Diagnosis and eradication of Helicobacter pylon in Patients with Duodenal Ulceration in the community

S. Z. Abbas (Gastrointestinal Unit. Royal Cornwall Hospital, Truro. UK.)
A. B. Abbas,J. English,D. McGovern,H. R. Dalton (Gastrointestinal Unit. Royal Cornwall Hospital, Truro,UK.)
A. Crawshaw (The Cornwall General Practice Training Group, Royal Cornwall Hospital, Truro. UK.)
S. Shaw (School of Mathematics and Statistics. University of Plymouth, Royal Cornwall Hospital, Truro. UK.)
G. Vivian (Nuclear Medicine Department, Royal Cornwall Hospital, Truro, UK)

Abstract

Objective: To determine the value of Helicobacter pylori (Hp) serology in diagnosis of active Hp infection in patients with documented duodenal ulcer (DU) and to directly compare the efficacy and side-effects profiles of metronidazole or tinidazole in a triple therapy regimen to eradicate active Hp infection.
Design of Study: Prospective, single-blinded, randomised trial.
Methods: One hundred patients from General Practice with documented DU and Hp seropositivity had a C14 Urea Breath Test (UBT). Those who tested positive were randomised to receive one-week, twice daily omeprazole 20 mgs and clarithromycin 250 mgs in combination with metronidazole 400 mgs (0CM) or tinidazole 500 mgs (OCT). Eradication was confirmed by a repeat UBT.
Results: Eighty five sero-positive patients had a positive pre-treatment UBT. On intention to treat basis, OCT (100%) had a significantly better eradication rate than 0CM (87.8%), p = 0.023. There was no difference in side effects.
Conclusion: (1) Positive Hp serology in patients with DU does not always mean active infection and (2) for patients in the community with active Hp and DU disease OCT is significantly better than 0CM for eradicating Hp (JPMA 53:90;2003).

Introduction

The discovery of the association of Helicobacter Py Pylori (Hp) infection and peptic ulcer disease (PUD) has revolutionised our therapeutic approach to PUD. The National Institute of Health Consensus Development Conference Statement therefore recommends antimicrobial agents to eradicate Hp infection in all patients with associated PUD.[1] The revised Maastricht Consensus Report by European Helicobacter Pylon Study Group (EHPSG) has also strongly recommended eradicating Hp in all infected PUD patients.[2] There are over 45 different regimens that have been used for the eradication of Hp, ranging from dual to quadruple therapy, lasting only 5 days to 2 weeks[3-5] and the quest to find a 'perfect' eradication regimen continues. These regimens have been reported to have Hp clearance rate of between 28%~10O%.[6,7]
One regime that achieves a reliably high rate of Hp eradication (>90%) is the

combination of omeprazole, clarithromycin and tinidazole (OCT) for one week only. This appears to be one of the most effective and acceptable combinations used so far8 and has set a standard against which all other regimes can be compared.[9] Tinidazole is a nitroimidazole antibiotic and is closely related to metronidazole. Although this combination was found highly effective in eradicating Hp8, the eradication rate was reported to be significantly lower among metronidazoleresistant strains.[10] These two drugs have similar antibacterial activity and side effects profiles. There is a significant difference in cost between these two drugs. In the UK, 20-tablets pack of tinidazole 500 mgs costs £11.50 , compared to a few pence for metronidazole (British National Formulary - September 2001). Tinidazole is also not available in some countries.[11] This study was designed to directly compare OCT with 0CM (replacing tin idazyle with metronidazole) in terms of efficacy and side-effects in patients with documented duodenal ulcer (DU) in the comm unity.

Hp serology testing is a non-invasive test and is investigation of choice in population studies.[12] However, there seems to be an increased prevalence of false-negative serology in elderly people.[13] It also may remain falsely positive for a long time after eradication of Hp.[14,15] This study also attempted to determine the value of a positive serology in diagnosing an active Hp infection prior to an intentional eradication treatment.

