Non-steroidal anti-inflammatory drugs and peptic ulceration

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There is no definite evidence that non-steroidal anti-inflammatory drugs (NSAIDs), apart from aspirin, cause peptic ulceration in man. In the case of aspirin, studies of large numbers of patients have established a true association between that drug and gastric ulcer [1-3a]. So far, there have been few studies of similar quality on other NSAIDs, although there is an abundance of case reports of NSAID users developing ulcers [4-8]. However, these do not prove a cause and effect relationship between NSAIDs and ulceration as they do not even establish a true association between such drugs and peptic ulcer. It is widely accepted that the relevant literature is inadequate [9,10]. This inadequacy is largely explained by peptic ulcer being relatively common in the general population [11,12]. To demonstrate an association between drugs and ulcers would ideally require a very large prospective study demonstrating that the incidence of peptic ulcer in patients using NSAIDs is higher than in a similar group of people not taking these drugs. The expense involved, as well as difficulties in establishing a valid control group, have been factors preventing such a study from taking place.

An alternative method of showing an association would be to analyse cases of peptic ulcer after presentation and demonstrate a higher use of NSAIDs in patients with peptic ulcer than in a similar group without peptic ulcer. This latter method forms the basis of our study which was confined to investigating the NSAID group as a whole. Limitation to one member of the group would have generated only a small patient sample with a resulting loss of statistical validity.

We restricted the study to elderly patients as they are the most frequent users of these drugs [13]. In addition, peptic ulcer is associated with a significant mortality in this age group [14]. Our earlier work [15] analysed the NSAID use of patients with various upper gastrointestinal lesions such as gastritis. Macroscopic diagnosis of mucosal inflammation is controversial and often does not correlate well with histological analysis [16,17]. The present study is thus limited to patients with definite macroscopic ulceration.

Methods

The Bolton hospitals provide an endoscopy service which includes a session exclusively for the elderly. In the period of the study from April 1980 to January 1984, approximately 400 patients aged 60 and over were examined. All patients were endoscoped for major indications as detailed in Table 1. The standard procedure for flexible upper gastrointestinal endoscopy was followed [18]. Diagnosis of peptic ulcer required visualisation of a gap in the mucosa with the presence of an ulcer crater. The term ulcer includes acute and chronic ulceration. Biopsies were taken routinely from all gastric ulcers. The endoscopists (A.K.B;G.O) had access to the case records at the time of examination.

Table 1. Indications for endoscopy.

| Symptom                | Controls (n = 52) | DU group (n = 64) | GU group (n = 57) |
|------------------------|------------------|------------------|------------------|
| Abdominal pain         | 32 (62%)         | 26 (46%)         | 19 (33%)         |
| Haematemesis/melaena   | 0*               | 27 (42%)         | 24 (42%)         |
| Vomiting/dyspepsia     | 5 (10%)          | 9 (14%)          | 7 (12%)          |
| Unexplained anaemia    | 4 (8%)           | 3 (5%)           | 8 (14%)          |
| Appetite and weight loss | 4 (8%)          | 1 (2%)           | 4 (7%)           |
| Other                  | 9 (17%)          | 3 (5%)           | 0 (-)            |

*Exclusion factor for control group.

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Analysis of the findings was conducted by one of the authors (D.C.) at a later date in a manner designed to eliminate observer bias. All cases were initially allocated to groups on the basis of the endoscopy finding (Fig. 1.) The information was obtained from the endoscopy sheet before the drug history or other clinical details were reviewed. Some cases were later withdrawn from the study on the basis of the criteria shown in Table 2. Those patients taking NSAIDs for less than a week were excluded to minimise the inclusion of people who take analgesics as a response to the symptoms of peptic ulcer [18]. Details of age, sex, smoking habit and alcohol consumption were recorded for members of both control and ulcer groups. Smokers who used 1–4 cigarettes daily were classified as ‘mild’ with 5–14 ‘moderate’, and over 15 as ‘heavy’. Mild alcohol intake was designated as being up to four pints of beer per week, or two glasses of spirits a week. Moderate intake was between this figure and 12 pints of beer or six glasses of spirits per week. Intake above this was classed as ‘heavy’ (see Table 3).

