Antiprostaglandin synthetase activity of nonsteroidal anti-inflammatory drugs and gastrointestinal micro-bleeding: a comparison of flurbiprofen with benoxaprofen

A. C. YEUNG LAIWAH,¹ T. E. HILDITCH,² P. W. HORTON,²
AND J. A. HUNTER³

From the ¹University Department of Medicine, Western Infirmary, Glasgow, the ²Department of Clinical Physics and Bio-Engineering, West of Scotland Health Boards, and the ³University Department of Medicine, Centre for Rheumatic Diseases, Glasgow

SUMMARY By using ⁵¹Cr-labelled erythrocytes and ¹⁴¹Ce-labelled microspheres to correct for daily variations in faecal output, gastrointestinal microbleeding was measured in hospital patients with rheumatoid arthritis before and after administration of 2 propionic acid derivatives. These were flurbiprofen and benoxaprofen, respectively a potent and a weak prostaglandin synthetase inhibitor. Increased faecal blood loss occurred consistently with flurbiprofen and not with benoxaprofen. Our results provide indirect evidence for the cytoprotective effect of prostaglandins on the gastrointestinal mucosa in man. The quantitative correlation between faecal occult blood loss as measured by the above techniques and the Haemocult slide test is also discussed.

In recent years many nonsteroidal anti-inflammatory drugs (NSAID) have appeared on the market with the claim that they produce fewer gastrointestinal side effects, the most important of which is gastric bleeding.¹⁻³ The majority of these drugs have been shown to have an inhibitory effect on prostaglandin (PG) synthesis as assessed by in-vitro tests; the suggestion has even been made that their clinical effectiveness as anti-inflammatory agents parallels their antiprostaglandin activity.^{4,5} Experiments using several animal models have firmly established that a large number of prostaglandin compounds exert a cytoprotective effect on the mucosa of the gastrointestinal (GI) tract.^{6,7} If prostaglandins were to have a similar cytoprotective effect in man, it might be argued that no antiprostaglandin analgesic would be completely free from producing gastric damage.

The discovery of benoxaprofen, a weak PG synthetase inhibitor,⁸ allowed us to compare its gastrointestinal effect with flurbiprofen, reputedly a potent prostaglandin synthetase inhibitor.⁹ Both

drugs are propionic acid derivatives. In this study we measured the amount of gastrointestinal micro-bleeding before and after administration of these two NSAID at therapeutic doses in patients suffering from rheumatoid arthritis.

Patients and methods

Six patients suffering from classical rheumatoid arthritis¹⁰ were entered into the study. None of them had any known cardiac, hepatic, or renal diseases. Particular care was taken to exclude patients with a previous history of prolonged dyspepsia, peptic ulcer, and gastrointestinal bleeding. Proctoscopy was carried out to exclude any local source of anorectal bleeding. The patients were selected for inpatient treatment with bed rest and physiotherapy; many of these patients had unsatisfactory social circumstances. The purpose of the study was fully explained to each patient, whose consent was obtained only after 3 days' stay in the research unit to assess the situation. The option to withdraw from the study at any time was given to the patient at the onset of the study period. The clinical details of the patients are given in Table 1.

A seventh patient with rheumatoid arthritis with a

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Correspondence to Dr A. C. Yeung Laiwah, University Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow G11 6NT.

Table 1 Clinical details of patients with rheumatoid arthritis

Case no.	Sex	Age (years)	Weight (kg)	Duration of disease (years)	Other diseases	Drug treatment on admission
1	M	72	60	20	Migraine	*NSAID, dihydrocodeine
2	F	74	68	30	Varicose veins	NSAID, diazepam
3	F	70	57	7	Nil	NSAID, diazepam
4	F	59	43	8	Nil	NSAID, penicillamine
5	F	57	63	5	Nil	NSAID, paracetamol, temazepam
6	M	60	61	5	Nil	NSAID, nitraxepam, prednisolone 5 mg/day
7**	F	65	62	6	Chronic duodenal and gastric ulcers	NSAID cimetidine

*NSAID = nonsteroidal anti-inflammatory drugs. **Case 7 not included in statistical analysis of results.

documented past history of duodenal and gastric ulcers was studied separately. Before admission she had been treated with numerous NSAID 'under cover' of cimetidine. Endoscopy carried out before the study period revealed no active lesions but evidence of healed gastric and duodenal ulcers. She was then maintained on cimetidine, 200 mg t.d.s. and 400 mg nocte throughout the study period.

