Long term follow up studies for one to four years have not shown any tolerance to the efficacy of the drug or any long term side effects (E H Reynolds *et al*, 18th epilepsy international congress, New Delhi, 1989).[21-23] Vigilance for possible long term toxicity should continue because early studies of toxicity in rats and dogs showed that microvacuoles suggestive of intramyelinic oedema were reversibly formed in the white matter in a dose related manner.[24 25] In dogs microvacuolation was accompanied by changes in the transmission time through the central nervous system of somatosensory evoked potentials, but such changes have not been observed in patients receiving long term treatment.[26 27] No evidence of intramyelinic oedema has been seen in six necropsies and 23 biopsy specimens taken from patients treated with vigabatrin for a mean of 25 months (D Scholey *et al*, Merrell Dow files, personal communication).

The clinical evaluation of vigabatrin has proceeded cautiously, and the drug will be available only for treating epilepsy that is not satisfactorily controlled by other anti-epileptic drugs. Nevertheless, it may prove to be a milestone in the treatment of epilepsy not only because it is the first new antiepileptic drug since the licensing of sodium valproate in 1973 but also because it is the first successful rational approach to the treatment of chronic epilepsy.

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# *Regular Review*

# Non-steroidal anti-inflammatory drugs and peptic ulcers

## *Facts and figures multiply, but do they add up?*

Evidence of an association between non-steroidal anti-inflammatory drugs and peptic ulceration in the elderly has prompted a search for effective prophylaxis.[1 2] The flood of publications giving guidance has, however, washed up some important new questions and inconsistencies.

### The story so far

Ever since aspirin was shown to injure the human gastric mucosa aspirin and non-aspirin non-steroidal anti-inflammatory drugs have been suggested as causes of peptic ulcers.[3] Changes in the rates of perforation and bleeding in parallel with changing patterns of prescribing have reinforced this suspicion.[4-8] Case-control and cohort studies from both Britain and the United States of patients with symptoms of gastric ulceration,[9-15] haematemesis and melaena,[10 13 16-25] perforations,[18 23-28] or death related to ulcers[18 23 24] have shown increased risks in patients taking these drugs. Endoscopic surveys have also reported a high prevalence[29-33] and incidence[1 2 34] of gastric and duodenal ulceration in patients taking non-steroidal anti-inflammatory drugs. Some have suggested that the type of arthritis has an influence, with gastric ulceration being especially common in patients with rheumatoid arthritis,[30 31 33] but others have rejected this suggestion.[12 29]

### How big is the risk?

CASE-CONTROL STUDIES

In general five end points have been used—presentation with gastric ulcer, presentation with duodenal ulcer (whether complicated or uncomplicated), presentation with upper gastrointestinal bleeding (sometimes restricted to presentation with bleeding peptic ulcer), perforation of an ulcer, and death attributable to peptic ulceration. The results of case-control studies have been consistent in associating both aspirin and non-aspirin non-steroidal anti-inflammatory drugs with the development of gastric ulceration (fig 1).

Because most studies have provided raw data an average relative risk can be derived from a simple meta-analysis by the Mantel-Haenszel technique with individual studies as separate strata.[30] When the risks for different periods of ingestion have been quoted in individual studies those for regular ingestion in the past one to four weeks have been used. In studies using both hospital and community controls data relating to community controls have been used. When 95%

confidence intervals were not quoted in the original studies they have been calculated by the method of Miettinen.[36]

Such an analysis puts the pooled relative risk for aspirin at 4·67 (table I) and for non-aspirin non-steroidal anti-inflammatory drugs at 4·03 (table II). For upper gastrointestinal bleeding the association is consistent for aspirin, with an average relative risk of 3·30 for three studies presenting raw data (fig 2; table III). For non-aspirin non-steroidal anti-inflammatory drugs the average relative risk of bleeding is 3·09 (fig 2; table IV) and of perforation 5·93 (fig 3; table V). Studies that record death from ulcers or their complications also show a fairly consistent association, the average relative risk for non-aspirin non-steroidal anti-inflammatory drugs being 7·62 (fig 4; table VI).

