Histological findings in gastric mucosa in patients treated with non-steroidal anti-inflammatory drugs

M Caselli, R LaCorte, L DeCarlo, A Aleotti, L Trevisani, M Ruina, F Trotta, V Alvisi

Abstract

Aims—To identify distinguishing and general histological features related to the use of non-steroidal anti-inflammatory drugs (NSAID).

Methods—Slides from gastric antral biopsies of 50 patients with osteoarthritis taking NSAID were compared with slides from antral biopsies of 50 control cases matched for age, sex, and race. Semithin sections stained with toluidine blue were used.

Results—Chronic gastritis was seen in 76% of the patients taking NSAID and in 58% of the control cases; active inflammation was detected in 10% of the NSAID treated patients and in 24% of the control cases, and it appeared closely related with *Helicobacter pylori* infection. Some histological features common to all slides of patients taking NSAID were recognised. These consisted of focal erosions of the gastric epithelium and macroerosions, and they seemed to represent successive steps of a process of "desquamation".

Conclusions—Some distinguishing morphological aspects appeared prominent; it is suggested that these may be related to the pathogenesis of NSAID linked peptic ulceration. On the other hand, epithelial damage due to NSAID appears very different from that due to *Helicobacter pylori*, another important factor involved in the aetiopathogenesis of peptic disease.

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Non-steroidal anti-inflammatory drugs (NSAID), widely used agents with a two billion dollar world market,¹ are closely linked to gastric bleeding and gastric peptic ulceration² and are the most frequent cause of adverse reaction to medication.³ These drugs are considered by others^{4,5} and by us⁶ to be one of the most important factors in peptic ulceration, together with *Helicobacter pylori* and cigarette smoking. According to our previous findings, however, these factors may play different and independent pathogenic roles in peptic disease, and NSAID might also have a protective effect against *H. pylori*.⁶ Furthermore, while NSAID mainly induce ulcerations in the stomach,⁷ *H. pylori* induces ulcers mainly in the duodenal bulb,⁸ and a meta-analysis of controlled studies has shown that duodenal ulcerations due to

NSAID are much more easily prevented than gastric ulcerations by using H₂ receptor blocking agents.⁹ Since knowledge concerning the histology of the gastric mucosa in NSAID treated patients is not clear and often discordant, we have examined the histological lesions in 50 patients with osteoarthritis taking NSAID for 15-30 days and compared the findings with those in 50 subjects not taking NSAID.

Methods

We examined slides from 50 outpatients with osteoarthritis taking NSAID for 15-30 days (28 males and 22 females; age range 24-79 years, mean age 51), and from 50 control outpatients undergoing endoscopy for symptoms referable to the upper gastrointestinal tract and not taking NSAID who were matched for age, sex, and race (28 males and 22 females; age range 25-76 years, mean age 50). None of the patients studied drank alcohol or took other drugs known to be harmful to the gastric mucosa. Among the patients taking NSAID, 24 were using diclofenac sodium, 18 ketoprofen, and eight naproxen sodium.

Three biopsy specimens of gastric antrum were taken in each case. To prepare the histological slides we used semithin sections stained with toluidine blue; in our experience¹⁰ this technique allows easy interpretation of the microscopy appearances. Chronic gastritis was graded according to the Whitehead *et al* classification.¹¹ The presence of neutrophil infiltrates in the lamina propria or the epithelial layers was used to indicate active inflammation.

For statistical analysis of the data a χ^2 test was performed.

Results

Chronic non-specific gastritis with superficial lymphocyte/plasma cell infiltration of the lamina propria was present in 38 of the NSAID treated patients (76%) and in 29 of the control cases (58%) ($p < 0.05$).

Active inflammation with evidence of mild to severe neutrophil infiltration was seen in five of the NSAID treated cases (10%) and in 12 of the control cases (24%) ($p = 0.03$); colonisation by *H. pylori* coexisted in all these patients with evidence of active gastritis. Distinguishing features of epithelial damage were found in all our patients taking NSAID and these features were never seen in control patients. These included focal erosions (fig 1) in 79 slides and extensive

University of
Ferrara, I-44100
Ferrara, Italy,
School of
Gastroenterology
M Caselli
L DeCarlo
L Trevisani
M Ruina
F Trotta

Department of
Rheumatology
R LaCorte
F Trotta
Centre of
Electron Microscopy
A Aleotti

Correspondence to:
Dr Michele Caselli,
C.so Biagio Rossetti,
I-44100 Ferrara,
Italy.

