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One Week Triple Therapy for *Helicobacter Pylori* Associated Duodenal Ulcer Disease

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ABSTRACT

Introduction: Eradication of *Helicobacter pylori (H. pylori)* cures and prevents the relapse of duodenal ulceration. Different treatment regimes for the eradication of *H. pylori* have been used and the most successful eradication regimens have been one week treatments with a proton pump inhibitor and two antibiotics.

Aim of Study: To examine the eradication rate of *H. pylori* with a one week regimen consisting of OCT (Omeprazole 20mg BD, Clarithromycin 250mg BD, Tinidazole 500mg BD). This treatment regimen has been used for *H. pylori* eradication in our department since the end of 1996.

Methods: Patients diagnosed to have duodenal ulcer in 1997 were retrospectively reviewed. Infection with *H. pylori* must be documented either by gastric biopsy or by a positive CLO test. Eradication of *H. pylori* was confirmed by negative ^{14}C urea breath test or by histology at least four weeks after cessation of therapy.

Results: The review was performed on 251 patients. There were 177 males, 74 females. The median age was 51 (18 – 77) years. *H. pylori* infection was confirmed by CLO test in 170 patients and by histology in 72 patients. Thirty patients did not undergo further investigation after therapy to confirm the eradication. Of the remaining 221 patients, *H. pylori* was successfully eradicated in 198 patients (89.6%) as confirmed by ^{14}C urea breath test (190 patients) or repeat gastroscopy and gastric biopsy (31 patients). There were no serious adverse events documented.

Conclusions: Our retrospective study showed that the one week regimen used in our department is effective for the eradication of *H. pylon* in nearly 90% of infected cases.

Keywords: *helicobacter pylori*, duodenal ulcer, eradication, triple therapy

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INTRODUCTION

Helicobacter pylori (H. pylon) infection is the major aetiological factor in peptic ulcer disease, and curing the infection dramatically reduces the ulcer relapse rate[1,2]. Approximately 95% of patients with duodenal ulcer and 50% of patients with non-ulcer dyspepsia are colonised with *H. pylori*[3,4].

The 'classical' triple therapy recommended by the World Congress of Gastroenterology in 1991[5] and the National Institute of Health Consensus[6] contains bismuth, tetracycline or amoxycillin, and metronidazole, all given for 14 days. A high incidence of side effects with this treatment has encouraged investigators to develop different treatment regimes which are less complex, with fewer side effects and of a shorter duration. The most successful eradication regimens so far have been one week treatments with a proton pump inhibitor and two antibiotics. Bazzoli et al showed an eradication rate of over 95% with one week regime comprising of clarithromycin 250mg twice daily, omeprazole 20mg once daily and tinidazole 500mg twice daily[7]. Since the end of 1996, our gastroenterological unit has adopted this regime for the eradication of *H. pylori* in our local population. In our protocol, the dosage of omeprazole was increased to 20 mg twice daily as several studies showed higher eradication rates with higher doses of omeprazole[8].

The aim of the current study was to investigate the efficacy of this regime in our local population.

METHODS

The review was conducted between January 1997 and end of December 1997. Patients diagnosed to have duodenal ulcer were identified from the database at our endoscopy unit. All patients had been evaluated for ulcer-like dyspeptic symptoms. The case notes of these patients were retrospectively reviewed to confirm the endoscopic findings and *H. pylori* infection.

All patients received triple therapy as described above for one week. Patients who were prescribed other regimes for *H. pylori* eradication were excluded from this analysis.

Endoscopy

Gastroscopy was performed after six hours of fasting under local anaesthetic agent (Xylocaine throat spray). One antral biopsy was placed into the agar gel of the CLO test (Delta West, Bentley, Western Australia). A positive test was recorded if there was a colour change from yellow to pink within 1 hour.

Histology

For histological examinations, haematoxylin/eosin stained antrum and corpus biopsies were examined. One antral and corpus biopsies were routinely taken for histology.

Urea Breath Test (UBT)

Liquid ^{14}C-urea was purchased from Sigma, St Louis, and preparation of ^{14}C was carried out according to the method as described by Marshall et al[9]. Patients were administered the ^{14}C-urea solution and a breath sample was obtained at 20 minutes into a liquid trap containing hyamine solution. The solution was then counted in a liquid scintillation counter (Wallac 1410, Pharmacia). This method has been previously validated with a sensitivity and specificity of 100% and 97.2% respectively when it was compared to histology[10].

H. pylori infection was considered to be present if the CLO test and /or histopathological results were positive. Eradication of the infection was defined as an absence of *H. pylori* on gastric tissue (by CLO test and histology) or negative UBT performed at least four weeks after the end of therapy.

