COMPARISON OF ONCE-A-DAY VERSUS TWICE-A-DAY CLARITHROMYCIN IN TRIPLE THERAPY FOR HELICOBACTER PYLORI ERADICATION

Marianne P Collado, Ma Fatima P Calida, Peter P Sy, Benedicto V Agbay

Department of Medicine, Section of Gastroenterology, Cardinal Santos Medical Center, San Juan, Metro Manila, Philippines

ABSTRACT

Background/Aim: Helicobacter pylori (H. pylori) eradication therapy with proton pump inhibitor, amoxicillin and clarithromycin immediate-release is used extensively. However, the efficacy of once-a-day, extended-release clarithromycin has not been determined. This study was conducted to compare the efficacy and safety profile of once-a-day clarithromycin with the standard twice-a-day clarithromycin in the triple therapy of H. pylori-infected patients.

Methods: This prospective, randomized, open-label, blinded endpoint (PROBE) study was conducted at the Cardinal Santos Medical Center from July 2005 to December 2005. A total of 51 patients who were H. pylori-positive by rapid urease test were included and randomly assigned to once-a-day vs. twice-a-day clarithromycin. Twenty-four patients were administered with once-a-day clarithromycin extended-release 500 mg including esomeprazole 40 mg b.i.d. and amoxicillin 1 g b.i.d. for seven days. Twenty-seven patients received a standard seven-day triple therapy consisting of esomeprazole 40 mg b.i.d., clarithromycin immediate-release 500 mg b.i.d. and amoxicillin 1 g b.i.d. The eradication rates were evaluated by the (13) C-Urea breath test at least four weeks after completion of a course of treatment.

Results: Forty-five patients completed the trial and six patients dropped out. The eradication rates in the twice-a-day and once-a-day groups using the intention to treat analysis [N=27/N=24] were 85% and 75% (p=0.250) and using the per protocol analysis [N=25/N=20] were 92% and 90% (p=0.795), respectively. Short lasting and self-limiting side effects including taste disturbance and diarrhea were reported in 11 patients (41%) in the twice-a-day group and 10 patients (42%) in the once-a-day group with p value of 0.414.

Conclusion: Once-a-day and twice-a-day clarithromycin-based triple therapies were both effective and safe in eradicating H. pylori in the patient population studied.

INTRODUCTION

Helicobacter pylori (H. pylori) infection, which is present in 30-60% of the population in developed countries and in more than 60% in developing countries, is established to be a major cause of gastritis, peptic ulcer disease and gastric cancer. It is a serious, chronic, transmissible infectious disease which is preceded by long asymptomatic periods.

H. pylori resides in the surface of the stomach within the mucus as well as attached to the mucus cells. H. pylori can also be found within the epithelial cells. These various niches provide a challenge for antimicrobial therapy. In addition, the gastric lumen is a hostile environment for antimicrobial therapy because the drugs must penetrate the thick mucus and may need to be active at pH levels below neutral. Despite these difficulties, relatively effective therapies have been identified, primarily through the process of trial and error.

Currently, therapy with proton pump inhibitors such as esomeprazole and two antibiotics, amoxicillin and clarithromycin, is the most frequently used therapy for the eradication...
of H. pylori. Non-recurrence of gastric and duodenal ulcer is strictly dependent on the success of H. pylori eradication and the persistence of infection is a negative prognostic marker, thus the need for effective H. pylori eradication. An obstacle to effective therapy is poor compliance with the prescribed medication as with any other disease requiring multiple drugs for therapy. Simplifying an effective therapy is ideal using less medication and/or a shortened duration of therapy.

The extended-release formulation of clarithromycin has demonstrated bioequivalence to the immediate-release formulation with respect to the area under the plasma concentration-time curve despite a lower maximum plasma concentration (C_{MAX}) and a longer time to maximum plasma concentration (T_{MAX}) for the extended-release tablets. The effectiveness of this new formulation of clarithromycin has not been established in H. pylori eradication.

Clarithromycin extended-release 500 mg tablets are formulated using a patented polymer-based matrix that slows the release of clarithromycin and extends absorption from the gastrointestinal tract after oral administration. The reformulation is intended to improve both patient compliance and tolerability.