Tests were performed to identify those factors that might contribute to an increased bleeding tendency, namely, platelet count, clotting profile, and leucocyte ascorbic acid level. Table 2 gives the results of investigations performed on admission. The 3 patients with subnormal leucocyte ascorbic acid levels were given vitamin C supplements throughout the study period.

Faecal blood loss was measured by a standard technique after an intravenous injection of ^{51}Cr labelled autologous erythrocytes (50 μCi) at the onset of the study period.¹¹ To correct the blood loss in each faecal collection for variations in daily faecal output the patient received a daily dose of 0.2 μCi cerium-labelled (^{141}Ce), inert, nonabsorbable microspheres (3M Company). The ^{141}Ce -activity was measured simultaneously with ^{51}Cr -activity in each

stool specimen and used to correct the blood loss to a 24-hour basis.¹² The radiation dose from the ^{51}Cr and ^{141}Ce was considered acceptable and approved by the Administration of Radioactive Substances Advisory Committee.

Every stool specimen passed was tested within 1 hour for faecal occult blood (FOB) by the Haemoccult (R) spot test. The aim was to compare the sensitivity of this method with the ^{51}Cr -haemoglobin stool content.

Design of study. This was an inpatient study over a 6-week period starting with 1 week's run-in prior to which all NSAID were stopped. This was followed by a treatment period of 2 weeks when the patient was given either flurbiprofen or benoxaprofen in an open, randomised, cross-over fashion. After the first treatment period there was a wash-out period of 1 week followed by the second treatment period of 2 weeks with the other drug.

Drug treatment. Flurbiprofen 1 $\times$ 50 mg tablets q.d.s. or benoxaprofen 1 $\times$ 600 mg tablet at night Paracetamol 1 g t.d.s. was prescribed regularly throughout the study period; additional doses of 1 g were given as required.

Clinical assessment. The standard measurements

Table 2 Laboratory data at beginning of study period

Case no.	Hb (g/dl)	Platelets ($10^9/l$)	Prothrombin and partial thromboplastin time	Leucocyte ascorbic acid (fmol/WBC) ($n=1.1-2.8$)	Whole blood folate (nmol/l)	Serum vit B ₁₂ (pmol/l)	ESR (mm 1st h)	RF titre	ANF titre	DNA binding capacity (%)
1	13.0	304	Normal	1.50	426	154	68	1/512	1/16	0
2	12.8	145	Normal	0.70	274	309	80	1/2048	1/256	0
3	12.5	312	Normal	1.20	453	575	85	1/256	0	0
4	10.8	210	Normal	1.00	537	472	64	1/1024	1/1000	6.6
5	15.6	160	Normal	1.20	342	413	27	1/128	0	0
6	12.3	300	Normal	1.20	351	310	56	1/16	1/16	0
7	12.4	368	Normal	0.80	206	502	74	1/512	0	0

Conversion: SI to traditional units: whole blood folate 1 nmol/l = 0.441 ng/ml. Serum vitamin B₁₂ pmol/l = 1.356 pg/ml. WBC = white blood cells. ESR = erythrocyte sedimentation rate. RF = rheumatoid factor. ANF = antinuclear factor.

used to assess efficacy of NSAID were performed at weekly intervals. These were: duration of morning stiffness, walking distance over 30 metres, articular index, joint circumference measurements, patient's assessment of pain on a visual analogue scale, patient's own overall assessment, and physician's overall evaluation.