Paracetamol has also been associated with gastric ulceration[12] and upper gastrointestinal bleeding (fig 2; table III).[16] A different interpretation is usually placed on this association. Most doctors believe that aspirin and non-aspirin non-steroidal anti-inflammatory drugs cause ulcers but that paracetamol consumption rises as a consequence of the ulcer—perhaps as self treatment for indigestion. This differential interpretation has been based more on belief than evidence but is supported indirectly by recent data showing aspirin to be associated with previously undiagnosed ulcers and paracetamol with those previously diagnosed.[37]

TABLE I—*Studies of gastric ulcer and aspirin*

| | Patients | | Controls | | Relative risk | | 95% Confidence interval |
|---|---|---|---|---|---|---|---|
| | No taking aspirin | No not taking aspirin | No taking aspirin | No not taking aspirin | Quoted | Derived | |
| Gillies and Skyring (1968)[9] | 57 | 43 | 22 | 78 | | 4·70 | 2·58 to 8·56 |
| Levy (1974)[10] | 5 | 21 | 1015 | 14 813 | 3·40* | 3·47* | 1·39 to 8·69* |
| Piper *et al* (1981)[12] | 17 | 39 | 2 | 55 | 17·3* | 12·00* | 3·35 to 42·94* |
| Duggan *et al* (1986)[15] | 17 | 78 | 6 | 89 | 3·0 | | 0·7 to 21·3 |
| Adjusted relative risk | 4·67 (3·06 to 7·14) | | | | | | |
| $\chi^2$ | 49·31 (p<0·0001) | | | | | | |
| Homogeneity $\chi^2$ | 2·47 (p>0·1) | | | | | | |

*Weighted relative risk given by authors but no confidence interval stated; values shown refer to derived relative risk.

TABLE II—*Studies of gastric ulcer and non-aspirin non-steroidal anti-inflammatory drugs*

| | Patients | | Controls | | Relative risk | | 95% Confidence interval |
|---|---|---|---|---|---|---|---|
| | No taking drugs | No not taking drugs | No taking drugs | No not taking drugs | Quoted | Derived | |
| Cooke and Thompson (1981)[11] | 37 | 165 | 10 | 210 | | 4·71 | 2·40 to 9·26 |
| McIntosh *et al* (1985)[14] | 23 | 81 | 8 | 200 | 6·4 | | 2·3 to 18·0 |
| Duggan *et al* (1986)[15] | 20 | 75 | 11 | 84 | 5·0 | | 1·4 to 26·9 |
| Griffin *et al* (1988)[23] | 11 | 23 | 429 | 3468 | 4·2 | | 1·9 to 9·0 |
| Adjusted relative risk | 4·03 (2·80 to 5·78) | | | | | | |
| $\chi^2$ | 55·45 (p<0·0001) | | | | | | |
| Homogeneity $\chi^2$ | 4·83 (p>0·1) | | | | | | |

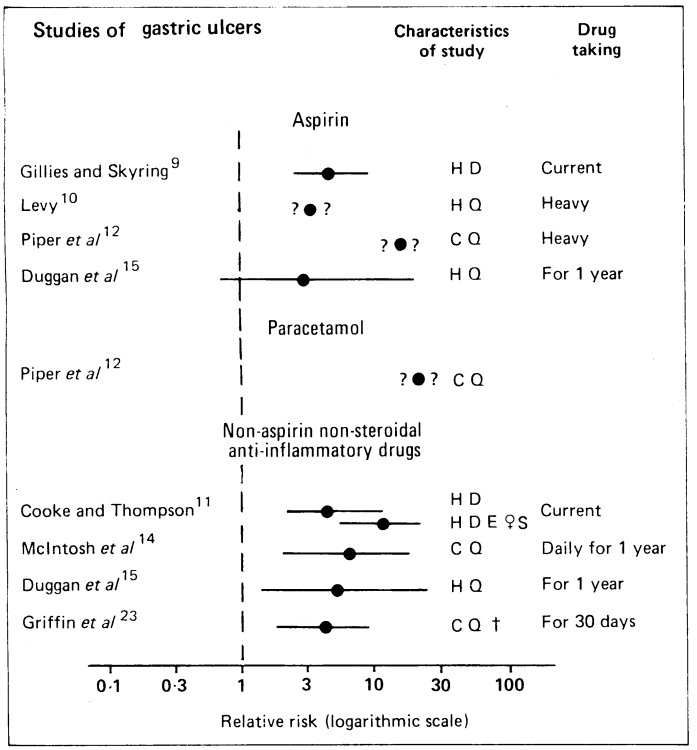


FIG 1—*Relative risks of gastric ulceration for patients taking aspirin, paracetamol, or non-aspirin non-steroidal anti-inflammatory drugs. H=comparison with hospital controls; C=comparison with community controls; Q=quoted values; D=derived values[35]; E=elderly patients (over 60 or 65); ♀=women; †=death attributable to ulceration; S=subgroup analysis; ?=confidence interval not given*