Table 2. Criteria for exclusion from study.

|   |   |
|---|---|
| 1. | Patients with pathology other than peptic ulcer. |
| 2. | Patients with normal endoscopy findings but history of haematemesis and melaena. |
| 3. | All patients on corticosteroids, ethacrynic acid or anticoagulants. |
| 4. | Patients with oesophageal ulceration on emepronium bromide or tetracyclines. |
| 5. | Uncertain drug usage. |
| 6. | Patients using NSAIDs less than 1 week prior to presentation. |

The drug history was obtained from the referring doctor’s letter, the medical casenotes and the nursing records. Patients coming to the Bolton hospitals as arranged admissions are requested to bring their medications with them, and details of all drugs are routinely recorded in the casenotes. Further enquiry took place in about 40 per cent of cases when the patient’s family doctor was contacted by one of the authors (D.C.) at the time of the retrospective study. Details on most of the cases involving use of NSAIDs were confirmed in this way. At the time of the study, all NSAIDs except aspirin were available only on prescription so prescribing records were available. In general, there was good correlation between the family doctors’ records, the hospital case-notes and the patients’ own accounts. However, a total of 15 cases were excluded because of the absence of a satisfactory drug history. Patients in both control and ulcer groups were designated as taking aspirin only if they were regular users of the drug on more than three days per week, in line with the findings of the Boston Collaborative Drug Surveillance Programme [1]. Our study was chiefly designed to assess the ulcerogenicity of NSAIDs other than aspirin. In any case, estimation of occasional use of non-prescribed aspirin would almost certainly have been inaccurate. Patients taking two NSAIDs at the time of presentation were classified as taking both. Patients who had been taking different NSAIDs within four weeks of presentation were also classified as taking both.

Statistical methods

Patients were classified as controls (no evidence of peptic ulceration), DU (duodenal ulcer), GU (gastric ulcer) or OU (oesophageal ulcer). A small number of patients had a combination of ulcers (Table 3) so the three ulcer groups were not mutually exclusive. Also, the smaller number of OU patients precluded a formal statistical analysis of this group; analysis was restricted to separate comparisons of the controls against the DU group and against the GU group.

The demographic data were analysed using the Chi-square test with Yates’ correction factor for frequency data and the Student unpaired t-test adjusted for unequal variances if appropriate for continuous data. The association between NSAID usage and peptic ulceration was assessed using the Mantel-Haenszel method for determining relative risks [20]. Significance was set at 5 per cent.

Results

A total of 175 people were eligible for inclusion in the study proper. These consisted of 52 controls, 57 patients with DU, 53 with GU, 7 with combined ulcers (predominately DU plus GU) and 6 with oesophageal ulcers. Their demographic details are summarised in Table 3. The ratio of males to females in the control group did not differ significantly from that of the DU and GU groups. The mean ages of the three groups did not differ significantly in either sex. Tobacco smoking and alcohol consumption tended to be heavier in the ulcer groups relative to the controls, the difference being more pronounced in female patients. However, no significant differences were found for either sex, possibly because no satisfactory user information was obtained from about one-third of those included in the study.

As shown in Table 4, over 30 per cent of the patients with either DU or GU were NSAID users compared with only 8 per cent of the controls. For the male patients the relative risk of both DU and GU was higher in NSAID users, but did not attain statistical significance. For the female GU group there was a significant association with
NSAID use which remained after the exclusion of heavy users of aspirin and after the further exclusion of users of indomethacin, phenylbutazaone and benoxaprofen. There was also an association between NSAID usage and DU in females. This association remained significant after the exclusion of heavy users of aspirin but became non-significant after the further exclusion of indomethacin, phenylbutazaone and benoxaprofen users. The overall increased risk of NSAID users of either sex developing a peptic ulcer regardless of type was estimated to be 6.68 (confidence limits 3.67-12.8); for non-aspirin NSAIDs the relative risk factor was 5.77 (3.31-10.07).

The indications for endoscopy are detailed in Table 1; 57 of the ulcer group were transfused with an average of four units of blood from the time of endoscopy and of these patients 31 (56 per cent) were using NSAIDs.

