Non-steroidal anti-inflammatory Drugs and Gastrointestinal Adverse Effects

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Non-steroidal anti-inflammatory drugs (NSAIDs) have often been said to cause various gastrointestinal adverse effects. Anecdotal case reports abound but, apart from aspirin, there is no definite proof that NSAIDs cause peptic ulcer in man[1]. This is because large studies are needed to prove that one adverse effect is due to one drug. These large numbers of patients are required because usage of these drugs and gastrointestinal pathology are relatively common[2]. Furthermore, serious adverse effects are probably uncommon. The Boston Collaborative Drug Surveillance Program (BCDSP) used over 16,000 admissions to prove an association between aspirin and various gastrointestinal pathologies[3-5].

While these methods approach the ideal, they are expensive to undertake and may not yield rapid results. With the proliferation of new NSAIDs, a number of case reports[6-9] have implicated them in various gastrointestinal lesions. We felt it necessary to attempt a quick assessment of these claims. To do this with statistical validity, we were limited to the question of whether the drug group as a whole was associated with a range of gastrointestinal adverse effects. We confined the study to elderly patients, as there is an active endoscopy service for the elderly at our hospital, the findings of which could be accurately studied retrospectively. Additionally, the elderly are probably the chief users of these drugs and are more prone than younger patients to the gastrointestinal adverse effects of NSAIDs[5,7,8].

Patients and Methods

Between April 1980 and April 1982 over 200 elderly patients were examined by flexible upper gastrointestinal endoscopy using standard procedure[10]. Every case in this period was eligible for inclusion in the study. All endoscopies were performed for a specific clinical indication (Table 1). A patient’s use of NSAIDs was never a deciding factor in the use of endoscopy. In most cases the endoscopists, G.O. and A.K.B., were unaware of the patients’ medications at the time of examination.

Consecutive case records were examined at a later date. To reduce any observer bias the notes were opened first at the pink endoscopy sheet. Allocation of patients, as indicated in Fig. 1, was done before other case details were examined. The allocation of consecutive cases was continued until the nearest large figure in each group was attained. The mean age of the 150 patients eligible was 75 years.

The term ulcer includes acute and chronic peptic ulcers. The mucosa had to be grossly red and inflamed for the diagnosis of oesophagitis, gastritis or duodenitis to be made. Patients on medications besides NSAIDs that might have caused the lesion were excluded, for example, patients with oesophagitis on tetracycline[11]. Those with lesions suspected of being malignant were also excluded. Cases included in the study were further analysed as far as possible for age, sex, alcohol intake, smoking habit and prevalence of other pathology.

A detailed drug history was obtained for each patient, using the referring doctor’s letter, the admitting doctor’s
Results

The results of the study are summarised in Table 2. Patients listed as taking NSAIDs include three in the lesion group taking their drug in suppository form. The various pathologies and drugs used in the lesion group are shown in Tables 3, 4 and 5. The mean and mode length of use of the drugs were around 15 months.

Table 2. Summary of results of study.

| Lesion Group | Control Group | No. of patients | No. on NSAIDs | (Excluding aspirin) | No. of patients with bleeding lesions on NSAIDs |
|--------------|---------------|----------------|---------------|----------------------|-----------------------------------------------|
| DU           | 50            | 5              | (5)           | 17/36                |                                               |
| GU           | 100           | 34             | (30)          | 3                    |                                               |

Table 3. Pathologies comprising lesion group.

| Pathology                  | No. |
|----------------------------|-----|
| Benign gastric ulcer (GU)  | 35  |
| Duodenal ulcer (DU)        | 33  |
| Oesophagitis               | 20  |
| Acute gastritis            | 5   |
| Combined lesions           | 7   |
| DU and GU                  | 3   |
| DU and oesophagitis        | 2   |
| Gastritis + duodenitis     | 2   |

Table 4. Drug usage in group associated with lesions. (Number in brackets = number using NSAID at same time.)

| Drugs                   | No. of patients | All lesions | Bleeding lesions |
|-------------------------|-----------------|-------------|------------------|
| Indomethacin            | 9(2)            | 5(2)        |                  |
| Piroxicam               | 7(3)            | 5(3)        |                  |
| Ibuprofen               | 5               | 1           |                  |
| Benoxaprofen            | 4(1)            | 3(1)        |                  |
| Naproxen                | 3               | 2           |                  |
| Azapropazone            | 2               | 2           |                  |
| Diflunisal              | 1(1)            | 1(1)        |                  |
| Magnesium choline trisalicylates | 1       | 1           |                  |
| Ketoprofen              | 1               | 1           |                  |
| Phenylbutazone          | 1(1)            | 1(1)        |                  |