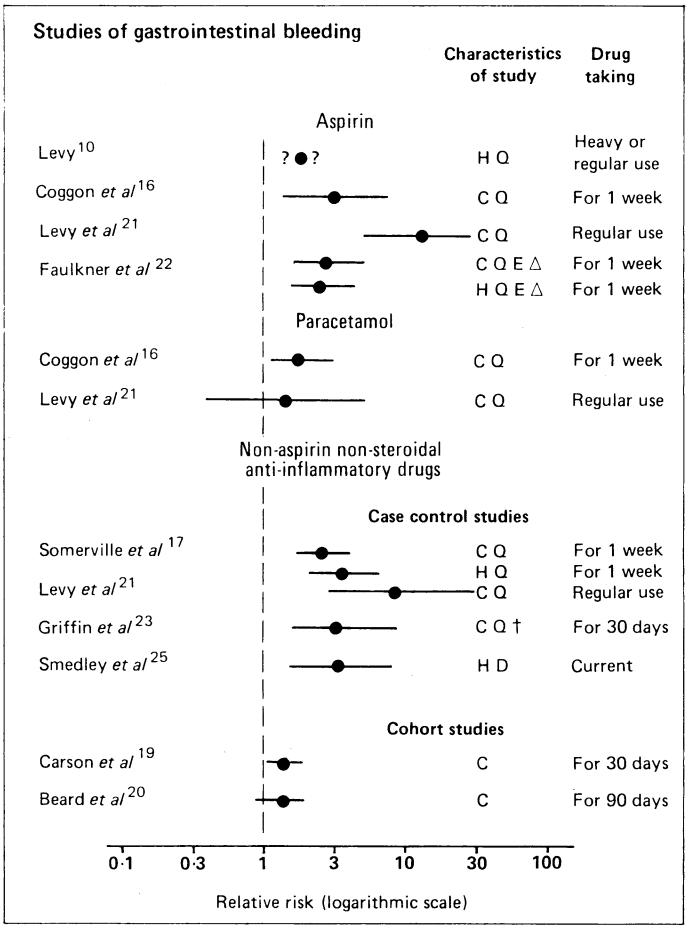


FIG 2—*Relative risks of upper gastrointestinal bleeding for patients taking aspirin, paracetamol, or non-aspirin non-steroidal anti-inflammatory drugs. H=comparison with hospital controls; C=comparison with community controls; Q=quoted values; D=derived values[35]; E=elderly patients (over 60 or 65); △=ulcer bleeding only; †=death attributable to gastrointestinal bleeding; ?=confidence interval not given.*

TABLE III—*Studies of upper gastrointestinal bleeding and aspirin*

| | Patients | | Controls | | Relative risk | | 95% Confidence interval |
|---|---|---|---|---|---|---|---|
| | No taking aspirin | No not taking aspirin | No taking aspirin | No not taking aspirin | Quoted | Derived | |
| Levy (1974)[10] | 14 | 74 | 1015 | 14 813 | 2·1* | 2·76* | 1·59 to 4·79* |
| Coggon *et al* (1982)[16] | 71† | ? | 19† | ? | 3·7 | | 2·2 to 6·4 |
| Faulkner *et al* (1988)[22] | 53 | 177 | 24 | 706 | 3·1 | | 1·8 to 5·8 |
| Levy *et al* (1988)[21] | 15 | 42 | 87 | 2 330 | 15·0 | | 6·4 to 34·0 |
| Adjusted relative risk | 3·30 (2·39 to 4·54) | | | | | | |
| $\chi^2$ | 51·88 (p<0·0001) | | | | | | |
| Homogeneity $\chi^2$ | 13·25 (p<0·01) | | | | | | |

*Weighted relative risk given by authors but no confidence interval stated; values shown refer to derived relative risk.
†Pairs in which both patient and control took aspirin were excluded; data were not included in meta-analysis.
?Value not given.

