Non-steroidal anti-inflammatory drugs as a possible cause of collagenous colitis: a case-control study

R H Riddell, M Tanaka, G Mazzoleni

Abstract

The use of oral non-steroidal anti-inflammatory drugs (NSAIDs) in 31 patients with collagenous colitis and in 31 matched control patients with irritable bowel syndrome or colonic diverticular disease who had also undergone colonoscopy and biopsy was investigated. The long term use (>6 months) of NSAIDs was significantly commoner in the study group (19/31) than in the control group (4/31) ($p < 0.02$), even assuming the most adverse drug history in six patients in whom this could not be established. In all patients with collagenous colitis taking NSAIDs, diarrhoea followed the use of these drugs, and by a mean (SD) of 5.5 (4.4) years (range 0.5 to 15 years). In three patients with collagenous colitis, diarrhoea improved after withdrawing NSAIDs; rechallenge in one was followed by a recurrence of diarrhoea, which improved after withdrawing the drug again. It is suggested that NSAIDs may play an aetiological role in the diarrhoea and thickened collagen band in some patients with collagenous colitis.

Collagenous colitis is an uncommon condition that affects the large bowel, primarily in middle aged and elderly women, and is characterised clinically by watery diarrhoea and histologically by thickening of the subepithelial collagen band with chronic inflammation. Its aetiology is still unclear, although a variety of associated diseases have been reported including not only gastrointestinal diseases such as coeliac disease,^{1,2} collagenous sprue,³ and enterovirus infection⁴ but also systemic diseases such as rheumatic syndromes,⁵⁻⁸ scleroderma,⁵ gout,^{6,7} and thyroid diseases.⁶ Two patients with collagenous colitis in whom there was prior use of non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics have been reported,⁷ and we have noted a similar association with NSAIDs in many of our patients. One report raised the question of an association with caffeine,⁹ which can cause an increase in the fluid load to the colon.¹⁰

In view of the association with many different types of arthritis, NSAIDs could theoretically be expected to be used more frequently in patients with collagenous colitis. Some of our patients seemed to benefit symptomatically from withdrawal of medications which included NSAIDs. We therefore wondered if the association between this disorder and NSAID use was more than coincidental because of their use in arthritis associated with collagenous colitis.

This study aimed to investigate whether there is a causal relationship between collagenous colitis and NSAID use in our patients, and if so the nature of the temporal relationship between

the onset of diarrhoea and the use of NSAIDs, the type of NSAID used together with the time for which it had been used, and whether any patient responded to withdrawal or rechallenge.

Methods

Patients with collagenous colitis were identified by review of the surgical pathology files of McMaster University Medical Centre and the records of weekly gastrointestinal biopsy conferences from 1985 to early 1990. The thickness of the subepithelial collagen band was measured in two well-oriented and thickest points of each colorectal biopsy specimen using haematoxylin and eosin slides (and trichrome stain if needed) and a calibrated eye piece graticule. The mean thickness of the collagen band (MTCB) was calculated at each site within the large bowel. From published reports, the normal collagen band is less than 7 μm ,^{5,11,12} and reported cases of collagenous colitis have a collagen band thicker than 10 μm .^{15,11} On the basis of these data, biopsy specimens with both a $\text{MTCB} \geq 10 \mu\text{m}$ and mucosal inflammation at any site within the large bowel, together with a history of diarrhoea for which no other cause could be found, were used as the diagnostic criteria for collagenous colitis. Patients with other conditions that might cause diarrhoea, such as radiation, infective and pseudomembranous colitis, and inflammatory bowel disease were excluded from this study by review of clinical records. However, two patients with collagenous colitis and coeliac disease that failed to respond fully to a gluten free diet were included.