Table 5. Number of NSAID users in different lesions.

| Lesion                  | NSAID users | % |
|-------------------------|-------------|---|
| DU                      | 14 of 33    | 42|
| GU                      | 13 of 35    | 37|
| Oesophagitis            | 3 of 20     | 15|
| Acute gastritis         | 1 of 5      | 20|
| Combined lesions        | 3 of 8      | 37|

These results and the various epidemiological data on patients in both groups were submitted for independent statistical analysis. As the probable causal role of aspirin in certain gastrointestinal lesions had already been well evaluated[3,4], we emphasised any correlation of gastrointestinal lesions and NSAIDs, excluding aspirin. Even when aspirin was excluded there was a highly significant association ($P = 0.002$) between the lesions and NSAID use, employing the chi-square test with Yates’ correction factor. When indomethacin, phenylbutazone and benoxaprofen users were also excluded from both groups, one of the control group and 15 of the lesion group were using other NSAIDs, and a significant association remained between NSAID use and upper gastrointestinal lesions ($P = 0.015$). There was a significantly higher proportion of women in the lesion group. In a comparison of women users of NSAIDs, excluding aspirin, the association of lesions with drug use remained, though with a lesser degree of significance. There were three NSAID users out of 22 women in the control group, compared with 26 users out of 55 women in the lesion group. Applying the chi-square test with Yates’ correction factor gave a $P$ value of 0.023.

There was no statistical difference between the control and lesion group when the parameters of age, smoking habit and alcohol intake were considered. The only notable differences in pathology between the two groups, apart from gastrointestinal lesions, were an increased incidence of osteoarthritis (14 per cent) and rheumatoid arthritis (9 per cent) in the lesion group. All patients with these diagnoses were on NSAIDs.

Discussion

We believe that the above data suggest a significant association between upper gastrointestinal pathology and NSAID use. This association remains even after exclusion of aspirin, benoxaprofen, indomethacin and phenylbutazone, all of which have been strongly implicated as causing some of these lesions[3,4,6,7]. Bleeding is an indicator of the acuteness and severity of gastrointestinal lesions; the high proportion of patients who bled on NSAIDs tends to support the conclusion of an association between lesions and drugs.

Several queries could be raised about the methods we used to arrive at these conclusions. As with all retrospective studies, observer bias is possible, although we made every attempt to minimise it, as outlined above. While designing the study, much consideration was given to constituting the most appropriate control group. The possibility of using patients admitted to our acute geri-
atrict medical wards without obvious gastrointestinal disease was considered. However, this group could have contained asymptomatic patients with 'silent' lesions, so it was decided to use patients with normal endoscopy findings even though the examination had been performed for a specific indication. The dilemma about which group to use as a control proved to be largely academic. Of 200 consecutive admissions of elderly patients, 23 were on NSAIDs. This usage is similar to that of the control group we used. The high proportion of women in the lesion group is not easily explained, though it is unlikely to alter the conclusion of our study, as women are less prone to peptic ulcer than men[2]. Female preponderance was also a feature of those with gastrointestinal haemorrhage in the BCDSP. It may reflect increased drug usage by women or a change in the previous epidemiological pattern of the lesions[13]. Another factor in our study was that the control and lesion group were not disease-matched. The excess of patients with osteoarthritis in the lesion group might be explained by their use of NSAIDs. A higher prevalence of peptic ulcer has been noted in rheumatoid arthritis sufferers[14]. However, the 9 per cent higher prevalence of patients with rheumatoid arthritis in our lesion group would not significantly alter the conclusions of our study. Moreover, all were taking NSAIDs.

No particular drug is indicted by the study. The drugs listed in Table 4 probably reflect usage and marketing of drugs in our area, as much as the safety of the named drugs. However, at least two drugs that have aroused some controversy recently, benoxaprofen[7] and piroxicam[8], are prominent on the list.

Proof that the association between NSAIDs and gastrointestinal lesions is causal awaits further studies. New studies are also required to assess the comparative incidence of adverse effects in younger compared to elderly patients. The licensing and release of these drugs is constantly under review. Of particular concern is that, once released, the overall effects of a new product should be carefully monitored in large numbers of the target population, which, with these drugs, usually contains a high proportion of elderly patients.

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