The different types of NSAIDs used by patients with ulcers are shown in Table 5. This table includes the results of an estimate of which NSAIDs were used in the catchment area of the Bolton hospitals over the period of the ulcer study [21]. Details of the exact duration of use were available from 33 NSAID users. There was a wide distribution ranging from seven weeks to nine years. Most NSAIDs (69 per cent) had been used for less than six months.

Some 100 cases were excluded from the study because endoscopy revealed lesions other than peptic ulceration. The majority (about 70 per cent) of these showed inflammation such as gastritis. Neoplasia, strictures and varices accounted for the remainder. Another 60 cases were not

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**Table 3. Epidemiological details of patients.**

| Group            | Number (M) (%) | Age (years) Mean (s.d.) | Tobacco users (%) | Alcohol users (%) |
|------------------|----------------|-------------------------|-------------------|-------------------|
|                  | M  | F  | M  | F  | M  | F  | M  | F  | M  | F  | M  | F  |
| All patients     | 74 | 101| 71 (6) | 73 (7) | 63 | 33 | 51 | 16 |
| No ulcer         | 24 | 32 | 72 (5) | 71 (6) | 65 | 50 | 50 | 10 |
| DU only          | 30 | 38 | 71 (6) | 74 (7) | 73 | 36 | 46 | 10 |
| GU only          | 14 | 22 | 69 (7) | 74 (9) | 100 | 33 | 100 | 33 |
| DU + GU          | 1 | 1 | 77 (-) | 69 (1) | NA | 25 | NA | NA |
| DU + OU          | 2 | 1 | 69 (12) | NA (-) | 67 | 33 | 33 | 0 |
| Total DU        | 32 | 43 | 71 (7) | 74 (7) | 67 | 47 | 54 | 31 |
| Total GU        | 17 | 23 | 69 (7) | 74 (8) | 75 | 36 | 50 | 13 |
| Total OU        | 5 | 7 | 73 (11) | 72 (10) | 67 | 25 | 33 | 0 |

NA = not available; M = male; F = female.

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**Table 4. Details of NSAID usage.**

| Group                      | Controls M | F | All DU patients M | F | All GU patients M | F | All OU patients M | F |
|----------------------------|------------|---|-------------------|---|-------------------|---|-------------------|---|
| No. of patients            | 24 | 28 | 32 | 32 | 17 | 40 | 5 | 4 |
| Users of NSAIDs            | 1 | 3 | 7 | 15 | 3 | 20 | 0 | 1 |
| Relative risk*             | - | - | 6.44 | 7.35 | 4.93 | 8.33 | - | - |
| (95% confidence interval)  | (0.73-56.4) | (1.84-29.4) | (0.47-52.1) | (2.16-32.1) |
| Users of NSAIDs excluding heavy aspirin users | 1 | 3 | 5 | 15 | 2 | 17 | 0 | 1 |
| Relative risk*             | - | - | 4.60 | 7.35 | 3.29 | 7.08 | - | - |
| (95% confidence interval)  | (0.304-24.2) | (1.84-29.4) | (0.27-39.7) | (1.82-27.6) |
| Users of NSAID excluding aspirin, indomethacin, phenylbutazaone, benoxaprofen | 1 | 2 | 3 | 6 | 1 | 12 | 0 | 1 |
| Relative risk*             | - | - | 2.76 | 4.41 | 1.64 | 7.50 | - | - |
| (95% confidence interval)  | (0.27-28.5) | (0.79-24.5) | (0.09-28.4) | (1.50-37.5) |

*c.f. control group

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**Table 5. Types of NSAID used by patients with ulcer.**

Numbers in parentheses indicate the number of patients using another NSAID at the same time.

