Enhanced gastric mucosal leukotriene B₄ synthesis in patients taking non-steroidal anti-inflammatory drugs

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Abstract

The effects of longstanding non-steroidal anti-inflammatory drug (NSAID) treatment on gastric mucosal synthesis of leukotriene B₄ (LTB₄), leukotriene C₄ (LTC₄), and prostaglandin E₂ (PGE₂) was studied. Gastric antral biopsies in 65 patients with arthritis taking NSAIDs and 23 control patients were taken and eicosanoid concentrations, stimulated by vortex mixing or calcium ionophore, were measured by radioimmunoassay. Median gastric mucosal synthesis of LTB₄ was increased in patients taking NSAIDs compared with non-users: (0.9 (0.2-2.5) pg/mg *v* 0 (0-0.6) pg/mg (*p*<0.001)). These differences persisted when subgroups of patients were analysed according to *Helicobacter pylori* colonisation or degree of mucosal injury. Synthesis of LTB₄ was strongly associated with the presence of type C (chemical) gastritis. Increased synthesis of LTC₄ was associated with *Helicobacter pylori* colonisation but not NSAID use. Synthesis of PGE₂ was decreased in patients taking NSAIDs compared with control patients (*p*<0.001). Enhanced gastric mucosal synthesis of LTB₄ in patients taking NSAIDs may represent a primary effect of these drugs and could be implicated in the pathogenesis of gastritis and ulceration associated with NSAIDs.

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Non-steroidal anti-inflammatory drugs (NSAIDs) are associated with gastric mucosal injury that may result in peptic ulceration, upper gastrointestinal haemorrhage, and perforation.¹ Mucosal injury is often ascribed to the well established ability of NSAIDs to inhibit synthesis of prostaglandins, as prostaglandins stimulate mucosal defence mechanisms such as secretion of mucus and bicarbonate and enhance mucosal blood flow.^{2,3} Profound inhibition of synthesis of prostaglandins can occur in the absence of mucosal injury,⁴ and depletion of mucosal prostaglandins may be only one of several factors responsible for the pathogenesis of injury related to NSAIDs.

Theoretically, as a result of substrate diversion of arachidonic acid, inhibition of cyclooxygenase by NSAIDs may lead to the increased formation of the leukotriene series through the 5-lipoxygenase pathway. Leukotrienes are known proinflammatory mediators and leukotriene B₄ (LTB₄) is a potent chemoattractant of polymorphonuclear cells and causes degranulation and release of lysosomal enzymes,^{5,6} which could play an important part in amplifying the

inflammatory response to NSAIDs. Similarly leukotriene C₄ (LTC₄) could mediate gastric mucosal damage both by its vasoconstrictive actions and its effects on vascular permeability promoting vascular stasis and subsequent reduction in tissue perfusion.^{7,8} Animal studies have shown a correlation between the gastric mucosal injury induced by ethanol or acid and increased synthesis of leukotrienes.⁸⁻¹¹ Some authors have shown that lipoxygenase inhibitors are protective in such protocols,¹²⁻¹⁴ but more recently this has been questioned.^{15,16} Where mucosal protection has been shown it does not correlate well with potency of inhibition of 5-lipoxygenase and could be due to another property such as oxygen radical scavenging. Enhancement of gastrointestinal synthesis of leukotrienes by NSAIDs in humans has not hitherto been shown and experimental evidence is conflicting; indomethacin has been reported to enhance synthesis of LTB₄,¹⁷ have no effect on synthesis of LTB₄,¹⁸ and inhibit synthesis of LTC₄, albeit to a lesser extent than its effects on prostaglandins¹⁹ in the rat stomach.

To clarify a possible role for synthesis of leukotrienes in damage caused by NSAIDs we investigated the effects of long term NSAID treatment on gastric mucosal LTB₄, LTC₄, and prostaglandin E₂ (PGE₂) concentrations in patients with arthritis compared with control subjects not taking NSAIDs. We correlated these findings with endoscopic mucosal damage, the presence or absence of *Helicobacter pylori*, and the degree of histological gastritis.

