

Triple therapy with clarithromycin, omeprazole, and amoxicillin for eradication of *Helicobacter pylori* in duodenal ulcer patients in Asia and Africa

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SUMMARY

Background: Studies assessing the efficacy of triple therapy containing clarithromycin and amoxicillin for the eradication of *Helicobacter pylori* infection and healing of duodenal ulcers in Asian and African countries are limited.

Aim: To determine the efficacy and safety of 1-week triple therapy with omeprazole, amoxicillin and clarithromycin for eradicating *H. pylori* infection in patients with active duodenal ulcer living in Asian and African regions.

Methods: This was an open-label, multicentre study in 11 centres in Asia and Africa. Patients with endoscopy-proven duodenal ulcer and who were *H. pylori*-positive were treated with clarithromycin 500 mg, omeprazole 20 mg, and amoxicillin 1000 mg, all given twice daily

for 7 days. Upper endoscopy was repeated at week 6 to check for ulcer healing and *H. pylori* status.

Results: A total of 117 patients were recruited. *H. pylori* eradication rates were 85% by per protocol analysis and 80% by intention-to-treat analysis. Ulcer healing was found in 94% of subjects (per protocol analysis). Clinical success, measured by change of pre-treatment ulcer symptoms, was strongly supported by complete resolution or improvement in 100% of the evaluable patients (per protocol analysis). Since treatment-related adverse events, when present, were largely mild or moderate, the triple therapy regimen was considered safe.

Conclusion: Seven-day triple therapy with omeprazole, amoxicillin, and clarithromycin was efficacious for treating Asian and African patients with duodenal ulcer disease associated with *H. pylori* infection, and the treatment regimen was well-tolerated.

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INTRODUCTION

Helicobacter pylori infection is recognized as a causative factor for development of duodenal ulcers. *H. pylori* eradication results in ulcer healing, prevention of ulcer recurrence, and decreased overall use of health care

resources.^{1–8} For *H. pylori* eradication, the use of various antibiotics—including tetracycline, amoxicillin, metronidazole, and clarithromycin—has been studied. Numerous clinical trials have been conducted to define the best drug combinations and duration of treatment. In general, short-term treatment regimens improve patient compliance, whilst triple drug treatment combinations are highly efficacious, especially against strains that are resistant to certain antibiotics.^{9–13}

Prevalence of *H. pylori* infection is high in regions of Africa and Asia, and therapy can be complicated by various factors including drug costs and availability, treatment side-effects, and the presence of bacterial strains that are antibiotic resistant.¹⁴ Some treatment regimens recommended elsewhere in the world are considered too expensive or may be unavailable in these regions. Standard bismuth triple therapy is available, but patients may not comply due to the common occurrences of side-effects.¹⁵ Metronidazole-containing regimens have limited effectiveness because of increasing prevalence of resistance to this drug; resistance rates as high as 74% have been reported in some areas in our region.^{16–20} Thus, non-metronidazole containing regimens are currently considered more suitable for eradicating *H. pylori* infection in Asia and Africa.¹⁴

Elsewhere in the world, clarithromycin-containing regimens which combine a proton pump inhibitor with amoxicillin have shown considerable success. When used for 7–10 days, these therapeutic regimens have achieved *H. pylori* eradication rates and ulcer healing rates greater than 90%. Furthermore, such therapy afforded a good safety profile and credible patient compliance.^{7, 9, 11–13, 21–23} However, the experience on the overall efficacy of these regimes in the Asian and African population is limited. Most of the results came from single centre studies in Hong Kong, Taiwan or Japan; data from Southeast Asia and Africa are lacking. The purpose of the present study was therefore to evaluate the efficacy and safety of 7-day triple therapy with omeprazole, amoxicillin, and clarithromycin for eradicating *Helicobacter pylori* and healing duodenal ulcers in a multicentre design in Asia and Africa.

