Chemical gastritis and *Helicobacter pylori* related gastritis in patients receiving non-steroidal anti-inflammatory drugs: Comparison and correlation with peptic ulceration

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Abstract

Aims: To evaluate the prevalence and significance of chemical gastritis, in comparison with gastritis related to *Helicobacter pylori* in patients receiving non-steroidal anti inflammatory drugs (NSAIDs).

Methods: Two hundred and eighteen patients were studied, 174 of whom were taking NSAIDs. Chemical gastritis was defined as the presence of foveolar hyperplasia, muscle fibres in the lamina propria, oedema and vasodilation, in the absence of a chronic inflammatory cell infiltrate.

Results: Chemical gastritis was found in 46 (26%) patients taking NSAIDs, and three (7%) in subjects not taking these drugs ($p < 0.01$). *H. pylori* was detected in 56 (32%) subjects taking NSAIDs compared with 22 (50%) not taking these agents ($p < 0.02$). Ulcers were found in 16 out of 72 patients (22%) taking NSAIDs and without *H. pylori* infection or chemical gastritis compared with 27 out of 56 (48%) with *H. pylori* related gastritis ($p < 0.01$), and 25 out of 46 (54%) with chemical gastritis ($p < 0.01$).

Conclusions: Peptic ulcers associated with the use of NSAIDs seem to occur more commonly in patients with chemical gastritis or *H. pylori* infection. Patients taking NSAIDs also seem to have a greater prevalence of chemical gastritis but a lower prevalence of *H. pylori* than those not taking these drugs.

The effect of non-steroidal anti-inflammatory drugs (NSAIDs) on gastric histology is not clear. Recent studies have reported some histological changes similar to those encountered in patients with previous gastric surgery.¹⁻³ They consisted of foveolar hyperplasia, vasodilatation, oedema, lack of inflammatory cells, and the presence of muscle fibres in the lamina propria. These features were initially called "reflux gastritis", referring to the effect of bile reflux on the stomach after surgery.³ Because other chemicals, such as NSAIDs, were also thought to be involved in changes in intact stomachs, the terms type C or "chemical" gastritis have been proposed.⁴ The aim of our study was to evaluate the prevalence

and significance of chemical gastritis, compared with gastritis related to *Helicobacter pylori*, in patients taking NSAIDs. It was also hoped that any interactions that might exist between *H. pylori* and NSAIDs in the gastric mucosa would also then become apparent.

Methods

Patients with adult onset rheumatoid arthritis were recruited at random from the rheumatology clinic provided that they had taken NSAIDs for a minimum of four weeks. Patients not taking NSAIDs were also accepted provided they had not taken these agents for at least a month. Patients who had received treatment for ulcers, antibiotics, or cytotoxic drugs were excluded, as were those with a history of previous gastric surgery. All patients were asked about their alcohol intake. This was considered heavy if 10 or more units a week were consumed.

Informed consent was obtained and endoscopy performed after the administration of 5-15 mg diazepam intravenously. The endoscopic findings were graded as follows: 0, normal or minor erythema; 1, one to five erosions; 2, six to 10 erosions; 3, frank ulceration measuring at least 5 mm in diameter.

On average, three biopsy specimens were obtained from healthy looking mucosa in the gastric antrum of each subject. The specimens were fixed in 10% formalin and processed routinely. Cuts were made at three levels in the paraffin wax sections, which were then stained with haematoxylin and eosin. Further sections were also made and treated with cresyl violet to help identify *H. pylori*.

The findings in each set of biopsy specimens were graded twice: first, according to the Whitehead classification of gastritis,⁵ modified to cover the newly described entity of lymphocytic gastritis⁶; and second, according to a system modified from Dixon *et al* for the diagnosis of chemical gastritis.³ Features of the modified Whitehead gastritis (figs 1 and 2) included neutrophilic infiltration, chronic inflammatory cells, lymphocytic aggregates, intestinal metaplasia and gland atrophy. Their degree was graded on a four point scale: 0, absent; 3, severe. A similar scale was applied to the following features of chemical gastritis (fig 3): (i) the degree of foveolar hyperplasia; (ii) the degree of oedema and the prominence of

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Figure 1 Antrum of stomach: chronic superficial gastritis, typical of *Helicobacter* related gastritis. It shows foci of active gastritis with degradation of the surface epithelium (haematoxylin and eosin).

muscle fibres in the lamina propria; (iii) the degree of vasodilatation and congestion; (iv) the inverse of the number of neutrophils (absence scoring 3); and (v) the inverse of the number of plasma cells (absence again scoring 3). Patients scoring 8 or more by the chemical score were considered to have chemical gastritis.

