Prevalence of *Helicobacter pylori* in NSAID users with gastric ulcer

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**Objective.** Regarding the interaction of *Helicobacter pylori* and non-steroidal anti-inflammatory drugs (NSAIDs), we cannot accept unanimous conclusions in inducing gastric ulcer. We therefore evaluated the role of *Helicobacter pylori* and NSAIDs in inducing gastric ulcer.

**Methods.** Dyspeptic patients receiving NSAIDs underwent endoscopic examination. Gastric ulcer formation and *H. pylori* status were investigated. Biopsy specimens from the antrum and lower body of the stomach were prepared for the rapid urease test and pathological evaluation. Anti-*H. pylori* antibody was measured by enzyme-linked immunosorbent assay.

**Results.** Two hundred and twenty-six patients receiving NSAIDs (220 chronic and six on-demand users) underwent gastrofibrescopic examination. There were 110 patients with gastric ulcer and 111 non-ulcer patients with gastritis. The remaining five patients had neither. NSAID users with gastric ulcer showed a low prevalence of *H. pylori* compared with those without them [55/110 (50.0%) vs 79/111 (71.2%), \( P < 0.01 \)]. The same tendency was seen when patients receiving low-dose aspirin and those with rheumatoid arthritis were analysed separately [13/29 (44.8%) vs 50/62 (80.6%), \( P < 0.01 \), and 11/33 (33.3%) vs 16/26 (61.5%), \( P < 0.06 \) with Yates’ correction, respectively].

**Conclusion.** *Helicobacter pylori* infection appeared to be a risk factor for developing gastritis, but we found no evidence that it increases gastric ulcer formation in NSAID users with dyspepsia.

**Key words:** Aspirin, Gastric ulcer, Gastritis, *Helicobacter pylori*, Non-steroidal anti-inflammatory drugs, Rheumatoid arthritis.

*Helicobacter pylori* and non-steroidal anti-inflammatory drugs (NSAIDs) are two major causes of gastroduodenal ulcers. Patients with rheumatoid arthritis (RA) often develop ulcers induced by NSAID use, and *H. pylori* may play a more minor role in inducing gastroduodenal ulcers in patients with RA than in patients without such a disease [1–3]. However, Chan et al. [4] reported the usefulness of *H. pylori* eradication in preventing peptic ulcers among patients planned to receive NSAIDs. Thus, there are disputes about the role played by the interaction of NSAIDs and *H. pylori* infection in the induction of gastroduodenal ulcers. Some investigators reported a deleterious effect of *H. pylori* in the development of gastroduodenal ulcers among NSAID users [5–7], whereas other investigators found no such untoward effects of *H. pylori* on NSAID gastropathy [8–13]. To further address this controversy, we evaluated the prevalence of *H. pylori* in dyspeptic patients currently...
taking NSAIDs with special reference to ulcer formation in the stomach.

Patients and methods

Patients

After providing informed consent, current NSAID users with dyspepsia underwent gastrofibrescopic examination with special reference to the detection of gastric ulcer (GU) and _H. pylori_ infection. GU was diagnosed when an open crater of stages A1 to H2 (mucosal break of more than 3 mm in diameter or length) in the gastric mucosa was verified endoscopically [14]. The diagnosis of gastritis was made according to the updated Sydney system [15]. Because _H. pylori_ plays a major role in inducing duodenal ulcer (DU), patients who had DU were excluded from the analysis. Patients with cancer, those who received eradication therapy against _H. pylori_ and those receiving antibiotics, proton-pump inhibitors or misoprostol were also excluded. In addition, patients currently suffering fever, abdominal pain or diarrhoea were excluded. As a control, specimens and sera from 114 age-matched NSAID non-users with GU were also analysed. Moreover, patients receiving low-dose aspirin (81 mg/day) and those with RA who were receiving NSAIDs were analysed separately.

Assessment of _H. pylori_ status

Biopsy specimens were obtained from the antrum and lower body in the greater curvature of the stomach and from the major lesions. The samples from the antrum and lower body were placed into rapid urease test (RUT) kits (CLO test; Tri-Med Specialties, Osborne Park, Australia) and the results were evaluated 24 h later. Samples were also prepared for haematoxylin–eosin (H&E) staining for pathological evaluation. Titres of _H. pylori_ IgG antibody were measured with an ELISA (enzyme-linked immunosorbent assay) kit (Determiner; Kyowa Medex, Tokyo, Japan) [16–18]. _H. pylori_-seronegative patients who had a positive result for RUT or H&E staining were re-evaluated, because anti- _H. pylori_ IgG antibody may be undetectable in serum in the early period of _H. pylori_ infection.