The control group, which closely matched the above patients for age and sex, was randomly sampled from patients with irritable bowel syndrome or colonic diverticular disease who also had endoscopically normal mucosa and in whom large bowel biopsy specimens had been taken. The diagnosis of irritable bowel syndrome was based on the Manning criteria.¹³

Clinical records and telephoned or written replies from physicians and/or collagenous colitis or control patients were obtained with the patients' consent and were reviewed to investigate whether and why NSAIDs had been taken. The temporal relationship with the use of NSAIDs and the specific NSAID used were also established. Patients were defined as having taken long term NSAIDs if they had done so for at least six months before colorectal biopsy in the control study, and six months before diagnostic biopsy in patients with collagenous colitis. In the latter group these specimens also had to have a $\text{MTCB} \geq 10 \mu\text{m}$. The use of NSAIDs for at least six months was chosen arbitrarily to exclude occasional use for other symptoms such as fever, headache, or dysmenorrhoea.

Department of
Pathology, McMaster
University Medical
Centre, Hamilton,
Ontario, Canada
R H Riddell
M Tanaka
G Mazzoleni

Correspondence to:
Dr R H Riddell, Department
of Pathology, McMaster
University Medical Centre,
1200 Main Street West,
Hamilton, Ontario, L8N 3Z5
Canada.

Accepted for publication
12 August 1991

The χ^2 test was used for statistical analysis of independent variable of positive and negative use of NSAIDs between patients with collagenous colitis and those in the control group.

Results

Thirty two patients with diarrhoea of unexplained aetiology and a MTCB $\geq$ 10 μ m and mucosal inflammation in colorectal biopsy specimens were identified. A 2 year old girl was excluded because of difficulty in finding an appropriate matched control patient. The study group consisted of 28 women and three men, with a mean (SD) age of 62.7 (13.0) years (range 33 to 87 years).

The control group consisted of 21 patients with irritable bowel syndrome and 10 with colonic diverticular disease. There were 28 women and three men, with a mean age of 61.3 (12.4) years (range 30 to 86 years). All of these patients had large bowel biopsy specimens with normal or minimally inflamed mucosa and a MTCB<4 μ m.

ASSOCIATION WITH THE USE OF NSAIDS

The use of oral NSAIDs and the type, dose, and length of ingestion in 31 patients with collagenous colitis and 31 control patients is summarised in the Table. In the study group, over a period of six months before their first biopsy specimen with a MTCB $\geq$ 10 μ m, NSAIDs had been taken by 19 patients (in the Table patients a-f had taken double or triple NSAIDs and details of the drug sequence in these patients are provided in the Figure) and 10 had no history of NSAID use. In the control group only four patients had taken NSAIDs and 23 had no history of NSAID use. NSAID use in two patients with collagenous colitis and four of the control group was unclear – the patients were unsure, the treating physicians could not be located, or the notes were unavail-

able. Statistical analysis showed that NSAID use was significantly more prevalent in patients with collagenous colitis than in control patients ($p<0.02$), even though we assumed that the most adverse drug history was present in the six patients with an unclear drug history – that is that the two patients in the collagenous colitis group had not been taking NSAIDs and the four in the control group had been taking them. Had these simply been excluded the p value would have been <0.0005 using Fisher's exact probability test. Both daily dosage and total dosage varied markedly (Table). The two patients with both collagenous colitis and coeliac disease had no history of NSAID use.

TEMPORAL RELATIONSHIP WITH NSAID USE

In all 19 patients with collagenous colitis taking NSAIDs, their use preceded the onset of diarrhoea. The period of NSAID use before the onset of diarrhoea varied from 6 months to 15 years, with a mean of 5.5 (4.4) years (Table and Figure) in these.¹⁹ In three patients (patients a, f, and h in the Figure) diarrhoea improved immediately after stopping NSAIDs but they did not undergo biopsy subsequently. These patients were also treated simultaneously with other medication for their symptoms, but none were taking drugs known to cause diarrhoea. Unrecognised rechallenge with ibuprofen in one patient (patient h) was followed by a recurrence of diarrhoea, which started after the same period of ingestion as before (six months) and improved again immediately after stopping ibuprofen. Changes in the type of NSAID (patients f and g) or a reduction in dose (patient b) seemed to have little effect (Figure).

