Chemical gastritis induced by naproxen in the absence of *Helicobacter pylori* infection

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Abstract

Aim—To evaluate the histological changes that occur in the antral mucosa of healthy male subjects before and after one week of naproxen administration, using a chemical gastritis score according to the *Helicobacter pylori* status.

Methods—Nineteen male subjects (mean age 31 years) underwent two endoscopies: one before and the other after one week of naproxen treatment (1 g daily). Antral biopsy specimens were assessed for the presence of *H pylori* infection and for chemical gastritis, defined as the presence of foveolar hyperplasia, muscle fibres in the lamina propria, oedema, and vasodilatation, in the absence of acute or chronic inflammatory cell infiltrate.

Results—Of the 19 subjects, eight had *H pylori* infection. After one week of naproxen treatment, none of those with *H pylori* infection developed chemical gastritis, while five of 11 (45%) of those without *H pylori* infection did. In the absence of *H pylori* infection there was no evidence of inflammation, either before or after naproxen administration.

Conclusions—A different pattern of antral histological change occurs following naproxen administration. This pattern is related to the presence or absence of *H pylori* infection, suggesting that *H pylori* status should be determined in histological studies of subjects taking non-steroidal anti-inflammatory drugs.

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The evidence concerning the effects of non-steroidal anti-inflammatory drugs (NSAIDs) on the gastric mucosa in subjects with *Helicobacter pylori* infection is conflicting. Some studies suggest that *H pylori* infection is an important factor,¹⁻³ while others do not support a role for *H pylori* in NSAID gastropathy.⁴⁻⁶ Lanza *et al*⁴ reported that volunteers with serological evidence of *H pylori* infection had similar macroscopic antral mucosal changes to those without *H pylori* infection after one week of naproxen or aspirin treatment. However, as macroscopic changes do not correlate well with the histological changes of the gastrointestinal mucosa,⁷ the above observations need to be confirmed at the histological level.⁴

The histological changes that occur in the intact stomach secondary to either bile reflux,

drugs, or other chemicals has been termed chemical gastritis (type C or reactive gastritis).^{8,9} This entity appears to be more prevalent in NSAID users.^{3,9,10} The latter histological studies examined biopsy specimens of patients after ingestion of NSAIDs. To date, however, there have been no prospective studies assessing the changes leading to chemical gastritis before and after administration of NSAIDs. The aim of this study was to assess any histological changes occurring in the antral mucosa, using a chemical gastritis score, depending on *H pylori* status both before and after one week of naproxen treatment.

Methods

Nineteen healthy men with a mean age of 31 years (range 25-41 years) were studied. They had no history of peptic ulcer disease, upper gastrointestinal symptoms, and had not received NSAIDs, bismuth, or antibiotics over the preceding three months.

The study was approved by the local ethics committee and informed consent was obtained from all subjects.

Each volunteer underwent two gastroscopies: one at entry and the other eight days later. Study medication comprised naproxen, 1 g daily, on days 0 to 7 which was taken at the same time each day following a meal. The subjects abstained from alcohol during the study period. Each gastroscopy was performed by one endoscopist who assessed the macroscopic appearance of the mucosa using the Lanza score¹¹ as follows: 0 = normal mucosa with no submucosal haemorrhage; 1 = a single submucosal haemorrhage; 2 = more than one submucosal haemorrhage; 3 = numerous areas of submucosal haemorrhage; and 4 = large areas of submucosal haemorrhage with active bleeding or widespread inflammation of the stomach.

At each endoscopy, two antral biopsy specimens were taken from an area of normal looking mucosa (2 cm from the pylorus): one for a rapid urease test (CLO test, Delta West Ltd., Bentley, Australia) to detect the presence of *H pylori* and the second for histological assessment. Specimens for histology were fixed in 10% formalin and embedded in paraffin wax. Sections from the paraffin wax blocks were stained with haematoxylin and eosin, and a further section was stained with Warthin-Starry for the identification of *H pylori*. Slides were examined by two pathologists. One (DH) recorded the presence or

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absence of chronic gastritis and *H pylori*. The second (MMcD), unaware of the findings of the first pathologist, assessed the histological features forming the basis of the chemical gastritis score.⁸ These features include the presence of foveolar hyperplasia (0–3), lamina propria oedema (0–3), and vascular congestion (0–3). These scores were added to two scores which assessed acute (0–3) and chronic (0–3) inflammatory cell infiltrate (3 = no inflammatory infiltrate; 0 = severe inflammatory infiltrate). The highest possible score was 15. A total score of 10 or more was indicative of chemical gastritis in accordance with the observations of Dixon *et al.*⁸ Both pathologists were blind to the day on which the biopsy specimens were taken, the endoscopic appearance of the gastroduodenal mucosa at the time of endoscopy, and the result of the rapid urease test.

Results

Of the 19 subjects, eight were infected with *H pylori*, as documented by a positive rapid urease test and the presence of *H pylori* on antral histology. *H pylori* status did not change following administration of naproxen for one week. Two of the *H pylori* positive and three of the *H pylori* negative subjects were smokers.

There was no evidence of macroscopic mucosal damage in any of the subjects at their first endoscopy. After one week of naproxen administration, the mean (SD) macroscopic score¹¹ was 1.6 (0.5) in those with and 2.0 (0.5) in those without *H pylori* infection. Of the subjects, 14 of 19 (74%) had some evidence of macroscopic inflammation after one week, six of whom were infected with *H pylori*. Changes in the macroscopic appearance of the gastroduodenal mucosa after naproxen administration were similar in the subjects with and without *H pylori* infection.