Patients and methods

Sixty five patients with rheumatoid arthritis (n=57) or osteoarthritis (n=7) on NSAIDs for >3 months (mean (SD): 4.7 (3.1) years) were recruited from a rheumatology clinic to undergo screening by upper gastrointestinal endoscopy before entry into a therapeutic trial, approved by the hospital ethics committee. Patients were not included in the study if they had undergone previous gastric surgery or if they were receiving cytotoxic drugs or >5 mg/day prednisolone. Patients receiving other second line agents – namely, gold, penicillamine, sulphasalazine, or hydroxychloroquine – were included in the study. Those taking H₂ receptor antagonists stopped this medication at least one week before endoscopy. The control subjects were 23 patients concurrently undergoing endoscopy for dyspeptic symptoms. The control subjects had received neither aspirin nor NSAIDs in the three months before study.

Informed consent was obtained before endo-

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scopy. At endoscopy, a visual assessment and video recordings were made of ulceration and gastropathy (Olympus GIF XV10). Nine antral gastric biopsies were taken 3–4 cm from the pyloric ring. One sample was placed in a CLO test (a gel based rapid urease test)²⁰ for assessment of *Helicobacter pylori* colonisation (a positive result was denoted by a colour change at four hours). Two samples were immediately fixed in 10% formalin for histological assessment. Paraffin wax sections were cut and stained by both haematoxylin and eosin and giemsa and assessed for evidence of gastritis and *Helicobacter pylori* organisms. Gastritis was defined according to the system proposed by Wyatt and Dixon.²¹ Type C (chemical) gastritis was characterised by the presence of foveolar hyperplasia and tortuosity, vasodilatation, and congestion with a paucity of inflammatory cells in the lamina propria layer. Type B gastritis (chronic active gastritis) was characterised by an increase in inflammatory cells (lymphocytes, plasma cells, histiocytes) in the lamina propria of the mucosa and polymorphonuclear neutrophils infiltrating the epithelium. Histopathology assessments were made without knowledge of the endoscopic or biochemical findings.

The remaining six biopsy samples were divided into pairs and washed in 1 ml of Tris saline buffer. Each pair was then vortex mixed for six seconds and centrifuged for 10 seconds, the supernatant stored, and the procedure repeated. A further 300 µl of Tris saline buffer was then added. Synthesis of eicosanoids was stimulated by vortex mixing for a further minute. After centrifugation for 10 seconds the supernatant was removed and stored at –70°C until assayed (within three months).²² In a subgroup of patients further biopsy samples were stimulated by calcium ionophore A23187 for a period of 20 minutes, as described elsewhere,²³ before the supernatant was stored. Immuno-reactive LTB₄, LTC₄, and PGE₂ were measured by radioimmunoassay and results were expressed as pg/mg wet weight of gastric biopsy sample. Chemicals for radioimmunoassay were from Amersham International except PGE₂ antiserum, which was from Sigma Chemical Company.

VALIDATION OF ASSAYS

Intra-assay coefficients of variation were 3.8% for LTB₄, 3.9% for LTC₄, and 2.5% for PGE₂ (n = 10). Interassay coefficients of variation were

7.6% for LTB₄, 5.3% for LTC₄, and 12.4% for PGE₂. Experiments with exogenous compounds showed a good correlation between amounts added and amounts measured. Overall correlations for measured *v* added were 0.998 for LTB₄, 0.988 for LTC₄, and 0.990 for PGE₂ (n = 6). Cross reactivity and sensitivity of all three radioimmunoassays has been previously described.^{22, 23} The lower limits of detection by radioimmunoassay were: LTB₄ 0.2 pg, LTC₄ 1 pg, and PGE₂ 2 pg.

STATISTICAL METHODS

The influence of age, sex, smoking, use of prednisolone or second line treatment, *Helicobacter pylori* colonisation, and NSAID use on each of the dependent variables was analysed by stepwise multivariate regression analysis with the SPSS programme (statistical package for social sciences). Non-parametric methods were used with significance determined at the 5% level. The Mann-Whitney U test was used for pairwise comparisons where the influence of independent variables was identified as significant by the multivariate analysis. Results are expressed as medians (interquartile ranges).

