Gastrosopic evaluation of anti-inflammatory agents*

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Summary and conclusions

Gastrosopy was performed in 164 patients with rheumatoid arthritis (RA) and 85 with osteoarthritis (OA) to assess the effects of anti-inflammatory agents on the stomach. The main criterion for entry into the trial was the absence of active gastric lesions on pretreatment endoscopy. The patients were divided into groups to receive one of 12 anti-inflammatory drugs or combinations of these. Gastrosopy repeated at three to six and at 12 months disclosed gastric lesions in 78 cases (31%), patients in both disease categories being similarly affected. Lesions occurred in 41 of the 177 patients (23%) receiving a single drug and in 37 of the 72 (51%) receiving combined treatment. All the anti-inflammatory drugs caused gastric damage, the greatest offender being aspirin (13 out of 26 patients) and the least sulindac and diflunisal (two out of 19 (11%) and two out of 20 (10%) patients respectively). Corticosteroids caused gastric damage in only three out of 21 patients (14%), a lower incidence than expected.

The indiscriminate prescribing of anti-inflammatory drugs to patients with OA is to be deplored. A lack of correlation between the patients' subjective complaints of gastric discomfort and the gastrosopic findings emphasises the unreliability of patients' complaints and the importance of gastrosopy in assessing gastric tolerance. It was not possible to assess minimal prescribing doses or minimum periods of treatment below which gastric damage may be guaranteed not to occur.

Introduction

Gastric injury is a major and undesirable side effect of most anti-inflammatory agents, be they corticosteroids or non-steroidal anti-inflammatory drugs.¹⁻² These drugs are generally thought to be capable of aggravating existing gastric disease and in some instances of actually causing peptic ulceration.³⁻⁸ Evidence exists suggesting that non-steroidal anti-inflammatory drugs, particularly aspirin, can cause acute gastric erosions and microbleeding,⁹⁻¹² but the results obtained in clinical trials and epidemiological studies designed to prove the existence of such a relation have not been conclusive.¹³⁻¹⁵ In clinical trials with patients suffering from rheumatoid arthritis (RA) and treated with various anti-inflammatory drugs the incidence of peptic ulcer has ranged from 4.6%¹⁶ to 31%.¹⁷ An incidence of 31% would appear to favour the hypothesis that patients with arthritis are particularly prone to develop peptic ulcer,¹⁷⁻¹⁸ but this is controversial.

We designed this study to determine the incidence of peptic ulcer in patients with RA or osteoarthritis (OA); the incidence of acute gastric erosions after prolonged treatment with various anti-inflammatory drugs (single- and multiple-drug treatment); and the relation between the gastric damage observed during

single-drug treatment and the drug dosage, duration of treatment, history of peptic ulcer, and sex of the patient.

Patients and methods

We chose for our study 249 men and women suffering from chronic RA (164 patients; 40 men, 124 women) or OA (85 patients; 28 men, 57 women), most of whom had received prolonged treatment with anti-inflammatory drugs. Table I shows the age and sex distributions of the patients. We were unable to include a control group because of the clinical conditions of all the patients studied (all had joint pain or impairment of joint function, or both). Moreover, the purpose of the trial was to assess the effect of long-term treatment, and such patients cannot be left untreated for a long time.

TABLE I—Age and sex distributions of patients studied

Age (years):	≤40	41-50	51-60	≥61	Total
Men ..	7	19	16	26	68
Women ..	24	36	50	71	181
Total ..	31	55	66	97	249

No significant difference in distributions (χ^2 test).

After undergoing endoscopy, at which no patient showed evidence of active mucosal lesions, the patients were allocated to receive either a single drug or combined treatment (table II) according to their clinical requirements, as is usual practice. For the purposes of evaluation in those patients receiving combined treatment we considered the base drug to be that of which the patient was receiving the greatest amount, and each patient was counted once only. Treatment was continued for a minimum of three months; a second endoscopy was performed between the third and sixth months of treatment, and a third endoscopy, when possible, after 12 months' treatment. Endoscopy was also performed whenever the patient complained of symptoms that suggested gastric disease.