RESULTS

Two hundred and ninety seven patients were identified to have duodenal ulcers on endoscopy during the study period. Medical notes of 263 patients were successfully retrieved. Of these patients, only 251 were identified to have received our standard triple therapy for the eradication of *H. pylori* associated duodenal ulcer disease. There were 177 males and 74 females. The median age of the group was 51 (18 – 77) years. *H. pylori* infection was confirmed by CLO test in 170 patients and by histology in 72 patients. Only 4 patients were on non-steroidal anti-inflammatory drugs (NSAID). Of the twelve patients who did not receive our triple therapy, eight patients were found to be *H. pylori* negative and did not therefore receive eradication therapy; five of these patients were on non-steroidal anti-inflammatory drugs. Four patients were *H. pylori* positive by CLO test but were prescribed dual therapy combinations by their attending physicians.

Thirty patients did not undergo further investigation after therapy to confirm the eradication and they were excluded from the analysis. The main reasons were either due to the patients' default of follow-up or physicians' discretion that further testing was not indicated due to successful symptomatic outcome after therapy.

The analysis was performed for the remaining 221 patients. *H. pylori* eradication was successfully achieved in 198 patients (89.6%) as assessed by either UBT or gastric histology. Post-therapy UBT was performed on 190 patients. Thirty-one patients underwent repeat gastroscopy and gastric biopsy after treatment to check on the healing of concomitant gastric ulcers. Eradication of *H. pylori* was confirmed if both CLO test and antral and corpus histology showed absence of *H. pylori* colonisation. As gastric histology is considered to be of lower sensitivity than UBT for the assessment of *H. pylori* eradication, subgroup analysis without this group was also performed. Of the total number of 190 patients who had UBT after therapy, 173 patients (91.1%) had negative UBT and were therefore successfully eradicated. Twenty-five out of 31 patients were considered to be eradicated by gastric histology. There was no serious adverse events documented in relation to therapy.

DISCUSSION

This retrospective study showed that a one week combination of a proton pump inhibitor with two antibiotics was highly effective, with the eradication of *H. pylori* infection in nearly 90% of patients with duodenal ulcers. The proportion of patients eradicated was comparable with that reported by other investigators using similar drug combinations[11,12].

Two large studies of one week, twice daily *H. pylori* eradication regimens were published[11,12]. The MACH 1 study was a European multicentre, double blind, randomised, placebo-controlled trial in 723 *H. pylori* patients with duodenal ulcer[11]. Treatment consisted of omeprazole 20 mg in combination with either placebo, or with two antimicrobiol agents twice daily: metronidazole 400 mg, amoxycillin 1 g, and clarithromycin 250 mg or 500 mg; all tablets taken twice daily for one week. The second study, a UK and Eire multicentre, randomised trial, involved 496 *H. pylori* patients with duodenal ulcer or non-ulcer gastritis[12]. Patients were randomised to either lansoprazole 30 mg plus two of clarithromycin 250 mg, amoxycillin 1 g, metronidazole 400 mg, or to omeprazole 20 mg plus amoxycillin 1 g and metronidazole 400 mg; all given twice daily for one week. These two large randomised comparative trials suggest that a one week, low dose twice daily triple therapy regimen containing a proton pump inhibitor with clarithromycin 250 – 500 mg and either amoxycillin 1 g or metronidazole 400 mg, will cure *H. pylori* infection in about 90% of patients.

The success of *H. pylori* eradication therapy depends to some extent on patient compliance[13,14], side effects and bacterial resistance to the antimicrobiol agents. Severe side effects leading to discontinuation of the treatment in 5% – 20% of cases have been reported[15]. The "classic" triple therapy containing bismuth and two antibiotics is more commonly associated with common side-effects and is unpopular among gastroenterologists. The regimens that have been studied to date have used a bismuth preparation, an H2-receptor antagonist, ranitidine bismuth citrate, or a proton pump inhibitor, in combination with one, two or three antimicrobiol agents[16,17].

From the Maastricht Consensus[18], it was agreed that therapy should be simple, well tolerated and achieve eradication rate of over 80% on an intention-to-treat basis. It was strongly recommended that eradication treatment should be with proton pump inhibitor based triple therapy for seven days, using a

proton pump inhibitor and two of the following: clarithromycin, a nitroimidazole (metronidazole or tinidazole) and amoxycillin. It was recommended that this regime replace classic bismuth based triple therapy as it is associated with fewer side effects, higher efficacy and better compliance[18]. Similar seven-day regimens have been recommended by the Asia Pacific Consensus[19]. In addition, ranitidine bismuth citrate (RBC) based therapy at 400 mg twice daily with combinations of two other antibiotics have also been recommended.