Results

PATIENTS

Overall 65 patients taking NSAIDs for arthritis and 23 control non-users were analysed. Table I shows characteristics of sex, age, smoking, and duration of NSAID use. Of 65 patients taking NSAIDs nine had endoscopic evidence of ulceration (six gastric, three duodenal), as defined by a mucosal lesion greater than 3 mm in diameter with definite depth. Seventeen had gastric erosions, mainly confined to the antrum. Sixteen patients had minor gastropathy consisting of submucosal or petechiae haemorrhage and the remaining 23 patients had endoscopically normal mucosa. Twenty five of the patients taking NSAIDs were positive for *Helicobacter pylori* as determined by histology and CLO test. Of the 23 control subjects who did not use NSAIDs ulceration was present in five (three gastric, two duodenal), five had erosions, and 14 had an endoscopically normal mucosa. Twelve of these controls were positive for *Helicobacter pylori*. Twenty (31%) patients taking NSAIDs had a histologically normal antral gastric mucosa. Twenty (31%) patients had a type C (chemical) gastritis, and the remaining 25 (38%) had a type B (active) gastritis. *Helicobacter* organisms were identified in all but two patients with type B gastritis and in two patients with type C gastritis. (Table II).

TABLE I Patient characteristics and *Helicobacter pylori* colonisation in patients on NSAID treatment and control subjects

	NSAIDs (n = 65)	Controls (n = 23)
Male:female	27:38	11:12
Mean (SEM) age (y)	58.0 (1.3)	58.9 (2.4)
Smokers (%)	16 (25)	8 (30)
Mean (SD) duration of NSAID treatment (y)	4.7 (3.1)	–
<i>Helicobacter pylori</i> colonisation (%)	25 (38)	12 (52)
Endoscopic injury:		
Ulcer	9	5
Erosions	17	5
Haemorrhages	16	0
Normal	23	13

TABLE II Relation of histology to NSAID use and *Helicobacter pylori* colonisation

	NSAID <i>Helicobacter pylori</i>		Controls <i>Helicobacter pylori</i>	
	+	–	+	–
Normal	0	20	0	12
Type C gastritis	2	18	0	0
Type B gastritis	23	2	12	0

Figure 1: Gastric mucosal synthesis of leukotriene B_4 (LTB_4) in 65 patients with arthritis on longstanding NSAID treatment compared with 23 controls. Medians denoted by bar lines.

EFFECT OF NSAID USE ON SYNTHESIS OF EICOSANOIDS

Leukotriene B_4

Treatment with NSAIDs, gastritis, and use of second line treatment were the only independent variables identified as exerting a significant influence on synthesis of LTB_4 in the multivariate analysis.

Median gastric mucosal synthesis of LTB_4 in patients taking NSAIDs as determined by vortex mixing was 0.9 (0.2–2.5) pg/mg ($n=65$). This was significantly higher than the value of 0 (0–0.6) pg/mg seen in controls ($n=23$, $p<0.001$, Fig 1). Similarly when synthesis of LTB_4 was stimulated by calcium ionophore there was also a significant increase in LTB_4 concentrations found in NSAID users (1.5 (0.3–2.6) pg/mg ($n=60$)) compared with non-users (0 (0–0.1) pg/mg ($n=14$)) ($p<0.01$).

The increase in synthesis of LTB_4 seen in patients taking NSAIDs remained significant when the subgroups who were *Helicobacter pylori* positive or negative were analysed separately. Among those patients who were *Helicobacter pylori* positive NSAID treatment was associated with synthesis of LTB_4 of 1.2 (0.4–2.6) pg/mg ($n=25$) compared with 0 (0–0.4) pg/mg in non-users ($n=12$, $p<0.005$). In those who were *Helicobacter pylori* negative NSAID use was associated with LTB_4 synthesis of 0.8 (0–2.2) pg/mg ($n=40$) compared with 0 (0–1.0) pg/mg in non-users ($n=11$) ($p<0.005$). Within the two groups, NSAID users and non-users, there were no significant differences between synthesis of LTB_4 in patients colonised or not colonised with the organism.

A similar pattern of results of enhanced synthesis of LTB_4 with NSAID use across all

subgroups was seen with calcium ionophore stimulation.

