Helicobacter pylori: a risk and severity factor of non-steroidal anti-inflammatory drug induced gastropathy

D Heresbach, J L Raoul, J F Bretagne, J Minet, P Y Donnio, M P Ramée, L Siproudhis, M Gosselin

Abstract
This prospective study aimed to determine the prevalence of Helicobacter pylori infection in relation to the occurrence and severity of NSAIDs induced gastropathy. A total of 111 patients were studied – 66 were taking NSAIDs and 45 were control patients. All patients underwent endoscopy during which antral biopsy specimens were taken to determine H pylori status (Gram and Giemsa staining, urease test, and cultures). The NSAID group comprised: group I, patients without mucosal damage (n=28); group II, patients with gastropathy (n=26); and group III, patients with bleeding associated with NSAID induced gastropathy (n=12). Control patients had neither dyspeptic symptoms nor endoscopic lesions. There were no differences in age, sex ratio, or presence of H pylori (26% vs 24%) between the NSAID and the control groups. Among patients taking NSAIDs, H pylori infection was more frequently (p<0.02) diagnosed in those presented with gastropathy (groups II and III: 37%) than in those without lesions (group I: 11%). The frequency of H pylori infection increased significantly with the severity of gastropathy (group I=11%; group II=31%; group III=50%; p<0.03). H pylori infection was associated with chronic active gastritis (group I=21%; group II=35%; group III=67%; p<0.05). These data suggest that H pylori may be a risk factor of NSAID induced gastropathy.

Methods
Gastrointestinal disturbance is a frequent side effect of non-steroidal anti-inflammatory drugs (NSAIDs). The high frequency of this complication and the cost of routine prophylactic treatment which it imposes are important economic considerations. The profile of patients at risk for this side effect of NSAIDs has not been completely determined. Patients with a history of peptic ulcer disease are most certainly at risk, but many patients without this history exhibit NSAID gastropathy too, and this may be the result of Helicobacter pylori infection. NSAIDs gastropathy and H pylori gastritis share certain common features such as the predominance of lesions in the antrum, an increase in frequency with age, and the putative pathogenic role of neutrophils.

Most of the studies in this area concern H pylori infection and any resultant dyspeptic symptoms or the endoscopic score of mucosal damage. Our prospective study aimed to determine the prevalence of H pylori infection in patients taking NSAIDs in relation to the occurrence and the severity of gastric lesions.

Patients and methods
Patients
Between March 1989 and July 1990 a series of 111 consecutive patients were included in this prospective study. All patients were French and were white. Sixty were women and 51 men and their mean (SD) age was 57.2 (17.7) years. Patients who presented with a history of peptic ulcer disease or who had taken either antibiotics or sucralfate in the two weeks before endoscopy were excluded.

Each patient underwent endoscopy of the upper digestive tract with routine biopsy specimens of the gastric antrum, regardless of whether they were taking NSAIDs or they had gastrointestinal side effects related to the use of NSAIDs (pain or upper bleeding).

Twenty one (32%) of the 66 patients taking NSAIDs were being treated for rheumatoid arthritis or ankylosing spondylitis, 35 (53%) for osteoarthritis and 10 (15%) for other reasons. These 66 patients were divided into three groups according to endoscopic data and the occurrence of bleeding. Group I was composed of patients without endoscopic lesions (n=28); group II of patients with gastroduodenal lesions detected by endoscopy (n=26); and group III of patients who presented with gastrointestinal bleeding related to mucosal damage (n=12). Fifty four patients were taking one NSAID, eight had a double therapy, and four were taking three different NSAIDs. The NSAID used was: indomethacin in 20 cases, pyroxican in 19, ketoprofen in 14, diclofenac in 12, and others in 17 cases. The control group was composed of the remaining 45 patients who were not taking NSAIDs. Endoscopy was performed because of weight loss or anaemia or immediately before an endoscopic retrograde cholangiopancreatography. Those patients had neither symptoms referable to the upper gastrointestinal tract nor any gastroduodenal lesion as determined by endoscopy.

Methods
At endoscopy the degree and the severity of NSAID induced gastroduodenal damage were assessed using the scoring system proposed by Lanza et al. Endoscopy was considered as abnormal if the score was higher than 1. Three biopsy specimens were taken from the greater
curvature of the antrum within 5 cm of the pylorus. Two were intended for bacteriological determinations and one for histological examination.