TYPE OF NSAID USED

Acetylsalicylic acid was most commonly used by patients with collagenous colitis (enteric coated aspirin in eight, aspirin in three), and was followed by naproxen in three, ibuprofen in three, indomethacin in two, sulindac in two, and others (Table).

ASSOCIATED DISEASES

Associated diseases for which NSAIDs had been administered to patients with collagenous colitis were rheumatoid arthritis in six, osteoarthritis in one, unspecified arthritis in nine, low back pain in two, and transient ischaemic attacks in one. No patient with collagenous colitis but no history of NSAID use had arthritis. Arthritis was present in six control patients four of whom had been taking NSAIDs.

Discussion

A relationship between arthritis and collagenous colitis is well recognised but, as in our series, many different types of arthritis have been reported,⁵⁻⁸ which makes it difficult to postulate a mechanism that would explain the association. Of our 19 patients with collagenous colitis taking NSAIDs, 18 were taking them for arthritis or low back pain and one was taking them for other

Use of non-steroidal anti-inflammatory drugs (NSAIDs) before symptoms in patients with collagenous colitis and control subjects

NSAIDs	Collagenous colitis			Control subjects		
	Patients (n=31)	Dosage (mg/day)	Years*	Patients (n=31)	Dosage (mg/day)	Years†
	19			4		
Salicylic acid, enteric-coated aspirin	8	650 1300 3900	5, 15 2, 5, 11 ^a 4 ^b , 6, 8 ^c	2	325 1300	3 5
Aspirin	3	650 2600	3, 15 ^d 2	1	325	5
Naproxen	3	250 500 750	2 10 5			
Ibuprofen	3	800 1200 2400	8 ^e 0.5 2 ^f			
Indomethacin	2	75 200	0.5 11 ^g			
Sulindac	2	400	1 ^h , 4 ⁱ			
Tiaprofenic acid	1	600	0.5 ^j			
Ketoprofen	1	200	3 ^k	1	150	5
Piroxicam	1	40	0.5 ^l			
Diclofenac sodium	1	100	2			
Tolmetin sodium	1	1200	4 ^m			
No use of NSAIDs	10			23		
Uncertain NSAID use	2			4		

*Years of ingestion before the onset of symptoms.
†Years of ingestion before the biopsy.
Superscript a-f: each represents the same patient; further details of the drug sequence in these patients are provided in Figure.

diseases (transient attacks). Twelve patients with collagenous colitis who had no or an unclear history of NSAID use had no arthritis. All four patients in the control group were taking NSAIDs for arthritis. In addition, in all patients with collagenous colitis taking NSAIDs, their use preceded the diarrhoea. We therefore postulate that the relationship between arthritis and collagenous colitis may be a NSAID associated colonic disease as a result of the treatment of arthritis (and other diseases), and that in some patients with collagenous colitis NSAIDs may play a major aetiological role.

In patients with collagenous colitis, biopsy specimens taken before the formation of a thickened collagen band often show mild to moderate colitis (microscopic colitis), sometimes accompanied by an increase in intraepithelial lymphocytes.^{18 14} These reports support an inflammatory disease with subsequent formation of a thickened collagen band. Furthermore, both 'microscopic colitis' and collagenous colitis are characterised clinically by watery diarrhoea, which is thought to be caused by reduced colonic absorption of water and electrolytes and may have a coexistent secretory component in some patients.¹⁵⁻¹⁷ We therefore suggest that in some

patients 'microscopic colitis' is also caused by NSAIDs ingestion.

There is preliminary evidence to support an association between the long term use of NSAIDs and colitis. Several cases of colitis associated with the use of mefenamic acid have been reported.¹⁸ In a further series, four of 43 new cases of colitis were associated with mefenamic acid or piroxicam ingestion.¹⁹ NSAIDs are also well recognised causes of both small and large bowel ulcers, with or without perforation.²²⁻³⁰ The mechanism may be different, but this provides supporting evidence that NSAIDs can affect the large as well as the small bowel. Small bowel ulceration may heal with multiple areas of stenosis (diaphragm disease),²⁰⁻²² but this has not been reported in the large bowel, nor is it clear whether these patients are predisposed to 'microscopic colitis' or collagenous colitis.