Leukotriene C_4

By contrast with LTB_4 , colonisation by *Helicobacter pylori*, but not NSAID use was associated with increased vortex stimulated LTC_4 synthesis. Among NSAID users those with *Helicobacter pylori* colonisation synthesised 3.1 (1.5–4.0) pg/mg ($n=23$) compared with 3.2 (0.6–5.3) pg/mg ($n=12$) in non-users. In those not colonised with the organism synthesis of LTC_4 was 2.0 (1.2–2.8) pg/mg ($n=32$) in NSAID users and 2.2 (0–2.6) pg/mg ($n=11$) in non-users. The values for synthesis of LTC_4 in those colonised with *Helicobacter pylori* were significantly higher ($p<0.04$) than in those not colonised (Fig 2).

Prostaglandin E_2

As found in previous studies patients taking NSAIDs synthesised less PGE_2 than those not taking these drugs. Median gastric mucosal synthesis of PGE_2 stimulated by vortex mixing was 16.2 (8.0–40.3) pg/mg ($n=65$) in NSAID users and 51.4 (22.3–75.0) pg/mg ($n=23$) in non-users ($p<0.001$). Concentrations of PGE_2 were not measured in samples stimulated by calcium ionophore because limited material was available.

CORRELATION OF SYNTHESIS OF LEUKOTRIENES WITH ENDOSCOPIC INJURY

Although there was a trend of higher synthesis of

Figure 2: Influence of *Helicobacter pylori* (HP) colonisation on gastric mucosal synthesis of leukotriene C_4 (LTC_4) in 55 patients with arthritis on longstanding NSAID treatment and 23 controls. Medians denoted by bar lines.

Figure 3: Influence of endoscopic mucosal injury on gastric mucosal leukotriene B₄ (LTB₄) in 65 patients with arthritis on longstanding NSAID treatment. Medians denoted by bar lines.

LTB₄ in those NSAID subjects with endoscopic evidence of more severe mucosal injury this did not reach statistical significance. Patients with ulceration or erosions synthesised 2.2 (0.1–3.0) pg/mg of LTB₄. In comparison those with only submucosal haemorrhages synthesised 1.0 (0.4–2.1) pg/mg and those with an endoscopically normal mucosa synthesised 0.7 (0.0–1.7) pg/mg ($p=0.11$, Fig 3). By contrast no such trend was seen with synthesis of LTC₄. In NSAID users with ulcers or erosions synthesis of LTC₄ was 1.9 (1.2–3.1) pg/mg LTC₄ ($n=22$) compared with 2.8 (1.2–3.7) pg/mg ($n=20$) in those with a normal mucosa ($p=0.4$).

CORRELATION OF SYNTHESIS OF LEUKOTRIENE WITH GASTRITIS

Synthesis of LTB₄ was also measured in patients according to the histological state of antral biopsies. All controls with type B (active) gastritis were *Helicobacter pylori* positive with LTB₄ values of 0 (0.0–0.4) pg/mg, whereas those who were *Helicobacter pylori* negative all had a normal histological appearance and values of 0 (0.0–1.0) pg/mg. In patients taking NSAIDs those with type C (chemical) gastritis synthesised LTD₄ concentrations of 2.2 (0.4–3.0) pg/mg, significantly higher than 0.6 (0.0–0.9) pg/mg in patients with a normal mucosa ($p<0.008$). Patients with type B gastritis synthesised 1.0 (0.4–2.6) pg/mg, again significantly higher than those with a normal mucosa ($p<0.02$, Fig 4).

By contrast there were no significant differences in synthesis of LTC₄ in NSAID users between those with type C gastritis (2.3 (1.5–3.0) pg/mg) compared with those with normal mucosa (1.8 (1.2–2.8) pg/mg) although enhanced synthesis in those with type B gastritis (3.2 (1.5–4.0) pg/mg) reflected the higher concentrations seen in patients colonised with *Helicobacter pylori* ($p<0.02$).

CORRELATION OF SYNTHESIS OF LEUKOTRIENES WITH SECOND LINE TREATMENT

The use of second line drugs in the management of rheumatoid arthritis was also identified as an independent variable that significantly influenced leukotriene concentrations. Thus in patients taking NSAIDs synthesis of LTB₄ was 2.2 (0.8–4.5) pg/mg ($n=24$) in those taking second line treatment compared with 0.8 (0.0–2.3) pg/mg ($n=41$) in patients not on these drugs ($p<0.006$). In patients taking NSAIDs but not taking second line treatment synthesis of LTB₄ was still significantly higher than in controls ($p<0.005$). Use of prednisolone, however, did not influence synthesis of LTB₄. Synthesis of LTC₄ was also unrelated to second line treatment (2.3 (1.4–3.5) v 2.8 (1.6–3.9) pg/mg).