Two further biopsy specimens were taken from the gastric antrum of each subject and examined for the presence of *H pylori* using both histological and microbiological methods, as previously described.⁷

Figure 2 Antrum of stomach: lymphocytic gastritis. There is a pronounced increase in lymphocytes in the surface and foveolar epithelium. There is also chronic superficial gastritis (haematoxylin and eosin).

The χ^2 test with the Bonferroni correction for multiple comparisons was used. Spearman's coefficient was also used to test for the correlation between the endoscopic and histological scores. The endoscopist, pathologist, and bacteriologist were unaware of the patients' drugs. Code numbers were used to facilitate randomisation of the biopsy specimens.

Results

A total of 218 patients were studied: 174 were taking NSAIDs. Their clinical details are shown in table 1. Patients not taking NSAIDs included 27 subjects with rheumatoid arthritis and 17 with other musculoskeletal disorders: 13 with osteoarthritis and four with ankylosing spondylitis.

The prevalence of chemical gastritis and *H pylori* in the presence or absence of NSAIDs is shown in table 1. Subjects receiving NSAIDs were more likely to develop chemical gastritis, but less likely to have *H pylori* than those not taking NSAIDs. Two of the three patients with evidence of chemical gastritis, but not taking NSAIDs, had a history of heavy alcohol intake. They both had rheumatoid arthritis.

Patients with chemical gastritis, *H pylori* infection, and those with neither of these findings in the NSAID group, tended to have similar demographic data (table 2). *H pylori* could not be detected in any of the patients with chemical gastritis. Histological findings, other than chemical gastritis, are presented in table 3. Chronic superficial gastritis was the major finding in all groups.

Patients not taking NSAIDs had a total of 14 ulcers—five gastric and nine duodenal, all of which were positive for *H pylori*. No erosions were found in this group. There was no significant difference in the distribution of ulcers, *H pylori*, or histological findings between

Figure 3 Antrum of stomach: "chemical" gastritis. Note the elongation of the foveolae, the virtual absence of inflammatory cells, and the presence of oedema and muscle fibres in the foveolar compartment. The "chemical score" was 10 (haematoxylin and eosin).

Table 1 Characteristics of patients with or without history of NSAID treatment

	Taking NSAIDs	Not taking NSAIDs
Number of patients	174	44
Age (years)	59	53
Median (interquartile range)	(51–65)	(34–65)
Males	29	23
Females	145	21
Smoker	35	20
Drinkers:		
Less than 10 units/week	36	17
10 or more units/week	3	8
Upper abdominal symptoms	63	42
Chemical gastritis—No (%)	46 (26%)*	3 (7%)
<i>H pylori</i> positive—No (%)	56 (32%)*†	22 (50%)

Significant rise compared with patients not taking NSAIDs:

* $\chi^2 = 7.95$; $p < 0.01$,† $\chi^2 = 4.43$; $p < 0.02$.

patients with rheumatoid arthritis or those with other musculo-skeletal disorders not taking NSAIDs. The distribution of ulcers in the NSAID histological subgroups is shown in table 2; NSAID related peptic ulcers are more likely to develop in the presence of *H pylori* or chemical gastritis. The correlation between the endoscopic and histological scores, however, was significant only in those with chemical gastritis (table 4). Erosions were found in 11 patients taking NSAIDs but without *H pylori* infection or chemical gastritis. Erosions in the other NSAID subgroups are shown in table 4. A total of 68 ulcers were diagnosed in the NSAID group—58 gastric and 10 duodenal. Twenty of 58 (34%) NSAID related gastric ulcers and five of 10 (50%) duodenal ulcers were positive for *H pylori*.

