Effect of *Helicobacter pylori* eradication on peptic ulcer healing

Humphrey J O’Connor, Chakravarthy Kanduru, Abdul S Bhutta, Judith M Meehan, Kenneth M Feeley, Kevin Cunnane

Summary

In a prospective study designed to assess the effect of *Helicobacter pylori* eradication on peptic ulcer healing, 85 consecutive patients with *H. pylori*-positive peptic ulcer disease were treated with a triple therapy regimen consisting of colloidal bismuth subcitrate 120 mg four times daily for 28 days, with metronidazole 400 mg three times daily and tetracycline 500 mg three times daily for the first seven days of treatment. *H. pylori* status was assessed by CLO test and histology at least four weeks after completing therapy. Of 75 patients (88%) *H. pylori*-negative after therapy, 69 (92%) had healed ulcers compared with only five of 10 patients (50%) who remained *H. pylori*-positive (p = 0.003). Cigarette smoking had no significant effect on ulcer healing. Our results suggest that *H. pylori* eradication may accelerate ulcer healing and provide further evidence that an effective helicobactericidal regimen is the treatment of choice in *H. pylori*-positive peptic ulcer.

Keywords: *Helicobacter pylori*, peptic ulcer

Introduction

The rediscovery of *Helicobacter pylori* has provoked a fundamental reevaluation of ideas on the aetiology and management of peptic ulcer. Perhaps the strongest evidence linking *H. pylori* and peptic ulcer is the fact that eradication of infection prevents ulcer relapse, effectively curing the disease. This seminal finding was first highlighted by Coghlan et al. Subsequent studies continued to focus on the effect of *H. pylori* eradication on ulcer relapse with less attention being paid to possible effects on ulcer healing. This prospective study was primarily designed to assess the effect of *H. pylori* eradication on peptic ulcer healing. A secondary aim of the study was to assess the impact of smoking and other factors on ulcer healing and *H. pylori* eradication.

Patients and methods

PATIENTS

Patients were eligible for inclusion in the study if they were over 18 years of age, in good general health, were found to have a gastric or duodenal ulcer at endoscopy, and had a gastric biopsy which gave a positive rapid urease test indicating the presence of *H. pylori* infection. An ulcer was defined as a circumscribed break in the mucosa measuring at least 5 mm in the longest diameter with apparent depth and covered with an exudate.

Patients were excluded if they had taken antibiotics or omeprazole in the preceding four weeks, bismuth-containing medication in the preceding three months, were on nonsteroidal anti-inflammatory drugs, had undergone peptic ulcer surgery, were pregnant, or had significant pathology at endoscopy other than gastric or duodenal ulcer. Prior to endoscopy, patients were questioned regarding current and past cigarette smoking. Ex-smokers were considered as nonsmokers for purposes of analysis in the study. All patients gave written informed consent for endoscopy and inclusion in the study.

ENDOSCOPY AND BIOPSIES

All the examinations were performed using an Olympus GIFIT 20 endoscope. If after inspection of the oesophagus, stomach, and duodenum, the patient was still considered eligible for inclusion in the study, three mucosal biopsy specimens were obtained using a standard biopsy forceps from the gastric antrum within 5 cm of the pylorus. One of the biopsy specimens was tested immediately for the presence of preformed urease activity using the CLO test (Deltawest, Perth, Australia). The remaining two specimens were fixed in 10% buffered formaldehyde, coded, and sent for histological evaluation.

Paraffin-processed histological sections were stained with haematoxylin and eosin and by a modified Giemsa stain method, and examined by an experienced pathologist blind to the clinical details and biopsy site. The modified Giemsa-stained sections were specifically examined for the presence of *H. pylori*, detected by the finding of characteristic curved bacilli on the mucosal surface.

THERAPY

Patients received a triple therapy regimen (see box). All medications were taken before meals.

Patients were counselled prior to starting therapy regarding the possibility of treatment-related gastrointestinal side-effects (nausea, taste disturbance, blackening of the stools),
specifically advised to abstain from alcohol for the first week of therapy, and the importance of good compliance to the success of therapy was emphasised.

Repeat endoscopy to assess ulcer healing and _H. pylori_ eradication was performed at least four weeks after completing therapy and at that time, patients were questioned regarding compliance and side-effects. Ulcer healing was defined as complete re-epithelialisation. _H. pylori_ eradication was defined as the inability to detect evidence of infection on both the CLO test and histological evaluation.

STATISTICS
Differences in ulcer healing and _H. pylori_ eradication between patient groups were tested for statistical significance using two-tailed Fisher’s exact test. A p-value < 0.05 was considered significant.