This therapeutic trial is designed to compare the efficacy (percentage of patients with successful eradication of H. pylori) and safety of once-daily dosing with the standard twice-daily regimen of clarithromycin in the triple therapy of H. pylori eradication.

**MATERIALS AND METHODS**

**Study Population**

Adult patients of either sex, with duodenal ulcer or erosive/superficial gastropathy, or both, who were H. pylori-positive (as determined by rapid urease test-Cu test) seen at the Endoscopy Unit of the Cardinal Santos Medical Center from July 2005 to December 2005 were included.

Patients with more than one previous attempt to eradicate H. pylori, and those with active bleeding from the upper gastrointestinal tract were excluded. Other exclusion criteria were regular treatment with non-steroidal anti-inflammatory drugs, concomitant intake of antimicrobial agents and allergy to any of the study drugs.

This study was approved by the Ethics Committee of the Cardinal Santos Medical Center before commencement of patient enrollment. Informed consent was obtained from patients before entering the study.

**Study Design**

This study was a prospective, randomized, open-label, blinded endpoint (PROBE) trial with parallel-group design. Eligible patients were randomized to 1 of 2 treatment groups (Table 1) by a process of transparent envelopes. Equivalent number of pieces of paper, determined based on the calculated sample size, were placed on sealed envelopes. Each paper indicated the group allocation of patients. Patients were allocated the next envelope once they have satisfied the inclusion criteria.

**Table 1. Therapeutic Groups**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Twice-a-day therapeutic group (mg)</th>
<th>Once-a-day therapeutic group (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole</td>
<td>40 BID</td>
<td>40 BID</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>1000 BID</td>
<td>1000 BID</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500 BID (Immediate release)</td>
<td>500 OD (Extended release)</td>
</tr>
</tbody>
</table>

Note: Triple therapy was administered for 7 days.

**Assessments**

At the first visit (VISIT 1), patients underwent endoscopy with biopsy specimen taken from the antrum and body, where rapid urease test (Cu test) was performed to confirm infection. Patients returned for a clinic visit (VISIT 2) after the seven-day treatment period for symptom, adverse event and compliance assessment. (13) C-Urea breath test (UBT) was performed four weeks after the end of treatment (VISIT 3). Eradication was defined as a negative UBT test four weeks after cessation of therapy.

Those patients included in the once-a-day therapeutic group with a positive UBT after four weeks of therapy (treatment failure) were given the standard treatment for H. pylori for another week.
The primary measure of efficacy was the eradication of H. pylori as determined by the results of UBT at Visit 3. The Fisher’s Exact Test was used to determine statistical significance. Success rate for the twice-a-day therapeutic group was set at 94% based on MACH 2 Study. The success rate for the once-a-day therapeutic group was projected at 80% on an intention to treat basis upon the recommendation of the Maastricht Consensus Report. The authors calculated a sample size of 90 patients to show equivalence between the two study groups, with a power of 80% with an \( \alpha = 0.05 \) (two-tailed).

Analysis was performed on an intention to treat (ITT) and per protocol basis. ITT patients included all those enrolled and randomized to the treatment groups. This included those who took no or incomplete medication, those lost to follow-up evaluation (not returning for visits 2 or 3) and those who had deviated significantly from the study protocol (e.g., intake of interval antibiotics). For the per protocol analysis, these patients were excluded.

The worst-case scenario was used where it was assumed that H. pylori had not been eradicated if the patient did not return for UBT at Visit 3.

### RESULTS

#### Patient Population

Fifty-one patients were initially recruited for the ITT analysis. Table 2 shows the baseline characteristics of the eligible patients. Demographic characteristics were similar in the two groups, as were the symptoms at initial assessment. Of these 51 patients, 45 patients were eligible for inclusion in the per protocol analysis. Four patients who were excluded had not attended visit 3, and the other two patients did not complete the treatment.