PATIENTS AND METHODS

Patients

This was a multicentre study including 11 major hospitals in Hong Kong, Pakistan, South Africa, and

Taiwan. Patients who met specific inclusion criteria were enrolled in the study. To be included, patients had to be aged between 18 and 80 years with an active duodenal ulcer of at least 5 mm in diameter. *H. pylori* infection was defined by a positive CLO test (Delta West, Bentley, West Australia) on endoscopic biopsy specimens from the antrum which was confirmed by at least one of two tests: histological examination of antral and body biopsy with Giemsa stain or ¹³C-urea breath test (¹³C-UBT). All patients gave written, informed consent according to the Declaration of Helsinki and applicable local laws. Patients were excluded from enrolment if they: had taken bismuth preparations or antibiotics within 4 weeks prior to the study; had endoscopy-based evidence of gastric ulcer, gastric malignancy, pyloric obstruction, oesophageal stricture requiring dilation, fresh clot, active bleeding, or perforated ulcers; had a history of previous gastric or duodenal surgery, underlying malignant conditions, allergy to proton-pump inhibitors, amoxicillin or clarithromycin; or if they had clinically significant cardiovascular, pulmonary, renal, hepatic, metabolic, gastrointestinal, neurological, endocrine, or psychiatric disease. Female patients were non-lactating and had a negative pregnancy test.

Study design

Patients enrolled in this open-label investigation were treated with clarithromycin 500 mg, omeprazole 20 mg, and amoxicillin 1000 mg, all given twice daily for 7 days. Antacid tablets were provided to each patient for the relief of pain or discomfort, as needed, and patients were instructed to report the usage. Symptoms were recorded at the initial visit, the end-treatment visit (day 8, 9, or 10), and at the follow-up visit (4–6 weeks post-treatment). ¹³C-urea breath test and endoscopy with biopsy for histology were performed at the follow-up visit. Samples for urea breath test and histology were sent and analysed by central reference laboratories. Global eradication was defined as negative results on both tests. The endoscopic examination also assessed ulcer healing. Compliance was assessed by count of returned tablets, and side-effects were determined by direct questioning on the end-treatment visit.

Patients who underwent therapeutic procedures that interfered with subsequent evaluation were excluded from efficacy evaluation, as were those who failed to take at least 70% of the tablets for each study medication.

Bacterial culture and antimicrobial susceptibility tests

Culture and antimicrobial susceptibility testing were performed on an antral biopsy specimen collected from each study participant at the pre-treatment visit. Specimens were placed in collection devices containing glycerol broth and frozen at -20°C or below, within 1 hour of biopsy. Specimens were transported on dry ice to the central laboratory where they were stored at -70°C . Culture was performed using fresh blood-based media, both selective and non-selective, at 37°C in 12% CO_2 in air with 98% humidity. *H. pylori* was identified by Gram stain, typical colony morphology, and biochemical properties (production of oxidase, catalase, and urease). In addition, the minimal inhibitory concentration for each isolate was determined with the epsilon meter test and agar dilution.

Ulcer and histological assessment

Endoscopic examinations were performed to document pre-treatment ulcer size and post-treatment ulcer healing. An ulcer was considered healed if the pre-treatment ulcer was completely healed, and no additional ulcers were present. The ulcer was considered unhealed if at least one ulcer was present or the index ulcer was not completely re-epithelialized. The condition was indeterminate if the ulcer was not reassessed.

At a reference laboratory, a pathologist who was blinded to the patients' clinical status performed the histological examination of gastric biopsy specimens. Pre-treatment examinations assessed for evidence of *H. pylori* infection and for evidence of chronic gastritis, including inflammation, gastric activity and atrophy, and intestinal metaplasia. Post-treatment examinations reassessed these same parameters.

Clinical response

Symptoms of epigastric pain or burning, belching, daytime abdominal pain, and night-time abdominal pain were assessed. All symptoms were rated as absent, mild, moderate, or severe. Mild symptoms were transient and easily tolerated. Moderate symptoms caused discomfort and disrupted normal activities. Severe symptoms caused considerable interference with usual activities or were incapacitating. The clinical response of each subject was assessed at the follow-up visit. A pre-treatment symptom was considered resolved if the

severity changed from mild, moderate, or severe to absent. A symptom was considered improved if it changed from severe to moderate or mild, or moderate to mild. A symptom was unresolved if it stayed the same or worsened. If all symptoms were resolved, the patient was classified as cured. Symptom 'improvement' was assigned when some pre-treatment duodenal ulcer symptoms were improved, whilst 'failure' was assigned when there was no improvement. The condition was indeterminate if the patient was asymptomatic before treatment or if patient symptoms were not reassessed.