| Drug                  | Number with peptic ulcer using drug | Percentage of prescriptions in Bolton |
|-----------------------|--------------------------------------|--------------------------------------|
| Indomethacin          | 12 (3)                               | 16                                   |
| Piroxicam             | 8 (3)                                | 11                                   |
| Aspirin*              | 6                                    | 7†                                   |
| Ibuprofen             | 6                                    | 36                                   |
| Naproxen              | 4                                    | 8                                    |
| Azapropazone          | 3                                    | 1                                    |
| Benoxaprofen          | 2                                    | 3                                    |
| Flufenamic Acid       | 2 (2)                                | 1                                    |
| Flurbiprofen          | 2 (1)                                | 4                                    |
| Ketoprofen            | 2 (1)                                | 1                                    |
| Diflunisal            | 2 (2)                                | 1                                    |
| Choline magnesium trisalicylate | 1 (1)    | 1                                    |
| Phenylbutazaone       | 1 (1)                                | 1                                    |

*See text
†Also available without prescription
Discussion

We believe our study points to a true association between the use of NSAIDs and peptic ulcer in the elderly. It is necessary to qualify this by pointing out that when subgroups are analysed, it is only in female patients with GU that the association with the NSAID group reaches statistical significance when aspirin and other notorious drugs are excluded. The increased relative risk in other categories of male and female users with both main types of peptic ulcer suggests that a valid association would be demonstrable with larger numbers.

Retrospective studies such as ours can be unreliable because of observer bias and recording inaccuracies. As outlined above, we made every effort to avoid bias. The diagnosis of peptic ulcer was made on the basis of specific macroscopic features as opposed to findings prone to subjective interpretation. Family doctors in our area were unaware of the investigation into NSAIDs until three months before its completion. The number of NSAID users referred for endoscopy did not rise significantly after this date. The endoscopists made no conscious selection for examination of patients on NSAIDs. All examinations were performed for specific reasons, usually for indications such as haemorrhage or abdominal pain. Had there been bias at either the referral stage or at selection for endoscopy, it should have been reflected by increased numbers of NSAID users in the control group as well as in patients with ulceration.

The accuracy of drug histories is crucial to the reliability of this kind of study. In our study, one author collated all the information, thus minimising differences in the intensity of questioning. Information on use of NSAIDs collected at the time of admission was, in most cases, verified at a later date. Apart from aspirin, we are confident about the accuracy of our data on the use of NSAIDs. Aspirin was available without prescription throughout the period of the study, so light aspirin use may have been under-recorded.

A valid control group is also important to the drawing of correct conclusions from the study. The three possible control groups available to us were (a) elderly patients with normal endoscopies, (b) consecutive admissions of elderly patients to hospital and (c) a random sample of 209 elderly people outside hospital collected in a separate study [22]. The number of NSAID users, excluding aspirin, in groups (b) and (c) were 23 and 16 respectively. We opted for the patients in group (a) with normal endoscopies as the other two groups could have contained patients with silent peptic ulcers to which this age group is prone [23,24]. In the event, the NSAID use of the three groups was similar, so it is unlikely that our conclusions would have been altered by use of a different control group. Another aspect of our study was that the control and ulcer groups were not disease matched. Our earlier work [15], which this study incorporates, demonstrated an excess of patients with osteoarthritis and rheumatoid disease in those with gastrointestinal lesions. However, the increased prevalence of rheumatoid arthritis was not sufficient to alter the conclusions of that study, even if one believes that there is a true increase in the prevalence of peptic ulcers in patients with rheumatoid arthritis [25].

The nature of the association between NSAIDs and peptic ulceration is uncertain. Whether it represents cause and effect or a coincidence requires further consideration. Bradford-Hill supplied guidelines for resolving the nature of such associations [26]. Particularly important among these was the strength of the association. Our work demonstrates a relative risk for elderly users of NSAIDs of about six, which is large compared to the estimated factor of 2.4 for corticosteroids [27]. A true temporal association of a drug with ulceration is another major pointer to a causal association. However, the ethical and other problems of mounting trials which will demonstrate evolution of ulceration in large numbers of humans taking a particular drug means that they are unlikely ever to be performed. The same applies to procedures involving rechallenging patients thought to be susceptible to the ulcerogenic effects of a drug. Dose-toxicity information for NSAIDs may become available in the future but satisfactory data are not presently available for most NSAIDs. Jick [28] has suggested a method that partly overcomes this lack of information on the time-relationship of drugs with ulceration. Haemorrhage from an ulcer is an indication that the ulcer is active as opposed to it being a long-standing fibrosed crater. Demonstration of an increased association of NSAIDs with active bleeding ulcers, as occurred in our study, thus provides some support for a causal relationship. The recent findings of McIntosh and his colleagues [3a] of a correct temporal relationship and the knowledge of local and systemic mechanisms by which NSAIDs can damage gastrointestinal mucosa [29–31] provide further support for this concept.