#### Table 2. Demographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Twice-a-day Therapeutic Group</th>
<th>Once-a-day Therapeutic Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (years)</td>
<td>60.20 (40-80)</td>
<td>57.85 (18-84)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men (%)</td>
<td>15 (56)</td>
<td>14 (58)</td>
</tr>
<tr>
<td>Range (%)</td>
<td>12 (44)</td>
<td>10 (42)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duodenal Ulcer (%)</td>
<td>6 (22)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Erosive/ Superficial Gastropathy (%)</td>
<td>21 (73)</td>
<td>20 (84)</td>
</tr>
</tbody>
</table>

#### Efficacy

The proportion of patients in whom H. pylori was successfully eradicated using the per protocol and the intention to treat analyses are shown in Table 3. In both the intention to treat and the per protocol analyses, the difference in efficacy of the twice-a-day and once-a-day clarithromycin triple therapy in the eradication of H. pylori was found not to be statistically significant (\( p = 0.25 \) and \( p = 0.795 \), respectively).

### Table 3. Proportion of patients with negative Urea Breath Test four weeks after treatment

<table>
<thead>
<tr>
<th>UBT Result</th>
<th>Twice-a-Day Therapeutic Group</th>
<th>Once-a-Day Therapeutic Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention to treat Negative (%)</td>
<td>N=27 23 (85)</td>
<td>N=24 18 (75)</td>
</tr>
<tr>
<td>Per protocol Negative (%)</td>
<td>N=25 23 (92)</td>
<td>N=20 18 (90)</td>
</tr>
</tbody>
</table>

#### Safety

The safety analysis was done on all 45 patients who had taken at least one dose of the medications. The most frequently reported adverse events were diarrhea and taste disturbance (Table 4).

Fifteen patients experienced diarrhea while six patients reported taste disturbance. There was no significant difference in terms of the
occurrence of adverse effects in the two groups (p=0.414). No patient withdrew from the study as a result of an adverse event.

Table 4. Patients Experiencing Adverse Events in Each Treatment Group

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Twice-a-Day Therapeutic Group N=27</th>
<th>Once-a-Day Therapeutic Group N=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Taste Disturbance</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Total (%)</td>
<td>11 (41)</td>
<td>10 (42)</td>
</tr>
</tbody>
</table>

**DISCUSSION**

This study has shown that once-a-day clarithromycin and twice-a-day clarithromycin triple therapy, given for seven days, effectively eradicates H. pylori. The proportion of patients in the once-a-day therapeutic group in whom H. pylori was successfully eradicated was comparable with the twice-a-day therapeutic group. This eradication rate is consistent with other studies using clarithromycin and proton-pump inhibitor triple therapies. Like many studies reported in Europe, a per protocol eradication rate of at least 90% was achieved in this study.

The results of this study suggest that giving either once-a-day or twice-a-day clarithromycin triple therapy results in comparable eradication rates. However, since the calculated sample size was not achieved in this study, it is possible that a beta error has occurred where because of a lack of statistical power to detect a difference, a difference in efficacy may not have been detected.

In an effort to improve tolerability, which is postulated to contribute better compliance, clarithromycin was reformulated as an extended-release tablet. The new formulation of clarithromycin provides a convenient once-daily dosing.

It has been suggested that eradication rates vary between patient subgroups. In particular, patients with non-ulcer dyspepsia have been reported to have lower eradication rates than patients with ulcer disease. In this study, a majority of the patients in the once-a-day and twice-a-day therapeutic groups showed high eradication rates in both intention to treat and per protocol populations despite being diagnosed with non-ulcer dyspepsia.

The use of Urea Breath Test (UBT) in the assessment of H. pylori eradication has been proven to have a very high sensitivity as reported by previous trials with a reported 95% agreement between UBT and histological assessments. This test is a highly sensitive method for assessing H. pylori status both before and after therapy and that the reliability of the method is such that a single post-therapy UBT is sufficient in most cases.

The number of patients reporting adverse effects was similar in both groups. No patient withdrew from the study because of these side effects, thus the treatments were regarded to be generally well tolerated. The high incidence of taste-related adverse events is a frequently reported occurrence with the use of clarithromycin and is thought to be dose-dependent. Taste disturbance, however, was not observed in a significant percentage of patients in this study. Diarrhea and GIT disturbances are also a well documented side effects of amoxicillin, a broad-spectrum penicillin antibiotic. Reports of this adverse events among the patients in this study were consistent with current knowledge with the use of these drugs.

**CONCLUSION**

Once-a-day and twice-a-day clarithromycin-based triple therapies were both effective and safe in eradicating H. pylori in the patient population studied.

**REFERENCES**