Evaluation of safety

Safety was assessed by recording adverse events, where an adverse event was any undesirable event, such as a sign, symptom, or laboratory finding, that was associated with the drug treatment regimen. The relationship of an adverse event to the study regimen was rated as probable, possible, or improbable.

Statistical analysis

Primary efficacy analyses for *H. pylori* eradication at 4–6 weeks post-treatment were performed for per protocol and intention-to-treat results, and data analyses were reported with 95% exact binomial confidence intervals. Secondary analyses were likewise determined for ulcer healing and symptom changes from pre-treatment to follow-up visits.

RESULTS

Subject enrolment and evaluation

A total of 119 subjects were enrolled in the study at sites in Hong Kong (37), Pakistan (27), South Africa (25), and Taiwan (30). Two subjects (one from Hong Kong and one from Taiwan) were excluded from the intention-to-treat analysis because they did not take the study drugs. For the per protocol analysis, eight subjects were excluded because they either failed to comply with the treatment regimen, or lacked follow-up endoscopy, or their follow-up examination was not timed correctly.

At 4–6 weeks post-treatment, patients were assessed for *H. pylori* status, clinical response, and ulcer healing. Results are summarized (Figure 1, Table 1) according to per protocol analysis and intention-to-treat analysis.

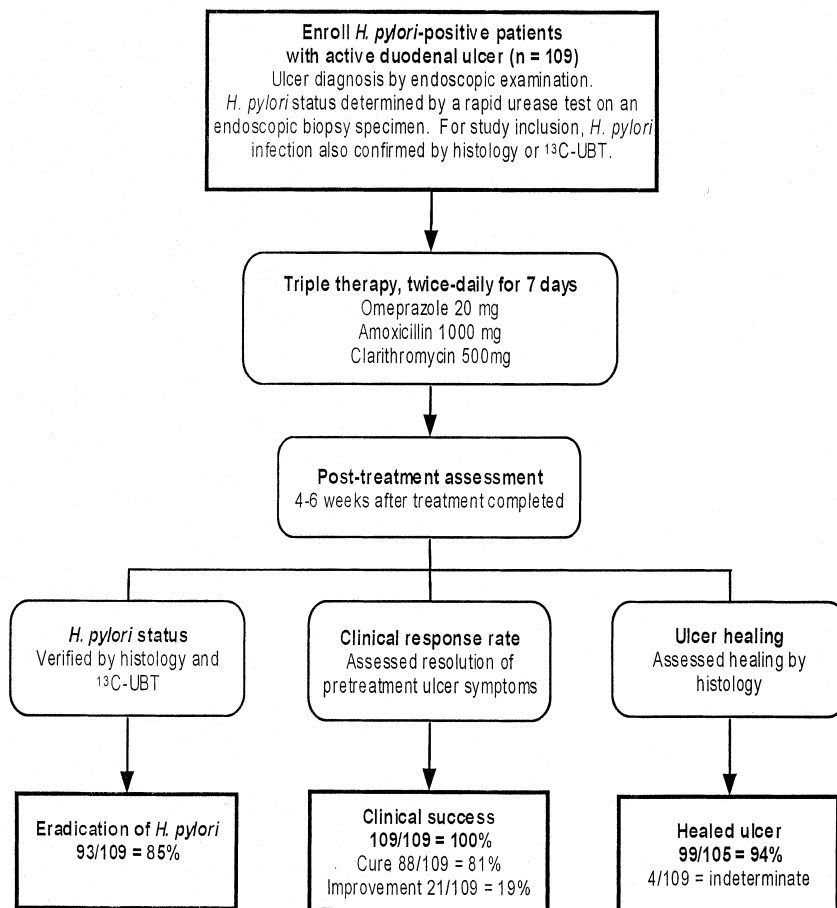


Figure 1. Protocol summary and per protocol analyses of results for patients receiving 7-day triple therapy.

H. pylori susceptibility to antibiotics

Primary resistance to metronidazole occurred in 54% (39 out of 72) of tested patients, whilst resistance to clarithromycin was less than 2.7% (2 out of 72), and resistance to amoxicillin was not observed.

H. pylori eradication

The overall eradication rates for the study were 85% (per protocol analysis) and 80% (intention-to-treat analysis; Table 1), although results varied markedly from site to site. Eradication rates ranged from 72% to 94% for per protocol analysis and from 67% to 92% for intention-to-treat analysis, with Hong Kong showing the highest rates, Pakistan the lowest, and South Africa and Taiwan at intermediate levels (Table 2).

