DEVELOPMENT OF MULTIFOCAL DUODENAL EROSIONS AFTER ANTI-HELIcobacter pylori TRIPLE THERAPY

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Background and Purpose: Anti-Helicobacter pylori triple therapy is effective for healing duodenal ulcer (DU) diseases and reducing disease recurrence. However, multifocal duodenal erosions or shallow ulcers may develop after triple therapy. The purpose of this study was to investigate the incidence and outcome of duodenal erosions that developed after triple therapy.

Methods: A total of 106 Taiwanese with active DU and with H. pylori infection were enrolled in this study. All patients received anti-H. pylori triple therapy (i.e., 2 weeks of antimicrobial agents combined with treatment for 4 to 6 weeks with acid suppression agents). Follow-up endoscopy was performed immediately after stopping treatment. The incidence of multifocal erosions or shallow ulcers over the bulb and/or second portion of the duodenum was studied. Additional acid suppression agent was given for 4 weeks whenever duodenal erosions or shallow ulcers were found.

Results: Out of 106 patients, 11 (10.4%) were found to have multifocal duodenal erosions and/or shallow ulcers on the duodenal bulb and/or second portion of the duodenum at the end of treatment. Ten of the 11 patients with newly developed erosions had healed DU in the S1 or S2 stage, and all 11 had successful H. pylori eradication. The duodenal erosions and/or shallow ulcers of these 11 patients were healed after an additional 4 weeks of histamine-2-receptor antagonist therapy.

Conclusions: Multifocal duodenal erosions and/or shallow ulcers were noted in around 10% of Taiwanese DU patients who received anti-H. pylori triple therapy. An additional 4 weeks therapy with acid suppression agents healed these lesions.

Key words: Anti-ulcer therapy, Duodenum, pathology, Duodenal ulcer, Helicobacter pylori


There is strong evidence implicating Helicobacter pylori as a pathogen in duodenal ulcer (DU) disease.1,2 It has been reported that the 1-year recurrence rate of DU reduced from 80% to 20% after eradication of H. pylori.3 Numerous treatment trials for eradicating H. pylori using many different antibiotics as either dual or triple therapies have been reported. Many side effects have been reported in the treatment of H. pylori with triple therapy or dual therapy, including nausea, dry mouth, diarrhea, flatulence, constipation, abdominal pain, skin rash, dizziness, disorientation, sore throat, fiery tongue, metallic taste, glossitis, and pseudomembranous colitis.4-7 In addition, we have also occasionally noted newly developed multifocal duodenal erosions or shallow ulcers in DU patients just after anti-H. pylori triple therapy in regular follow-up examinations at our clinic. This phenomenon has not been reported in the traditional treatment of DU using antacids or histamine-2-receptor antagonists (H2RAs) alone. Recently, Shiotani et al reported that small duodenal erosions developed in H. pylori-eradicated patients within 4 weeks to 6 months after cessation of medication.8 The nature of these duodenal lesions may be different to that of extensive duodenal erosions or shallow ulcers that are noted after triple therapy. Furthermore, Shiotani et al.8 did not discuss the outcome of duodenal erosions in their report. This study investigated the incidence of

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multifocal duodenal erosions and/or shallow ulcers on the duodenal bulb and/or second portion of the duodenum after anti-*H. pylori* triple therapy in DU patients, and investigated the outcome of these duodenal erosions.

**Methods**

This study was approved by the Human Subjects Committee at our institution, and informed consent was obtained from all subjects prior to participation. A prospective design was used and endoscopists were blinded to the findings of previous endoscopic examination and the regimen of subsequent treatment. Patients with active DU on initial endoscopy who were *H. pylori*-positive were eligible for participation. DU patients with duodenal erosions found on initial endoscopy or accompanied by conditions that may induce duodenal erosions (liver cirrhosis, diabetes mellitus, or renal insufficiency) were excluded from this study. 106 patients including 62 males and 44 females, with ages ranging from 21 to 78 years (mean, 49.8 years) were enrolled in the study. They received anti-*H. pylori* and acid suppression for treatment of active DU. The regimen consisted of amoxicillin 500 mg 4 times daily, metronidazole 250 mg 4 times daily and H2RA treatment [cimetidine 400 mg, ranitidine 150 mg, or famotidine 20 mg] twice daily for 2 weeks followed by H2RA for 4 weeks (94 patients) or amoxicillin 500 mg 4 times daily, metronidazole 250 mg 4 times daily and proton-pump inhibitor (PPI) [omeprazole 20 mg] once daily for 2 weeks followed by PPI for 2 weeks (12 patients).

Patients were not permitted to receive non-steroidal anti-inflammatory drugs or steroids during the period of this therapy. At the end of treatment, follow-up upper gastrointestinal endoscopy was performed using an Olympus GIF-XQ200 endoscope (Olympus Optical Co., Ltd, Tokyo, Japan). Four biopsies were taken from the gastric antrum and body, 2 specimens were for urease test, and the other 2 were for histological examination using hematoxylin and eosin staining. Eradication of *H. pylori* was considered to be successful when both the urease test and the histological examination were negative. The duodenal condition and the success rate of *H. pylori* eradication were evaluated.