Methods

Patients with previously documented DU, either by barium meal or at endoscopy, were identified as part of a local initiative by the Cornwall GP Trainers Workshop to offer such patients eradication therapy should they be Hp positive. Patients were identified from general practice from computerised records. After obtaining informed consent to participate in the study, these patients were tested for serum Hp lgG antibodies by ELISA. All positive patients were randomly allocated to receive either OCT (omeprazole 20 mgs, claithromycin 250 mgs and tinidazole 500 mgs) or 0CM (replacing tinidazole with metronidazole 400 mgs) -all twice a day for 1 week - after having a positive C14 Urea Breath Test (UBT) confirming an active Hp infection. The patients knew which treatment they received, but the doctors did not (single-blind design). Compliance was checked by a tablet count and a questionnaire and side effects were monitored by a questionnaire. Six to eight weeks following treatment patients had a repeat UBT to check for eradication of the organism.

Out of the 100 patients who tested positive for H. pylon serology, 64 had their DU diagnosed previously by barium meal and 36 at endoscopy. Of these patients 80 were men and 20 were women. Their mean age was 61 years (range 24-79).

Exclusion Criteria

1) Patients under 1 8 or over 80 years of age.
2) Patients who had had previous Hp eradication therapy.
3) Patients who needed to continue receiving drugs that may interact with the study drugs e.g. warfarin, carbamazepine and lithium.
4) Patients with hypersensitivity to the study drugs.
5) Pregnant and breast-feeding mothers.
6) Patients with mental impairment who could not comply or consent.

Statistical Analysis

Analysis was performed on an intention-to-treat basis. The treatment success was compared between the two groups using Fishers exact test. The side-effects profiles were compared using the chi-squared test; 95% Confidence Intervals (95% CI) were also calculated. Mean ages were compared using t-test. P values <0.05 were considered significant.
Assuming 90% of patients responded to OCT treatment, this study had a power of 91% for detecting a difference of 20% (i.e. down to 70%) in the 0CM group for a one-tailed test at the 5% level. Assuming 30% of patients had side effects in the OCT group, the study had a power of 47% for detecting a difference of 20% (i.e. up to 50°/o or down to 10%) in the 0CM group for a two-tailed test at the 5% level. Ethical committee approval for this study was obtained from the Cornwall Ethics Committee. Informed consent was obtained from all patients.

Results

One hundred patients were identified with documented DU and positive Hp serology. Of these patients, 9 tested negative (5 men ; 4 women), 6 equivocal (5 men; I woman) and 85 positive (70 men 15 women) oii UBT. Four of those who tested negative, had had an antibiotic (amoxycillin, trimethoprim, clarithromycin or doxycycline) for a chest or a urinary tract infection while still on acid suppressing treatment (3 on omeprazole, 1 on ranitidine) at a mean of 8 months before the initial UBT. The average ages of the UBT-negative and the UBT-positive groups were 65.8 .years (SD 7.6) and 59.5 years (SD = 11.3) respectively -p = 0.044. The 85 positives were randomly allocated treatment with either 0CM or OCT. Their demographic characteristics are as listed in the table.
Hp infection was successfully eradicated in 36 out 41 patients treated with 0CM as diagnosed by a normal post-treatment UBT (87.8%; 95% Cl 77.8-97.8%). Of the 5 failures, I had non-compliance with the tablets due to vomiting. In the OCT group , all 44 patients had a normal post-treatment UBT, indicating 100% success rate (95% Cl 93.4-100%-one-tailed interval). This was significantIy better than the success rate with 0CM (p = 0.023 - Fisher's exact test).
All patients who had successful eradication of Hp, had no problem with compliance with the trial drugs. Among those who failed to respond 2 were women and 3 men (p = 0.21 - Fisher's exact test). The average ages of those who had successful eradication of Hp was 59.9 years (SD = 11 .4) and of those in treatment failure group was 53 years (SD = 8.6)- p 0.19.
patients in the 0CM group reported one or more side-effects during the treatment as compared to 23 of the 44 (52.2%; 950/0 Cl = 37.5 - 67.0%) patients in the OCT group. This was not statistically significant (pO.32). The side-effects reported are shown in the

table.

Table. Comparison of the two H. pylori eradication groups.

