (n= 27) with *H. pylori* infection. 19 patients had upper gastrointestinal bleeding before the study. Six patients were excluded from the study (5 were lost to follow-up and 1 developed skin rash during the first week of treatment).

Table 1. Mean peptic ulcer symptom scores at entry, second, fourth, and eighth or twelfth week.

Symptom	Mean score			
	Week 0	Week 2	Week 4	Week 8/12
Anorexia	1.282	1.051*	1.128	1.000*
Epigastric pain	1.897	1.070*	1.070*	1.070*
Gastric fullness	1.846	1.179*	1.205*	1.128*
Nausea and Vomiting	1.410	1.051*	1.026*	1.000*
Heartburn	1.154	1.026	1.000*	1.000*
Total	7.590	5.385*	5.436*	5.205*

Remark:- * = $p<0.05$

There were 39 patients who completed this study (30 men, 9 women). Twenty-six patients had duodenal ulcer and 13 patients had gastric ulcer (28 patients had a single ulcer, 11 patients had multiple ulcers). The ages were between 26-84 years (52.4 ± 15.01, mean ± SD). There were 12 patients and 9 patients who smoked and took NSAIDs, respectively.

Mean total peptic ulcer symptom scores (mean ± SD) were 7.59±1.916, 5.38±0.847, 5.44± 0.788 and 5.20±0.522 at entry, second, fourth and eighth or twelfth week, respectively. Significant symptom improvement was observed after 2 weeks of treatment. (Table 1)

In duodenal ulcer patients the ulcers were healed in 24 (92%) and 23 (88%) at the fourth and eight weeks after treatment, respectively (one developed a 0.3 cm gastric ulcer at the eighth week after a duodenal ulcer had healed at the fourth week but *H. pylori* was eradicated) and *H. pylori* was eradicated in 21. (81%)

In gastric ulcer patients, the ulcers were healed in 12 (92%) and 11 (85%) at the eighth and twelfth weeks, respectively (one had delayed ulcer healing after the eighth week, one had ulcer relapse and one developed a 0.3 cm duodenal ulcer after the gastric ulcer was healed but *H. pylori* was eradicated in all of these patients) and *H. pylori* was eradicated in 10 patients (77%). The overall healing rate of gastric ulcer and duodenal ulcer was 87 per cent and eradication rate was 79 per cent.

Mild side effects were observed in 6 patients (15.4%) including diarrhea in two, metallic taste in one, skin in one, dizziness in one and fainting in one. Only one patient had to stop treatment because of skin rash.

DISCUSSION

Eradication of *H. pylori* has been clearly shown to alter the natural history of duodenal and gastric ulcer disease. The annual relapse rate of patients with *H. pylori* positive was reduced from 58 per cent to 2.6 per cent in duodenal ulcer patients and from 53 per cent to 2 per cent in gastric ulcer patients if *H. pylori* was eradicated[4].

Since 1991 the Gastroenterology Unit, Department of Medicine, Chulalongkorn University Hospital has used the CLO® test for detecting H. pylori infection in peptic ulcer patients. We found *H. pylori* infection in only 69 per cent of 295 duodenal ulcer patients and 53 per cent in 114 gastric ulcer patients. The lower prevalence of *H. pylori* infection in peptic ulcer patients in our center is similar to other centers in Thailand and may be due to the liberal use of NSAIDs and antibiotics in Thailand. In most cases of *H. pylori* associated peptic ulcer patients we used a proton pump inhibitor combined with two antibiotics. The antibiotics that we often use are amoxicillin, clarithromycin and metronidazole or tinidazole but the efficacy of these regimens in Thailand has not been well established.

The impact of metronidazole resistance on the eradication of *H. pylori* with a proton pump inhibitor plus amoxicillin and metronidazole has been reported. Bell et al performed two studies with a 14 day regimen of omeprazole plus amoxicillin and metronidazole. The rate of eradication decreased from 96-100 per cent for metronidazole susceptible strains to 75 per cent for metronidazole resistant strains[9-10]. Lerang et al reported similar results with 10 days of the same regimen[11]. Thijs et al used a 7 day regimen of omeprazole plus amoxicillin and tinidazole. They found the rate of eradication decreased from 95 per cent for metronidazole susceptible strains to 69 per cent for metronidazole resistant strains[12].

Metronidazole resistance is an important factor in *H. pylori* eradication efficacy, but we did not study metronidazole or tinidazole resistance in this study. In Thailand, we reported 52 per cent of metronidazole resistance[6] and the rate of 51 per cent was similarly reported by Phaosawasdi K et al[8] which are relatively high. The proportion of metronidazole resistant strains in a population

depends on the history of that population's exposure to imidazoles[14]. Our high rate of metronidazole resistance reflects the liberal use of antimicrobial agents in Thailand. There is cross resistance between metronidazole and tinidazole but in this study we still have an acceptable rate of *H. pylori* eradication even though the local rate of metronidazole resistance is high. There have been some studies reporting regimens of lansoprazole, amoxicillin, and metronidazole that can eradicate *H. pylori* in 73-95 per cent of *H. pylori* infected patients[7]. The result of our study is comparable to previous reports.

To overcome the metronidazole resistance of *H. pylori* the combination of at least two antibiotics and a proton pump inhibitor should be used. There has been recommendation that to enhance the eradication rate clarithromycin should be used because it can partially negate the effect of metronidazole resistance[15]. But we also have the rate of 13.3 per cent of clarithromycin resistance in Thailand[8] and clarithromycin resistant *H. pylori* is associated with lower cure rates than those of metronidazole resistance when clarithromycin and metronidazole based therapies were used in the treatment regimens respectively[16]. Presently there is not enough data about a proton pump inhibitor plus clarithromycin and metronidazole or amoxicillin in Thailand.

