Eradication of H. Pylori by Quadruple or Triple Therapy A comparative study

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Background: Quadruple therapy appears to be more effective than standard therapy in management of patients with helicobacter pylori infection. No data is available on the relative efficacy of triple and quadruple drug regimens from Pakistan. **Methods:** Consecutive patients with peptic ulcer and H. pylori infection were randomized to receive omeprazole 20 mg twice daily along with either amoxycilline (500 mg four times daily) and clarithromycin (500 mg twice daily) (Group A) or tri-protassium dicitrate hismuthate (120 mg four times daily), metronidazole (400 mg thrice daily) and tetracycline (500 mg 4 times daily) {Group B} for 10 days. Presence H. Pylori infection was looked for using an fecal antigen test before treatment and 30 days after completion of treatment. **Results:** 17 of 21 patients in Group A and 16 of 23 in Group B had eradication of infection (80.9 and 69.56% respectively by protocol analysis). Side effects occurred in 2 (1%) and 4(2%) patients in Group A and B, respectively. Discontinuation of drug was not required in any patient. **Conclusion:** Quadruple therapy for initial therapy of H. Pylori infection does not offer any advantage over standard triple therapy.

Key words: Quadruple triple therapy, H. pylori,

Beliefs concerning the cause and treatment of peptic ulcer disease have undergone numerous changes over the past 75 years. In the early part of this century, the disease was thought to be related to stress and dietary factors, so treatment consisted of bed rest and a bland diet. Later came an understanding of the injurious effects of gastric acid, and treatment focused on neutralizing the acidic environment of the stomach with antacids and antisecretory agents[1]. Although the introduction of histamine[2] (H2) receptor antagonists revolutionized treatment of peptic ulcer disease, disturbingly high recurrence rates forced many patients to continue long-term acid-suppression therapy[2]. Recent development of proton pump inhibitors added a more effective therapeutic option but did not solve the problem of recurrent disease. Finally, the realization that peptic ulcer disease is usually the result of *Helicobacter pylori* infection has brought the promise of long-term cure by eradication of the organism[3].

Anti Helicobacter pylori therapy is currently recommended for all patients with peptic ulcer who test positive for H Pylori. (1 4)HP eradication therapy consists of antibiotics and anti-secretory drugs[4,6]. (Table I)

The goal of *H. pylori* treatment is the complete elimination of the organism. Once this has been achieved, reinfection rates are low; thus, the benefit of treatment is durable. Clinically relevant *H. pylori*–eradication regimens must have cure rates of at least 80 percent (according to intention-to-treat analysis) without major side effects and with minimal induction of bacterial resistance. Such goals have not been achieved with antibiotics alone. Because luminal acidity influences the effectiveness of some antimicrobial agents that are active against *H. pylori,* antibiotics are combined with proton-pump inhibitors or ranitidine bismuth citrate. So-called triple therapies, combinations of one antisecretory agent with two antimicrobial agents for 7 to 14 days, have been extensively evaluated, and several regimens have been approved by the Food and Drug Administration (FDA)[4,6] (Table II)

Resistance to antibacterial agents, which is an important determinant of outcome of therapy, is common in isolates from several parts of the world, especially developing countries [5,6,7,8]. Some studies from our region reported sub-optimal results with the commonly recommended regimes. Thus, questions have been raised about the usefulness of the low dose, short course treatment regimens for eradication of H. Pylori in populations in which drug resistance is common. Failure of initial treatment increases the risk of development of resistance to the agents used.

High response rates have been reported with second-line, quadruple therapy with a PPI, a bismuth compound, tetracycline and an imidazole, in the face of resistance to imidazoles. We hypothesized that in a population with high prevalence of such resistance and consequently lower eradication rates with standard drugs, the quadruple therapy would lead to better results. The present study was designed to compare the quadruple therapy including metronidazole with a PPI-based triple therapy for initial treatment of H. Pylori infection.

Methods

44 consecutive patients with endoscopically proved active peptic ulcers, or healed ulcers with previously documented active ulcer, seen in OPD were included in the study. Those with complications precluding oral drug therapy were excluded. Patients on any type of anti-ulcer medication were tested for fecal antigen 4 weeks off these drugs. Each patient gave a written informed consent.

All the Patients had fecal antigen for H. Pylori tested.