The definition of _H. pylori_ infection required two or more of the following findings to be positive: RUT, pathology, and anti- _H. pylori_ IgG antibody.

Statistical analysis

Statistical significance was evaluated with the χ² test, and _P_ values less than 0.05 were accepted as significant.

Results

In total, 245 NSAID users with dyspepsia received gastrofibrescopic examination. There were 19 patients with DU (eight with RA and 11 non-RA patients), and these patients were excluded from the analysis. There were 59 RA patients and 91 patients receiving low-dose aspirin as anticoagulation therapy. There were no significant differences in age and smoking habit among the patients with GU, those without ulcer, and the control group (Table 1). Women were predominant among RA patients (female:male ratio 46:13). Among the 226 NSAID users with dyspepsia, 110 had GU and 111 had gastritis without ulcer formation. Only five patients had normal endoscopic findings, and these were enrolled in the non-ulcer group. One patient who was seronegative for _H. pylori_ had a positive RUT and pathological results, although a follow-up study was positive for _H. pylori_ serology. Only half of the NSAID users with GU were infected with _H. pylori_ (Table 2A). Compared with NSAID users without ulcer, those with GU manifested a low prevalence of _H. pylori_ (55/110 (50.0%) vs 79/111 (71.2%), _P_ < 0.002) (Table 2A). The same tendency was found when patients receiving low-dose aspirin and those with RA receiving NSAIDs were analysed separately [13/29 (44.8%) vs 50/62 (80.6%), _P_ < 0.01; 11/33 (33.3%) vs 16/26 (61.5%), _P_ < 0.06] (Tables 2B and C). Compared with GU patients who were NSAID non-users, NSAID users manifested a low prevalence of _H. pylori_ (55/110 (50.0%) vs 91/114 (79.8%), _P_ < 0.0001).

The NSAIDs that were prescribed for the patients consisted of low-dose aspirin (91 patients), diclofenac (42 patients), loxoprofen (21 patients), mefenamic acid (seven patients), sulindac (seven patients), indomethacin (six patients) and others. There were no differences in the prevalences of _H. pylori_ and GU in patients receiving diclofenac or loxoprofen compared with those receiving low-dose aspirin.

Discussion

In the present study, we found that only half of NSAID users with GU were infected with _H. pylori_. GU patients receiving NSAIDs had a lower prevalence of _H. pylori_ than non-ulcer patients receiving NSAIDs. Even when patients receiving low-dose aspirin and those with RA receiving NSAIDs were analysed separately, the same tendency was found. Among patients with gastroduodenal ulcer, Mizokami et al. [19] reported that the prevalence

<p>| Table 1. Characteristics of NSAID users with dyspepsia and controls |
|------------------------|----------|---------|--------|</p>
<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>F:M</th>
<th>Age (yr)</th>
<th>Smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric ulcer</td>
<td>110</td>
<td>67:43</td>
<td>62.0±12.6</td>
<td>35.4%</td>
</tr>
<tr>
<td>No ulcer</td>
<td>111</td>
<td>75:36</td>
<td>65.5±10.4</td>
<td>38.7%</td>
</tr>
<tr>
<td>Controls</td>
<td>114</td>
<td>48:66</td>
<td>60.5±6.8</td>
<td>33.3%</td>
</tr>
</tbody>
</table>

Controls were non-users of NSAIDs who had GU.

