Triple therapy with pantoprazole, clarithromycin and amoxicillin for eradication in patients with Helicobacter pylori positive duodenal ulcers

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ABSTRACT

Objective: To assess the effectiveness of a 7-day pantoprazole 40 mg twice a day (bid) plus clarithromycin 500 mg bid and amoxicillin one gram bid therapy in the eradication of *Helicobacter pylori* (*H. pylori*) in patients with *H. pylori* positive duodenal ulcers.

Methods: The present study was a prospective, non-comparative and open-label designed. After confirming duodenal ulcer by endoscopy, patients with evidence of *H. pylori* infection with *Campylobacter* like organism (CLO) test, histology or culture were given eradication treatment for 7 days. Successful eradication was confirmed with second endoscopy after 4 weeks unless all CLO test, histology or culture were negative. Relief of symptoms and any adverse effects were recorded. The trial took place between February 2002 and April 2002 at King Hussein Medical Center, Royal Medical Services, Amman, Jordan.

Results: Eradication rate of *H. pylori* was 94% at 4 weeks after treatment was given. There was an improvement in gastrointestinal symptoms and adverse events were recorded in 5 patents only; however, in no case was withdrawal of treatment necessary.

Conclusion: This study demonstrates that a 7-day pantoprazole 40 mg bid plus clarithromycin 500 mg bid and amoxicillin one gram bid therapy is an effective and well tolerated therapeutic approach for *H. pylori* eradication.

Saudi Med J 2004; Vol. 25 (8): 1006-1009

Since the rediscovery of *Helicobacter pylori* (*H. pylori*) by Warren and Marshall in the early 1980s, there has been a paradigm shift in our understanding of the pathogenesis of many common and uncommon gastrointestinal disease processes, as well as therapy of *H. pylori* related diseases.[1-3] Indeed, the whole concept of ulcer disease was possibly related to a bacterial infection and had been summarily dismissed until the observations made by these Australian investigators resurrected the premise. Since that event, a better understanding regarding the epidemiology, pathogenesis, disease association and treatment of this infection has been determined.[4-8] *Helicobacter pylori* infects approximately half the world's population. The estimated prevalence of the infection in the United States population is 30-40%.[9-11] The regional and subgroup differences in *H. pylori* prevalence are probably correlated with the observed differences in *H. pylori*-related clinical manifestation.[10] The human host is the only known reservoir for the infection. Transmission occurs by both person-to-person contact, oral-oral, and fecal-oral routes. Infection is most commonly acquired in

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Received 3rd November 2003. Accepted for publication in final form 13th March 2004.

