Gut, 1985, **26**, 359–363

Non-steroidal anti-inflammatory drugs and peptic ulcer perforation

D ST J COLLIER AND J A PAIN

From the Ipswich Hospital, Ipswich, Suffolk

SUMMARY A retrospective study is reported in which the ingestion of non-steroidal anti-inflammatory drugs (NSAID) in 269 patients with perforated peptic ulceration and 269 age/sex matched controls admitted between 1973–1982 was compared. A highly significant statistical difference was found ($p<0.001$) in those aged over 65. There was no statistical difference, however, in those aged under 65. Furthermore we have shown a highly statistically significant correlation ($p<0.0001$) between the annual number of patients aged over 65 with perforated peptic ulcers taking NSAID and the annual number of prescriptions issued for these drugs in the region. No such correlation was found for patients aged under 65 years. We suggest that the elderly especially women are unduly susceptible to NSAID associated peptic ulcer perforation, and discuss factors that may account for this.

A number of studies have suggested that non-steroidal anti-inflammatory drugs (NSAID) may play an important role in the aetiology of perforated peptic ulcers.[1–3] Non-steroidal anti-inflammatory drugs inhibit the synthesis of prostaglandins which have cytoprotective effects[4–6] in the upper gastrointestinal tract, as well as suppressing gastric acid secretion.[7–10] It has been suggested that the adverse effects of aspirin have been overemphasised,[11 12] and in recent leading articles[13 14] the evidence for NSAID in predisposing to peptic ulceration was questioned.

Although epidemiological studies have reported a fall in the incidence of perforated peptic ulcers[15–17] the decrease in the incidence in men and increase in women alluded to by others[17–20] have not been adequately explained.

The aim of this investigation was to study both the incidence of perforated peptic ulcers and the prescribing patterns of NSAID to observe if any relationship exists.

Methods

PATIENTS

A retrospective study has been performed on all patients admitted with perforated peptic ulcers to this hospital between 1973 and 1982. This hospital provides all the acute services for a population of 300 000. Overall there were 269 patients and they were compared for NSAID ingestion with 269 age/sex matched controls. The diagnosis of perforation was based on operative findings in 235, radiological findings in 15 and at necropsy in a further 19 patients. The data on NSAID intake were obtained by retrospective note review.

Controls were obtained from the hospital admissions register and the first entry matched for age, sex, month, and year of admission was selected. The controls had all been admitted as surgical emergencies, but the diagnosis was not recorded in the register and therefore did not influence selection. Numbers of prescriptions for NSAID to specific age and sex groups have been provided by Intercontinental Medical Statistics Ltd (IMS) – these were based on figures for the United Kingdom (1977–1982 inclusive).

Comparison of NSAID ingestion between patients and controls was assessed by χ^2 test. Information of the annual prescribing pattern of NSAID in the region from 1973–1982 was obtained from the Department of Health and Social Security. These estimates were based on a sample of 1 in 200 prescriptions written by general practitioners and dispensed by retail chemists in this region. Comparison of these figures with the number of patients taking NSAID was assessed by a Spearman's rank test.

Address for correspondence: Department of Surgery, University of Cambridge Clinical School, Addenbrookes Hospital, Hills Road, Cambridge.

Received for publication 8 June 1984

Results

The mean annual incidence of perforated peptic ulcers was 26·6 per year from 1973–1977 (8·9 per 100 000 population per year) and was 27·2 per year from 1978–1982 (8·9 per 100 000). Table 1 shows the annual numbers of patients with perforated peptic ulcers who were recorded as taking NSAID on admission – these totalled 69 (32%) patients with perforated duodenal ulcers and 23 (44%) patients with perforated gastric ulcers. Among patients with perforated peptic ulcers, 19 of 23 with rheumatoid and 73 of 78 with osteoarthritis were taking NSAID and in controls two of three with rheumatoid and 16 of 25 with osteoarthritis were taking these drugs. Age distribution of patients is shown in Table 2. Of patients with perforated duodenal ulcers 63% were men and of those with perforated gastric ulcers 42% were men.

In those aged over 65 there was a statistically significant difference in the recorded ingestion of NSAID between patients with perforated peptic ulcers and age/sex matched controls ($p<0·001$), however, in those aged under 65 there was no statistical difference ($p<0·5$) Table 3. If those patients and controls with arthritis who were not recorded as taking NSAID are assumed to have done so then again the statistical difference remains for those over 65 and is absent for those under 65 years.

A highly statistically significant correlation ($p<0·0001$) was found between the annual number of patients aged over 65 with perforated peptic ulcers taking NSAID and the annual number of prescriptions issued for these drugs in the region. No such correlation was found for patients aged under 65 years (Table 4).