Discussion

In this paper we have shown that longstanding NSAID treatment in patients with arthritis is associated with increased gastric mucosal synthesis of LTB₄ compared with controls. This increase was seen whether synthesis was stimulated by vortex mixing or by calcium ionophore and persisted across subgroups of patients with or without mucosal damage and with or without *Helicobacter pylori* colonisation. Our study also shows that NSAID treatment results in reduced gastric mucosal synthesis of PGE₂, as is well known,²⁴ but no significant changes in synthesis of LTC₄ related to NSAIDs.

Although age and sex did not influence the results, enhanced synthesis of lipoxigenase products has been reported in the synovial fluid and

Figure 4: Relation between gastritis as assessed histologically and gastric mucosal synthesis of leukotriene B₄ (LTB₄) in 65 patients with arthritis on longstanding NSAID treatment. Medians denoted by bar lines.

tissue of patients with rheumatoid arthritis or spondyloarthritis²⁵ and it is possible that this was a confounding variable. As most patients with rheumatoid arthritis take NSAIDs it may be difficult to discriminate between these factors. We also found an independent correlation between second line treatment and increased LTB₄ concentrations that may either reflect a pharmacological effect or a correlation with disease activity. The confounding use of second line drugs does not explain the increased synthesis of LTB₄ seen in patients taking NSAIDs overall. Dexamethasone has also been reported to suppress leukotriene activity in vitro¹¹ although we found no effect of low dose prednisolone in this study. Similarly, although smoking is known to suppress gastric mucosal cyclo-oxygenase activity^{26,27} we found no correlation with synthesis of LTB₄.

Accurate assessment of mucosal eicosanoid concentrations is notoriously difficult. Biopsy trauma is itself a stimulus to the synthesis of eicosanoids, but tissue fragments used for short incubation periods overcome the problems of tissue viability and both mechanical and chemical stimulation of synthesis of leukotriene are well established methods of generation under standardised conditions.^{28,29} Extraction procedures were the same in patients and controls and values can be regarded as an index of the capacity of the mucosa to synthesise eicosanoids.

Previous studies in humans have shown that synthesis of leukotrienes correlates with gastroduodenal mucosal injury. In patients with duodenal ulcers gastric and duodenal mucosal synthesis of LTB₄ and synthesis of LTC₄ were raised compared with controls and were significantly reduced after the ulcer healed.³⁰ Similarly we found a trend towards higher synthesis of LTB₄ in patients with endoscopic evidence of injury. Increases of both LTB₄ and LTC₄ have also been reported with gastritis associated with *Helicobacter pylori*.^{31,32} We also found enhanced synthesis of LTC₄ associated with *Helicobacter pylori* colonisation. There was, however, no significant enhancement of LTB₄ associated with *Helicobacter pylori* colonisation among patients taking NSAIDs. Values were too low to judge whether there was any effect associated with *Helicobacter pylori* colonisation in controls.

Our study does not identify the mechanism by which NSAID treatment leads to enhanced synthesis of LTB₄. Although the possibility that inhibition of cyclo-oxygenase results in diversion of the substrate arachidonic acid down 5-lipoxygenase pathways has been much discussed it has been difficult to confirm. In vitro concentrations of indomethacin that completely block cyclo-oxygenase seem to increase production of 5-hydroperoxy-eicosatetraenoic acid (5-HETE), another lipoxygenase product in leukocytes.³³ Peskar, however, found that high doses of indomethacin actually inhibited synthesis of LTC₄ in rat gastric mucosa.¹⁹ As this inhibition was less than the accompanying inhibition of PGE₂ it was possible to argue that some substrate diversion might have occurred, although weak inhibition of the 5-lipoxygenase enzyme by indomethacin seems a simpler and more plausible explanation. Clayton and col-

leagues have reported findings in isolated rat stomach antrum in vitro where indomethacin enhanced the release of LTB₄ as well as LTC₄, LTD₄, and LTE₄ in the presence of calcium ionophore A23187,¹⁷ but other studies by Wallace *et al* have failed to show any increase in gastric mucosal synthesis of LTB₄ after acute administration of indomethacin.¹⁸ We have shown enhanced LTB₄ with no significant effect on LTC₄ in patients on NSAID treatment. This raises the possibility that a mechanism other than substrate diversion is involved or that the various eicosanoids arise from different cellular sources and substrate diversion only occurred in a cell capable of synthesising LTB₄ but not LTC₄. Synthesis of LTB₄ by gastric mucosal epithelial cells has been reported³⁴ and it is possible that these are an important source of the increased concentrations we have seen in patients taking NSAIDs.