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childhood;[10] yet, many controversies in the management of *H. pylori* infection is still remain.[12] The combination of proton pump inhibitors (PPIs) and 2 or more antibiotics for 10-14 days became standard therapy for *H. pylori* based on the efficacy of this regimen as well as its tolerability and convenience.[2,9,10] Much remains to be learned before we know the optimal treatment approach to this common important infection. *Helicobacter pylori* treatment has been a slow process of experimentation and evolution. There has certainly been a treatment learning curve; we have abandoned multiple suboptimal therapies. We have increased the number of agents from monotherapy, to dual therapy with 2 antibiotics, but now a day they used triple antimicrobial-based therapy.[2,4,11] Proton pump inhibitors have both direct and indirect effects on *H. pylori* eradication.[13,14] The PPIs directly affect *H. pylori* by reducing its density and causing lysis of the *H. pylori* at neutral pH in the presence of urea. Indirectly, PPIs increase antibiotic concentration in gastric juice by reducing the volume of gastric-acid secretion. They increase the permeability of gastric juice by decreasing its viscosity, and they reduce the degradation of acid-labile antibiotics in the stomach by increasing intragastric pH. Proton pump inhibitor triple therapy was first introduced in 1993[13] and the efficacy of combining a PPI and 2 antibiotics - specifically clarithromycin and tinidazole was demonstrated. Three times daily dosing regimen was highly effective, had no side effects, and patients had good compliance. Proton pump inhibitors are substituted benzimidazole derivatives that selectively and irreversibly inhibit the gastric hydrogen-potassium adenosine triphosphatase (H^+K^+ -ATPase) pump mechanism.[15,16] Omeprazole is the first available PPIs that has been used for nearly 2 decades. More recently, other members of the PPI family, including pantoprazole, lansoprazole, and rabeprazole were developed. These agents are used to treat gastroesophageal reflux disease, peptic ulcer disease, Barrett's esophagus, and Zollinger-Ellison syndrome. They are also administered as part of combination regimens to eradicate *H. pylori.* Pantoprazole sodium is a gastric $^+K^+$ -ATPase inhibitor.[17] It is the fourth orally available PPI for clinical administration in the United States. It shares the same core structure and common chemical mechanism as other PPIs. Like the other PPIs, pantoprazole inhibits ATPase only when acid secretion is occurring. Due to a low pK value, PPIs accumulate in the secretary canaliculus of the parietal cell when the cell is secreting acid. Pantoprazole is an acid-activated prodrug, as pronations required to form the active compound, which is capable of reacting with free SH groups on the ATPase enzyme.[18] The covalent binding of PPIs to $^+K^+$ -ATPase irreversibly inhibits hydrogen ion transport.

Methods. The present study was a prospective, non-comparative; open-label designed to assess the effectiveness of Pantoprazole based triple eradication therapy, having healing rate as a primary endpoint. Secondary objective of the study was assessment of relief of symptoms.

Inclusion criteria were male and female patients, aged $\geq$18 years with florid duodenal ulceration by endoscopy and evidence of *H. pylori* colonization. Exclusion criteria included the following 1. Women who are pregnant, lactating or using hormonal contraception. 2. History of any previous H Pylori treatment within the last 4 weeks prior to the study. 3. Duodenal ulcer complication. 4. History of upper gastrointestinal surgery. 5. History of reflux esophagitis proven by endoscopy. 6. Malignant disease of any kind. 7. History of known allergies to any of the participating drugs. 8. Concomitant use of none steroidal anti inflammatory drugs or steroids. Patients received pantoprazole 40 mg bid plus clarithromycin 500mg bid and amoxicillin one gram bid (pantoprazole, clarithromycin, amoxicillin group, n=57) administered for 7 days. At baseline visit (V0), clinical history and physical examination as well as concomitant medication if any were recorded; blood samples for biochemical and hematological analyses were drawn and informed consent was obtained from patients as well. The next visits were after completion of the 7-day study treatment (V1), and at 28 days after treatment completion (V2), at those visits clinical history and physical examination were repeated with special attention to improvement of symptoms, adverse effects and compliance. At endoscopies (V0 and V2), 2 antral (approximately 3 cm pre-pyloric) biopsies were taken and placed together on a *Campylobacter* like organism (CLO) test® slide,[19,20] additionally 2 corporal (middle of the posterior gastric wall) biopsies were sent to histology where a modified Giemsa and hematoxylin and eosin stains were used. Likewise, an additional biopsy was sent for culture, which was sent for none selective horse agar plate blood cultures and *H. pylori* specific colombia base blood culture.[21,22] In order to determine the presence of any adverse effects, patients were asked the standardized question at each assessment such as "Did the drug administered cause any complaint"? The severity of adverse effects judged by the observer as unrelated, improbably related, possibly related, probably related or definitely related to the study drug was classified as mild (signs or symptoms easily tolerated by the patient), moderate (discomfort enough to cause interference with the patient's activities), or severe (discomfort incapacitating the ability to undertake any activity or causing the patient to leave the study). Compliance with treatment was assessed by pill count. Post-treatment *H. pylori* status was assessed

by a second endoscopy at final visit (V3). And patients were considered cured of *H. pylori* infection if all cultures and histology stains were negative otherwise patients with *H. pylori* infection was considered as treatment failures.[23,24] Ranitidine 150 mg was permitted as a rescue medication during the one month follow-up period. The trial took place between February 2002 and April 2002.

