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

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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% v 24%) between the NSAID and the control groups. Among patients taking NSAIDs, *H. pylori* infection was more frequently (p<0.02) diagnosed in those who 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.

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Gastrointestinal disturbance is a frequent side effect of non-steroidal anti-inflammatory drugs (NSAIDs).¹⁻⁴ The high frequency of this complication and the cost of routine prophylactic treatment which it imposes are important economic considerations.⁵⁻⁷ 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,⁸ 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.⁹

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 deter-

mine 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, pyroxicam 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.*¹⁰ Endoscopy was considered as abnormal if the score was higher than 1. Three biopsy specimens were taken from the greater

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TABLE I Epidemiological characteristics of the study groups

	Age (years)		Sex ratio	Duration (days) of NSAID use		No of NSAIDs used		
	Mean	(SD)		Mean	Range	1	2	3
NSAID group:								
Group I	56.0	(17.7)	10/18	91 (130)	5-365	21	4	3
Group II	56.2	(14.3)	12/14	119 (180)	3-720	22	3	1
Group III	65.5	(18.1)	8/4	108 (159)	10-365	11	1	0
I + II + III	58.8	(19.2)	30/36			54	8	4
Control group	55.8	(19.3)	21/24					

TABLE II Endoscopic data in patients with NSAID induced gastropathy

	Group II		Group III		Total
	No	(%)	No	(%)	No
Location of lesions:					
Stomach alone	18	(69)	7	(58)	25
Duodenum alone	5	(19)	3	(25)	8
Stomach and duodenum	3	(12)	2	(17)	5
Total	26		12		38
Location of the most severe lesion:					
Fundus	3	(12)	2	(17)	5
Antrum	17	(64)	7	(58)	24
Duodenum	6	(24)	3	(25)	9
Total	26		12		38

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 microaerophilically 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 system¹¹: topographic classification was not undertaken

TABLE III Relationship between dyspeptic symptoms and endoscopic data in patients taking NSAIDs

	Dyspeptic symptoms				Total no
	Present No	(%)	Absent No	(%)	
Group I	17	(61)	11	(39)	28
Group II	13	(50)	13	(50)	26
Group III	7	(58)	5	(42)	12
Total	37	(56)	29	(44)	66

TABLE IV Characteristics of the four tests used in detecting Helicobacter pylori infection

	Sensitivity	Specificity
Histological determination	71%	92%
Gram staining	93%	94%
Urease test	89%	98%
Culture growth	68%	100%

Patients were deemed *H. pylori* positive if at least two of the four tests were positive.

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.¹²

Official authorisation for this study was given by the medical ethics committee of the Rennes University Hospital.

ANALYSIS

Patients were considered *H. pylori* positive when at least two of the microbiological and histological studies were positive.

Values were expressed as mean (SD) percentages. Comparison between the groups was by the χ^2 test. Statistical significance was set at the 5% level.

Results

The patients taking NSAIDs and the control group were similar in terms of age and sex ratio and there were no differences between groups I, II, and III (Table I) of the NSAIDs patients.

In patients from groups II and III, the most severe lesion (according to the endoscopic scale of Lanza *et al*¹⁰) was located more often in the stomach than in the duodenum ($p < 0.01$) and more often in the antrum than in the fundus ($p < 0.001$) (Table II). The degree and the severity of the mucosal damage were not correlated to the presence of dyspeptic symptoms (Table III).

The sensitivity and specificity of the four tests used to detect *H. pylori* infection are shown in Table IV. Direct examination had the best sensitivity and culture the best specificity.

The frequency of *H. pylori* infection was similar in the control group and in those taking NSAIDs (24% *v* 26% respectively). In patients taking NSAIDs: (a) *H. pylori* infection was not associated with the presence of dyspeptic symptoms and (b) *H. pylori* infection was more frequent in those with gastropathy (groups II and III; 37%) than in those without (group I; 11%) ($p < 0.02$).

The occurrence of chronic active gastritis was significantly ($p < 0.001$) associated with *H. pylori* infection in the population as a whole as well as in both subgroups (Table V). In the NSAID group, active gastritis tended ($p = 0.06$) to be more frequently observed in those with gastropathy diagnosed by endoscopy (45%) than in those without gastropathy (21%). The occurrence of chemical gastritis was similar in control and NSAID groups (11% *v* 12%).

Both the frequency of *H. pylori* infection and chronic active gastritis increased significantly with the severity of the mucosal damage ($p < 0.05$) (Figure).

TABLE V Relationship between *Helicobacter pylori* (HP) status and antral mucosa pathology

	Histologic features of antral mucosa										Total patients
	Normal		Chronic gastritis		Chronic active gastritis		HP gastritis		Drug induced gastritis		
	No	(%)	No	(%)	No	(%)	No	(%)	No	(%)	
<i>H. pylori</i> +ve:											
Control group	1	(9)	3	(27)	7	(64)	7	(64)	1	(9)	11
NSAID group	1	(6)	2	(12)	14	(82)	14	(82)	1	(5)	17
Total	2	(7)	5	(12)	21	(75)	21	(75)	2	(7)	28
<i>H. pylori</i> -ve:											
Control group	15	(44)	14	(41)	5	(15)	0	(0)	4	(12)	34
NSAID group	20	(41)	20	(41)	9	(18)	0	(0)	7	(14)	49
Total	35	(42)	34	(41)	14	(17)	0	(0)	11	(13)	83
Total patients	37	(33)	39	(35)	35	(32)	21	(19)	13	(12)	111

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).^{13,14} Patients with a previous history of peptic ulcer disease or epigastric pain were also excluded, so the study population were 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.¹⁵ 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.¹⁵ 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.¹⁶

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.^{17,21} 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*.²² However, it now seems that gold therapy does not decrease the prevalence of *H. pylori* infection in rheumatoid arthritis patients.²³ Moreover, it seems that gastroduodenal mucosal damage and bleeding occur primarily during the first months of NSAID treatment,²¹ 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*¹⁷ who suggested that there is no association between *H. pylori* infection and NSAID use.

In previous studies,^{17,21} 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%¹⁸ to close to 90%.¹⁹ 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 chemical gastritis in patients on NSAIDs that was shown by Taha *et al*.¹² 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 authors¹⁹ but refuted by others,^{17,20} 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*.¹⁹ 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.²¹

These results permit us to suggest that *H. pylori* infection may increase the NSAIDs own gastrotoxicity. This hypothesis is supported by several experimental findings. NSAID induced gastroduodenal mucosal damage depends mainly on

Frequency of *Helicobacter pylori* infection and chronic active gastritis as a function of severity of mucosal damage.

the presence of neutrophils⁹ 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 leukotriene B₄ induced by NSAIDs which is further increased by *H pylori* infection.²⁵ 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*.²⁶

In view of this hypothesis it is reasonable to assume that *H pylori* eradication could lead to a decrease in NSAID gastrototoxicity. 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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