Discussion

This study shows that patients taking NSAIDs have a higher prevalence of chemical gastritis

but a lower prevalence of *H pylori* than those not taking NSAIDs. The presence of chemical gastritis or *H pylori* seems to increase the likelihood of having NSAID related peptic ulceration. There was also a positive correlation between the endoscopic and histological chemical scores in subjects taking NSAIDs.

Histological appearances, now regarded as consistent with chemical gastritis, have been reported in patients with bile reflux after gastroduodenal surgery.^{3,8} Subsequent studies have, on the other hand, found that there was no correlation between the reflux of bile and the development of chemical gastritis in the intact stomach.⁴ This would suggest that bile reflux has not significantly influenced the prevalence of chemical gastritis in our study. We also believe that we have corrected for the possible effect of bile by including in our analysis patients who were not taking NSAIDs.

Features of chemical gastritis were also described in patients with alcoholic haemorrhagic gastritis.⁹ Two cases of chemical gastritis, in patients not taking NSAIDs, had a history of heavy alcohol intake in our study. The development of chemical gastritis in the NSAID group is unlikely to have been totally related to alcohol consumption, as judged from the demographic data of our patients (tables 1 and 2).

The prevalence of chemical gastritis among our patients was comparable with that found by another group.⁴ The scores regarded as being attributable to chemical effects in our study were lower than those found by Sobala *et al.*,⁴ this being justified on the basis of some possible differences in interpretation between the two centres. Moreover, despite being on the lower side, the chemical scores in our study still correlated positively with the endoscopic scores. Had we included only those patients with high chemical scores (greater than 8 or 9), the prevalence of chemical gastritis would have been lower, but the correlation with the endoscopic scores would have become even more significant. We could not accept, however, that patients with chemical scores of 8 or 9 should be regarded as having normal gastric histology.

In addition to chemical gastritis, NSAIDs work in several ways which can lead to gastric mucosal damage. These include inhibition of prostaglandin synthesis,¹⁰ interference with mucosal blood flow,¹¹ and disruption of the

Table 2 Patients taking NSAIDs subgrouped according to main histological findings

	Chemical gastritis	<i>H pylori</i> related gastritis	No <i>H pylori</i> and No chemical gastritis
Number of patients	46	56	72
Age (years)	60	57	62
Median (interquartile range)	(52–69)	(50–65)	(57–65)
Males	6	9	14
Females	40	47	58
Smoker	7	11	17
Drinkers:			
Less than 10 units/week	10	11	15
10 or more units/week	0	2	1
Upper abdominal symptoms	15	19	29
Second line agents:			
Gold	6	5	8
Sulphasalazine	6	3	6
Penicillamine	3	3	8
Hydroxychloroquine	3	2	5
Ulcers No (%)	25 (54%)*	27 (48%)*†	16 (22%)

Significant rise compared with patients without *H pylori* or chemical gastritis:* $\chi^2 = 12.72$; $p < 0.01$,† $\chi^2 = 9.09$; $p < 0.01$.

Table 3 Histological findings in patients without chemical gastritis

	Patients taking NSAIDs			Patients not taking NSAIDs
	<i>H pylori</i> present	No <i>H pylori</i> no chemical gastritis	Total	
Number of patients	56	72	128	41
Normal	0	16	16	7
Chronic superficial gastritis	48	44	92	31
Chronic atrophic gastritis	5	10	15	1
Chronic lymphocytic gastritis	3	2	5	2

Table 4 Correlation between endoscopic and histological scores in patients taking NSAIDs with chemical gastritis or *H pylori*

Histological scores	Endoscopic scores			
	0	1	2	3
Chemical:*				
8	8	4	2	3
9	2	0	1	10
10	2	1	1	10
11	0	0	0	2
<i>H pylori</i> related:†				
3–5	9	6	0	12
6–8	8	3	1	11
9	1	1	0	4

*: $r = 0.51$; $p < 0.05$ †: $r = 0.0023$; not significant.

