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

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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 weeks³⁵ and the quest to find a 'perfect' eradication regimen continues. These regimens have been reported to have Hp clearance rate of between 28%~100%⁶⁷. 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 far and has set a standard against which all other regimes can be compared. Tinidazole is a nitroimidazole antibiotic and is closely related to metronidazole. Although this combination was found highly effective in eradicating Hp, the eradication rate was reported to be significantly lower among metronidazoleresistant strains. 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. This study was designed to directly compare OCT with 0CM (replacing tinidazole with metronidazole) in terms of efficacy and side-effects in patients with documented duodenal ulcer (DU) in the community.

Hp serology testing is a non-invasive test and is investigation of choice in population studies. However, there seems to be an increased prevalence of false-negative serology in elderly people. It also may remain falsely positive for a long time after eradication of Hp. 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 IgG antibodies by ELISA. All positive patients were randomly allocated to receive either OCT (omeprazole 20 mgs, clarithromycin 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. pylori 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 18 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 (amoxyccillin, 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% CI 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% CI 93.4-100%-one-tailed interval). This was significantly 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%; 95/0 CI = 37.5 - 67.0%) patients in the OCT group. This was not statistically significant (pO.32). The side-effects reported are shown in the
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 infection7,17 several

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

<table>
<thead>
<tr>
<th>OCM</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>57(109)</td>
<td></td>
</tr>
<tr>
<td>Successful</td>
<td>36(87.8%)</td>
<td></td>
</tr>
<tr>
<td>Patients reporting side effects</td>
<td>23(52.2%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Bad taste</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Mouth ulcers</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Headaches</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Personality changes</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

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 infection7,17 several
other investigators have successfully used the combination of a proton pump inhibitor and clarithromycin with a nitroimidazole. However, only few studies have compared tinidazole with metronidazole in the above combination in chronic DU associated with H. pylori. Goddard et al 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. 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. While the resistance reported is to be very high in developing countries in a multicentre European survey, it varied from 7% to 45%. 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. 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 of nitroimidazole. 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. Although given in three times a day (tds) dose for various infections, Metronidazole is effective in a bd dose in various Hp eradication regimens. 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. 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. 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%. The commonest reason for false negative tests is breath testing too soon after a course of antibiotics, bismuth or omeprazole. Proton pump inhibitors have weak direct antibacterial effect on HP and also they inhibit urease. Stopping acid suppression therapy at least 1 month before the UBT is therefore generally advised. 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\(^%\) 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 1 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.

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