Based on histology, all evaluable subjects initially had evidence of inflammation, and 97% had gastritis activity present in gastric biopsy samples. Atrophic changes were noted in more than half of the subjects

(53%, 57 out of 107), and intestinal metaplasia was observed in some subjects (12% mild, 8% moderate, and 1% severe). Four to six weeks after completion of the 7-day triple therapy, 75%, 91%, 48% and 65% resolution or improvement were found in inflammation, activity, atrophy and intestinal metaplasia, respectively.

Clinical response rate

The ulcer-related symptoms reported most frequently at the baseline visit were epigastric pain (78%), daytime abdominal pain (67%), night-time abdominal pain (64%), and belching (56%). The majority of symptoms, more than 74% in each symptom category, were of mild or moderate severity. Following treatment, 81% of study patients experienced a cure and 19% experienced an improvement in symptoms by per protocol analysis, thus providing a 100% total clinical response rate. By intention-to-treat analysis, the total clinical response rate was 94%, including cure (76%) and

Table 1. Summary of efficacy results for duodenal ulcer patients receiving 7-day triple therapy

Efficacy result	% of subjects (n/n), [95% CI]
<i>H. pylori</i> eradication	
Per protocol	85% (93/109) [77.3%, 91.4%]
Intention-to-treat	80% (94/117) [72.0%, 87.1%]
Clinical response rate	
Per protocol	
TOTAL Cure + Improved	100% (109/109)
Cure	81% (88/109) [72.1%, 87.7%]
Improvement	19% (21/109)
Failure	0% (0/109)
Intention-to-treat	
TOTAL Cure + Improved	94% (110/117)
Cure	76% (89/117) [67.3%, 83.5%]
Improvement	18% (21/117)
Failure	2% (2/117)
Indeterminate	4% (5/117)
Ulcer healing	
Per protocol*	
Healed	94% (99/105) [88.0%, 97.9%]
Unhealed	6% (6/105)
Indeterminate	(4/109)
Intention-to-treat	
Healed	85% (99/117) [76.8%, 90.6%]
Unhealed	8% (9/117)
Indeterminate	7% (9/117)

*For the per protocol analysis, subjects were not included in computation of the ulcer healing rate if the healing status was indeterminate.

improvement (18%). By symptom, epigastric pain and daytime or night-time abdominal pain were relieved in 98%, 96% and 100% of patients, respectively. Belching remained a problem for just 11% of the patients.

Ulcer healing

Healing of the index duodenal ulcer at the post-treatment follow-up visit was observed in 94% (99 out of 105) of the per protocol subjects and in 85% (99 out of 117) of the intention-to-treat subjects (Figure 1, Table 1). For the per protocol analysis, subjects with a status of indeterminate were not included for computation of the healing rate. In the intention-to-treat analysis, however, indeterminate cases were treated as unhealed for computation.

Table 2. Stratification of *H. pylori* eradication results by country and by test criteria

Efficacy result	% of subjects (n/n), [95% CI] ¹³ C-UBT and Histology
Hong Kong	
Per protocol	94% (32/34) [80.3, 99.3]
Intention-to-treat	92% (33/36) [77.5, 98.2]
Pakistan	
Per protocol	72% (18/25) [50.6, 87.9]
Intention-to-treat	67% (18/27) [46.0, 83.5]
South Africa	
Per protocol	86% (19/22) [65.1, 97.1]
Intention-to-treat	76% (19/25) [54.9, 90.6]
Taiwan	
Per protocol	86% (24/29) [64.2, 94.2]
Intention-to-treat	83% (24/29) [64.2, 94.2]
TOTAL	
Per protocol	85% (93/109) [77.3, 91.4]
Intention-to-treat	80% (94/117) [72.0, 87.1]

Overall drug safety and specific treatment-related adverse events

A total of 46% (54 out of 117) of the subjects reported treatment-related adverse events; a majority of these events were considered by the investigator to be mild or moderate in severity. The most commonly reported adverse events were taste perversion (24%), diarrhoea (16%), dizziness (6%), and nausea (5%).

The safety of this 7-day triple therapy was indicated by excellent compliance to the treatment regimen, with over 90% of the study subjects taking at least 90% of their prescribed medications. No clinically significant changes in haematology or serum chemistry values or in vital signs were observed during the study.