Results

Variations in the daily rate of blood loss in the 6 patients treated with benoxaprofen and flurbiprofen are shown in Figs. 1 and 2. The data are combined and plotted in Fig. 3. It is clear that in all cases gastrointestinal microbleeding was increased after treatment with flurbiprofen as compared with benoxaprofen. In most cases the maximal effect of flurbiprofen seemed to occur during the second week of treatment. Individual response in terms of the maximal faecal daily blood loss varied considerably over the range of 3–14 ml/day. There is suggestion, especially from the histogram of case 4, that a wash-out period of 1 week may not always be adequate. In

Fig. 1 Corrected daily faecal blood loss for patients given benoxaprofen first.

Fig. 2 Corrected daily faecal blood loss for patients given flurbiprofen first.

the histogram of case 3 an increase in faecal blood loss occurred during the first week of treatment with benoxaprofen. It is interesting that this happened at a time when the patient had an influenza-like illness with looseness of the stools for a 3-day period.

For statistical analysis the mean daily blood loss over the last 4 days of each week of study was calculated. The results are shown in Table 3, where the patients are grouped according to which of the 2 drugs they were given first. Faecal blood loss was calculated from the last 4 days of each week of study for the following reasons: (i) this would compensate for the time taken for the effect of treatment to be reflected in the counting of the stool specimen; (ii) any tendency for there to be a carry-over effect from previous therapy would be minimised; (iii) this would give some indication of how the effect of the drug increased with time; (iv) the use of this measure would enable this study to be compared with other recently published work on gastrointestinal blood loss in which stool collections were made for limited periods of study.

Fig. 3 Combined results for mean daily faecal blood loss for each study week. Each line represents mean results of 3 patients.

Because of the small number of patients in each group nonparametric tests could not be applied to each group separately. The data were therefore combined, but to minimise the carry-over effect of the first drug treatment only results from the second week of each drug treatment period were examined. The small increase in faecal blood loss that followed treatment with benoxaprofen as compared with the run-in period (0.39 and 1.07 ml/day in the 2 groups) was not significant overall ($p > 0.1$ by the Wilcoxon test for pair differences). With flurbiprofen, however, the observed increase in blood loss (6.70 and 4.33 ml/day in the 2 groups) was found to be significant ($p < 0.05$ by both Wilcoxon and the sign test). When the treatment periods with the 2 NSAID were compared, significantly greater gastrointestinal blood loss ($p < 0.05$) occurred with flurbiprofen. Comparison of the rate of blood loss in the first and

Table 3 Estimates of mean daily faecal blood loss (ml) over last 4 days of each study week

Case no.	Run-in week	Benoxaprofen		Washout week	Flurbiprofen	
		Week 1	Week 2		Week 1	Week 2
1	0.85	1.02	1.70	1.81	7.85	12.56
2	0.76	0.39	1.71	0.74	1.33	3.07
3	1.14	2.19	0.53	0.68	2.12	7.24
Mean	0.92	1.20	1.31	1.08	3.77	7.62
SD	0.20	0.91	0.68	0.64	3.56	4.76

		Flurbiprofen			Benoxaprofen	
		Week 1	Week 2		Week 1	Week 2
4	0.90	5.00	10.32	10.80	2.41	3.15
5	0.80	5.22	2.07	1.04	1.04	1.24
6	0.92	2.48	3.22	0.78	1.02	1.42
Mean	0.87	4.23	5.20	4.21	1.49	1.94
SD	0.06	1.52	4.47	5.71	0.80	1.05

second weeks of treatment with flurbiprofen gave no significant difference ($p > 0.1$), though in 5 cases the rate of blood loss was greater in the second week.

Table 4 gives the amount of ^{141}Ce -microspheres retrieved from the same 4-day period stool collections. Clearly with the irregular bowel habits of some patients accurate blood loss estimates would not have been possible without the cerium count.