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Figure 1 Semithin section stained with toluidine blue. Focal erosion of luminal epithelium with a sharp transition between the erosive area and normal looking epithelial cells ($\times 1300$).

Figure 4 Semithin section stained with toluidine blue. Among the *H pylori*-like bacterial bodies seen near an erosive area numerous coccoid forms are recognisable. ($\times 965$).

Figure 2 Semithin section stained with toluidine blue. A more extensive erosive area involving the luminal part of a gland. Prominent capillaries are seen in suberosive areas. ($\times 985$).

Figure 3 Ultrathin section showing the progressive process of "desquamation" of gastric epithelial cells ($\times 3285$).

erosions (fig 2) in 71 slides. Focal and macro-erosive epithelial lesions seemed to be successive steps of a process of "desquamation" (fig 3). The transition between injured and normal looking cells appeared to be sharp. This

epithelial damage mainly involved the luminal epithelium with resulting exposure of the lamina propria and frequent erosions of the superficial part of the glands, while the underlying deeper glandular epithelium almost always appeared to be conserved in our slides, even in the presence of extensive erosions. Damage involving the deeper glandular epithelium was seen in slides of only two patients (4%). Another evident aspect is the constant presence of capillaries prominent in suberosive areas of the lamina propria. *H pylori*-like bacterial bodies were seen in seven of the patients taking NSAID (14%) and in 16 of the control patients (32%) ($p=0.03$), confirming the previous finding of low prevalence of *H pylori* in patients taking NSAID.⁷

In two cases where bacterial bodies were seen near the erosive areas numerous coccoid forms were recognisable (fig 4), suggesting bacterial infection.

Distinguishing and general aspects of the gastric antral mucosa in this group of NSAID treated patients are summarised in the table.

Discussion

Recent investigation has confirmed that in NSAID treated patients no correlation exists between the presence or absence of upper

General and distinguishing features of gastric antral mucosal histology in NSAID treated patients

Distinguishing histological features	General histological features
- Focal erosion of luminal epithelium	- Normal - Quiescent chronic gastritis (1+ to 3+) - Active chronic gastritis (1+ to 3+)
- Macroerosion of luminal epithelium (with frequent involvement of the superficial part of the gland)	
- Erosion involving the deeper glandular epithelium	
- Capillaries prominent in suberosive areas of lamina propria (features related to all grades of epithelial erosion)	

gastrointestinal symptoms, the endoscopic findings, and the histological appearance of the gastric mucosa.¹²

In our histological study some distinguishing morphological aspects appear prominent. General aspects related to cellularity do not appear to be helpful and neutrophilic infiltration seems to be closely linked to the presence of *H. pylori* infection. Epithelial damage, on the other hand, with focal erosions and macroerosions as result of a progressive process of desquamation of contiguous epithelial cells, and with a fairly sharp transition between damaged and normal looking cells, appears to be a common and distinguishing finding. Since cell proliferation and DNA synthesis have been found to be significantly reduced in patients taking NSAID by different investigators,^{13,14} this may explain the persistence of epithelial damage even when regenerative sites are not injured. The epithelial involvement is similar to that seen in animal models,^{15,16} and the impairment of the tight junction complexes between viable gastric epithelial cells may represent the first step.¹⁶ The large number of capillaries in suberosive areas seems to contrast with the reported reduction of angiogenesis in gastric tissue damaged by NSAID¹⁷; however, this finding may play a role in the mucosal "adaptation hypothesis". If the regenerative sites of the gastric glands are conserved, the process of "restitution" can occur with re-epithelisation of gastric mucosal surface,¹⁸ and this process may require increased neovascularity of the subepithelial tissue.

We suggest that damage of local vascular regeneration together with damage to the deeper glandular epithelium with involvement of regenerative sites, may be critical events for the inhibition of a rapid "restitution" and for the development of NSAID linked gastric peptic ulceration. If these events do not occur when NSAID are given over several days, a "mucosal adaptation" may become established¹⁹ and gastroerosions are seen to lessen.²⁰ Epithelial damage due to NSAID, however, appears very different to that due to *H. pylori*. The latter is characterised by penetration of the bacterium at the intercellular junctions and glandular lumens—inducing microerosive lesions—and in advanced stages of the infection by microvillar loss, depletion

of apical mucoid granules, and cytoplasmic vacuolisation.²¹ Although differing considerably in form, a type of local epithelial damage together with other conditions that inhibit rapid re-epithelisation may be the common pathogenic route by which different factors might induce peptic ulcer.

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