OCM			
Number of patients	41		
Males	31		
Females	10		
Mean age (SD) (10.9)	57		
Successful eradication	36 (87.8%)	44 (100%)	p = 0.023
Patients reporting side effects	23 (52.2%)	17(41.5%)	p=0.32
Details of side effects reported by the patients:			
Diarrhoea	8		
Abdominal discomfort	7		
Bad taste	5		
Mouth ulcers	2		
Nausea	2		
Headaches	4		
Personality changes	1		

Other side-effects reported by 2 or less patients included tiredness, vomiting, sore throat, off-colour, constipation. urine odour. polyuria. cramps, vertigo, mouth ulcers. insomnia, dark tongue and hallucinations.

Discussion

There is a scarcity of data on eradication of Hp in the setting of primary care, where large number of patients with symptomatic DU are treated for by their general practitioners. Many of these patients are on long-term acid suppression treatment and most of them do not attend hospital gastroenterology clinics on a regular basis. This is one of the few studies in the community to investigate Hp eradication in patients with DU disease.'6 Patients were recruited as part of local initiative by their general practitioners to offer such patients eradication therapy should they be Hp positive.

Since Bazzoli reported the efficacy of OCT in the treatment of Hp infection[7,17] several

other investigators have successfully used the combination of a proton pump inhibitor and clarithromycin with a nitroimidazole.[18-22] However, only few studies have compared tinidazole with metronidazole in the above combination in chronic DU associated with H. pylori. Goddard et al[23] compared the efficacy and side effects profiles of these two regimens (OCT vs. 0CM) directly in eradicating Hp. In the absence of any significant differences in the efficacy and side effects, 0CM being cheaper was chosen for Hp eradication. However, their study was hospital based and was not performed in the setting of chronic duodenal ulceration requiring symptomatic treatment in the community.

This study shows that OCT is more effective than 0CM which may not be due to metronidazole resistance alone. Metronidazole and tinidazole are pharmacologically similar and cross-resistance is likely to occur between the two drugs.[24,25] Although both the drugs have been very successfully used in Hp eradication regimens, the small treatment failure rate has at least partially been attributed to the wide use of metronidazole and the development of resistant strains to this drug.[10,24,26-28] While the resistance reported is to be very high in developing countries[29,30] in a multicentre European survey, it varied from 7% to 45%,[31] Although antibacterial sensitivities were not tested, this is still the most likely cause for the treatment failure in all 5 patients in this study. Metronidazole resistance is more frequent in young people.[32] Although the average age of successful eradication group was higher than the failure group in this study. this did not reach statistical significance (59.9 vs 53 years - $p = 0.19$) The superiority of OCT compared to 0CM in this study can perhaps be explained by the theory of overcoming the resistance of Hp by increasing the dose ofnitroimidazole. This study used both tinidazole and metronidazole in a bd dose (500 mgs and 400 mgs respectively). Treatment with tinidazole in the conventional doses of 500 mgs twice daily (bd) results in universally excellent success rates.[7,17-18,22,22] Although given in three times a day (tds) dose for various infections, Metronidazole is effective in a bd dose in various Hp eradication regimens.[19,20,23] However, Bell et al used metronidazole in a tds dose in combination with amoxycillin and omeprazole for 14 and 7 days and successfully eradicated Hp in 96.4% and 91.1% cases respectively. The above combination in the same doses successfully eradicated 75% and 88.2% Hp infections with metronidazole resistant organisms.[33,34] This suggests that using a tds dose of metronidazole somehow overcomes the resistance of Hp and may prove to be a better treatment than when it is used in a bd dose. Increasing the dosage of metronidazole from 800 mgs to 1600 mgs, increased the cure rate both in sensitive and in resistant Hp strains.[35] Consequently, it is possible that a higher dose of metronidazole than was used in this study. might have been proven more effective.

Nine out of 100 patients in this study, who had proven duodenal ulcer and positive Hp serology, had a negative UBT before they had eradication therapy. The UBT is very specific and its sensitivity ranges between 90-100%.[12,36] The commonest reason for false negative tests is breath testing too soon after a course of antibiotics, bismuth or omeprazole.[12] Proton pump inhibitors have weak direct antibacterial effect on HP[37] and also they inhibit urease.[38] Stopping acid suppression therapy at least I month before the UBT is therefore generally advised.[12] Accordingly. all the patients in this study stopped such drugs 6 weeks prior to the UBT test date.