Fig. 4 illustrates the pattern of blood loss in case 7. At the end of the flurbiprofen treatment period endoscopy was repeated: both gastric and duodenal ulcer sites had remained healed; the whole gastric mucosa appeared hyperaemic, but no erosions were noted. A pentagastrin stimulation test was also performed while the patient remained on cimetidine. Gastric acid secretion was found to be greatly reduced, reaching a maximal acid output of 3.4 eq/h after overnight fasting.

Testing for faecal occult blood. The Haemocult test was found to be positive in cases 1 and 4 only when maximal faecal blood loss of more than 10 ml/day occurred as measured by ^{51}Cr activity. The other stool specimens were all negative by

Table 4 Recovery of ^{141}Ce (% daily dose) in last 4 days of each week of study

Case no.	Run-in week	Benoxaprofen		Washout week	Flurbiprofen	
		Week 1	Week 2		Week 1	Week 2
1	317	265	265	419	297	448
2	501	463	234	284	317	268
3	219	287	318	337	458	413

		Flurbiprofen			Benoxaprofen	
		Week 1	Week 2		Week 1	Week 2
4	409	498	376	237	506	400
5	304	433	186	385	433	331
6	75	178	377	125	251	452

Fig. 4 Corrected daily blood loss in patient receiving cimetidine throughout the study period.

Haemoccult testing as directed by the manufacturers' instructions.

No serious side effects were encountered with either drug used. Case 2 developed a mild photosensitive, itchy rash over the face and arms during the second week of treatment with benoxaprofen. The rash rapidly resolved on stopping the drug. Although the present study was not designed to test the efficacy of the NSAID used, both were found to be equally more effective in giving some symptomatic benefit than paracetamol used alone. There was no significant difference in the number of extra paracetamol tablets given to the patients when they were treated with either flurbiprofen or benoxaprofen.

Discussion

It has been shown in several animal models that prostaglandins and some of their methyl analogues exert a cytoprotective effect on the gastric mucosa.^{6,7} Protection was conferred not only against damage from oral and parenteral treatment with NSAID that had antiprostaglandin activity, but also from subsequent local application of necrotising agents as varied as boiling water, absolute ethanol, concentrated salt solution, strong HCl, and strong NaOH solution.¹³ Extrapolation of animal experimental data to man should be made with caution: in rats NSAID can cause severe small intestinal ulceration culminating in fatal peritonitis,^{14,15} yet such complication has not been recognised in man despite widespread use of these drugs.

There is a dearth of evidence for the cytoprotective effect of prostaglandins in man, though such evidence is rapidly accumulating. Recently Cohen¹⁶ and Johansson *et al.*¹⁷ reported that giving PGE₂ orally along with aspirin and indomethacin respectively

prevented the increased faecal blood loss induced by aspirin or indomethacin given alone. The relative antiprostaglandin synthetase activity of benoxaprofen and flurbiprofen is given in Table 5. Our results would give additional indirect support that prostaglandins exert a cytoprotective effect in patients with rheumatoid arthritis in that flurbiprofen, the potent PG synthetase inhibitor, caused increased faecal blood loss consistently, whereas benoxaprofen, the weak inhibitor, did not. Other workers have reported that several NSAID such as indomethacin, aspirin, fenoprofen, and naproxen, which have varying degrees of in-vitro PG synthetase inhibitory activity, also caused increased micro bleeding from the gastrointestinal tract.¹⁶⁻²⁰ Benoxaprofen, probably the weakest antiprostaglandin drug of the group, caused no significant increase in faecal blood loss at the present dose used. It is important to note that in recent clinical trials the same dose of benoxaprofen was found to have comparable analgesic and anti-inflammatory effects to the more established drugs such as aspirin, naproxen, indomethacin, and ibuprofen at therapeutic doses.²¹