Patients with H. Pylori infection were randomized to received one of two t/m regimens. Omeprazole 20mg twice daily, amoxycillin 500 mg four times daily and clarithromycin twice daily (Group A); and Omeprazole 20mg twice daily tripotassium dicitrobismuthate 120mg 4 times daily metromidazole 400mg thrice daily and tetracycline 500mg per times daily (group B). The drugs were administered for 10 days, no t/m was allowed for next 30 days, after which fecal antigen test was repeated.

The primary end-point was eradication of H. Pylori infection compliance was defined as return of 10% or fever of prescribed tablets. Chi-squared test with Yates, correction was used for statistical analysis.

Results

Out of total 50 patients seen of peptic ulcer 6 were excluded because of absence of H. Pylori infection or presence of complication (bleeding 2 patients) of 44 patients included in the study 21 were randomized to Group A and 23 to group B. All patients had active or healed ulcers. Two groups had similar baseline characteristics. 1 patient was lost to follow up (Group B) and no patient discontinued drug. All patients had good compliance (Table I).

The two groups had similar H. Pylori eradication and ulcer healing rates. Adverse effects were almost equal in two groups; these include fissuring and burning sensation on tongue, constipation, diarrhoea, headache, fatigue and distaste for food.

Table:1 Baseline characteristics and results in two groups treated with different ani-H. Pylori drug regimens.

Parameters	Triple therapy (Gp.A)	Quadruple therapy (Gp. B)
Total patients.	21	23
Male : Female	17.4	20.3
Mean age range (years)	41.7(19.69)	37.5 (18.64)
Ulcer location duodenal:	14:4:2	21:2:0
Gastric: pyloric channel	32:4:1	32:2:0
Lost of follow up	0	0
Discontinued drugs	0	0
Complete protocol	21	22
H.Pylori eradication intention-to-treat basis	17/21	16/23
Side effect	2 (1%)	4(2%)

**Some patients had more than one type of ulcer p=ns*
**Includes the two patients who discontinued therapy.*

Discussion

An ideal H. Pylori eradication regimen should have an intention –to-treat response rate exceeding 80%. In our study, quadruple therapy using a PPI, bismuth, metronidazole and tetracycline gave suboptimal results. The two groups had similar eradication rates and side effects. A previous study using a combination of secnidazole, amoxycillin, PPI and bismuth gave similar results. Tetracycline, a drug that is used less commonly now as compared to amoxycillin, and consequently less likely for H. pylori to harbor resistance against, did not give better results.

Some previous reports have shown that similar quadruple regimes are useful for initial treatment. However, when resistance to metronidazole was proved or was likely, the outcome of quadruple therapy was found to be variable. When used for re-treatment, the results of imidazole-containing quadruple therapy appear to depend on whether the previous regime included an imidazole or not.

Thus, two factors appear to adversely affect the outcome of quadruple drug therapy reuse of an antibacterial agent included in a previous regime that failed and, in the event of initial therapy, use of an agent to which the resistance rates are high in a given population. The suboptimal response to four drugs in our study can be explained by the high prevalence of metronidazole resistance in our region. Since some studies have shown excellent cure rates despite the presence of resistance to the drugs, used the role of other factors that might have an influence on the outcome needs further evaluation.

The individual drugs in various H. pylori eradication regimes have been sued in different doses. The effect of differing doses of a given drug on eradication is not fully understood. When clarithromycin is used in combination with a PPI and amoxycillin, a dose of 500 mg twice daily is usually recommended. We chose to use all the drugs in doses that are in the higher end of the range recommended for eradication therapy.

The effect of duration of treatment on outcome is controversial. Treatment for 14 days is still recommended by some. Seven-day therapy may be inadequate if metronidazole resistance is common and treatment with clarithromycin and amoxycillin for 14 days has the disadvantage of high cost. We therefore decided to treat our patients for 10 days.

It is possible that our study overlooked a difference between the two groups because of the small number of patients studied. With response rates with triple drug regimen approaching 80%, one would need 145 patients per group to detect a 10% difference in response rate in a comparison group; this is difficult to achieve in any single center and suggests the need for multi-center trials.

The differences between our results and those reported from the West emphasize the need for region specific trials, based on antimicrobial drug resistance patterns in that region.

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