TABLE II—Distribution of patients by treatment

Drug given	Single-drug treatment	Multiple-drug treatment	Total
Aspirin (ASA) ..	26	9	35
Indomethacin ..	20	4	24
Ketoprofen ..	11	1	12
Naproxen ..	11	5	16
Diclofenac ..	10	3	13
Ibuprofen ..	17	10	27
Oxyphenbutazone ..	13	4	17
Corticosteroids ..	21	31	52
Sulindac ..	19	1	20
Diflunisal ..	20	0	20
Indoprofen ..	5	0	5
Corticotrophin ..	4	4	8
Total ..	177	72	249

Before endoscopy anaesthesia of the fauces and posterior pharyngeal wall was obtained by persuading the patient to gargle with 2 ml of a 2% xylocaine solution. Immediately before intubation diazepam was given by slow intravenous injection at the rate of 2.5 mg/30 s until the patient became drowsy (usually 10-15 mg). Endoscopy was performed with an oblique-viewing gastroduodenoscope (Olympus GIF-K) and with the patient in the left lateral position. The endoscopic findings were recorded photographically, and the gastric mucosa was evaluated at gastrosopy by the endoscopist (GBP), who was at all times unaware of the drugs being taken. The photographic and gastrosopic observations made referred to tissues lying immediately ahead of or distal to the advancing endoscope. Thus artefacts such as "scope

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tracks" and other evidence of trauma caused by a retreating endoscope were not recorded and any abnormalities could, with greater certainty, be attributed to the drugs ingested.

Patients were seen at monthly intervals, when their general well-being, the state of affected joints, and any dyspeptic symptoms were assessed and noted. Results were assayed by the χ^2 test and Fisher's exact test.

Results

Fifteen of the 164 patients with RA (three men, 12 women; 9%) and nine of the 85 with OA (five men, four women; 11%) showed signs of healed peptic ulcers on endoscopy before treatment (overall incidence 24 out of 249 patients; 10%). Differences between men and women were not significant. Thirty-six patients (including the 24 mentioned above) had a clinical history of peptic ulcer or erosion, or both: 22 (seven men, 15 women) had RA and 14 (six men, eight women) OA. After three months' treatment gastric erosions were present in 41 of the 177 patients receiving a single drug (23%) and in 37 of the 72 receiving multiple-drug treatment (51%), an overall incidence of 31%.

Table III relates the incidence of gastric lesions to the duration of disease. There were no significant differences between the groups. The incidence of lesions was similar in both diseases, being 29% (25/85) in patients with OA and 32% (53/164) in those with RA. The overall incidence was 31%.

TABLE III—Distribution of gastric lesions according to duration of disease. Figures are numbers (%) of patients

Mean duration of disease (and range) (years)							Total			
≤1								1 (1-3)	3 (1-5)	5 (1-10)
<i>Osteoarthritis</i>										
Gastric lesions	..	11 (44)	11 (44)	3 (12)						25
No lesions	..	22 (37)	21 (35)	7 (12)	6 (10)	4 (7)				60
Total	..	..	33 (39)	32 (38)	10 (12)	6 (7)	4 (5)			85
<i>Rheumatoid arthritis</i>										
Gastric lesions	..	11 (21)	15 (28)	6 (11)	16 (30)	5 (9)				53
No lesions	..	..	31 (28)	29 (26)	17 (15)	28 (25)	6 (5)			111
Total	..	..	42 (26)	44 (27)	23 (14)	44 (27)	11 (7)			164

In the 177 patients who received a single drug (table II) the incidence of gastric erosions or ulceration, or both, with each drug was as follows: aspirin (ASA) 50% (13 patients); indomethacin 30% (six); ketoprofen 27% (three); naproxen 27% (three); diclofenac 20% (two); ibuprofen 18% (three); oxyphenbutazone 15% (two); corticosteroids 14% (three); sulindac 11% (two); diflunisal 10% (two); indoprofen 40% (two); and corticotrophin nil. Thus aspirin, indomethacin, ketoprofen, naproxen, and diclofenac can apparently damage the gastric mucosa, while corticosteroids were better tolerated than expected. Too few patients were taking indoprofen and corticotrophin for any conclusions to be reached on these drugs.

When aspirin, which was associated with the highest incidence of gastric lesions, was taken as a reference and the other drugs compared with it the incidence of gastric lesions was significantly lower with corticosteroids, sulindac, and diflunisal ($P < 0.01$) and with oxyphenbutazone and ibuprofen ($P < 0.05$), but not with naproxen, ketoprofen, diclofenac, and indomethacin.