The definition of multifocal erosions and/or shallow ulcers in the study was apparent duodenal mucosa damage showing whitish mucosal lesions of variable size which may mix with hemorrhagic spots in the bulb and/or second portion of the duodenum (Fig. 1). Erosions were defined as small whitish mucosal damage, and shallow ulcers were defined as relatively extensive lesions with a larger area of superficial mucosa damage.

For quality control, the initial and follow-up endoscopies were performed by 2 experienced endoscopists. Serial endoscopic photographs were obtained during each endoscopy for subsequent review by the endoscopists of our study group at a weekly meeting.

When multifocal erosions or shallow ulcers were found on the follow-up examinations, the photographs of the initial endoscopy were reviewed again to confirm the absence of erosions or shallow ulcers before triple therapy (Fig. 2A and 2B); an additional 4 weeks of acid suppression therapy was given to treat these lesions. Endoscopy was performed again at the end of treatment to investigate the outcome of these erosions or shallow ulcers.

Statistical analysis was conducted using Student’s t test or Fisher’s exact test.

**Results**

Out of 106 patients in this study, 92.5% had endoscopically documented healing of DU (S1 or S2 stage) and 94% had successful eradication of *H. pylori*. However, 11 (10.4%) of these 106 patients (including 9 of 94 patients who received H2RA-based triple therapy and 2 of 12 patients who received PPI-based triple therapy) were noted to have multifocal erosions and/or shallow ulcers on the duodenal bulb and/or second portion of the duodenum. *H. pylori* could not be detected in these 11 patients using both the urease test and histology of 2 biopsies, and the original DU had been
healed in 10 of the 11 patients. There were no significant differences in mean age, gender ratio, healing rate of original DU, or eradication rate of *H. pylori* between the 11 patients with multifocal duodenal erosions or shallow ulcers and the 95 patients free of newly developed lesions (Table 1). The demographic characteristics of the patients with multifocal duodenal erosions or shallow ulcers are shown in Table 2.

The 11 patients with newly developed duodenal erosions and/or shallow ulcers after anti-*H. pylori* triple therapy.

### Table 1. Characteristics of patients with and without multifocal duodenal erosions and/or shallow ulcers after anti-*H. pylori* triple therapy.

<table>
<thead>
<tr>
<th></th>
<th>Multifocal erosions or ulcers (n = 11)</th>
<th>No multifocal erosions or ulcers (n = 95)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD age (years)</td>
<td>55.4 ± 12.9</td>
<td>49.2 ± 13.0</td>
<td>0.844</td>
</tr>
<tr>
<td>Male/female (n)</td>
<td>6/5</td>
<td>56/39</td>
<td>0.510</td>
</tr>
<tr>
<td>Healing of original ulcer (n)</td>
<td>10/11 (100%)</td>
<td>88/95</td>
<td>0.597</td>
</tr>
<tr>
<td><em>H. pylori</em> eradication (n)</td>
<td>1/11 (9.1%)</td>
<td>89/95 (93.7%)</td>
<td>0.509</td>
</tr>
<tr>
<td>Treatment regimen (H2RA/PPI; n)</td>
<td>9/2</td>
<td>85/10</td>
<td>0.790</td>
</tr>
</tbody>
</table>

H2RA = histamine-2-receptor antagonist; PPI = proton-pump inhibitor.

### Table 2. Clinical characteristics of patients with multifocal duodenal erosions or shallow ulcers.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Eradication regimen</th>
<th><em>H. pylori</em> status after triple therapy</th>
<th>Location of multifocal erosions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>M</td>
<td>44</td>
<td>AMC</td>
<td>Negative</td>
<td>Bulb</td>
</tr>
<tr>
<td>2*</td>
<td>M</td>
<td>54</td>
<td>AMC</td>
<td>Negative</td>
<td>Bulb and second portion</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>74</td>
<td>AMC</td>
<td>Negative</td>
<td>Bulb</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>67</td>
<td>AMR</td>
<td>Negative</td>
<td>Bulb</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>44</td>
<td>AMC</td>
<td>Negative</td>
<td>Bulb</td>
</tr>
<tr>
<td>6*</td>
<td>M</td>
<td>51</td>
<td>AMR</td>
<td>Negative</td>
<td>Bulb</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>32</td>
<td>AMF</td>
<td>Negative</td>
<td>Bulb</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>72</td>
<td>AMC</td>
<td>Negative</td>
<td>Bulb</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>52</td>
<td>AMR</td>
<td>Negative</td>
<td>Bulb</td>
</tr>
<tr>
<td>10*</td>
<td>M</td>
<td>64</td>
<td>AMO</td>
<td>Negative</td>
<td>Bulb</td>
</tr>
<tr>
<td>11*</td>
<td>F</td>
<td>55</td>
<td>AMO</td>
<td>Negative</td>
<td>Bulb</td>
</tr>
</tbody>
</table>

* With smoking habit.
† With previous ulcer history.