gastric mucosal barrier in a manner that allows the potentially damaging back diffusion of hydrogen ion.^{12,13} Despite the considerable interest that has recently been shown in some of the above mechanisms, probably because of their therapeutic potential,¹⁴ no correlation has been found between peptic damage and the activities of NSAIDs such as prostaglandin inhibition.^{15,16} This should emphasise the importance of identifying chemical gastritis, because of the positive correlation between the endoscopic and the histological chemical scores, as shown by our study. Chemical gastritis alone is unlikely to explain all cases of NSAID related peptic ulceration, probably due to the fact that multiple mechanisms are involved in such cases.¹⁰⁻¹³

A link, probably causal, has been thought to exist between gastritis and gastric ulcers, as suggested by several previous studies.¹⁷⁻²⁰ Such a relation has been extended to include cases of gastritis found in association with *H pylori*.²¹ The situation in patients taking NSAIDs has not been clear: it might have been complicated by not taking into consideration the presence of chemical gastritis,²² owing to the failure of Whitehead's classification to cover such a histological entity.⁵ The finding of a greater number of NSAID related gastric ulcers in patients with chemical gastritis strengthens the broader relation between gastritis in general and gastric ulcers.¹⁷⁻²¹ Patients taking NSAIDs but without *H pylori* infection or chemical gastritis (table 3) had a total of 56 cases of gastritis (78%), but the least number of ulcers (fig 2). This might suggest that gastritis has a strong association with NSAID induced gastric ulcers only when it is chemical in nature, or if it is associated with *H pylori*.

Patients taking NSAIDs included a smaller proportion of cases positive for *H pylori* than those not taking NSAIDs. The reason for this is not clear. NSAIDs might be directly toxic against *H pylori* or might indirectly change the natural habitat of these organisms. NSAIDs affect the rate and the characteristics of the mucus layer in the stomach. Aspirin²³ and indomethacin²⁴ inhibit mucus secretion. It was also suggested that aspirin could increase pepsin mediated proteolysis of mucus, decrease mucus viscosity, and increase the permeability of mucus to hydrogen ion.²⁵ Indomethacin was also found to inhibit active bicarbonate secretion by the gastric mucosa.²⁶ The mucus layer, commonly accepted as the natural habitat of *H pylori*,²¹ might be rendered less hospitable by the above changes.

In the NSAID group patients positive for *H pylori* had a greater number of ulcers than those without *H pylori* or chemical gastritis. This might suggest a synergistic effect between NSAIDs and *H pylori* in causing gastric damage. Examples of this synergism have been shown with other bacteria in the intestines of laboratory animals. The ability of NSAIDs to induce ulcers could be reduced by antibiotic treatment.²⁷ Germ-free animals were also found to be resistant to intestinal lesions induced by indomethacin.²⁸ More recently, we have shown that the combination of indometh-

acin and *H pylori* culture filtrate reduced human gastric mucosal viability and its PGE₂ production to a greater extent than indomethacin alone in vitro.²⁹ On the other hand, it is worth noting that, of 58 gastric ulcers identified in patients taking NSAIDs in our current study, only 20 (37%) were positive for *H pylori*. This is lower than the previously reported prevalence of *H pylori* in gastric ulceration unrelated to NSAIDs, which generally varied between 63%³⁰ and 77%.^{21,31} It is, however, consistent with other findings in this study, which suggest that NSAIDs might reduce the prevalence of *H pylori* infection. One cannot exclude the possibility that at least some of our ulcer patients might have become negative for *H pylori* at some stage during their long term intake of NSAIDs, although there was no evidence of this in our study.

In conclusion, chemical gastritis occurs more commonly in patients receiving NSAIDs than in those not taking these agents. The importance of identifying this histological entity stems from its positive correlation with NSAID-related gastric ulceration. Although *H pylori* was isolated in only 32% of subjects taking NSAIDs, its presence was associated with a greater number of ulcers than in patients taking NSAIDs without *H pylori* infection or chemical gastritis. These findings might contribute to our understanding of the interaction between NSAIDs and *H pylori*.

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