Results
Eighty-five patients were included in the study (see box).

HEALERS AND ERADICATION
Ulcers healed in 74 patients (87%) but failed to heal in 11 (duodenal ulcer, 10; gastric ulcer, 1). Sixty duodenal ulcer patients had healed ulcers (82%) compared with nine gastric ulcer patients (90%). Seventy-five patients were _H. pylori_-negative after therapy (88%) and 10 remained _H. pylori_-positive. Of the 75 patients _H. pylori_-negative after therapy, 69 (92%) had healed ulcers compared with only five of the 10 patients (50%) who remained _H. pylori_-positive (p = 0.003) (figure).

There was no significant difference in age or gender between the _H. pylori_-positive and _H. pylori_-negative groups (table 1). Three of the 10 gastric ulcer patients (30%) remained _H. pylori_-positive after therapy compared with only seven of the 73 duodenal ulcer patients (10%) (p = 1.0). Both patients with combined gastric and duodenal ulcer were _H. pylori_-negative after therapy.

SMOKING, HEALING, AND ERADICATION
Of the 46 patients who smoked, 38 (83%) had healed ulcers compared with 33 (92%) of the 36 nonsmokers (p = 0.332). Thirty-eight of the smokers (83%) were _H. pylori_-negative after therapy compared with 34 (94%) of the nonsmokers (p = 0.175).

SIDE-EFFECTS AND COMPLIANCE
Three patients (duodenal ulcer, 2; gastric ulcer, 1) admitted to noncompliance with the treatment regimen. One patient misunderstood the treatment instructions and failed to take the antibiotics prescribed for the first week of therapy. Two patients prematurely discontinued antibiotic therapy because of nausea. Two of the three noncompliant patients were cigarette smokers. All three patients remained _H. pylori_-positive after therapy. All of the 75 patients who were _H. pylori_-negative after therapy said they complied with therapy whereas three of the 10 patients who were _H. pylori_-positive after therapy were noncompliant (p < 0.001) (table 2).

<table>
<thead>
<tr>
<th><strong>Triple therapy regime</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- colloidal bismuth subcitrate (120 mg qid for 28 days)</td>
</tr>
<tr>
<td>- metronidazole (400 mg tid for 7 days)</td>
</tr>
<tr>
<td>- tetracycline (500 mg tid for 7 days)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Treatment group – 85 patients</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- 64 male</td>
</tr>
<tr>
<td>- mean age 47, range 22–74 years</td>
</tr>
<tr>
<td>- 46 smokers</td>
</tr>
<tr>
<td>- 73 duodenal ulcers</td>
</tr>
<tr>
<td>- 10 gastric ulcers</td>
</tr>
<tr>
<td>- 2 duodenal and gastric ulcers</td>
</tr>
</tbody>
</table>

**Figure** Effect of _H. pylori_ eradication on peptic ulcer healing

**Table 1** Comparison of the patient groups _H. pylori_-negative and _H. pylori_-positive after therapy

<table>
<thead>
<tr>
<th></th>
<th><em>H. pylori</em>-negative</th>
<th><em>H. pylori</em>-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>75</td>
<td>10</td>
</tr>
<tr>
<td>Mean age (range) (years)</td>
<td>45 (22–74)</td>
<td>37 (33–53)</td>
</tr>
<tr>
<td>Male:female</td>
<td>57:18</td>
<td>7:3</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>66 (90%)</td>
<td>7</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>7 (70%)</td>
<td>3</td>
</tr>
<tr>
<td>Combined duodenal and gastric ulcer</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 2** Compliance and _H. pylori_ eradication

<table>
<thead>
<tr>
<th></th>
<th>Compliant</th>
<th>Noncompliant</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. pylori</em>-negative</td>
<td>75</td>
<td>0</td>
</tr>
<tr>
<td><em>H. pylori</em>-positive</td>
<td>7</td>
<td>3</td>
</tr>
</tbody>
</table>