AMC = amoxicillin 500 mg 4 times daily + metronidazole 250 mg 4 times daily + cimetidine 400 mg twice daily; AMR = amoxicillin 500 mg 4 times daily + metronidazole 250 mg 4 times daily + ranitidine 150 mg twice daily; AMF = amoxicillin 500 mg 4 times daily + metronidazole 250 mg 4 times daily + famotidine 20 mg twice daily; AMO = amoxicillin 500 mg 4 times daily + metronidazole 250 mg 4 times daily + omeprazole 20 mg once daily.
triple therapy received an additional 4 weeks of H2RA treatment. All of the duodenal erosions and/or shallow ulcers disappeared after cessation of this additional treatment.

**Discussion**

At present, DU disease must be considered an infectious disease and treated accordingly. Not eradicating *H. pylori* means withholding a potential cure in an otherwise chronic relapsing and risky disease. However, the ideal anti-*H. pylori* treatment does not exist, since triple therapy is associated with problems of compliance and significant side effects, which are seen in 30% or more of patients. In this study, 11 of 106 patients who received anti-*H. pylori* triple therapy developed the complication of multifocal duodenal erosions or shallow ulcers on the duodenal bulb and/or the second portion of the duodenum, regardless of whether the original ulcer had been healed or not. The incidence of this complication was around 10%. There were no significant differences between the 11 patients who developed the complication and the other 95 patients with regard to mean age, gender ratio, healing rate of DU, treatment regimen, and eradication rate of *H. pylori*.

These multifocal duodenal erosions and/or shallow ulcers are rarely seen with acid suppression therapy. The mechanism by which anti-*H. pylori* triple therapy induces duodenal erosions and/or shallow ulcers is not clear. Antimicrobial agents such as amoxicillin or metronidazole may directly damage the duodenal epithelium or induce an idiosyncratic reaction in these patients. In an animal model of experimental DU, cysteamine-HCl could induce duodenal erosions at a dose less than 30 mg/100 g and induce DU without gastric lesion at a dose of 35 mg/100 g in rats. However, a very large dose of cysteamine (over 45 to 50 mg/100 g) could also induce gastric erosions in addition to a very deep (or perforated) DU. The mechanism of the development of duodenal lesion induced by cimetidine is not completely clear, though many possible causes (including inhibition of acid neutralization, increase in hydrogen ion back-diffusion in duodenal mucosa, and decrease of Brunner’s gland secretion) have been postulated. Similar dose-related effects might also occur with other chemical agents or some antibiotics. In our series, the gastric epithelium was spared from damage by antibiotics despite the development of duodenal lesion; a higher dose of antibiotics might cause gastric lesion in addition to duodenal erosions.

Shiotani et al recently reported that duodenal erosions may develop after *H. pylori* eradication in patients with the initial diagnosis of DU, gastric ulcer, or atrophic gastritis. The frequency of development of new duodenal erosions was found to be significantly higher in patients with DU (27.8%) compared with those with gastric ulcer (6.7%) or atrophic gastritis (1.4%). A high level of pepsinogen I pretreatment was found to be predictive of the development of duodenal erosions. These data suggest that development of duodenal erosions after *H. pylori* eradication might reflect gastric acid hypersecretion in the absence of concomitant use of antacid medications. In this study, about 10% of DU patients developed multifocal duodenal erosions or shallow ulcers after triple therapy. This incidence of duodenal lesions was slightly lower than in the study of Shiotani et al (27.8%). However, as shown in Fig. 1, the duodenal damage found in this study was extensive multifocal duodenal erosions or shallow ulcers rather than small erosions. This damage was perhaps a more severe category than the multiple small erosions reported by Shiotani et al. Furthermore, in contrast to the small duodenal erosions reported by Shiotani et al that were noted 4 weeks or 6 months after cessation of triple therapy, all 11 affected patients in our series were found to have duodenal erosions immediately after receiving continuing treatment with H2RA for 6 weeks or PPI for 4 weeks combined with antimicrobial agents for the first 2 weeks. There was no reason to suggest that the newly developed erosions or shallow ulcers of our series were caused by hyperacidity.

It is generally accepted that false-negative *H. pylori* tests may occur when patients are treated with acid suppression agents after antimicrobial therapy. In this study, follow-up endoscopy was performed immediately after stopping acid suppression therapy. Therefore, *H. pylori* may not have been detected on the limited areas sampled. The high eradication rate (up to 94%) in this study may thus have included some false-negative *H. pylori* test results.

In summary, around 10% of patients with active DU developed new multifocal duodenal erosions and/or shallow ulcers after receiving anti-*H. pylori* triple therapy. The mechanism of this complication is still not clear. Further follow-up study is needed to determine whether these patients are more likely to develop complications. In this series, an additional 4 weeks therapy with acid suppression agents healed these lesions.

**References**

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