This unexpected result (positive serology but negative UBT before treatment) may be due to initiation of an irreversible process by Hp towards atrophic gastritis intestinal

metaplasia and achlorhydria accompanied by a dramatic reduction or even demise of the organism. Superficial gastritis may advance over 20-30 years into atrophic body gastritis.[39-40] Therefore there is a group of older patients who have Hp related atrophy but are no longer infected.[39] The Hp serology however is known to remain positive for a long time[14,15] and the length of time required for Hp antibody concentration to decrease below defined sero-positive cut-offs is not known. In this study patients with positive serology and normal UBT were significantly older than those with both the tests positive (mean ages 65.8 years (SD = 7.6; 95% CI = 60.0 - 71.6) and 59.5 years (SD = 11.3, 95% CI = 57.1- 62.0) respectively (p 0.044).

An alternative explanation for this discrepancy in the UBT and serology test results could be inadvertent eradication of the bacteria by taking an antibiotic as a treatment for a concomitant infection. If such patients taking proton pump inhibitors developed an upper respiratory tract infection and received amoxycillin, they would effectively have had 'dual therapy'. Dual therapy regimens such as Omeprazole with Amoxycillin have been reported to give eradication rates varying between 28%4 to 92%.41 In this study, at least 4 out of the 9 patients who had a discrepancy in the serology and UBT results. did have antibiotic treatment while on acid suppressing agents (3 on omeprazole and I on ranitidine) at a mean of 8 months before the pretreatment UBT for a variety of reasons including chest and urinary tract infections.

It is concluded that for our population OCT is a significantly better treatment than 0CM for eradicating Hp in patients with documented DU in the community, and is as well tolerated. It would also appear that positive Hp serology does not necessarily mean active Hp infection even in the setting of documented duodenal ulceration.

Acknowledgements

The authors gratefully acknowledge the help of Tracy Clayton-Smith at the Medical Physics department, Royal Cornwall Hospital, Truro, UK and all the general practitioners Truro. in Cornwall, UK, and the patients who took part in the study. This study was funded by Astra Pharmaceuticals.

References

1.Anonymous: Helicobacter pylori in peptic ulcer disease. NIH Consensus Statement 1994; 2:1-23.

2.Sjolund K. Ljungh A. Report from an international consensus conference in Maastricht. Management and treatment of Helicobacter pylori infection. Lakartidningen 2001:98:1235 - 8.

3.HaITis AW. Misiewicz JJ. Eradication of Helicobacter pylon. In: Calam J. ed. Clinical gastroenterology Helicobacter pylori, Philadelphia: Bailliere Tindall. W B Saunders,1995. pp 583-613,

4.Gisbert JP, Marcos S. Gisbert JL. et al. High efficacy of ranitidine bismuth citrate, amoxycillin.. claithromycin and metronidazole twice daily for only five days in Helicobacter pylon eradication. Helicobacter 2001;6:157-62.

5.Kamberoglou D, Polymeros 0. Sanidas I, et al. Comparison of I-week vs. 2-or 4-week therapy regimens with ranitidine bismuth citrate plus two antibiotics for Helicobacter

