A Randomised Trial of Amoxycillin Versus Clarithromycin in Combination with Omeprazole for Eradication of Helicobacter Pylori Infection in Singapore

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ABSTRACT

Dual therapy has been reported to produce H.pylori eradication rate of 75 - 80%. This study is designed to determine the efficacy of omeprazole 20mg bd in combination with amoxycillin 500mg tid (Group A), amoxycillin 750mg tds (Group B) and clarithromycin 500mg tid (Group C) in Singapore.

One hundred and forty-eight patients with H.pylori positive duodenal ulcers between ages of 22 and 69 were enrolled from two centres. There were 48 patients in Group A, 50 patients in Group B and 50 patients in Group C. The medication was given for 14 days. The patients were re-evaluated with an upper GI endoscope 4 weeks after cessation of treatment. Successful eradication was defined as H.pylori negative on histology and culture. Based on intention to treat analysis, the eradication rate was 47.8% in Group A, 68% in Group B and 66% in Group C. The difference between Group A and B were statistically significant (p=0.04). Based on all patient treated analysis, the eradication rate was 57.5% in Group A, 70.7% in Group B and 75% in Group C. The difference in eradication rates was not statistically significant. Adverse events were reported in 21% of all patients with no difference in the adverse event rate between all groups. The eradication rate achieved with dual therapy in this study was similar to that attained in Western population. Higher dose amoxycillin regime gives a significantly higher eradication than a lower dose amoxycillin.

Keywords: Omeprazole, amoxycillin, clarithromycin, Helicobacter pylori

Singapore Med J 2000 Vol 41(10):482-484

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INTRODUCTION

It is now widely accepted that Helicobacter pylori infection of the human gastric mucosa leads to chronic gastritis and ulceration. There is also evidence that Helicobacter pylori is associated with atrophic gastritis and gastric cancer[1]. Eradication of Helicobacter pylori results in a dramatic decrease in the recurrence rates of duodenal and gastric ulcer[2,3]. Eradication therapy in Asia has been using bismuth based triple therapy with bismuth compounds, metronidazole and tetracycline, which is complicated in dosage and may lead to difficulty with compliance. Furthermore, such regime involves the use of metronidazole. The incidence of metronidazole resistance of Helicobacter pylori in Asia has been reported to be much higher than in the West[4,5] and this can lead to a decrease in eradication rate. Clarithromycin is a relatively new macrolide which when used in combination with a proton pump inhibitor has been reported to achieve eradication rates as high as 75 - 80%[6]. There has also been reports from Germany of a high efficacy of a combination of omeprazole and amoxycillin in the order of 80%, although eradication rates have been lower outside Germany[7-9]. Reports on the efficacy of these regimes from Asia have been limited. The primary objective of this study was to determine the efficacy of omeprazole 20mg bd in combination with amoxycillin 500mg tds (low dose) and 750mg tds (high dose) and omeprazole 20mg bd in combination with clarithromycin 500mg tds. The secondary objective was to compare the adverse effects of the treatment regimes.

PATIENTS AND METHODS

Patients

Patients aged between 22-69 years with proven duodenal ulcer on endoscopy with positive rapid urease (CLO) test were eligible for entry into the study. The presence of Helicobacter pylori was further confirmed by histology and culture. Patients were excluded if they had gastric ulcer, previous gastric surgery, hypersensitivity to study medication, taking medication known to be ulcerogenic, suffering from serious illness, or if they are pregnant. Four weeks after completion of treatment, a repeat endoscopy was performed and biopsies, taken from antrum and corpus, were sent for culture and histopathological examination. The study protocol was approved by the local Ethics Committee of the participating centres. Written consent was obtained.

Study Design

The study- a randomised study involving two centres. The physicians, pathologists and microbiologists were unaware of the medication that the patients were given.

Table I. Characteristics of intervention groups.