Quadruple therapy (omeprazole plus colloidal bismuth subcitrate or bismuth subsalicylate and two antibiotics) has been recommended for treatment of metronidazole resistant *H. pylori*[17]. Increasing the dosage of metronidazole in a proton pump inhibitor based triple therapy also seems to improve the eradication rate of metronidazole resistance *H. pylori*[18].

In this study we failed to cure duodenal ulcers in 2 patients. The reasons for healing failure were smoking in one and failure to eradicate *H. pylori* in the other. We also had one patient whose duodenal ulcer was healed at the fourth week but developed a small gastric ulcer at the eighth week even though the *H. pylori* was eradicated and the patient did not have any factor that influenced ulcer healing or ulcer recurrence. There were 2 gastric ulcer patients whose ulcers were healed at the fourth week but recurred at the eighth week, both of them were cigarette smokers. One gastric ulcer patient had delayed ulcer healing (after the eighth week) and we found *H. pylori* eradication failure in this patients.

The optimum duration of a proton pump inhibitor based triple therapy is still a controversial issue in Thailand. Asia Pacific Consensus stated that 7 days regimen is adequate[19] for *H. pylori* eradication. However, this may not be long enough and may lead to more *H. pylori* resistant strains and has a significant chance of treatment failure especially in the area of high prevalence of antibiotic resistant strains like Thailand. We recommend at least 10-14 days regimen of a proton pump inhibitor triple therapy for *H. pylori* eradication in Thailand. There have been reports that one week regimen of *H. pylori* eradication therapy is sufficient for both duodenal and gastric ulcer healing [20,21] but in our study we had many patients who had peptic ulcer complicated with upper gastrointestinal bleeding so that only week of triple therapy is not suitable. We recommend that complicated peptic ulcer patients should receive an acid suppression drug until the ulcer is healed.

In conclusion, a two-week regimen of lansoprazole, amoxicillin and tinidazole resulted in a relatively high healing rate of both gastric and duodenal ulcer (87%) and acceptable readication rate of *H. pylori* (79%) even though there is high metronidazole resistance in our area. More studies are needed to determine the best and cheapest regimen for *H. pylori* eradication in Thailand and we also have to study more on metronidazole resistance.

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การกำจัดเชื้อ*เฮลิโคแบ็คเตอร์ พัยลอริ* ด้วยสูตรยาแลนโสปราโซลร่วมกับยาอื่นรวม 3 ขนานในผู้ป่วยแผลในกระเพาะอาหารและลำไส้เล็กส่วนต้น

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ผู้ป่วยแผลในกระเพาะอาหารหรือในลำไส้เล็กส่วนต้น 39 ราย (แผลในลำไส้เล็กส่วนต้น 26 ราย, แผลในกระเพาะอาหาร 13 ราย, อายุเฉลี่ย 52.4±15.01) ซึ่งตรวจพบว่ามีการติดเชื้อ *H. pylori* ได้รับการรักษาด้วยยา lansoprazole 30 มิลลิกรัม ร่วมกับ amoxicillin 1000 มิลลิกรัมและ tinidazole 500 มิลลิกรัม โดยรับประทานวันละ 2 ครั้งเป็นเวลานาน 2 สัปดาห์ หลังจากนั้นผู้ป่วยจะได้รับยา lansoprazole 30 มิลลิกรัมต่ออีก 2 สัปดาห์ ในผู้ป่วยแผลในลำไส้เล็กส่วนต้น และอีก 6 สัปดาห์ ในผู้ป่วยแผลในกระเพาะอาหาร ตามลำดับ ได้ทำการติดตามผลการรักษาในผู้ป่วยโดยการส่องกล้องดูภายในกระเพาะอาหารและลำไส้เล็กส่วนต้นหลังเริ่มการรักษา 4 และ 8 สัปดาห์ในผู้ป่วยแผลในลำไส้เล็กส่วนต้น หรือ 8 และ 12 สัปดาห์ในผู้ป่วยแผลในกระเพาะอาหาร การตรวจว่าผู้ป่วยมีการติดเชื้อ *H. pylori* หรือไม่ ตรวจโดยการใช้ rapid urease test (CLO® Test) และโดยวิธีวิทยาฮิสโต จากชิ้นเนื้อที่ได้จากการส่องกล้องครั้งแรกก่อนการรักษาและครั้งสุดท้ายหลังการรักษา พบว่าในการส่องกล้องครั้งสุดท้าย แผลในกระเพาะอาหารหาย 11 ราย (85%) และแผลในลำไส้เล็กส่วนต้นหาย 24 ราย (92%) และพบว่าสามารถกำจัดเชื้อ *H. pylori* ได้ 31 ราย (79%) โดยพบผลข้างเคียงจากยาเล็กน้อย 15% โดยสรุป การรักษาแผลในกระเพาะอาหารและในลำไส้เล็กส่วนต้นด้วยยาสูตร lansoprazole ร่วมกับ amoxicillin และ tinidazole สามารถที่จะทำให้แผลหายได้ในอัตราสูง (90%) และสามารถกำจัดเชื้อ *H. pylori* ได้ในอัตราที่สูงพอสมควร (79%) แม้ว่าประเทศไทยจะมีอุบัติการของเชื้อ *H. pylori* ที่ดื้อต่อยา metronidazole สูงก็ตาม

คำสำคัญ : *H. pylori*, Lansoprazole, Triple Therapy, Peptic Ulcer

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