The biopsy specimens were immediately transferred to a transport solution and a microbiological study was begun within four hours at the latest after endoscopy. This study comprised: (a) a direct examination after Gram staining; (b) a urease test detecting urease activity after immersion of a biopsy specimen in a 2% urea broth; (c) inoculation into Teillard and Martin medium incubated microaerophically at 37°C for five days.

A histological examination was carried out after fixation in formalin, sectioning (5 μm), and staining by standard methods with Giemsa. All slides were carefully examined under oil immersion by the same pathologist (MPR) under single-blind conditions. *H pylori* was identified by its pathognomonic curved or spiral form seen beneath or within the mucosal layer overlying the gastric epithelium. Classification of chronic gastritis and grading of activity were according to the histological division of the Sydney system: topographic classification was not undertaken because the three biopsy specimens were taken from the antrum. Reactive or chemical gastritis was defined as the presence of following signs: foveolar hyperplasia, vasodilatation, oedema, paucity of inflammatory cells; and presence of muscle fibres in the lamina propria.Official authorisation for this study was given by the medical ethics committee of the Rennes University Hospital.

**TABLE II**

<table>
<thead>
<tr>
<th>Location of lesions:</th>
<th>Group I</th>
<th>Group II</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach alone</td>
<td>18 (69)</td>
<td>7 (58)</td>
<td>25</td>
</tr>
<tr>
<td>Duodenum alone</td>
<td>5 (19)</td>
<td>3 (25)</td>
<td>8</td>
</tr>
<tr>
<td>Stomach and duodenum</td>
<td>3 (12)</td>
<td>2 (17)</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>12</td>
<td>38</td>
</tr>
</tbody>
</table>

**TABLE III**

<table>
<thead>
<tr>
<th>Dyspeptic symptoms</th>
<th>Present (%)</th>
<th>Absent (%)</th>
<th>Total no</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>(61)</td>
<td>(39)</td>
<td>28</td>
</tr>
<tr>
<td>Group II</td>
<td>(50)</td>
<td>(50)</td>
<td>26</td>
</tr>
<tr>
<td>Group III</td>
<td>(58)</td>
<td>(42)</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>(56)</td>
<td>(44)</td>
<td>66</td>
</tr>
</tbody>
</table>

**TABLE IV**

<table>
<thead>
<tr>
<th>Characteristics of the four tests used in detecting <em>Helicobacter pylori</em> infection</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histological determination</td>
<td>71%</td>
<td>92%</td>
</tr>
<tr>
<td>Gram staining</td>
<td>93%</td>
<td>94%</td>
</tr>
<tr>
<td>Urease test</td>
<td>89%</td>
<td>98%</td>
</tr>
<tr>
<td>Culture growth</td>
<td>68%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Patients were deemed *H pylori* positive if at least two of the four tests were positive.
TABLE V  Relationship between Helicobacter pylori (HP) status and antral mucosa pathology

<table>
<thead>
<tr>
<th>Histologic features of antral mucosa</th>
<th>Normal</th>
<th>Chronic gastritis</th>
<th>Chronic active gastritis</th>
<th>HP + gastritis</th>
<th>Drug induced gastritis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>(*)</td>
<td>No</td>
<td>(*)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>H pylori +ve:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>1</td>
<td>(9)</td>
<td>3 (27)</td>
<td>7 (64)</td>
<td>7 (64)</td>
<td>1</td>
</tr>
<tr>
<td>NSAID group</td>
<td>4</td>
<td>(6)</td>
<td>1 (12)</td>
<td>13 (82)</td>
<td>14 (82)</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>(7)</td>
<td>5 (12)</td>
<td>20 (75)</td>
<td>21 (75)</td>
<td>2</td>
</tr>
<tr>
<td>H pylori -ve:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>15</td>
<td>(44)</td>
<td>14 (41)</td>
<td>5 (15)</td>
<td>0 (0)</td>
<td>4</td>
</tr>
<tr>
<td>NSAID group</td>
<td>20</td>
<td>(41)</td>
<td>20 (41)</td>
<td>9 (18)</td>
<td>0 (0)</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>(42)</td>
<td>34 (41)</td>
<td>14 (17)</td>
<td>0 (0)</td>
<td>11</td>
</tr>
<tr>
<td>Total patients</td>
<td>72</td>
<td>(53)</td>
<td>39 (53)</td>
<td>35 (52)</td>
<td>21 (19)</td>
<td>152</td>
</tr>
</tbody>
</table>