The mechanism by which NSAIDs cause colitis and subepithelial collagen band thickening remains unclear. However, injected ¹¹¹Indium labelled neutrophils localise to the terminal ileum in up to two thirds of patients with rheumatoid arthritis on long term NSAIDs but not in untreated patients, and this finding is accompanied by an increase in intestinal permeability demonstrated by an excess absorption of ⁵¹Cr-EDTA (ethylenediaminetetra acetic acid).²³⁻²⁵ Although one study²⁶ has suggested a possible primary role of rheumatoid arthritis in the intestinal inflammation, another study using healthy volunteers has shown that intestinal permeability after NSAID ingestion increases significantly compared with control values.²⁷ In addition, normal intestinal absorption of EDTA, which is absorbed primarily through the paracellular pathway rather than across the cell, can be greatly reduced by coadministration of a prostaglandin analogue (misoprostol).²⁸ Prostaglandin is also thought to be able to prevent indomethacin induced small intestinal inflammation.^{29 30} It is therefore possible in some patients that in the large bowel as well as the small, NSAIDs open the paracellular pathway at least sufficiently for the luminal contents to enter the lamina propria, thereby inducing mucosal inflammation. Although this is also the site of collagen band thickening, the mechanism by which this occurs remains obscure. Local abnormalities of collagen synthesis related to the pericryptal fibroblastic sheath and decreased cell turnover time have been considered as another possible mechanism of collagen band thickening.^{2 8 31 32}

Because 12 patients with collagenous colitis had no history of NSAID use, there may be a variety of aetiological factors in this disease. Other have reported an association with coeliac disease,^{1 2} collagenous sprue,³ or caffeine use.⁹ In our series two patients also had coeliac disease, but neither was taking NSAIDs. Because diarrhoea in both patients failed to respond fully to a gluten free diet but their symptoms were controlled by other means, we doubt that gluten is involved in the mechanism of collagenous colitis.

An intriguing factor in respect of this hypothesis is the long latent interval between the start of NSAID use and the development of symptoms. Assuming that the data are reason-

Temporal relationship of NSAID ingestion in patients who had a complicated drug history, a relationship between withdrawal and cessation of diarrhoea (a, f, h), rechallenge (h), and demonstration that change in the type of drug had no effect on symptoms (f, g).

↑ indicates onset of diarrhoea, ↑↑ its cessation and * time of diagnosis of collagenous colitis.

Uncertain drug use is indicated by dashed lines.

ASA (E): enteric coated aspirin, DIC: diclofenac sodium, IBU: ibuprofen, IMN: indomethacin, KET: ketoprofen, PIR: piroxicam, TOL: tolmetin sodium, TPA: tiaprofenic acid, SUL: sulindac.

ably accurate, the mean was more than five years but in some patients reached 15 years. If a relationship existed with NSAIDs, we expected that it would have been dependent on the dose used or the length of time the drugs had been taken. However, the Table shows that while the disease certainly occurred in patients taking high doses of NSAIDs, it also occurred in those taking relatively small amounts for short periods of time. In view of the relative rarity of collagenous colitis in a population in whom about 10% may be taking NSAIDs, this seems to be a rare complication and may simply reflect an unfortunate individual idiosyncratic sensitivity to the drug. More probably, collagenous colitis is a multistep disease, in which inflammation caused by NSAIDs sets the stage for a further, as yet undetermined, insult that precipitates the disease. Fortunately, our minimum length of time that could be accepted as long term NSAID use (six months) is also the minimum interval between the onset of diarrhoea following the use of NSAIDs. The possibility that some patients taking NSAIDs more than just occasionally could have been excluded because NSAID use was less than six months was investigated by reviewing all the data again: this did not seem to have been the case. The total cumulative dose of NSAIDs could also be important. However, the fact that our patient 'C' required six months of treatment on both occasions, and stopped for nine months only suggests that if this is the case any cumulative effect is lost rapidly after stopping the drugs.