Table IV shows the relations between gastric injury, daily dosage of drug given, and duration of treatment. Again the sample size precluded statistical evaluation, but some interesting trends were seen. In patients receiving aspirin the incidence of gastric lesions appeared to be higher in the higher-dosage group (> 3 g/day) than in the lower-dosage group. In the higher-dosage group most lesions were observed during the first month of treatment. A dose-dependent effect may also have existed with indomethacin: four out of eight patients taking over 100 mg/day developed gastric injury compared with two out of 12 receiving 100 mg daily. The patients receiving 100 mg daily, however, were all treated with suppositories, whereas in those receiving more than 100 mg/day the drug was administered by mouth and per rectum. In the patients receiving corticosteroids gastric lesions were observed only in those who had been taking more than 10 mg prednisone or equivalent daily for over six months. In the patients receiving ibuprofen no lesions were observed in 10 patients treated with 900 mg,

TABLE IV—Incidence of gastric lesions by daily dosage and duration of treatment in patients receiving single-drug treatment (with six selected drugs)

Dosage	Months of treatment						Total
	1	3	≤6	6	>6	12	>12
<i>Sulindac</i>							
<400 mg		0/6		0/3			0/9
400 mg		1/4		1/4		0/2	2/10
		1/10		1/7		0/2	2/19
<i>Diflunisal</i>							
500 mg				1/4			1/4
750 mg		0/11		0/1		1/4	1/16
		0/11		1/5		1/4	2/20
<i>Ibuprofen</i>							
900 mg		0/6		0/4		1/2	1/12
1200 mg		1/2				1/3	2/5
		1/8		0/4		2/5	3/17
<i>Aspirin</i>							
≤3 g	2/6	4/6		0/2			6/14
>3 g	6/6	1/5		0/1			7/12
	8/12	5/11		0/3			13/26
<i>Corticosteroids</i>							
5-7 mg			0/4		0/7		0/11
>10 mg			0/5		3/5		3/10
			0/9		3/12		3/21
<i>Indomethacin</i>							
100 mg	0/1			1/3		0/3	2/12
>100 mg	2/4					2/3	4/8
	2/5			1/3		2/6	6/20

of whom six received treatment for three months and four for six months. Lesions were observed, however, in two out of five patients who received the drug for 12 months or more. In addition, one patient treated with 1200 mg/day showed gastric lesions within the first three months.

Table V relates endoscopic findings and subjective symptoms: 17 of the 41 patients (41%) in whom lesions were seen endoscopically had no clinical complaints, while 28 of the 136 patients (21%) who complained of gastric discomfort had no endoscopic signs of gastric damage. The incidence of gastric lesions was higher in men than women.

Table VI shows that recurrence was seen in 14 (39%) of the 36

TABLE V—Incidence of gastric lesions in patients with or without subjective complaints

	Patients without complaints but with lesions		Patients with complaints but without lesions	
Aspirin ..	..	8/13	..	4/13
Indomethacin ..	..	1/6	..	1/14
Ketoprofen ..	..	1/3	..	3/8
Naproxen ..	..	1/3	..	1/8
Diclofenac ..	..	1/2	..	1/8
Ibuprofen ..	..	2/3	..	5/14
Oxyphenbutazone ..	..	0/2	..	1/11
Corticosteroids ..	..	1/3	..	6/18
Sulindac ..	..	1/2	..	4/17
Diflunisal ..	..	0/2	..	0/18
Others ..	..	1/2	..	2/7
Total ..	..	17/41 (41%)	..	28/136 (21%)

TABLE VI—Recurrence of gastrointestinal lesions in 36 patients with history of ulcer or erosions and in 24 patients with healed ulcers at pretreatment endoscopy

			Recurrence			No recurrence			Total
			Men	Women	Total	Men	Women	Total	
<i>Patients with history of ulcer</i>									
Rheumatoid arthritis	..		4	6	10	3	9	12	22
Osteoarthritis	..	..	2	2	4	4	6	10	14
Total	..	..	6	8	14	7	15	22	36
<i>Patients with healed ulcers before treatment</i>									
Rheumatoid arthritis	..		3	4	7		8	8	15
Osteoarthritis	..	..	4	2	4	3	2	5	9
Total	..	..	7	6	11	3	10	13	24

patients with a history of ulcer or erosions, or both; but in only two of these patients did we observe, along with this recurrence, a new gastric ulcer that could unquestionably be attributed to drug treatment. A recurrence of peptic ulcer was observed in 11 (46%) of the 24 patients with healed peptic ulcers at pretreatment endoscopy (table VI). There was no significant difference between men and women with either RA or OA in recurrence of gastric disease (table VII).

