Histological study of the effects of three anti-inflammatory preparations on the gastric mucosa

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SUMMARY Patients with osteoarthritis were entered into a single-blind trial comparing the effects on the gastric mucosa of a four week course of indomethacin, sulindac and a compound of paracetamol and dextropropoxyphene (Distalgesic). The presence and severity of both acute and chronic gastritis were assessed by histological examination of endoscopic biopsy specimens taken from five standard sites in the stomach of each patient before and at the end of the four week period.

The presence and severity of chronic gastritis was not affected by the treatment in any of the groups. The pattern of acute gastritis was complex, many of the patients having acute inflammatory changes in their initial biopsy specimens. At least one patient in each treatment group developed marked acute gastritis during the treatment period, but a significant overall increase in the severity of these changes was only found in the group treated with sulindac.

A number of anti-inflammatory agents which are not related to corticosteroids have been developed in recent years, and it has been reported that all of them may damage the mucosa of the gastrointestinal tract. One of the first was indomethacin. This has proved to be effective in relieving rheumatic symptoms but it is liable to cause gastric symptoms and to increase the loss of blood from the gastrointestinal tract by an appreciable amount.¹ Attempts have been made to find derivatives of indomethacin equal in anti-inflammatory activity but potentially less damaging to the gastrointestinal mucosa. One such derivative is sulindac which has been found to be much less damaging to the gastrointestinal tract in rats, dogs, and monkeys.² Initial clinical experience with sulindac has been encouraging.¹

The purpose of our study was to compare the effects on the human gastric mucosa of indomethacin, sulindac and a compound of paracetamol and dextropropoxyphene (Distalgesic) in patients with osteoarthritis. Distalgesic was used as a "control" treatment since it was considered unreasonable to expect patients complaining of pain to take dummy tablets, and it is generally believed that this preparation has no gastrointestinal side-effects.

The effect of anti-inflammatory agents on the gut varies from species to species, so that extrapolation of data from one species to another is often mis-

leading. Studies on human subjects are therefore particularly important. Most of the human data on this subject are confined to reports on symptoms of patients participating in therapeutic trials, and studies of gastrointestinal blood loss.¹ Endoscopic studies have been made, but these have relied on the macroscopic appearance of the mucosa³ which we know to be misleading, at least in the case of chronic gastritis. In our study, endoscopy and endoscopic biopsy were used in every case to assess the effect of the three agents on the gastric mucosa.

Material and methods

Thirty-two patients volunteered for and completed the study having given their informed consent. Initially each was treated with Distalgesic (2 tablets tds) for one week, at the end of which an endoscopic examination was made with an Olympus GIF-K endoscope. Any focal lesions were noted and biopsy specimens taken from five standard sites in the stomach, namely the prepyloric antrum (site 1), the mid-lesser curve (site 2), the mid-greater curve (site 3), high on the lesser curve (site 4), and the fundus (site 5). Each patient was then randomly allocated to one of three groups, taking indomethacin (25 mg tds), sulindac (200 mg bd), or Distalgesic (2 tablets tds) respectively, for four weeks. At the end of this treatment period, a further endoscopic examination was made and biopsy specimens taken as before. The

study was “single-blind”—that is, each patient was aware of which drug he or she was taking, while the investigators were not.

The biopsy specimens were floated off the biopsy forceps into normal saline and transferred on to filter paper. They were then uncurled with a pair of needles and orientated so that the mucosal surface was uppermost. After fixation in formol sublimate solution, they were embedded in wax and 5 µm sections were cut. Two sections from each specimen were stained with haematoxylin and eosin, and periodic acid-Schiff-alcian blue respectively, for histological examination.

Acute and chronic inflammatory changes were regarded as separate conditions and were assessed separately in sections from each specimen. To facilitate analysis of the findings, a numerical grading was ascribed to the degree of gastritis found at each site, one relating to the chronic inflammatory changes and another relating to the acute inflammatory changes.

The degree of chronic gastritis was graded according to a scheme based on a simplified version of the classification proposed by Whitehead *et al.*,⁴ which was as follows:

- Grade 0 = normal
- Grade 1 = chronic superficial gastritis
- Grade 2 = mild atrophic gastritis
- Grade 3 = moderate atrophic gastritis
- Grade 4 = severe atrophic gastritis.

A chronic gastritis index could then be calculated.⁵ This is the mean numerical grading ascribed to any

group of biopsy sites, multiplied by 25, resulting in a possible range of 0 to 100. For example, the “overall gastritis index” is defined as the mean of the gradings ascribed to the five sites biopsied at one examination multiplied by 25. Similarly, a gastritis index for one standard site could be calculated from a number of patients. For example, the gastritis index for the prepyloric antral site (site 1) in a group of five patients could be calculated as follows:

Patient	Grading for site 1
1	1
2	3
3	2
4	1
5	0

Gastritis index = $\frac{(1 + 3 + 2 + 1 + 0)}{5} \times 25 = 35$.