pylori eradication. Aliment Pharmacol Ther 2001; 15:1493-7.
6.Logan RPH, Rubio MA. Gummett PA: Oineprazole and a us o x y c i I I I n suspension for Helicobacterpylori (abstract). Irish J Med Sci 1992; 161 (Suppl l0):l6.
7.Bazzoli F, Zagari RM, Fossi S. et al. Efficacy and tolerability of a short-tenn, low-dose triple therapy for eradication of Helicobacter pylon (abstract]. Gastroenterology 1993: 104 (4): A40.
8.Axon ATR. Eradication of Helicobacter pylori. Scand J Gastroenterol 1996: 31(Suppl 214):47-53.
9.Goddard A . Logan R. One week low-dose triple therapy: new standards for Helicobacter pylori treatment; Eur J Gastroenterol Hepatol 1995: 7:1-3.
10.Ling KL. Luman W. Ho B, Ng HS. Efficacy of a nitroimidazole containing triple therapy regime in Singapore. Singapore Med J 2001:42:317-21.
11.Tracy JW, Webster IT. Jr. Chemotherapy of parasitic infections. In: Hardman JG. Limbird LE. Molinoff PB, et al., eds. The pharmacological basis of therapeutics. New York: McGraw-Hill, 1996, pp. 955-64.
12.Atherton IC. Spiller RC. The urea breath test for Helicobacter pylon. Gut 1994: 35:723-5.
13.Newell DG, Hawtin PR, Stacey AR, et al. Estimation of prevalence of Helicobacter pylori infection in an asymptomatic elderly population comparing tireas breath test and serology. J Clin Pathol 1991:44:385-7.
14.Hirschl AM, Brandstatter G, Dragosics B, et al. Kinetics of specific lgG antibodies for monitoring the effect of anti-Helicobacter pylon Chemotherapy J Infect Dis 1993:168:763-6.
15.Kosunen TO, Seppala K. Sarna S. et al. Diagnostic value of' decreasing IgG IgA and 1gM antibody titres after eradication of Helicobacter pylori. Lancet I 992:1:893-5.
16.Phull PS. Ryder SD. Halliday D. et al. The economic and quality-of-life benefits of Helicobacter pylori eradication in chronic duodenal ulcer disease -a community-based study. Postgrad Med J 1995: 7l,4l3-8
17.Bazzoli F. Zagari RM. Fossi S. et at. Short-term, low-dose triple therapy for eradication of Heticobacter pylon: Eur .J Gastroenterol and Hepatol 1994. 6:773-7.
18.Moayyedi P, Tompkins DS, Axon ATR. Determination of the optimum dose of omeprazole in a new triple therapy regime for eradicating Helicobactei pylon. Gut 1994; 35 (suppl.5): W63.
19.Labenz J. Stolte M. RuhI GH, et al. One week low-dose triple therapy for the eradication of Helicobacter pylori. Euri Gastroenterol and Hepatol 1995:7: 9-Il
20.Lind T. Megraud F. Unge P. et al. The MACH 2 study: role of omeprazole in eradication of Helicobacter pylon with W eek triple therapies Gastroenterology 1999: 116:248-53
21.Lind T, Veldhuywen van Zanten SJO. Unge P. et al. 'the MAC I I studs optimal one-week treatment for H. pylon is defined? Gui 995: 37 (Suppl I). .14.
22.Zuberi BF. Lal S. Sheikh RM Low dose. short-term. triple therapy for Helicobacier pylon associated peptic ulcer. J Pak Med Assoc 1997,47:228-30
23.Goddard AF, Logan RPH, Lawes S. et al. Randomised controlled comparison of nitroiinidazoles for the eradication of Helicobacter pylon and relief of ulcer-associated and non-ulcer dyspepsia. Aliment Pharmacol Ther 1999:13:637-42
24.Malfertheiner P. Compliance, adverse events and antibiotic resistance m Helicobacter