The mean annual numbers of patients admitted with perforated peptic ulcers in both halves of the study within specified age/sex groups is presented in Table 5. A fall is shown in the mean annual number of men aged under 65 and an increase in women over 65 – there being little change in the other two groups (Fig. 1). Perforated peptic ulceration is uncommon in females under 65 years. The number of patients taking NSAID on admission is greater in those aged over 65 and this is especially so in women. The number of prescriptions for NSAID to the same specified age/sex groups in the national population between 1977–1982 is illustrated in Figure 2, and shows an increase to all age/sex groups – the highest level of ingestion being in women aged under 65 years.

Corticosteroids were taken by 16 (7%) of patients with duodenal perforations and 10 (19%) of patients with gastric perforations – however, 15 of these patients were also taking NSAID. In the control group nine patients were taking corticosteroids. Five patients with perforated peptic ulcers, none of whom were taking NSAID, were recorded as taking a full dose of cimetidine on admission.

Table 1 *Numbers per year of patients with perforated peptic ulcers taking NSAID on admission. Number of patients with perforated peptic ulcers admitted in parentheses*

Year	*Duodenal ulcers*	*Gastric ulcers*
1973	3 (22)	2 (7)
1974	6 (20)	1 (4)
1975	5 (29)	2 (2)
1976	9 (19)	0 (2)
1977	8 (20)	2 (8)
1978	6 (20)	1 (2)
1979	5 (22)	1 (3)
1980	14 (24)	1 (3)
1981	4 (20)	9 (15)
1982	9 (21)	4 (6)
Total	69 (217)	23 (52)

Table 2 *Age distribution of patients with perforated peptic ulcers taking NSAID on admission. Number of patients with perforated peptic ulcers admitted in parentheses*

Year	*Perforated duodenal ulcers*	*Perforated gastric ulcers*
20>	0 (4)	0 (0)
20–29	0 (9)	0 (1)
30–39	0 (9)	0 (0)
40–49	3 (23)	0 (1)
50–59	2 (27)	1 (6)
60–69	22 (44)	3 (9)
70–79	27 (67)	12 (21)
79<	15 (34)	7 (14)
Total	69 (217)	23 (52)

Table 3 *Ingestion of NSAID in patients with perforated peptic ulcers compared to age/sex matched controls; for specified age groups*

	Taking NSAID	*No NSAID*	*Total*
*Under 65**			
Controls	6	95	101
Patients with perforated ulcer	13	88	101
Total	19	183	202
Over 65†			
Controls	12	156	168
Patients with perforated ulcer	79	89	168
Total	91	245	336

* $\chi^2 = 2·09$; DF = 1; $p<0·50$ NS with Yates correction.
† $\chi^2 = 67·65$; DF = 1; $p<0·001$.

Table 4 *Annual numbers of perforated peptic ulcers in patients taking NSAID by age group and the annual number of prescriptions for NSAID in this region*

Year	Patients taking NSAID		Prescriptions for NSAID '000s
	Under 65	Over 65	
1973	0	5	262*
1974	3	4	307*
1975	2	5	322
1976	2	7	359
1977	1	9	429
1978	1	6	405
1979	0	6	409
1980	1	14	471
1981	0	13	471
1982	3	10	515

* Old therapeutic classification underestimates by approximately 5%.

Spearman's Rho

Patients aged under 65	Patients aged over 65
RHO = −0·19	RHO = 0·93
t = −0·53	t = 7·01
DF = 8	DF = 8
p NS	p<0·0001

Table 5 *Mean numbers of patients with perforated peptic ulcer in specified age and sex groups admitted annually. Percentage taking NSAID in parentheses*

	1973–1977	1978–1982
Women aged under 65	1·8 (22%)	2·0 (20%)
Women aged over 65	7·8 (51%)	10·6 (66%)
Men aged under 65	9·6 (14%)	6·8 (8%)
Men aged over 65	7·4 (27%)	7·8 (35%)

Discussion

The data on patients and controls were obtained from retrospective note review and there are therefore biases inherent in using such a method. All note reviews were performed by the authors and based on the criteria that NSAID were taken regularly, this information being based on data obtained from referring general practitioners' letters, patients' clinical notes, drug charts, and discharge drug letters. We accept that there may be a small bias underestimating the number of controls on NSAID due to the fact that they had surgical conditions not thought to be drug related. We feel, however, that such biases would not substantially alter the results.