Fisher’s exact test (two-tailed), p < 0.001.
Table 3  Effect of *H. pylori* eradication on peptic ulcer healing, previous studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Therapy</th>
<th>Patients (n)</th>
<th>Ulcer healing (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marshall et al²</td>
<td>CBS vs CBS + TIN</td>
<td>100</td>
<td>HP-positive 61 HP-negative 92</td>
</tr>
<tr>
<td></td>
<td>vs CIM vs CIM + TIN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graham et al⁶</td>
<td>RAN vs RAN + AMOX + TET + MTZ</td>
<td>105</td>
<td>84 98</td>
</tr>
<tr>
<td>Hentschel et al⁸</td>
<td>RAN vs RAN + AMOX + MTZ</td>
<td>104</td>
<td>75 92</td>
</tr>
<tr>
<td>Hosking et al¹⁰</td>
<td>OM vs OM + CBS + TET + MTZ</td>
<td>155</td>
<td>78 95</td>
</tr>
<tr>
<td>McCarthy et al¹¹</td>
<td>OM + MTZ + TET</td>
<td>43</td>
<td>34 66</td>
</tr>
</tbody>
</table>

AMOX = amoxicillin; CBS = colloidal bismuth subcitrate; CIM = cimetidine; HP = *H. pylori*; MTZ = metronidazole; OM = omeprazole; RAN = ranitidine; TET = tetracycline; TIN = tinidazole.

Discussion

The patients included in this prospective study represent a homogenous consecutive group, all of whom had *H. pylori*-positive peptic ulcer disease and received a standard triple therapy regimen. *H. pylori* status was assessed using the CLO test and histology, both accurate methods for the detection of the presence or absence of infection.⁶

The principal finding was that patients *H. pylori*-negative after therapy had significantly more healed ulcers than patients who remained *H. pylori*-positive (92% vs 50%). This finding is in accord with data already available on the effects of *H. pylori* eradication on peptic ulcer healing (table 3).²⁻¹¹ The beneficial effect of *H. pylori* eradication on ulcer healing was evident for both duodenal and gastric ulcer. The mucosal damage and inflammatory response which accompany *H. pylori* infection regresses quickly after eradication of infection.¹² Rapid restoration of mucosal integrity may explain how eradication of *H. pylori* could facilitate the ulcer-healing process.

This study also afforded the opportunity to assess patient factors which might influence *H. pylori* eradication. Age and gender had no apparent effect on eradication but it is of interest that 30% of gastric ulcer patients remained *H. pylori*-positive after therapy compared with only 10% of duodenal ulcer patients. Cutler and Schubert,¹³ using a triple therapy regimen, reported a 64% eradication rate in gastric ulcer compared with 91% in duodenal ulcer patients. About 70% of gastric ulcers are *H. pylori*-positive compared with over 90% of duodenal ulcers¹⁴ but differences in virulence or antibiotic sensitivity¹⁵ have not been detected between *H. pylori* strains isolated from gastric and duodenal ulcer patients. It is possible that differences in the intragastric milieu between gastric and duodenal ulcer patients might influence the helicobactericidal efficacy of treatment regimens.¹⁷

Cigarette smoking is more common in patients with peptic ulcer disease than in non-ulcer controls.¹⁸ Fifty-four per cent of our patients were regular cigarette smokers compared with a reported population prevalence of 27%.¹⁹ We found that cigarette smoking had no significant effect on ulcer healing but cigarette smokers had a lower *H. pylori* eradication rate than nonsmokers (83% vs 94%). Cutler and Schubert¹³ reported a similar finding, while Unge et al²⁰ found that smoking also had a significant adverse effect on *H. pylori* eradication in patients treated with omeprazole and amoxicillin. Witterman et al²¹ have reported that *H. pylori* in smokers acquire secondary metronidazole resistance more readily than *H. pylori* in nonsmokers. This novel finding might explain why *H. pylori* eradication therapy seems less effective in smokers than nonsmokers.

Although efficacious, triple therapy is a cumbersome multidrug regimen which does not encourage good compliance. That only three of our patients (4%) admitted to noncompliance may reflect the time and care spent counselling patients about the importance of compliance and the side-effects to expect with triple therapy. Our results, however, reiterate the critical relationship between noncompliance and treatment failure.²² All three non-compliant patients remained *H. pylori*-positive after therapy whereas good compliance was associated with successful eradication and ulcer healing.

It is now firmly established that *H. pylori* eradication prevents peptic ulcer relapse, altering the natural history of the disease.²³ The fact that *H. pylori* eradication also accelerates ulcer healing adds further weight to the conclusion that an effective helicobactericidal regimen is the treatment of choice in *H. pylori*-positive peptic ulcer disease.

Summary points

- more healed ulcers were found in patients rendered *H. pylori*-negative after triple therapy
- cigarette smokers have a lower *H. pylori* eradication rate than nonsmokers

Sincere thanks are due to the Nursing Staff of the Endoscopy Unit, General Hospital, Tullamore, and to Mrs Iris Martin for typing the manuscript.
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