DISCUSSION

The present study is among the first in the world to determine the efficacy and safety of 7-day triple therapy comprising of standard dose omeprazole, amoxicillin and clarithromycin in a multicentre setting for patients who live in areas of Asia and Africa. The treatment regimen was considered efficacious because high rates of *H. pylori* eradication (85%), clinical success (100%), and ulcer healing (94%) were achieved on per protocol analyses of study findings. Patient compliance was high, and treatment-related adverse events, when present,

were largely mild or moderate. Thus, this triple therapy regimen was also considered safe.

In general, our multicentre study yielded results consistent with those reported for similar trials conducted elsewhere in the world. Desired thresholds for *H. pylori* eradication therapy were established recently as 90% eradication for data analysed on a per protocol basis or 80% eradication for data analysed on an intention-to-treat basis.¹⁴ Our study showed an eradication rate of 85% for per protocol analysis and 80% for intention-to-treat analysis. Recent 7-day triple therapy trials in Europe, Canada, the United States, the United Kingdom, and Taiwan generated eradication rates that ranged from 89% to 98% for per protocol analyses vs. 80% to 91% for intention-to-treat analyses (Table 6).^{9–11, 21, 24, 25} Some study-to-study differences may be attributed to different drug combinations in triple therapy, whilst others may be due to differing use of rapid urease testing, ¹³C-urea breath test results, and histopathological findings as criteria for eradication. If the regional prevalence of metronidazole resistance is high, *H. pylori* eradication rates can be reduced in metronidazole-containing regimens.²⁶ Reported metronidazole resistance in Asia and Africa has ranged from 20% to 74%, consistent with 54% of metronidazole resistance in this study.^{17–20}

There are, however, some notable differences in the data from the present study compared to other world studies. In particular, *H. pylori* eradication rates for the study centre in Pakistan were lower than expected, with 72% per protocol analysis and 67% intention-to-treat analysis. By contrast, eradication rates for Hong Kong were high, with 94% per protocol analysis and 92% intention-to-treat analysis. Although further studies will be necessary to pinpoint reasons for these differences, there are several possible explanations.

First, the numbers in individual centres were relatively small to make any meaningful or valid comparisons between countries. Second, differences may be due to variations in conduct of the study; to varying characteristics of the patient populations (nutrition, general health); or to properties of endemic bacterial strains (strain virulence, antibiotic resistance). In addition, Harris *et al.* raised the issue that not all duodenal ulcers are caused by *H. pylori*.²⁴ A third possibility is that 7-day treatment may not be fully effective for all individuals at all sites. Whilst comparisons of identical

regimens for 7, 10, and 14 days have generally been lacking, *H. pylori* eradication rates generally appear to increase directly with the duration of twice-daily triple therapy.¹⁰ Since it has been established that the most cost-effective therapy for *H. pylori* infection and duodenal ulcers is the treatment that is most effective for eradication, it will be necessary to determine whether longer treatment intervals or altered treatments are needed in specific sub-populations such as those in Pakistan.²⁵ It may also be necessary to provide local monitoring for bacterial strains and health conditions that may require additional treatment or alterations in the standard regimen.

The stringent protocol design for this study considered subjects who dropped out or had data missing as 'treatment failures' for their bacteriological, clinical, and ulcer healing responses, thus contributing to low apparent efficacy rates at some study sites. For example, of the 25 South African subjects included in the intention-to-treat analysis analyses, five subjects did not return or were too late for their follow-up visit, and three subjects were missing biopsy specimens from pre-treatment or follow-up visits. Likewise, of the 27 Pakistan subjects included in the intention-to-treat analysis analyses, one subject experienced a serious adverse event of chest pain and withdrew from the study. Another subject discontinued on their own accord. Furthermore, five subjects had missing biopsies on follow-up. It is possible that regional conditions which limited protocol adherence may have reduced the apparent successfulness of bacteriological, clinical, and ulcer healing responses in this study.

Overall, 7-day triple therapy with omeprazole, amoxicillin, and clarithromycin is efficacious for treating Asian and African patients who have duodenal ulcers associated with *H. pylori* infection. The treatment provides good compliance, and produces only mild side-effects. Such treatment thus represents a reasonable choice for clinical practice in regions of Asia and Africa, as is the case elsewhere in the world.

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