By measuring faecal blood loss during the whole 6-week study period it became apparent that maximal blood loss with flurbiprofen occurred in

Table 5 Drug concentrations (IC₅₀ μM) required to inhibit prostaglandin synthetase activity by different in-vitro methods^{8,9}

	Bovine seminal vesicles	Guinea-pig lung	Sheep seminal vesicles	Human rheumatoid synovium
Benoxaprofen	130-210	300-400	150-200	
Flurbiprofen	0.02-7.0	0.7	0.7	0.17
Indomethacin	0.07-20	0.61-3.5	0.45-2.0	0.003-2.2

most cases during the second week of treatment and that more than 1 week would be required after stopping the drug for the increased bleeding tendency to return to base-line. In some previous studies, in which the NSAID tested was given for only 1 week, the increased blood loss might not have reflected maximal mucosal damage.^{17 19 20}

The cytoprotective effect of prostaglandins on the gastric mucosa was shown to be mediated independently of the acid-reducing properties possessed by some prostaglandins.²² The pattern of blood loss seen in case 7, in whom increased faecal blood loss occurred despite cimetidine therapy, might indicate that a similar situation occurs in man. This would question the practice of some physicians to prescribe cimetidine regularly 'to cover' the use of NSAID in patients with previous peptic ulcer or prolonged dyspepsia.²³

CLINICAL SIGNIFICANCE OF INCREASED GASTROINTESTINAL MICROBLEEDING

Chernish *et al.*²⁰ found a good correlation between the measurements of faecal blood loss and endoscopic assessment of gastroduodenal mucosal damage after administration of aspirin and fenoprofen. Measurement of faecal blood loss was, however, a more sensitive indicator of mucosal damage. Most patients who lose about 2–10 ml blood daily can probably compensate for this loss provided they ingest a satisfactory diet, but prolonged loss of more than 10 ml blood/day can cause iron deficiency despite a normal Western diet. Unfortunately many patients with rheumatoid arthritis have a deficient diet because of either a reduced intake or an inability to look after themselves properly. Furthermore, in areas where iron deficiency is common, even the additional loss of less than 5 ml/day may contribute significantly to the anaemia of the rheumatoid patient.

The other important question that remains to be answered is whether a relationship exists between GI microbleeding, the presence of gastric lesions as assessed endoscopically, and acute upper GI haemorrhage. Acute upper GI haemorrhage is relatively rare^{24 25} in contrast to microbleeding, which occurred in all our patients treated with flurbiprofen, and to observable gastric lesions, which have been reported in as many as 50% of patients treated with various NSAID.^{26 27} The possibility remains that other factors such as a subscorbic state,²⁸ alcohol,²⁹ or other as yet unidentified factors, as seen in case 3, may have an additive damaging effect to the mucosa to precipitate a significant haemorrhage. So long as the NSAID in use has anti-PG activity the risk of haemorrhage will probably exist, particularly in those individuals who may have an increased susceptibility

to mucosal damage by these drugs. Already the addition of supplementary prostaglandin to NSAID has been proposed as a means of preventing gastric mucosal damage.¹⁷ Further investigations are needed to determine not only the effects of such a measure on other metabolic pathways but also whether the added prostaglandin would not impair the anti-inflammatory effect of these drugs.

The high false negative results obtained with the impregnated guaiac slide test—Haemoccult—highlight the difficulties inherent in the use of this test to detect faecal occult blood. This is important, as this is being widely advocated as a screening method for colonic cancer.³⁰ The Haemoccult test was positive in 2 of our patients only when faecal blood loss exceeded 10 ml/day, in keeping with the observation of Stroehlein *et al.*³¹ that at least 10 ml blood/day was necessary to obtain a positive test in the majority of cases. Winawer³² recommended that several precautions should be taken when using this test—for example, the avoidance of ascorbic acid supplements, which may cause a false negative result. Three of the patients in our study were given ascorbic acid supplements without knowledge of this fact at the time.

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