

Leading article

Helicobacter pylori and non-steroidal anti-inflammatory drugs: uncomfortable partners in peptic ulcer disease

Recent studies have suggested that *Helicobacter pylori* and non-steroidal anti-inflammatory drugs (NSAIDs) are capable of interfering with various protective mechanisms in the gastroduodenal mucosa. Whereas NSAIDs are recognised for their acid stimulating activity, the effect of *H pylori* on gastric acid secretion remains highly speculative despite its association with hypergastrinaemia. Both *H pylori* and NSAIDs have, however, been shown to influence the production rate and the quality of gastric cyclic AMP, the mucus layer, mucosal prostaglandins, blood flow, and platelet activating factor. Characteristic histological abnormalities have also been identified. Also NSAID related peptic ulcers seem to develop more commonly in patients infected with *H pylori* despite the apparent reduction in the prevalence of these organisms in chronic NSAID users, hence the uncomfortable relation between the two aetiological factors. It remains to be seen whether the eradication of *H pylori* would reduce the frequency of peptic ulcers induced by NSAIDs or prevent their recurrence.

Helicobacter pylori and NSAIDs are probably the commonest known exogenous factors in the aetiology of peptic ulcer disease. This paper describes the pathogenetic mechanisms common to *H pylori* and NSAIDs and discusses the possibility of a synergistic relation between them. The importance of such a relation, if present, relates to its potential to provide a new therapeutic approach to the common, but yet unresolved, problem of ulcers induced by NSAIDs.

Effect of NSAIDs and *H pylori* on gastric acid secretion

Because of the widely accepted importance of gastric acid in the pathogenesis of ulcers in general, it was only natural for many workers to investigate the possible effects of NSAIDs and, more recently, *H pylori* on acid secretion. NSAIDs (indomethacin and aspirin in particular) were found to increase basal and maximally stimulated gastric acid secretion^{1,3}; they seem to bypass the H₂ and muscarinic receptors and interact with secretagogues at a locus between the catalytic subunit of adenylate cyclase activation and the proton pump.⁴ The potentiation of secretagogue stimulated acid secretion by non-salicylate NSAIDs has also been found to be dependent on calcium.⁴

The situation is not so well defined in the case of *H pylori*. Because of its association with hypergastrinaemia, it was speculated that *H pylori* could increase the parietal cell mass that is characteristic of patients with duodenal ulcers.⁵ To date, the evidence for an increase in gastric acid secretion by *H pylori* has, however, been lacking.^{5,6} On the contrary, there is a consensus that acute exposure to *H pylori* causes hypochlorhydria.⁷⁻¹¹

Recent evidence indicates that hypergastrinaemia associated with *H pylori* might not be directly related to the function of the parietal cells,¹² the number of antral G cells,¹³ or to the bacterium's urease activity.¹⁴ It is more likely to be related to local inflammation¹³⁻¹⁵ or products of the T lymphocyte such as interleukin-2 and γ -interferon.¹⁶ Gastric

acid secretion in chronic NSAID users who are infected with *H pylori* has not been studied, but indomethacin has been shown to potentiate the inhibitory effect of *H pylori* protein on gastric fundic cyclic AMP, which in turn mediates acid secretion in vitro.¹⁷ This might explain, at least in part, the tendency of many arthritic patients to develop a degree of hypochlorhydria,¹⁸ and the limitations of acid inhibition in the management of NSAID related ulcers.^{19,20}

The mucus layer

The ability to change the characteristics of the gastric mucus layer is common to both NSAIDs and *H pylori*. Aspirin²¹ and indomethacin²² were found to inhibit mucus secretion. Aspirin can also increase pepsin mediated proteolysis of mucus, decrease mucus viscosity, and increase the permeability of mucus to hydrogen ion.²³ Indomethacin was shown to inhibit active bicarbonate secretion by the gastric mucosa.²⁴ It was also suggested that NSAIDs could cause disruption of the gastric mucosal barrier, which in turn allows back diffusion of hydrogen ion with its damaging results.²⁵⁻²⁷

Similarly, it has recently been shown that incubation of a culture filtrate of *H pylori* with gastric mucus could lead to a gradual loss of viscosity of mucus,²⁸ which might impair the ability of the mucus to retard the diffusion of hydrogen ions. It was concluded that the degenerative changes produced in the gastric mucus gel by *H pylori* might be a contributing factor to the pathogenesis of gastritis and peptic ulcers.²⁸

Mucosal prostaglandins

It is generally accepted that NSAIDs, with few exceptions,²⁹ are capable of suppressing gastric and duodenal mucosal prostaglandin (PG) synthesis, although no correlation has been found between the degree of inhibition of PG and the endoscopic abnormalities.^{29,30}