Besides patient compliance and side effects of therapy, bacterial sensitivity to antimicrobiol agents is an important factor determining success of eradication. Resistance to metronidazole, the mainstay of many eradication regimens, is well documented. A multicentre European study on the prevalence of metronidazole resistance in vitro showed that nearly 27.5% (7 – 49%) of the strains tested were resistant[20]. A significantly impaired eradication efficacy of triple[12] and quadruple[21] therapy in cases of metronidazole resistance have been documented. In Singapore, clarithromycin resistance rate remains low at 2% – 3%[22,23]. However, metronidazole resistance is as high as 52% and has been increasing in recent years after the introduction of nitroimidazole based triple therapy[23]. Despite this high prevalence of metronidazole-resistance in our locality, an eradication rate of over 80% was achieved with our nitroimidazole-based regime. An eradication rate of 86% was also achieved in a group of local patients with metronidazole resistant strain following therapy with a combination of lansoprazole, metronidazole and clarithromycin[24]. Misiewicz et al reported eradication rate of 75% with the regime containing lansoprazole, clarithromycin and metronidazole in patients with the metronidazole resistant strains[12].

There are several possible explanations for the high success rates achieved with nitroimidazole containing triple therapy despite the presence of resistant strains. Firstly, there have been speculations whether in vitro resistance is an unstable phenomenon[25,26]. A strain found to be resistant in vitro could become a sensitive strain in vivo through some as yet unknown mechanism. Secondly, some form of synergy is known between clarithromycin and omeprazole, and this synergy may overcome in vitro resistance of metronidazole[27].

We did not document any serious adverse events in relation to our therapy as defined by the ICH GCP criteria ie. any adverse event that is life-threatening or resulted in death, inpatient hospitalisation or significant disability. There certainly could have been an under recording of side effects (non serious adverse events) due to the retrospective nature of our study. However, it is unlikely that we have under-reported serious adverse events as these would certainly be recorded in the casenotes.

Thirty patients were excluded from the analysis as they did not undergo further testing to check on their eradication status. In the majority of cases, the physician in charge did not feel that further testing was indicated due to an improvement in the patients' symptoms. Although it is generally advisable to determine the outcome of attempted *H. pylori* eradication in uncomplicated peptic ulcer and non-ulcer dyspepsia, this may not be necessary when symptoms resolve[18,19]. In duodenal ulcer disease, symptom assessment at three and six months has been shown to be as valuable as the ^{13}C-UBT[16,28]. Complete resolution of symptoms at three months was found to be a strong predictor of the eradication of *H. pylori* infection for patients with peptic ulcer disease[28].

Non-recurrence of gastric and duodenal ulcer is strictly dependent on the success of *H. pylori* eradication[29]. This is also true for relapses of ulcer complications such as bleeding[30,31]. Both the European and Asia Pacific Consensus guidelines[18,19] strongly recommend the eradication of *H. pylori* for uncomplicated and complicated (bleeding and perforations) peptic ulcer disease, low grade MALT lymphoma, gastritis with severe macro- and microscopic abnormalities and following resection of early gastric cancer. This retrospective study shows that our regimen eradicated *H. pylori* infection in nearly 90% of cases in our local population.

REFERENCES

1. Peterson WL. Helicobacter pylori and peptic ulcer disease. N Engl J Med 1991; 324:1043-8.
2. Rauws EAJ, Tytgat GNJ. Cure of duodenal ulcer associated with eradication of Helicobacter pylori. Lancet 1990; 335:1233-5.
3. Marshall BJ, McGechie DB, Rogers PA, Glancy RG. Pyloric campylobacter infection and gastrointestinal disease. Med J Aust 1985; 142:439-44.
4. Talley NJ. Is Helicobacter pylori a cause of nonulcer dyspepsia? In: Malfertheiner P, Ditschumeit H, eds. Helicobacter pylori, gastritis and peptic ulcer disease. Berlin: Springer Verlag, 1990;
5. Axon ATR. Helicobacter pylori therapy: effect on peptic ulcer disease. In: Working party Report to the World Congress of Gastroenterology. J Gastroentyerol Hepatol 1991; 6:131-8.
6. NIH Consensus Development Panel. Helicobacter pylori in peptic ulcer disease. JAMA 1994; 272:65-9.
7. Bazzoli F, Zagari RM, Fossi S, et al. Short-term low dose triple therapy for the eradication of Helicobacter pylori. Eu J Gastroenterol Hepatol 1994; 6:773-7.
8. Bayerdorffer E, Miehlke S, Mannes GA, et al. Double-blind trial of omeprazole and amoxycillin to cure Helicobacter pylori in patients with duodenal ulcers. Gastroenterology 1995; 108:1412-7.
9. Marshall BJ, Plankey MW, Hoffman SR, et al. A 20-minute breath test for Helicobacter pylori. Am J Gastroenterol 1991; 86:438-45.
10. Yu WK, Chow PKH, Tan SY, et al. 5 micro-curie urea breath test for the diagnosis of Helicobacter pylori infection: evaluation in a South-East Asian population. Aus NZ J of Surgery 1998; in press:
11. Lind T, Velduyzen van Zanten SJO, Unge P, et al. Eradication of Helicobacter pylori using one week triple therapies combining omeprazole with two antimicrobiols. The MACH 1 study. Helicobacter 1996; 1:138-44.
12. Misiewicz JJ, Harris AW, Bardhan KD, et al. One week triple therapy for Helicobacter pylori: a multicentre comparative study. Gut 1997; 41:735-9.
13. Graham DY, Lew GM, Malaty HM, et al. Factors infleuncing the eradication of Helicobacter pylori with triple therapy. Gastroenterology 1992; 102:493-6.