pylori treatment. Scand J Gastroenterol 1993:28 (Suppl l96):34-7
25.Rubinstein G. Dunkin K. Howard A.t The susceptibility of Helicobacter pvtori to 12 antimicrobial agents. omcprazole and bismuth salts J Antimicrob Chernother 1994: 34: 409-13.
26.Banatvala N, Davies GR. Abdi Y. et al. High prevaletice of Ilelicobacter pylon metronidaole resistance in migrants to east London. relation with previous nitnoimidazole exposure and gastroduodenal disease Gut 1994; 35:1562-6.
27.Laniouliatte HC. Cayla R, Megraud F, ci al. Amoxycillin - clarithromycin - omeprazole: the best therapy for Helicobcater pylori infection? Acta Gastroenterol BeIg 1993: 56(Suppl):140.
28.Wong BC, Xiao SD, Hu FL. et al. Comparison of lansoprazole-based triple and dual therapy fon treatment of Helicobacter pylon-related duodenal ulcer an Asian multi-centre double-blind randomized placebo controlled studs Al iment Phannacol Ther 2000:14:217-24
29.Wongkusottham P. Vilaichone RK. Kullavannava jays P et al Eradication rates of H el icobacter pylori between metron idazot c-sensitive and metronidazole- idazol eresistant strains with metnonidazole containing regimen in That patients with peptic ulcer disease. J Med Assos Thai 2001:84 (Suppl I):S474-80
30.Harries AD, Stewart M, Deegan KM. ci al. Helicobacter pylori in Malawi, Centnal Africa. J Infect I 992;24:269-76.
31.European Study Group on Antibiotic Susceptibility of Helicobacten pylon. Results of a multicentre European survey in 1991 of metronidazole resistance in Helieobacter pylon. Eun J Chin Micnobiol Infect Dis 1992:11:777-81.
32.Parsons HK, Carter MJ, Sanders OS, et al. Heilcobacter pylori antimicrobial resistance in the United Kingdom: the effect of age. sex and socio-economic status. Aliment Phannacol Then 2001:15 1473-8.
33.Bell GD, Powell KU, Burridge SM. et al. Heticobactei pylori eradication' efficacy and side-effect pnofile of a combination of omeprazole. atnoxycillin and metronidazole compared with four alternative regime Q .1 Med 1993: 86: 743-50.
34.Bell GD, Powell KU, Bumdge SM, et al. Rapid eradication of Helicobacten pylon infection: AIlment Phannacol Then 1995: 9:41-6.
35.Bandhan KD, Bayendonifer E, Dehchier J, et al. H. pylon (Hp) eradication with omepnazole (o), metronidazole (M) and amoxycillin (A) : the impact of drug dosing and nesistance on efficacy - the HOMER story (absti'.) Gastroenterologv 1998: 114: MS.
36.Tewari V, Nath G, Gupta H, et al 14C-urea breath test for assessment of gastric Helicobacten pylori colonization and eradication lnd J Gastroenterol 2001:20(4):140 -3 .
37.Iwahi T. Satoh H. Nakao M, et at. Lansoprazole, a novel benziimidazole proton pump inhibitor and its related compounds have selective activity against Helicobacter pylon. Antimicrob Agents Cheinother 1991 35:490-6.
38.Sioschus B. Dominguez-Munoz JE. Kaihori N. et at. Effect of omeprazole on Helicobacter pylori urease activity in vtvo. Eur 3 Gastroenterol Hepatol 1996: 8 811-13.
39.Karves WE Jr. Sainloff IM, Siurala M, et at. Positive senim antibodies and negative tissue staining for Helicobacter pylon in subjects with atrophic body gastritis. Gastroenterology 1991:101: 167-74.
40.Kekki M. Varisk K, Pohjanpaio H, et at. Course of anirum and body gastritis in pernicious anemia families. Dig Dis Sci l983; 28:698-704.

41.Labenz J, Stolte M, Domain C. et al. Omeprazole plus amoxycillin or ctarithromycin for eradication of Helicobacter pylon in duodenal ulcer disease (abstract). Acta Gastroenterol Beig 1993; 56 (Suppl):131 Iwahi T. Satoh H. Nakao M, et at. Lansoprazole, a novel benziimidazole proton pump inhibitor and its related compounds have selective activity against Helicobacter pylon. Antimicrob Agents Cheinother 1991 35:490-6.
38.Sioschus B. Dominguez-Munoz JE. Kaihori N. et at. Effect of omeprazole on Helicobacter pylori urease activity in vtvo. Eur 3 Gastroenterol Hepatol 1996: 8 811-13.
39.Karves WE Jr. Sainloff IM, Siurala M, et at. Positive senim antibodies and negative tissue staining for Helicobacter pylon in subjects with atrophic body gastritis. Gastroenterology 1991:101: 167-74.
40.Kekki M. Varisk K, Pohjanpaio H, et at. Course of anirum and body gastritis in pernicious anemia families. Dig Dis Sci l983; 28:698-704.
41.Labenz J, Stolte M, Domain C. et al. Omeprazole plus amoxycillin or ctarithromycin for eradication of Helicobacter pylon in duodenal ulcer disease (abstract). Acta Gastroenterol Beig 1993; 56 (Suppl):131.