Because of its strong association with gastritis and neutrophilic infiltration, *H pylori* is expected, at least in theory, to stimulate PG production, as human neutrophils and macrophages are capable of synthesising PGs.³¹ Also gastritis – like any other inflammation – is associated with raised PG values irrespective of *H pylori* status.^{32,33} It was surprising, therefore, to find that patients with *H pylori* related gastritis had PG values similar to those without *H pylori*.³³⁻³⁵ This led to speculation that *H pylori* infection might result in at least a partial block in PG synthesis at the level of the neutrophils, mucosal cells, or both.³³ Indeed, some workers reported reduced concentrations of stable metabolites of PGI₂ in patients infected with *H pylori*,³⁶ but this was not confirmed by others.³³⁻³⁵ It was also interesting to find that, in vitro, the combination of indomethacin and *H pylori* culture filtrate reduced gastric antral mucosal PGE₂ and epithelial viability to a greater degree than indomethacin alone.³⁷ This in turn might suggest a synergistic relation between *H pylori* and NSAIDs in causing mucosal damage.

Mucosal blood flow

Several studies have shown that short courses of NSAIDs could reduce gastric mucosal blood flow in laboratory animals.^{2,38,39} The situation is not clear in patients on long term NSAIDs, who could have other factors that might alter blood flow. Also, little is known about the duodenal micro-circulation in such patients. It has been shown, however, that duodenal, but not gastric, mucosal blood flow is lowest in NSAID patients who smoke, or those with duodenal ulcers or *H pylori*⁴⁰; no correlation could be found with age or sex. Further analysis of the data in this study⁴⁰ showed that the suppressive effect of smoking and *H pylori* on duodenal blood flow in NSAID patients was independent of ulceration and other demographic variables. Although such findings do not dispute the capacity of NSAIDs to lower mucosal blood flow in general, they might represent another aspect of the synergistic relation thought to exist between NSAIDs and *H pylori*, at least for duodenal blood flow.

Histological and endoscopic abnormalities

Active chronic gastritis is the classic histological picture found in association with *H pylori* in most infected subjects. It is best remembered as the main abnormality seen after the deliberate ingestion of the organisms to fulfil Koch's postulates for the pathogenicity of *H pylori*,^{7,8} and in epidemic gastritis.⁹ It is also the commonest histological finding in patients treated with NSAIDs.⁴¹ Neutrophilic infiltration, common to most cases of NSAID and *H pylori* gastritis, could be related to the capacity of NSAIDs and *H pylori* to stimulate the production of platelet activating factor.^{42,43} As well as its ulcerogenic actions,⁴² platelet activating factor might be involved in the aggregation and activation of neutrophils,⁴⁴ which might subsequently contribute to ulcer formation: neutropenic rats are less likely to develop gastric mucosal injury from indomethacin or naproxen.^{44,45} These interesting findings might not apply, however, to patients with chemical gastritis, another histological abnormality characteristic of chronic NSAID intake.^{41,46} Not unlike bile reflux gastritis in patients with a history of gastroduodenal surgery,⁴⁷ it is characterised by foveolar hyperplasia, vasodilatation, oedema, lack of inflammatory cells, and the presence of muscle fibres in the lamina propria.^{41,46-49} *H pylori* is very rare in cases of chemical gastritis,^{41,46,47} and the histological picture can be found in about 25% of chronic NSAID users.^{41,46} The importance of such an entity stems from the positive correlation between the histological chemical scores and the degree of endoscopic damage: peptic ulcers related to NSAIDs and measuring 5 mm in diameter were found more commonly in patients with chemical gastritis or gastritis associated with *H pylori* than in those without either of these conditions.⁴¹ This is in agreement with other studies,^{50,51} that found a greater number of gastric ulcers in NSAID patients infected with *H pylori* compared with patients either taking NSAIDs or infected with *H pylori*. The prevalence of NSAID related ulcers in *H pylori* positive patients has also been found to be twice that in *H pylori* negative subjects, but the differences were not significant due to the small numbers of patients and ulcers studied.^{52,53} Graham *et al*⁵² found a greater number of submucosal haemorrhages and erosions in *H pylori* negative NSAID users, unlike the results of another report, which suggested that the presence of *H pylori* had no influence on the prevalence of such lesions after the acute administration of naproxen or aspirin in healthy volunteers.⁵⁴ Also, Shallcross *et al*⁵³ found more duodenal than gastric ulcers in their NSAID patients, which is not typical of NSAID related damage, and could be explained by the fact that they included in their study patients who were able to stop their NSAID within a month before endoscopy. This would in

turn raise concern about the suitability of such subjects for analysis and their need for and compliance with NSAID intake, which can determine the extent of peptic damage. A more recent study in asymptomatic NSAID users from the community has found that *H pylori* infection was not related to the severity of the endoscopic findings, but to higher degrees of gastritis,⁵⁵ which in the long term might progress to ulceration.⁵⁶