It is unclear how representative our small control group is of the general population, particularly with regard to their use of NSAIDs. In our control group, 4 of 31 patients (13%) were taking NSAIDs. This is similar to the figure obtained by Langman, *et al*¹⁸ in their study in which 8% of their 268 control patients aged over 40 and 10% of those aged over 60 were also taking NSAIDs. Our control group is therefore likely to be reasonably representative of the general population, and the prevalence of NSAID ingestion is unlikely to be artificially low.

In conclusion, this study suggests that NSAIDs may be an aetiological factor in collagenous colitis in a major subgroup of patients (61% in this study) with this disease. Patients taking NSAIDs therefore may warrant investigation for collagenous colitis if they develop watery diarrhoea. When diagnosed as having the disease, stopping NSAIDs should be considered. However, in view of the frequency with which NSAIDs are taken long term in the general population, this is probably an uncommon complication.

We would like to express our thanks to numerous colleagues in the section of Gastroenterology at McMaster University Medical Centre for their constructive suggestions and support. These include Dr R H Hunt, Dr R Goodacre, Dr J Irvine, Dr S Crowe, Dr K Croiteru, Dr B Salena and Dr S Collins. We also thank Mrs Janice Butera for typing the manuscript and Mrs Lydia Wilson for her help in obtaining data.

- 1 Sylwestrowicz T, Kelly JK, Hwang WS, Shaffer EA. Collagenous colitis and Microscopic Colitis: the watery diarrhoea-colitis syndrome. *Am J Gastroenterol* 1989; **84**: 763-8.