An alternative explanation of the raised synthesis of LTB₄ is that it is a secondary consequence of gastritis or injury related to NSAIDs. The multivariate analysis showed significantly increased synthesis of LTB₄ in NSAID users, however, compared with controls independent of the degree or type of the accompanying gastritis. Again there was a dissociation between LTB₄ and LTC₄ with significant increases in LTB₄ being particularly associated with type C gastritis and increases in LTC₄ with type B gastritis associated with *Helicobacter pylori*. Increases in LTC₄ could be secondary to the invasion of inflammatory cells that accompanies *Helicobacter pylori* colonisation and that characterises type B gastritis. By contrast type C gastritis is characterised by foveolar hyperplasia and elongation and tortuosity of vessels together with oedema, vasodilatation, and congestion with a paucity of inflammatory cells. Our data confirm the previous reports of an association with NSAID use.³⁵⁻³⁷ The paucity of inflammatory cells in the lamina propria that is usually seen with this type of gastritis makes it difficult to argue that the increased synthesis derives from inflammatory cells. If gastric mucosal epithelial cells are the main source of LTB₄,³⁴ enhanced synthesis could simply be a consequence of the hyperplastic epithelium characteristic of chemical gastritis. Conversely, these hyperplastic features could be taken to imply epithelial remodelling possibly under the influence of a chemical mediator. Our data raise the possibility that LTB₄ is a candidate for this role as it is plausible that LTB₄ contributes to the vascular changes and oedema that characterise type C gastritis.

If NSAIDs directly enhance leukotriene synthesis this may also contribute to mucosal injury. Whereas removal of prostaglandin dependent mucosal defence mechanisms remains a central mechanism in the development of gastric mucosal injury related to NSAIDs, this could be enhanced by increased synthesis of leukotriene, as LTB₄ attracts and activates polymorphonuclear leucocytes^{5,6} and peptidoleukotrienes are potent vasoconstrictors capable of increasing vascular permeability and causing microcirculatory stasis.^{7,8} Establishment of a causal role for leukotrienes in the pathogenesis of

mucosal damage has, however, remained elusive. Studies in rats have shown a correlation between gastric damage induced by ethanol and other agents and endogenous LTC₄ concentrations,^{8,9,11} and infusion of peptidoleukotrienes can potentiate ethanol mediated gastric damage.¹⁰ Although some studies have shown lipoxygenase inhibitors to be protective,¹²⁻¹⁴ more recent studies have not.^{15,16} Dietary replacement of arachidonic acid by eicosapentaenoic acid results in an enhanced resistance to ethanol induced gastric damage. This might be due to the accompanying reduction in synthesis of the 4 series leukotrienes.³⁸

More recent reports suggest that acute indomethacin induced gastric mucosal injury in rats is accompanied by neutrophil adherence to mesenteric microvascular endothelium and that the severity of gastric injury can be greatly reduced by prior neutrophil depletion with neutrophil antibodies.²⁶ Moreover neutrophil adhesion to the endothelium seems to correlate with increased LTB₄ concentrations and adhesion is prevented by inhibitors of the synthesis of leukotrienes.³⁹ This finding suggests a direct interaction between NSAIDs, synthesis of LTB₄, and mechanisms of subsequent mucosal injury. Measurement of gastric mucosal leukotrienes in humans after acute dosing with indomethacin and other NSAIDs and investigation of the effects of other inhibitors of 5 lipoxygenase will be necessary to define more precisely the role of leukotrienes in mucosal injury related to NSAIDs.

In conclusion, we have shown that enhanced in vitro synthesis of LTB₄ by human gastric mucosa occurs with NSAID use and is strongly associated with type C gastritis. There are reasons to believe that the association may be a primary affect of drug treatment, which could mediate some of the pathological changes associated with NSAID use rather than a secondary consequence of these changes.

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