<table>
<thead>
<tr>
<th>Table 2. Prevalence of <em>H. pylori</em></th>
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<tbody>
<tr>
<td>Anti- <em>H. pylori</em> antibody</td>
</tr>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>(A) NSAID users with dyspepsia</td>
</tr>
<tr>
<td>GU (%)</td>
</tr>
<tr>
<td>No GU (%)</td>
</tr>
<tr>
<td>(B) Non-rheumatic patients</td>
</tr>
<tr>
<td>receiving low-dose aspirin</td>
</tr>
<tr>
<td>(81 mg/day)</td>
</tr>
<tr>
<td>GU (%)</td>
</tr>
<tr>
<td>No GU (%)</td>
</tr>
<tr>
<td>(C) GU patients with RA receiving</td>
</tr>
<tr>
<td>NSAIDs</td>
</tr>
<tr>
<td>GU (%)</td>
</tr>
<tr>
<td>No GU (%)</td>
</tr>
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* _P_ = 0.0012 (part A); _P_ = 0.0057 (part B); ** _P_ = 0.0300 ( _P_ = 0.0574 with Yates’ correction) (part C).
of *H. pylori* was lower in RA patients receiving NSAIDs than in non-rheumatic patients who were not receiving NSAIDs. In a study of 217 patients, Ng et al. [20] also found a lower prevalence of *H. pylori* in GU patients receiving NSAIDs than in those not receiving them (71 vs 92%, *P* < 0.0002). We also found such a tendency when we used serodiagnosis and RUT without the bacterial cultures (Table 2). In both of these previous studies, *H. pylori* infection was evaluated by bacterial culture and pathological findings, but without serodiagnosis. This might underestimate the prevalence of *H. pylori*, although in the early period of the infection some patients may be missed, as we report in the Results section. In addition, both reports compared the prevalence of *H. pylori* in ulcer patients receiving NSAIDs with that in those not receiving them, irrespective of the presence of rheumatic diseases. In contrast, we compared the prevalence of *H. pylori* in patients with GU with that in those without ulcer formation, both groups receiving NSAIDs. Although the backgrounds of these three study groups differed, NSAID use is apparently associated with a low prevalence of *H. pylori* in patients with GU compared with patients without GU. Thus, *H. pylori* infection may not increase the prevalence of GU formation in NSAID users. If we accept the idea that GU can be induced by damage additional to that produced by established gastritis, *H. pylori* might play a partially protective role in preventing GU induced by NSAIDs.

We observed a low prevalence of DU in NSAID ulcers compared with that of 252 non-NSAID ulcers, including the 114 patients in the control group [19/109 (17.4%) vs 71/252 (28.2%)], although the difference was not significant. We also observed a low prevalence of DU in RA patients with NSAID ulcers [8/41 (19.5%)]. Contrary to our results, Grigoriadou et al. [21] recently reported a relatively high prevalence of DU among NSAID users with RA. As in our results, Belaiche et al. [22] reported a low prevalence of DU among NSAID users in a nationwide study in Belgium. We and Belaiche et al. made endoscopic examinations in unselected NSAID users, including RA patients, whereas Grigoriadou et al. evaluated them in RA patients. In addition, it is well known that the Japanese are more likely to develop GU than DU. Differences in existing morbidity and race could contribute to the difference in the prevalence of DU.

The three groups receiving low-dose aspirin, diclofenac or loxoprofen did not differ in the prevalence of *H. pylori* infection and that of GU formation. They might contribute equally to *H. pylori* infection and GU development, although the sample size may not be large enough to draw definite conclusions.

Because of the complex networks involved in cytokine cascades [12, 23–25], the molecular mechanism of the interaction between *H. pylori* and NSAIDs that causes gastroduodenal ulcer remains unclear. *Helicobacter pylori* and NSAIDs have been reported to share some properties relating to cytokine production and secretion, by which the gastroduodenal mucosa could be damaged [23, 24]. Either of them induces the production of tumour necrosis factor α (TNF-α), interleukin (IL)-1β, IL-8 and leukotriene B4 (LTB4), which harm the alimentary mucosa [26, 27], although IL-1β might play a partially protective role against peptic ulcer due to its antacid activity [28].

Concerning the deleterious effects of NSAIDs, most NSAIDs are acidic in aqueous solution, whereas their pH values are higher than that of hydrochloric acid secreted from parietal cells. NSAIDs, therefore, move into mucosal cells because of a pH gradient that favours their uptake when gastric acid is secreted into the lumen. Thus, in addition to the shortage of prostaglandin, NSAIDs damage the gastric mucosa by hyperacidity and direct toxicity against such cells. The ability of *H. pylori* to protect against mucosal damage is probably related to the secretion of *H. pylori* urease, which can neutralize gastric acid and thus protect against mucosal injury caused by hyperacidity or direct toxicity. Moreover, *H. pylori* induces prostaglandin secretion, which is blocked by NSAIDs [29]. *Helicobacter pylori* also induces IL-1 and some growth factors that accelerate the proliferation of mucosal cells, although there are some discrepancies in the data concerning this finding among previous results. Overall, the presence of *H. pylori* in the stomach does not constitute supporting evidence of ulcer formation among NSAID users, although *H. pylori* is likely to be associated with gastritis. Thus, at present it may be unreasonable to accept *H. pylori* eradication as a gold standard in the prevention of NSAID-induced GU, especially in chronic NSAID users.

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**References**