- 2 Hwang WS, Kelly JK, Shaffer EA, Hershfield NB. Collagenous colitis: a disease of pericryptal fibroblast sheath? *J Pathol* 1986; **149**: 33-40.
- 3 Eckstein RP, Dowsett JF, Riley JW. Collagenous enterocolitis: a case of collagenous colitis with involvement of the small intestine. *Am J Gastroenterol* 1988; **83**: 767-71.
- 4 Rams H, Rogers AI, Ghandur-Mnaymneh L. Collagenous colitis. *Ann Intern Med* 1987; **106**: 108-13.
- 5 Esselinckx W, Brenard R, Colin J-F, Melange M. Juvenile scleroderma and collagenous colitis. The first case. *J Rheumatol* 1989; **16**: 834-6.
- 6 Jessurun J, Yardley JH, Giardiello FM, Hamilton SR, Bayless TM. Chronic colitis with thickening of the subepithelial collagen layer (collagenous colitis): histopathologic findings in 15 patients. *Hum Pathol* 1987; **18**: 839-48.
- 7 Giardiello FM, Hansen III FC, Lazenby AJ, Hellman DB, Milligan FD, Bayless TM, *et al*. Collagenous colitis in setting of nonsteroidal antiinflammatory drugs and antibiotics. *Dig Dis Sci* 1990; **35**: 257-60.
- 8 Fausa O, Foerster A, Hovig T. Collagenous colitis. A clinical, histological, and ultrastructural study. *Scand J Gastroenterol* 1985; **20** (suppl 107): 8-23.
- 9 Sloth H, Bisgard C, Grove A. Collagenous colitis: a clinicopathological follow-up study. *Eur J Gastroenterol Hepatol* 1989; **1**: 73-6.
- 10 Wald A, Back C, Bayless TM. Effect of caffeine on the human small intestine. *Gastroenterology* 1976; **71**: 738-42.
- 11 Giardiello FM, Bayless TM, Yardley JH. Collagenous colitis. *Compr Ther* 1989; **15**: 49-54.
- 12 Gledhill A, Cole FM. Significance of basement membrane thickening in the human colon. *Gut* 1984; **25**: 1085-8.
- 13 Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. *BMJ* 1978; **ii**: 653-4.
- 14 Giardiello FM, Lazenby AJ, Bayless TM, *et al*. Lymphocytic (microscopic) colitis. Clinicopathologic study of 18 patients and comparison to collagenous colitis. *Dig Dis Sci* 1989; **34**: 1730-8.
- 15 Bo-Linn GW, Vendrell DD, Lee E, Fordtran JS. An evaluation of the significance of microscopic colitis in patients with chronic diarrhoea. *J Clin Invest* 1985; **75**: 1559-69.
- 16 Rask-Madsen J, Grove O, Hansen MGJ, Bukhave K, Scient C, Henrik-Nielsen R. Colonic transport of water and electrolytes in a patient with secretory diarrhoea due to collagenous colitis. *Dig Dis Sci* 1983; **28**: 1141-6.
- 17 Giardiello FM, Bayless TM, Jessurun J, Hamilton SR, Yardley JH. Collagenous colitis: physiologic and histopathologic studies in seven patients. *Ann Intern Med* 1987; **106**: 46-9.
- 18 Hall RI, Petty AH, Cobden I, Lendrum R. Enteritis and colitis associated with mefenamic acid. *BMJ* 1983; **287**: 1182.
- 19 Tanner AR, Raghunath AS. Colonic inflammation and nonsteroidal anti-inflammatory drug administration. An assessment of the frequency of the problem. *Digestion* 1988; **41**: 116-20.
- 20 Langman MJS, Morgan L, Worrall A. Use of anti-inflammatory drugs by patients admitted with small or large bowel perforations and haemorrhage. *BMJ* 1985; **290**: 347-9.
- 21 Nagaraj HS, Sandhu AS, Cook LN, Buchino JJ, Groff DB. Gastrointestinal perforation following indomethacin therapy in very low birth weight infants. *J Pediatr Surg* 1981; **16**: 1003-7.
- 22 Lang J, Price AB, Levi AJ, Burke M, Gumpel LM, Bjarnason I. Diaphragm disease: pathology of disease of the small intestine induced by non-steroidal anti-inflammatory drugs. *J Clin Pathol* 1988; **41**: 516-26.
- 23 Bjarnason I, Williams P, So A, *et al*. Intestinal permeability and inflammation in rheumatoid arthritis: effects of non-steroidal anti-inflammatory drugs. *Lancet* 1984; **ii**: 1171-4.
- 24 Bjarnason I, Zanelli G, Smith T, *et al*. Non-steroidal anti-inflammatory drug-induced intestinal inflammation in humans. *Gastroenterology* 1987; **93**: 480-9.
- 25 Rooney PJ, Jenkins RT, Smith KM, Coates G. ¹¹¹Indium-labelled polymorphonuclear leucocyte scans in rheumatoid arthritis: an important clinical cause of false positive results. *Br J Rheumatol* 1986; **25**: 167-70.
- 26 Segal AW, Isenberg DA, Hajirousou V, Tolfree S, Clark J, Snaith ML. Preliminary evidence for gut involvement in the pathogenesis of rheumatoid arthritis? *Br J Rheumatol* 1986; **25**: 162-6.
- 27 Bjarnason I, Williams P, Smethurst P, Peters TJ, Levi AJ. Effect of non-steroidal anti-inflammatory drugs and prostaglandins on the permeability of the human small intestine. *Gut* 1986; **27**: 1292-7.
- 28 Bjarnason I, Smethurst P, Fenn CG, Lee CE, Menzies IS, Levi AJ. Misoprostol reduces indomethacin-induced changes in human small intestinal permeability. *Dig Dis Sci* 1989; **34**: 407-11.
- 29 Fang W-F, Broughton A, Jacobson ED. Indomethacin-induced intestinal inflammation. *Am J Dig Dis* 1977; **22**: 749-60.
- 30 Robert A. An intestinal disease produced experimentally by a prostaglandin deficiency. *Gastroenterology* 1975; **69**: 1045-7.
- 31 Grouls V, Vogel J, Sorger M. Collagenous colitis. *Endoscopy* 1982; **14**: 31-3.
- 32 Widgren S, Jliidi R, Cox JN. Collagenous colitis: histologic, morphometric, immunohistochemical and ultrastructural studies. Report of 21 cases. *Virchows Arch [A]* 1988; **413**: 287-96.