	Group A **(n = 48)**	Group B **(n = 50)**	Group C **(n = 50)**	Remarks
Age - mean	40.69	45.26	42.34	No sig diff
- median, range (years)	40 (22-65)	48 (23-68)	41.5 (22-69)	(1-way ANOVA p=0.17)
Ethnic group (%)				
Chinese	40 (83.3)	45 (90.0)	44 (88.0)	p=0.29 (chi-sq)
Malay	5 (10.4)	0 (0.0)	3 (6.0)	
Indian	2 (4.2)	3 (6.0)	3 (6.0)	
Others	1 (2.1)	2 (4.0)	0 (0.0)	
Smoking Status (% smokers)	31 (64.6)	29 (58.0)	30 (60.0)	p=0.79 (chi-sq)
Alcohol intake (% non-drinkers)	30 (62.5)	37 (74.0)	38 (76.0)	p=0.47 (chi-sq)
First presentation of ulcer disease (% first presentation)	28 (58.3)	30 (60.0)	25 (50.0)	p=0.56 (chi-sq)
Duration of ulcer	54.6	92.8	77.7	No sig diff
disease (months) median, range	36 (12-240)	48 (1-432)	48 (0.75-360)	(Kruskal-Wallis p=0.53)

Group A = (Omeprazole plus 1.5g Amoxycillin) Group B = (Omeprazole plus 2.2g Amoxycillin) Group C = (Omeprazole plus 1.5g Clarithromycin)

The patients were randomly allocated to one of the following regimes. The trial medication were randomised by the sponsors. (A) Forty-eight patients received Omeprazole (20mg bd) and Amoxycillin(500mg tds). (B) Fifty patients received Omeprazole (20mg bd) and Amoxycillin (750mg tds). (C) Fifty patients received Omeprazole (20mg bd) and Clarithromycin (500mg tds).

Medication were given for 14 days. Successful eradication of Helicobacter pylori was defined as negative culture and histology from antral biopsies obtained 4 weeks after cessation of treatment. Adverse events occurring during treatment were recorded in diary given to the patients. Patients were also asked to return their drug packets at the end of treatment and compliance checked. Eradication rates were analysed according to all patients treated and intention to treat basis.

Table II. Outcome of intervention by APT.

Global comparison	% eradicated (n)	95% Confidence interval
Group A (n=40)	**57.5% (23)**	*(40.9 - 73.0)*
Group B (n=48)	**70.8% (34)**	*(55.9 - 83.1)*
Group C (n=44)	**75.0% (33)**	*(59.7 - 86.8)*

Pairwise comparisons: Group B vs Group A: p=0.19
Group C vs Group A: p=0.09
Group B vs Group C: p=0.65

Table III. Outcome of intervention by intention to treat.

Global comparison	% eradicated (n)	95% Confidence interval
Group A (n=48)	**47.9% (23)**	*(33.3 - 62.8)*
Group B (n=50)	**68.0% (34)**	*(53.3 - 80.5)*
Group C (n=50)	**66.0% (33)**	*(51.2 - 78.8)*

Pairwise comparisons: Group B vs Group A: p=0.04
Group C vs Group A: p=0.08
Group B vs Group C: p=0.83

Statistical Methods

Statistical analysis was performed using the level of statistical significance set at $p \leq 0.05$. The statistical packages used were SPSS for windows and CIA (Gardner MJ 1989)

RESULTS

A total of 148 patients entered the study. The patients were comparable in terms of age, racial-mix, smoking and alcoholic intake (Table I). About 50% - 60% of the patients were suffering from "first time ulcers". The duration of ulcer symptoms appear to differ in duration and was longest in Group B. We have adjusted for this difference in the analysis.

Sixteen patients withdrew from the study. Four withdrew because of an adverse event. Twelve failed to return for repeat endoscopy. One patient who complained of headache was found to be suffering from a pituitary tumour.

Eradication rate

The eradication rate by all patients treated analysis was 57.5% for Group A (Omeprazole plus 1.5gm amoxycillin daily), 70.8% for Group B (Omeprazole plus 2.2gm amoxycillin daily) and 75.0% for Group C (Omeprazole plus 1.5 gm Clarithromycin daily) patients. (Table II). The difference between the three groups were, statistically, not significant.