Discussion

Our results show that the prevalence of H pylori infection in patients taking NSAIDs is similar to that in control patients of the same age distribution and sex ratio. Furthermore, in those taking NSAIDs, the prevalence of H pylori infection is correlated to the degree and severity of gastroduodenal mucosal damage. This result is free of age or sex bias, or bias resulting from the recent prescription of antibiotics or sucralfate (see exclusion criteria). Patients with a previous history of peptic ulcer disease or epigastric pain were also excluded, so the study population was all receiving a routine prescription of NSAID. In short, the control and NSAID populations were very similar.

In our study diagnosis of H pylori infection depended on a positive result in two of four tests, as reported elsewhere. With regard to the sensitivity and specificity of the tests used to detect H pylori infection, our results are very similar to those in the reports and confirm the low sensitivity of culture growth. In two cases, the urease test alone was positive and in these patients a second direct examination excluded the presence of H pylori and another spiral shaped bacteria was suspected.

Little work has been done on H pylori infection in patients taking NSAIDs. In most studies on this subject patients suffered from rheumatoid arthritis or chronic rheumatism – diseases that require long term NSAID therapy. They differ completely from our study. In our NSAID group the underlying cause for NSAID prescription was osteoarthritis, less than one third of the patients suffered from chronic rheumatoid arthritis. This explains why only a few patients had received long term NSAID therapy. Furthermore, patients with long standing rheumatoid arthritis sometimes undergo gold therapy which is known to have an in vitro antimicrobial activity against H pylori. However, it now seems that gold therapy does not decrease the prevalence of H pylori infection in rheumatoid arthritis patients. Moreover, it seems that gastroduodenal mucosal damage and bleeding occur primarily during the first months of NSAID treatment, and complications become fewer in long term therapy probably because of an adaptive process. These facts may explain why our results differ from those of Graham et al who suggested that there is no association between H pylori infection and NSAID use.

In previous studies, chronic active gastritis is frequently reported. In patients with chronic active gastritis the frequency of H pylori infection varies considerably, ranging from less than 30% to close to 90%. Our results are intermediary in patients taking NSAIDs as well as in the controls, thus it seems unlikely that NSAIDs alone induce chronic active gastritis. Moreover, we were unable to find the greater prevalence of chronic gastritis in patients on NSAIDs that was shown by Taha et al. Published reports are also conflicting with regard to the relationship between H pylori infection and dyspeptic symptoms. A significant association has been reported by some authors but refuted by others as in the present study. The lack of correlation between dyspeptic symptoms and gastroduodenal mucosal damage shown by our results is well known and explains why epigastric pain is not usually predictive of complications such as upper digestive bleeding.

The association between gastroduodenal mucosal damage and H pylori infection has also been studied by Upadhyay et al. They showed a trend towards a greater frequency of H pylori infection in patients with mucosal damage diagnosed by endoscopy (64%) than patients free of lesions (38%), although the difference did not achieve statistical significance. This result seems to have been confirmed in the most recent study on this subject reported by the same group.

These results permit us to suggest that H pylori infection may increase the NSAIDs own gastrointestinal toxicity. This hypothesis is supported by several experimental findings. NSAID induced gastroduodenal mucosal damage depends mainly on
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the presence of neutrophils which are numerous in cases of chronic active gastritis caused by *H pylori* infection. In addition, toxicity might be the result of the increased synthesis of leukotrienes B4 induced by NSAIDs which is further increased by *H pylori* infection. Furthermore, as demonstrated in in vitro conditions, the depression of cell viability and prostaglandin E2 production by indomethacin is increased by a toxin produced by *H pylori*.

In view of this hypothesis it is reasonable to assume that *H pylori* eradication could lead to a decrease in NSAID gastrotoxicity. With this in mind, a prospective study concerning the possible prophylaxis of NSAID induced gastropathy by anti-*H pylori* therapy should be undertaken in the near future.

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