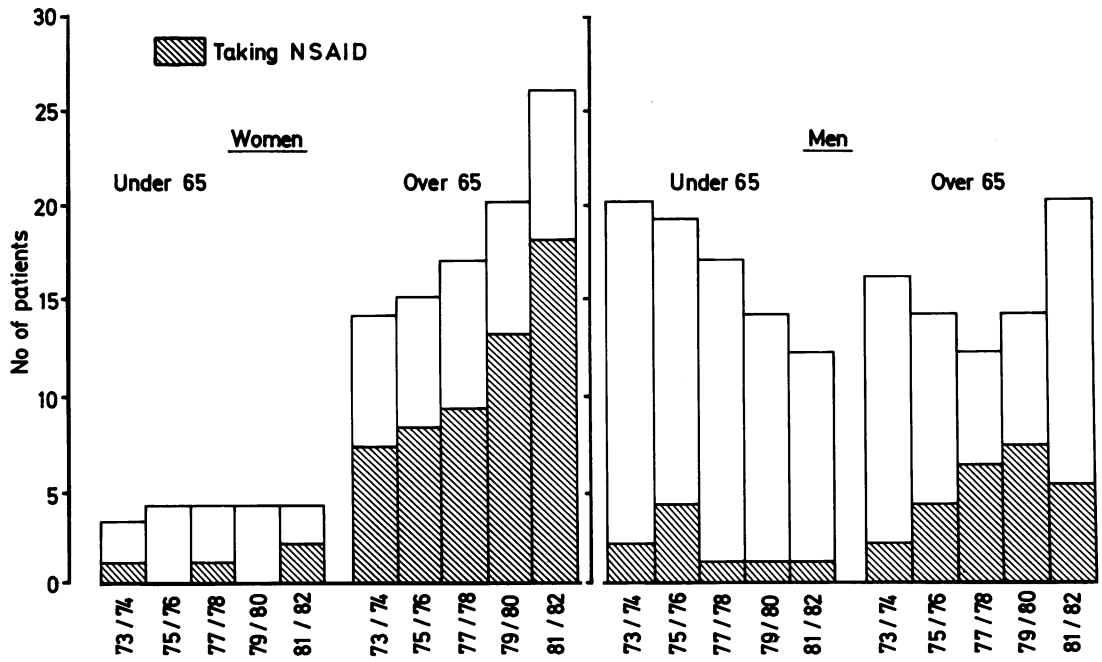

Fig. 1 *Numbers of perforated peptic ulcers in specified age and sex groups.*

Fig. 2 *Annual number of prescriptions for NSAID issued to specified age and sex groups in the United Kingdom between 1977–1982.*

The mean annual incidence of perforated peptic ulcers has remained unchanged between the first and second half of the period studied, there being no change since the introduction of cimetidine in 1977. Overall 34% of patients were taking NSAID and our results, together with the known pharmacological actions of NSAID, add further evidence to implicate them in the pathogenesis of perforated peptic ulceration.

The specified age/sex groups (Table 5), however, show marked differences in the prevalence of patients with perforated peptic ulcers taking NSAID. These differences cannot be explained by the prescribing patterns of NSAID in the United Kingdom (Fig. 2). The largest number of prescriptions for NSAID in the UK were issued to women aged under 65 yet the overall incidence of perforations in this group was very low. Furthermore there was an increase in prescribing of NSAID to every group, yet the percentage of patients with perforations taking NSAID only increased in those aged over 65, especially women. Therefore the elderly, particularly women, appear to be unduly susceptible to the effects of NSAID. This maybe because of pathophysiological changes associated with aging or alterations in external factors such as diet.

Some of the relevant pathophysiological factors associated with aging may include atherosclerosis, hormonal changes or alterations in pharmacokinetics. Local ischaemia caused by atherosclerosis may predispose to ulcer formation[21] and this could be compounded by NSAID which inhibit prostaglandin synthesis so further reducing gastric mucosal blood flow.[22 23] Elderly women seem to be particularly susceptible to perforation and this raises the possibility that postmenopausal hormonal changes may be involved in the pathogenesis. Oestrogens have been used successfully in the treatment of peptic ulceration.[24] As oestrogens and progestogens increase the production of mucus within the stomach[25] postmenopausal women may have a lowered mucus production, and this could be further decreased by the action of NSAID[26] thereby losing cytoprotection. Conversely hormonal protection may account for the low incidence of perforations in women aged under 65 years. Another factor that may influence the action of NSAID is the altered pharmacokinetics that occur in the elderly.[27] No sex difference in the rate of phenylbutazone metabolism, however, has been found.[28]

Relevant external factors may include smoking,[29] diet (low fibre intake,[30 31] low vitamin C,[32] and coffee[33]) and a single cohort effect.[34] It is difficult to assess the importance of any factor in isolation as there is likely to be a complex inter-relationship, and in addition most published work has examined the influence of these factors in non-perforated peptic ulceration.

In conclusion our study offers evidence that NSAID are associated with perforated peptic ulceration in those aged over 65, especially women. We have shown no association between NSAID ingestion and perforated peptic ulceration in those under 65 years. We suggest that certain factors predispose the elderly to be unduly susceptible to NSAID associated perforated peptic ulceration. Further studies should be carried out to identify these factors so that patients at risk may be recognised. If these factors cannot be modified then NSAID should be avoided or protection provided by the concurrent administration of oral prostaglandins or analogues.

We thank Mr W G Hartfall, Mr H M Adair, Dr J L Day and Dr D T Coady, Consultants at Ipswich Hospital, for their helpful advice, Dr R Hanka for statistical analysis and Miss M A Aldridge for secretarial assistance. Figures furnished by the Department of Health and Social Security are Crown copyright and reproduced with the permission of the Controller of Her Majesty's Stationery Office.

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