Therefore, the association between NSAIDs and peptic ulceration does seem to represent cause and effect. Extrapolation of this conclusion to younger patients cannot be assumed. Our study supports the recent report of an association of NSAIDs with bleeding ulcers which was also performed in patients aged over 60 [31a]. The finding in that study was that non-aspirin NSAIDs were taken over twice as often by patients with bleeding ulcers as by controls. This is fully compatible with our estimation of a six-fold increased risk of developing a clinically significant ulcer, as only some of these will bleed profusely.

The association of NSAIDs with DU as well as GU in our study is initially surprising as some large studies with aspirin have found the association to be limited to GU. However, it does seem that mucosal protection in the duodenum is similar to that in the stomach [32–34], and so there is no theoretical reason why the duodenum should be totally spared the damaging effects of some of the more potent NSAIDs. The information about the different types of NSAID shown in Table 5 is of limited use. However, the availability of information on drug use in the area where the study was carried out does add...
proportion to some of the findings. The numbers are too small to draw any conclusions about individual drugs but may serve as a pointer for future studies. The demonstration with statistical validity of an association between the NSAID group and peptic ulcer has implications for testing and safety of members of the group. This study and the other mentioned above [31a] have estimated the relative risk for elderly people using drugs of the NSAID group as a whole. Similar estimates of risk are now required for individual NSAIDs.

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The College’s 400th anniversary

Fifty years ago the College was contemplating its 400th anniversary in the midst of war. Various things, from a dinner to up-dating the Roll of the College, were discussed but it was finally agreed that ‘under the present conditions caused by the War it is inexpedient at the present time to arrange for any public celebration, and recommend that the question of commemorating the Quatercentenary should be postponed for six months.’ As it happened, the first World War was four weeks from its armistice when the College slipped quietly into the fifth century of its existence.

The idea of an unofficial celebration came to a group of Fellows serving as physicians to the armies in France. Thanks to the enthusiasm of Michael Foster and Jex-Blake, a dinner was arranged at the Officers’ Club in Boulogne. On the 18th of October, 1918, sixteen Fellows sat down to what proved to be an excellent dinner. Apart from the Old Brown Sherry, the Clos d’Estournelle 1906, Veuve Clicquot 1906 and Dow’s Port 1906 must have gone down well. Sir William Herrington took the chair, the others diners being W. Pasteur, J. Rose Bradford, J. H. Thursfield, J. A. Nixon, A. J. Jex-Blake, W. P. S. Branson, Gordon Holmes, T. R. Elliot, Michael Foster, Charles Miller, C. J. Martin, W. E. Hume, Henry MacCormac, S. W. Curl and A. M. H. Gray. The longest survivor of this dinner, by then Sir Archibald Gray, was assembling his notes on the celebration to record them for the College’s 450th anniversary when he died just before that event.

Over the port the Fellows signed an address, written in elegant Latin by Jex-Blake, to send to the College in London. The address lamented that the College was so little regarded despite producing men of eminence. It went on to describe the medical havoc of war; the verminous trenches and the effects of poison gas were transmuted by the Latin to pediculi necon muscae and vapores noxii. It ended with a greek quotation from Pheidippides: ‘Rejoice for we are victorious.’ Michael Foster carried the address to London and presented it to the President of the College, Dr Norman Moore, after the Harveian Oration. Not to be outdone, the President sat down and wrote a reply, Epistola a dilectissimis Societ nostri in Gallia bellum gerentibus accepta. In this he thanked the Fellows for their dutiful conduct to the College in the midst of danger and ended with the hope of peace with honour, Adsit utinam fausta illa dies, quum ad patriam ad domos ad Collegium redeuntes pacem cum honore referetis. A phrase that rang sadly in the ears of a later generation.