- Acute gastritis was graded as follows:
- Grade 0 = no evidence of acute gastritis
 - Grade 1 = mild acute inflammatory changes (Fig. 1)
 - Grade 2 = severe acute inflammatory changes (Fig. 2)
 - Grade 3 = acute inflammatory changes with evidence of erosion.

Specimens were considered to show evidence of erosion if part of the surface epithelium was replaced by slough consisting of fibrin and polymorphonuclear leucocytes (Fig. 3), or if regenerative epithelium was

Fig. 1 Body mucosa showing mild acute gastritis. There is a focus of acute inflammatory cells in the central part of the figure. Haematoxylin and eosin × 150.

Fig. 2 Body mucosa showing severe acute gastritis. There is a marked acute inflammatory infiltration of the lamina propria, migration of polymorphonuclear leucocytes through the epithelium (arrow) and evidence of epithelial damage. Haematoxylin and eosin $\times 100$.

Fig. 3 Pyloric mucosa showing an erosion with fibrin and polymorphonuclear leucocytes (arrow) replacing surface epithelial cells. Haematoxylin and eosin $\times 50$.

seen. An immature appearance, with decreased cytoplasmic mucin content and increased mitotic activity, was regarded as evidence of regeneration (Fig. 4).

The sum of the acute gastritis gradings ascribed to each of the standard sites biopsied at any one examination was defined as the overall acute gastritis grading. This was used as a measure of the overall degree of acute gastritis, the range being from 0 to a possible maximum of 15.

The protocol for the present study was approved

by the Ethical Committee of the Oxfordshire Area Health Authority (Teaching).

Statistical analysis

Wilcoxon's signed rank sum test was used to test the null hypothesis.

Results

Table 1 shows that the treatment groups were well matched in terms of numbers, mean age, and the

Fig. 4 Regenerative epithelium in pyloric mucosa. Immature cells deficient in mucin and with many mitotic figures are arranged in a pseudovillous pattern. Haematoxylin and eosin $\times$ 170.

incidence and severity of chronic gastritis. The endoscopic findings are summarised in Table 2. An erosion was found at the initial examination of one patient. At the second examination, one or more erosions were found in five patients, at least one of whom came from each of the three treatment groups. Other focal lesions were seen on nine occasions. These consisted of red antral spots in eight instances, and small, sessile polypoid lesions in the antrum in the remaining patient.

Table 1 The three treatment groups

	Distalgesic	Indomethacin	Sulindac
No of patients	12	10	10
Mean age (yr)	57.5	55.6	55.1
Male:female ratio	1:2	1:1	
% of group with chronic gastritis	50	60	1:2:3 60
Mean overall gastritis index (chronic)	20.4	25	20

Table 2 Endoscopic findings in patients of three treatment groups

Endoscopic findings	First (pretreatment) endoscopy			Second (post-treatment) endoscopy		
	Dist	Indo	Sul	Dist	Indo	Sul
No focal lesion	8	10	9	7	6	9
Focal lesion	4	0	1	5	4	1
Erosion	1	0	0	2	2	1

Dist = distalgesic.
Indo = indomethacin.
Sul = sulindac.

Fig. 5 Chronic gastritis index for each biopsy site before and after treatment of 32 patients with one of three anti-inflammatory agents for four weeks. There was no significant change in the severity or distribution of chronic gastritis during the treatment period for the group as a whole.

CHRONIC GASTRITIS
More than half (56%) of the patients had some degree of chronic gastritis in their initial set of biopsy specimens. There was no significant change in the degree or distribution of chronic gastritis at the second examination when all 32 patients were considered together (Fig. 5). There was no significant change in the overall gastritis index in any of the

Fig. 6 Overall chronic gastritis index before and after treatment of patients in each treatment group. The open circles represent patients without chronic gastritis on either occasion.

Table 3 Gastritis index and grading for each patient in three treatment groups

Age	First (pretreatment) endoscopy	Second (post-treatment) endoscopy	Overall gastritis index (chronic)	Overall acute gastritis grading
Distalgesic				
66	85	6	85	4
45	55	4	35	0
46*	40	3	15	0
50*	30	0	30	4
61*	25	6	50	6
62*	10	0	10	1
58*	0	0	0	0
65*	0	0	0	0
64	0	0	0	0
62*	0	0	0	0
45*	0	0	0	0
66*	0	0	0	10
Indomethacin				
62	60	3	50	0
54*	50	3	45	2
66	45	11	55	11
62	45	0	20	0
54	40	0	30	2
58*	10	0	25	0
66	0	0	0	0
35	0	0	0	3
64	0	0	0	10
35*	0	0	0	9
Sulindac				
64	55	6	60	9
44	55	4	45	6
64*	45	5	35	4
54*	20	0	25	0
65*	20	0	25	6
67	5	0	0	0
40*	0	0	0	0
58*	0	0	0	0
46	0	0	20	4
49	0	0	10	10

*Treated with an anti-inflammatory agent during the 30 days before entering the trial.

treatment groups when these were considered separately (Fig. 6).