All of the subjects with *H pylori* infection had mild or moderate chronic gastritis. None of these subjects had chemical gastritis. Of the 11 *H pylori* negative subjects, one had chemical gastritis. The remaining subjects, with chemical gastritis scores of 10 or less and no evidence of chronic gastritis, were regarded as histologically normal. None of the subjects had concurrent chemical and chronic gastritis.

None of the *H pylori* positive subjects ($n = 7$; one subject did not have an adequate specimen for examination and was excluded from subsequent analysis) had chemical gastritis scores greater than 10 following naproxen administration. Indeed, three subjects had a lower score, reduced by one point in each case. This was because of an increase in the severity of chronic gastritis which was noted in four subjects. Three subjects had an increased chemical gastritis score (by two, four and five points, respectively) which occurred in one case despite a concurrent increase in chronic inflammation, which obviously depresses the score. The score remained unchanged in one case.

Of the 11 *H pylori* negative subjects, two had a reduced chemical gastritis score, by one

and two points, respectively. Six (55%) subjects had an increased score (by one, one, three, three, four, and five points, respectively) and in five (45%) of these cases, the resulting score now fulfilled the criteria for chemical gastritis. The score remained unchanged in three cases, none of whom had concurrent chemical and chronic gastritis.

Discussion

Previous studies have confirmed that chemical gastritis occurs in NSAID users.^{3,9,10} However, this is the first report highlighting that chemical gastritis develops after just one week of treatment. The study is strengthened by its prospective design which assessed a single anti-inflammatory drug—naproxen. We also identified differences in the histological changes occurring in the antral mucosa of *H pylori* positive and negative subjects. Those with *H pylori* infection did not have or develop chemical gastritis, while 45% of those without *H pylori* infection developed chemical gastritis following treatment with naproxen. Conversely, as previously reported,¹² chronic gastritis was strongly associated with *H pylori* infection and those without *H pylori* infection did not have chronic gastritis either before or after naproxen administration.

Recently, Quinn *et al.*¹⁰ reported that chronic and chemical gastritis co-exist in a subgroup of patients. While the possibility that the two conditions were distinct entities occurring concurrently was considered, the preferred explanation was that this mixed category represented an overlap of the spectrum of the two diseases. Such an overlap, however, was not observed in any of the subjects included in this study. This discrepancy is almost certainly because of the different methods used to assess chemical gastritis. In the scoring system proposed by Dixon *et al.*⁸ the presence of an inflammatory cell infiltrate leads to a reduction in the overall chemical gastritis score. Only in very exceptional circumstances (not encountered in our relatively small study group), where the inflammatory cell infiltrate is very mild and the other measured histological features are severe, is it possible to exceed a score of 10. Therefore, the points system makes the diagnosis of chronic and chemical gastritis almost mutually exclusive. Such an interpretation is supported by the strong association demonstrated in this study and in others³ between colonisation by *H pylori* and chronic gastritis on the one hand and the absence of *H pylori* and chemical gastritis on the other. At present, the importance of increases in the chemical gastritis score which fail to reach a threshold of 10 points is uncertain.

The less formal system adopted by Quinn *et al.*¹⁰ where the individual histological features of reactive gastritis are still sought but no scoring system is employed, enables the pathologist to make the combined diagnosis. However, because the histological features comprising chemical gastritis are non-specific and may be seen in other gastric pathologies,¹⁰

such a method runs the risk of interpreting non-specific findings as chemical gastritis.^{8 10} We would propose, therefore, that the diagnosis of chemical gastritis be made only when all of the histological features, including a lack of inflammatory cell infiltrate, are present and that, unless further studies clarify the situation, types B and C gastritis remain, histologically at least, mutually exclusive.

The relation between *H pylori* and NSAID gastropathy is similarly unclear, although there is in vitro evidence that NSAIDs are more damaging to the antral mucosa in the presence of *H pylori*.¹³ In a study of 218 patients,³ of whom 174 were taking NSAIDs, there was a higher incidence of ulceration in NSAID users with than in those without *H pylori* infection, suggesting that NSAIDs and *H pylori* infection act synergistically.¹⁴ In this study macroscopic lesions were observed with equal frequency in both *H pylori* positive and negative subjects. Microscopically, chemical gastritis, the pattern of gastric damage now thought to be associated with NSAID administration, was not observed in those with *H pylori* infection. However, prevalence of chronic gastritis, a pattern strongly associated with *H pylori* infection, was increased following administration of naproxen as observed in four of seven subjects with *H pylori* infection. Although the numbers in this study are small, these results suggest that administration of NSAIDs increase the inflammation associated with established *H pylori* infection, rather than that *H pylori* infections increases NSAID gastropathy.

Macroscopic mucosal lesions were present in 14 (74%) subjects following naproxen administration. There was no evidence of macroscopic inflammation before ingestion of the drug. As *H pylori* gastritis is poorly correlated with macroscopic lesions^{7 15 16} and because chemical gastritis can occur in patients taking NSAIDs, histological evaluation of the gastric mucosa is important for assessing mucosal changes in patients taking NSAIDs, who may also be infected with *H pylori*. Macroscopic lesions are unlikely to be related to the presence of *H pylori* infection in patients with rheumatoid arthritis who have been taking NSAIDs chronically,¹⁷ again suggesting that histological assessment of the mucosa is necessary. The macroscopic scores in this study were similar to those obtained by Lanza *et al.*,⁴ with both *H pylori* positive and negative subjects having an increased macroscopic score; however, in this study these changes did not correlate with the histological changes observed.

In conclusion, this study has documented the pattern of histological changes occurring in the antral mucosa after one week of naproxen treatment and has recorded differences between subjects with and without *H pylori* infection. Clearly, *H pylori* infection should be identified and considered in all studies evaluating the effects of NSAIDs on the gastric mucosa.

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