Statistical analysis were carried out using the statistical software package SAS, data analysis were performed descriptively. The eradication rate was computed as point estimate with its 95% confidence limits.

Results. Fifty-four subjects were recruited, 23% of patients were female and 77% were males. The mean age was 39 ± 13. Weight was 71 ± 11 kg, 48% were none smokers, 1.5% were occasional smokers and 50.5% were daily smokers. The median time since gastrointestinal symptoms were known was 5 years, the minimum was 62 days and the maximum was 30 years. Six patients (11%) had concomitant disease, most frequent were diabetes mellitus and migraine (2 patients each), for the 2 other patients one had psoriasis and the other coronary artery disease. The most concomitant medication was paracetamol. The patient was considered *H. pylori* positive if at least one of the tests (CLO test, histology and microbiology was positive).[22] Out of the 54 patients at V0 only 5 patients were still *H. pylori* positive at V3. The major gastrointestinal symptoms at V0 included epigastric pain 94.5% (51), nausea 40% (22), vomiting 15% (8) and heart burn 78% (42). At V1, the symptoms were epigastric pain 13% (7), nausea 4% (2), vomiting 4%(2) and heart burn 6% (3). At visit 2 (final visit) the gastrointestinal symptoms were epigastric pain 17% (9), nausea 8% (4), vomiting 6% (3) and heart burn 33% (18). Adverse events included diarrhea in 3 patients (5%), headache in one (1.8%) and dry mouth in one (1.8%).

Discussion. Proton pump inhibitors represent the most important recent advance in the treatment of acid-related gastrointestinal diseases.[25,26] Based on efficacy profiles superior to those of histamine H2-receptor antagonists (H_2RA), sucralfate, and cisapride, PPIs are now considered the drugs of choice in managing patients with peptic ulcer disease and triple therapy including 2 antibiotics and a PPI is the preferred therapeutic choice for eradication of *H. pylori* in those patients.[26] Proton pump inhibitor-based triple therapy, including amoxicillin and clarithromycin, was recommended as first-line therapy for *H. pylori* eradication by the Maastricht 2-2000 Consensus.[27,28] The primary objective of this non-comparative open-label with intention to treat study was to assess the effectiveness and tolerability profile of pantoprazole based triple therapy in the management and eradication of patients with duodenal ulcers. The response rate was assessed primarily by the eradication rate of *H. pylori* after treatment, which required that all CLO test. Histology and culture were negative and secondarily by the improvement in gastrointestinal symptoms. The tolerability was assessed by the frequency of adverse effects.

This study confirms the effectiveness of pantoprazole based triple therapy in patients with h pylori positive duodenal ulcers. At the end of the 4-week treatment period, 94% of patients were *H. pylori* negative, which is in keeping with previous studies using PPIs with clarithromycin and amoxicillin.[29,30,31] Gastrointestinal symptoms including heartburn, nausea, vomiting and epigastric pain showed improvement after treatment. Prior to treatment the most common symptom was epigastric pain (94.5%) followed by heartburn (78%) then nausea (40%) and least common vomiting (15%). Pantoprazole based triple therapy was well tolerated and produced minimal adverse effects. There were 3 patients with diarrhea, one with headache, and one with dry mouth in which these adverse events were considered possibly related to the studied medication by the investigator but a casual relation with the studied medication was not ruled out for all patients. However, there are no cases withdrawn during the treatment as no serious adverse events were reported.

In conclusion, this non-comparative, open-label, prospective with intention to treat study, Pantoprazole based eradication therapy has shown clinical effectiveness in eradicating *H. pylori* in patients with duodenal ulcers and in reducing the frequency and intensity of associated symptoms. Pantoprazole regimen was also well tolerated.

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