The eradication rates by intention-to-treat analysis was 47.9% for Group A, 68.0% for Group B and 66.0% for Group C (Table III). The difference between Group B versus Group A was statistically significant ($p = 0.044$). The comparisons between Group C and Group A, ($p = 0.08$) was not significant.

Adverse Events

Altogether 33 patients (21%) complained of side effects, 12 patients in Group A, 9 in Group B and 12 in Group C. In 4 patients the adverse effects were sufficient to cause the patients to withdraw from the trial. Of these, 3 patients were on low dose Amoxycillin and 1 was on Clarithromycin. The adverse events with Amoxycillin were peri-orbital oedema, urticaria and headache, which

on investigation showed a pituitary tumour in one patient. Other adverse events encountered with Amoxycillin were diarrhoea. Tinnitis was the adverse event responsible for the single drop out from Clarithromycin. A bitter taste (8%) was the commonest adverse event reported by patients receiving Clarithromycin.

DISCUSSION

This study evaluated the efficacy of omeprazole in combination with clarithromycin, and with high and low dose amoxycillin. There were two noteworthy points from our study. The eradication rate achieved was highest in patients treated with omeprazole-clarithromycin at 75% on APT analysis and lowest in patients treated with omeprazole-low dose amoxycillin combination. The eradication rates of 74.7% attained in our study with omeprazole-clarithromycin is consistent with the results of a double blind placebo controlled study[10]. Further, we have found that with omeprazole amoxycillin combination, eradication rates achieved was significantly higher with high dose amoxycillin than with low dose amoxycillin (ITT analysis 68.0 vs 47.9 p=0.04). This is consistent with a recent study using pooled data that showed eradication rates with high dose amoxycillin were 10% higher than with low dose amoxycillin[11]. Our results also showed a trend in favour of clarithromycin compared with low dose amoxycillin although this did not reach statistical significance and this is different from the result of Katelaris who found no difference in eradication rates between omeprazole-clarithromycin and omeprazole-low dose amoxycillin[12]. An important point to note is that adverse events were found in 21% of patients and evenly distributed amongst the three trial groups suggesting that higher dose did not produce more side effects. It is also relevant to note adverse events resulted in stopping treatment in only 2% of patients.

Is there a role for dual therapy in treatment of H. pylori in Asia? Our results suggest that as much as 25% to 30% of patients will have failed therapy. This failure rate by itself appears to be high although in relation to classic triple therapy, it is only 5 - 10% lower. Twice daily dosage makes patient compliance easier and from a cost effectiveness perspective, Vakil has analysed that dual therapy using clarithromycin is effective in regime where metronidazole resistance is high (>36%)[13]. There are, however, newer triple therapies which can improve eradication rate. By adding metronidazole or amoxycillin to dual therapy, there can be a 10 - 20% increase in eradication rates. Combinations of PPI with both amoxycillin and clarithromycin can also produce similar if not greater increase in eradication rates. Our study, however, has suggested that for triple therapy involving amoxycillin, a higher dose of amoxycillin-omeprazole combination is likely to result in higher eradication rate than low dose amoxycillin-omeprazole combination. We did not perform a comparison of low dose clarithromycin versus high dose clarithromycin, although current literature does suggest better eradication rates with higher dose clarithromycin[14].

In conclusion, our study has shown that the eradication rate of H.pylori using dual therapy in Singapore is comparable to those found in the West and that with a lower-dose of amoxycillin there is a decrease effectiveness in eradication rate, just as is found in the West. Treatment regimens based on dual therapy in Singapore did not attain the high eradication rates as seen in Germany. Safety profile of dual therapy regimen was satisfactory with no major adverse effects. Their role in the treatment of H.Pylori have been overtaken by the new triple therapy using PPI and two antibiotics.

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