The interpretation of the findings related to submucosal haemorrhages or erosions is made difficult by the chronic nature of *H pylori* infection, its association with ulcers, and the lack of evidence that such minor lesions can really progress to ulcers. Another possible explanation for the differences in the findings of these studies^{41,50-55} is the failure to correct for the presence of chemical gastritis, which appears to act as an independent factor, and the use of serological tests of unproved value in patients treated with NSAIDs. Diagnostic titres of *H pylori* IgG antibodies could still be detected in patients with chemical gastritis, with its high prevalence of NSAID ulcers, despite the failure to confirm the presence of the organisms by culture, histology, or urease activity.^{57,58} Also serology might not be reliable enough in predicting the presence of *H pylori* or ulcers in NSAID patients, unlike other categories of patients,^{59,60} because: firstly, NSAID ulcers can be completely without symptoms^{61,62}; secondly, the specificity of some IgG tests might be low in patients receiving NSAIDs^{57,58}; thirdly, despite the apparent synergistic relation between *H pylori* and NSAIDs, the intake of such drugs might be associated with a reduced prevalence of *H pylori* infection^{41,57,63-65}; this could be due to a direct toxic action, or indirectly related to the increase in acid secretion¹⁻⁴ and the interference with the mucus layer²¹⁻²⁷ rendering the natural habitat of *H pylori* organisms unsuitable for their survival.

The virulence of *H pylori* strains might also explain some of the differences in the reported rates of ulcer formation. Western blotting analysis of systemic IgG or IgA responses to *H pylori* has shown the antigenicity of 110-120 kDa, 89 kDa, 61 kDa, 54 kDa, and 31 kDa proteins, although there is substantial variability among subjects.⁶⁶⁻⁷⁰ The 120 kDa protein, which is recognised systemically in 83% of *H pylori* positive subjects, is a surface protein not expressed in some *H pylori* strains.⁶⁸

It has been suggested that 120 kDa positive strains have pathogenetic features associated with active gastritis and peptic ulcerations.⁷⁰ Infection with 120 kDa negative strains might explain why peptic ulceration develops in only a proportion of subjects infected with *H pylori*.⁷⁰ A vacuating cytopathic agent has also been described in some strains of *H pylori*.⁷¹ It is not, however, known whether these important findings would apply to patients receiving long term NSAIDs.

Therapeutic considerations

The role of eradicating *H pylori* in the healing or the prevention of NSAID related peptic ulcers has not been studied. As well as their antibacterial activity, however, agents currently used in the treatment of *H pylori* infection were previously found to possess properties relevant to the mechanisms of NSAID induced mucosal damage. Colloidal bismuth subcitrate was shown to stimulate gastric and duodenal alkaline secretion through a prostaglandin dependent mechanism.⁷² The same agent was also found to have a protective action against aspirin induced micro-bleeding, and this protection occurred despite a pronounced suppression of mucosal prostaglandin production.⁷³ Also, it was shown that the ulcerogenic effect of NSAIDs could be reduced in animals by treatment with antibiotics,⁷⁴ and that germ free animals were resistant to indomethacin induced intestinal lesion.^{75,76}

The common nature of NSAID related ulcers in association with *H pylori* colonisation, especially in elderly patients, should act as an incentive to devise an effective therapeutic approach. In 1983, enough NSAIDs were made available to treat almost three million people daily in the United States,⁷⁷ and 22 million prescriptions were issued for such agents in the United Kingdom.⁷⁸

About half of the NSAIDs prescribed were for persons over 60 years old.⁷⁸ *H pylori* infection can be identified in about 80% of people of this age group⁷⁹ although in the presence of NSAIDs the prevalence of *H pylori* might fall to 30% to 50%, according to data collected at our unit between 1987 and 1992.

It is estimated, therefore, that between 25% and 40% of all NSAID users and 30–50% of elderly patients taking NSAIDs could be infected with *H pylori* and, as a result, are at special risk of developing peptic ulcers. The management of ulcers in this large number of patients is not only essential but might also need to be different from that of other types of ulcers. Its effect on ulcer complications, especially in elderly patients, also needs to be clarified.

Despite the evidence for a low prevalence of *H pylori* in chronic NSAID users, it has to be emphasised that the possible use of NSAIDs to eradicate *H pylori* should not be considered, knowing that such eradication might involve the impairment of the mucus layer with its damaging consequences.

In conclusion, the evidence for a synergistic relation between NSAIDs and *H pylori*, despite being contested, should not be ignored because of its potential therapeutic implications. Also, the suggestion that NSAIDs might influence the prevalence of *H pylori* would indicate that the two factors are uncomfortable partners in peptic ulcer disease.

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