TABLE VII—Incidence (%) of endoscopic lesions by sex and history in patients receiving single-drug treatment

	All patients	Patients with history of peptic ulcer	Patients with healed ulcers before treatment
All patients . . .	23 (41/177)	39 (14/36)	46 (11/24)
Men . . .	41 (21/51)	46 (6/13)	55 (5/9)
Women . . .	16 (20/126)	35 (8/23)	40 (6/15)
Significance*	P<0.01	NS	NS

*Significance of difference between men and women.
NS = Not significant.

Discussion

The overall incidence of endoscopically confirmed gastric lesions during treatment with anti-inflammatory drugs in this prospective study was 31%. The incidences were similar in patients with OA (29%) and RA (32%) (table III). The duration of disease did not appear to be an important predisposing factor (table III). The high incidence of gastric damage in patients with OA, a disease for which no particular susceptibility to gastric injury has ever been claimed, was most probably due to the increasing use of anti-inflammatory drugs by these patients. The incidence of gastric injury ranged from 23% in patients receiving a single drug to 51% in patients receiving multiple-drug treatment. Even though the patients receiving several drugs (mainly cortisone derivatives, aspirin, indomethacin, and ibuprofen) included those with the most severe disease, we believe that the concomitant administration of these drugs was directly related to the incidence of gastric damage. All these drugs have the same mechanism of action¹⁹—that is, they remove prostaglandin-supported defence mechanisms.

The tendency of rheumatologists to coadminister several drugs to reduce the cortisone dosage is justified only when such drugs have different modes of action and affect different stages of the inflammatory process. This, however, was probably not the case with the drugs in this study. The incidence of peptic ulcers per se was 10%, which is lower than the 14% observed in the general population.²⁰ In addition, the number of new ulcers developing during this study was extremely low (two out of 249 patients). Most of the patients had already been receiving anti-inflammatory drugs for varying periods of time, so that this complication occurred in subjects who were possibly predisposed to it. The risk of recurrence of old ulcers, however, was high (46%—table VI). This finding emphasises even further the need for caution in treating rheumatic patients with a history of peptic ulcer. If it is true that the use of anti-inflammatory drugs is inevitable in most patients with RA, it is even truer that their use in OA should and can be strictly limited. Indiscriminately using combinations of these drugs is usually unjustifiable in this disease, particularly when a previous peptic ulcer is known or suspected.

In this survey aspirin and indomethacin were the two drugs most frequently associated with gastric toxicity (50% and 30% respectively). Aspirin given to six patients in doses exceeding 3000 mg/day (table IV) caused gastric damage in all six. The 100-mg indomethacin suppository, a most popular route of administration, particularly for the evening dose in RA, was well tolerated: two of 12 patients showed endoscopic evidence of gastric lesions. The newer drugs ketoprofen, naproxen, and diclofenac (at daily dosages of 200, 750, and 125 mg respectively) were not significantly better tolerated than the classical drugs, which contrasts with the findings of other investigators.¹²

Oxyphenbutazone (200–300 mg/day) and ibuprofen (ranging from 900 to 1200 mg/day) were slightly better tolerated than aspirin. We found that at “physiological” doses (5–7 mg of prednisone or equivalent/day) over long periods corticosteroids rarely cause endoscopically detectable gastric injuries, which agrees with the findings of Conn and Blitzer.²¹

The drugs best tolerated by the stomach appeared to be sulindac and diflunisal. The good gastric tolerance of sulindac might be related to its pro-drug property. In effect, it is absorbed in the gastric tract in the inactive form (sulfoxide) and subsequently metabolised in the liver into the active form (sulfide). This process would circumvent the inhibiting action of these drugs on gastric prostaglandins, which probably protect the mucosa. The relatively good tolerance of diflunisal, a derivative of salicylic acid, might be due to its increased pharmacological potency as compared with aspirin. In our experience²² 750 mg of diflunisal is at least as effective as 3000 mg aspirin in treating OA.

The incidences of gastric lesions associated with the various drugs were compared with the incidence associated with aspirin (the highest seen); only corticosteroids, diflunisal, and sulindac differed significantly from aspirin.