ACUTE GASTRITIS

The overall gastritis index (chronic gastritis) and the overall acute gastritis grading are shown for each patient at each examination in Table 3. Specimens taken at the initial examination of a number of patients in each group showed acute gastritis. It is interesting to note that all of these patients also had an appreciable degree of chronic gastritis. Seventeen of the patients had been taking anti-inflammatory agents of various sorts in the 30 days before entering the study. Some patients had acute gastritis at the first examination and this raised the question of the effects of previous medication possibly persisting beyond the one week interval between stopping such treatment and the initial endoscopy. This does not appear to be so since these 17 patients seemed to have had no greater chance of having acute changes in their initial biopsy specimens than the remaining patients who had not been taking anti-inflammatory drugs before entering the study.

Six patients, whose biopsy specimens obtained at the first examination were entirely normal, developed acute gastritis during the treatment period, this being severe and widespread in four instances. This occurred in patients from each treatment group. Fig. 7 shows the overall acute gastritis grading before and after treatment for each patient. Taking the 32 patients as a whole, there was a significant increase in the overall acute gastritis grading during the treatment period ($p < 0.025$). Taking each treatment group separately, there was no significant difference in the overall acute gastritis grading for the patients taking Distalgesic. Of the 10 patients who were given

Fig. 7 Overall acute gastritis grading before and after treatment in each treatment group. The open circles represent patients without evidence of acute gastritis on either occasion. Some patients from each treatment group developed acute gastritis, but a significant increase in the acute gastritis grading was found only in the sulindac group.

indomethacin, the acute gastritis remained unchanged in one, improved in two, but deteriorated in four. This apparent overall deterioration was not statistically significant. There was, however, a significant deterioration in the acute gastritis found in specimens obtained from the patients who were treated with sulindac ($p = 0.03$): five patients showed an increase in the degree of acute gastritis, and only one showed a slight improvement.

Discussion

The findings in relation to acute gastritis were unexpected as sulindac is less damaging than indomethacin to the gut of various animals and as sulindac is reported to be relatively free from side-effects when used in human subjects. It has been pointed out, however, that there are marked species differences with respect to the gastrointestinal side-effects of anti-inflammatory agents. Furthermore, it seems likely that acute gastritis, like chronic gastritis, is often a symptomless condition. In our study, erosions were seen endoscopically on six occasions. The patient had complained of gastrointestinal symptoms in only two instances. Acute inflammatory changes were seen in the biopsy specimens taken at endoscopy in five of the six cases. The presence in the remaining patient of an erosion seen endoscopically without any acute inflammatory changes in the biopsy specimens suggests that acute gastritis may be patchy in its distribution.

The association between chronic gastritis and acute gastritis is interesting. The fact that acute gastritis was only seen in association with appreciable degrees of chronic gastritis before the treatment period suggests that there is a relation between these two forms of gastritis. On the other hand, the most dramatic acute gastritic changes occurred in patients whose initial biopsy specimens were entirely normal.

Various prostaglandins have a remarkable ability to protect the gastric mucosa against the effects of a number of noxious agents in rats.⁶ It has been reported that endoscopic biopsy specimens from patients with chronic gastritis contain increased amounts of prostaglandins.⁷ Indomethacin is a powerful inhibitor of prostaglandin synthetase activity, as is a metabolite of sulindac.² Paracetamol also exhibits a degree of prostaglandin synthetase inhibition under some circumstances.⁸

It is tempting to speculate that the dramatic occurrence of severe, generalised, acute gastritis seen in at least one patient in each treatment group was caused by inhibition of gastric mucosal prostaglandin synthesis by the anti-inflammatory drugs they were given. If the amount of prostaglandin in mucosa affected by chronic gastritis is greater than

that in normal mucosa, this might explain the absence of similar dramatic occurrences in patients with chronic gastritis. If this is so, however, there must be at least one additional mechanism by which acute gastritis can develop to explain its common association with chronic gastritis.

Conclusion

Acute inflammatory changes, which may lead to erosion of the surface epithelium, can be found in gastric biopsy specimens in the absence of chronic gastritis, although the two conditions frequently coexist. In many instances, the patient has no symptoms, and no abnormalities can be detected endoscopically. As in the case of chronic gastritis, acute gastritis is not always evenly distributed within the stomach. Endoscopic biopsy from multiple sites within the stomach is therefore a highly suitable method for studying this condition.

Acute gastritis developed during the treatment period in patients from each group, but a statistically significant overall increase in acute gastritis was only seen in the group given sulindac. This suggests that, in contrast to its effect on the gastrointestinal tract of other species, sulindac is a cause of acute gastritis in man. The pattern of acute gastritis in the study group of patients suggests that the pathogenesis of this condition is complex.

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