14. Cathbert AF, Schubert TT. Patient factors affecting Helicobacter pylori eradication with triple therapy. Am J Gastroenterol 1993; 88:505-9.
15. de Boer WA, Tytgat GN. The best therapy for Helicobacter pylori infections: Should efficacy or sideeffect profile determine our choice? Scand J Gastroenterol 1995; 30:401-7.
16. Unge P. Review of Helicobacter pylori eradication regimes. Scand J Gastroenterol 1996; 31 (suppl 215):74-81.
17. Unge P. What other regimens are under investigation to treat Helicobacter pylori infection? Gastroenterology 1997; 113:S131-S148.
18. Current European concepts in the management of Helicobacter pylori infection. The Maastricht Consensus Report. Gut 1997; 41:8-13.
19. Lam SK, Talley NJ. Report of the 1997 Asia Pacific Consensus Conference on the management of Helicobacter pylori infection. J Gastroentrol Hepatol 1998; 13:1-12.
20. European study group on antibiotic susceptibility of Helicobacter pylori: results of a multicentre European survey in 1991 of metronidazole resistance in Helicobacter pylori. Eur J Clin Microbiol Infect Dis 1992; 11:777-81.
21. van der Hulst RWM, van der Ende A, Homan A, Roorda P, Dankert J, Tytgat GNJ. Influence of metronidazole resistance on efficacy of quadruple therapy for Helicobacter pylori eradication. Gut 1998; 42:166-9.
22. Fock KM, Tan AI, Khor CJL, Ng TM, Teo EK, Lee YM. Susceptibility and resistance of H. pylori to clarithromycin in Singapore. J Gastroenterol and Hepatol 1998; 13 suppl:D20(Abstract).
23. Yeoh KG, Hua J, Lim SG, et al. Rising metronidazole resistance among Helicobacter pylori strains in Singapore from 1995-1997. J Gastroenterol and Hepatol 1998; 13 suppl:D21(Abstract).
24. Yeoh KG, Gwee KA, Lim SG, et al. A low dose triple therapy combination is effective for eradicating Helicobacter pylori in Asian patients despite a high rate of metronidazole resistance. J Gastroenterol Hepatol 1998; 13(supple):D37.
25. Cederbrant G, Kahlmeter G, Ljungh A. Proposed mechanism for metronidazole resistance in Helicobacter pylori. J Antimicrob Chemother 1992; 29:115-20.
26. Smith MA, Edwards DI. Redox potential and oxygen concentrations as factors in the susceptibility of Helicobacter pylori to nitroheterocyclic drugs. J Antimicrob Chemother 1995; 35:751-64.
27. Gustavsson LE, Kaiser JF, Edmonds AL, et al. Effect of omeprazole on concentrations of clarithromycin in plasma and gastric juice at steady state. Antimicrob Agents Chemother 1995; 39:2078-83.
28. McColl KEL, El-Nujumi A, Murray LS, et al. Assessment of symptomatic response as predictor of Helicobacter pylori status following eradication therapy in patients with ulcer. Gut 1998; 42:618-22.
29. Hopkins RJ, Girardi LS, Turney EA. Relationship between Helicobacter pylori eradication and reduced duodenal and gastric ulcer recurrence: a review. Gastroenterology 1996; 110:1244-52.
30. Jaspersen D. Helicobacter pylori eradication: The best long term prophylaxis for ulcer bleeding recurrence? Endoscopy 1995; 27:622-5.
31. Rokkas T, Karameris A, Mavrogeorgis A, Rallis E, Giannikos N. Eradication of Helicobacter pylori reduces the possibility of rebleeding in peptic ulcer disease. Gastrointest Endosc 1995; 41:1-4.