Another important feature in assessing side effects of these drugs is the presence of subjective symptoms related to objectively proved gastric lesions. In the group receiving a single drug 17 of the 41 patients (41%) without subjective complaints had endoscopic evidence of gastric lesions (table V). This emphasises the importance of endoscopic control during anti-rheumatic treatment and questions the reliability of previous work in which the gastric tolerance of antirheumatic drugs was assessed exclusively on the basis of clinical symptoms. On the other hand, dyspeptic symptoms without any endoscopic evidence of gastric injury were present in 28 (21%) of 136 patients. This suggests that the correlation between subjective symptoms and the presence of ulcerative lesions is not always clear-cut. When each single drug was analysed separately, using subjective complaints as the parameter, aspirin appeared to have the highest, most pronounced gastric toxicity and the most complaints, while indomethacin was associated with the highest number of patients with no complaints (table V).

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Mini-pump: method of diabetic control during minor surgery under general anaesthesia

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Summary and conclusions

A simple method for maintaining diabetic control during and after minor surgery requiring a general anaesthetic was studied in 20 insulin-treated diabetics. Long-acting insulin was omitted on the night before the operation, and a mini-pump delivering insulin at a rate of 0.5 units/h was strapped to the arm early on the morning of the operation regardless of the time of operation. Insulin was infused at this rate throughout the day, the usual evening dose of insulin given and followed by supper, and the pump then stopped. In all 20 patients studied blood glucose concentrations fell steadily throughout the day. Hypoglycaemia did not occur.

The mini-pump is simple to use and with the same standard insulin dose for all patients maintains satisfactory blood glucose concentrations throughout the day of operation.

Introduction

Many regimens for managing insulin-dependent diabetes during surgery have been described.¹ Unfortunately, blood glucose concentrations tend to fluctuate unpredictably and inadequate control or hypoglycaemia may occur. We have devised a regimen for managing diabetics on the day of operation for those patients undergoing operations requiring a general anaesthetic but no intravenous fluids and after which they may reasonably be expected to be eating and drinking by evening. Our regimen enables the operation to be performed at any time during the day and not necessarily first on the list.

Patients and methods

We studied 20 insulin-dependent diabetics (12 female and 8 male) undergoing surgery. The criteria for selection were that each patient would require a general anaesthetic but no intravenous fluids, and that he would be eating or drinking by the evening of the operation.

The operations performed included photocoagulation in seven patients, removal of a lower-segment caesarean section scar, liver biopsy in a child, teeth extraction in two patients, cleaning and debridement of a bed sore, cauterisation of vulval warts, antral washout, various other ENT procedures in four patients, metatarsal osteotomy, and removal of a retinal detachment implant. We also studied a control group of eight insulin-dependent diabetics (five female and three male) undergoing similar types of surgery (three photocoagulation, two teeth extraction, one antral washout, and two orthopaedic drainage procedures).

The patients in both groups were longstanding diabetics (duration of diabetes seven to 50 years). All apart from one in the test group had been receiving insulin from the time of diagnosis of diabetes. Sixteen of the patients in the test group and seven controls had had at least one episode of ketoacidosis during their lives, and in all the diabetes had been diagnosed before the age of 30 years. The mean ($\pm$ SD) daily requirement of insulin in the test group was 48.2 ± 15.2 (range 24-80) units and in the controls 44.5 ± 15.2 (range 24-72) units. The mean age of the patients in the test group was 41.8 ± 17.1 (range 9-71) years and in the control group 44.1 ± 16.8 (range 13-65) years.

The regimen used for the test group is as follows. Only soluble insulin is given on the evening before operation and the medium-acting insulin omitted. The mini-pump is set up first thing in the morning and blood glucose concentrations measured. The mini-pump is so called because it is light and portable and may be attached by a strap around the arm or by a holster for long periods; it is a miniature version of larger insulin infusion pumps used in acute diabetic emergencies. There are several models: we used the Mill Hill Infuser (fig 1) (Muirhead Ltd, Beckenham, Kent), but a good alternative is the Syringe Driver type MS16 (Pye Dynamics). Both pumps are battery operated and drive a syringe in which soluble insulin is diluted in physiological saline with no additives. The pump is connected to a peripheral arm vein by means of a "butterfly" indwelling needle. Insulin is infused at a standard rate of 0.5 units/h throughout the day of operation. The operation may conveniently be performed at any time during the day. Feeding is resumed that

FIG 1—Mini-pump attached to arm and connected to peripheral vein by "butterfly" indwelling needle.

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