Whether particular groups are especially vulnerable is also not clear. Some studies have found associations only with bleeding from ulcers and perforation in elderly patients. Others have reported associations of comparable magnitude in groups containing patients of all ages (figs 2 and 3). Apparent age differences may arise because younger patients are less likely to take non-steroidal anti-inflammatory drugs so that an association becomes harder to show. Alternatively, when an age difference has been found by subgroup analysis it remains possible that it may have arisen by chance.

What case-control studies have failed to establish is whether non-steroidal anti-inflammatory drugs cause uncomplicated duodenal ulcers. Four studies of aspirin have not found an association (fig 5; table VII),[9-11 15] but those relating to non-aspirin non-steroidal anti-inflammatory drugs are conflicting (fig 5; table VIII). One study found no association with uncomplicated duodenal ulceration,[15] but the results of studies of patients presenting with complications—where risks of duodenal ulcer have been expressed separately—have been inconsistent. Two recent studies found bleeding or perforation, or both, to be greater with gastric ulcers than with duodenal ulcers,[24 25] but another study reported a higher relative risk for death from duodenal ulcer than gastric ulcer.[23]

These uncertainties about whether non-steroidal anti-inflammatory drugs induce duodenal ulcers raise the possibility that in some cases at least their action is not to induce ulceration but to cause complications in pre-existing (possibly silent) ulcers. This is one possible explanation for the observation that many patients taking non-steroidal anti-inflammatory drugs who present with complications have not previously experienced dyspepsia. For bleeding at least this is biologically plausible because non-steroidal anti-inflammatory drugs interfere with platelet function and prolong the bleeding time. Such an action might account for five observations. Firstly, the risk of upper gastrointestinal bleeding from

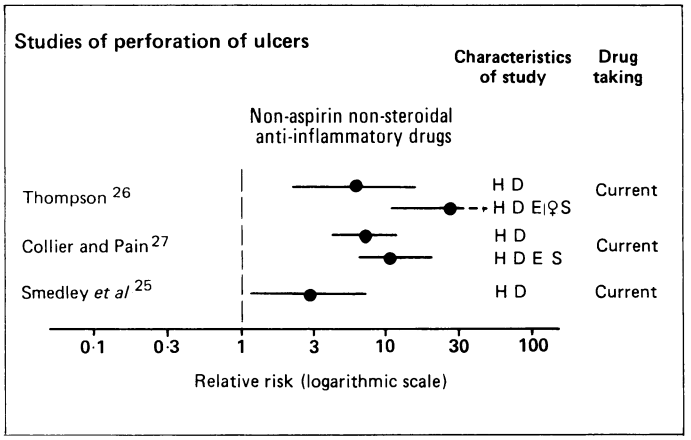


FIG 3—*Relative risks of perforation for patients taking non-aspirin non-steroidal anti-inflammatory drugs. H=comparison with hospital controls; D=derived values[35]; E=elderly patients (over 60 or 65); ♀=women; S=subgroup analysis*

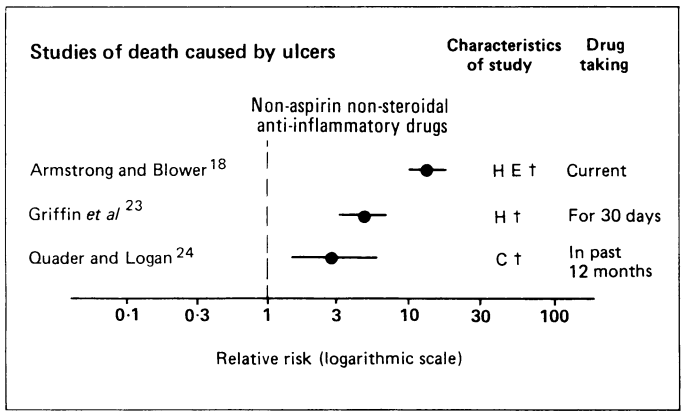


FIG 4—*Relative risks of death for patients taking non-aspirin non-steroidal anti-inflammatory drugs. H=comparison with hospital controls; C=comparison with community controls; E=elderly patients (over 60 or 65); †=death attributable to ulceration*

TABLE IV—*Studies of upper gastrointestinal bleeding and non-aspirin non-steroidal anti-inflammatory drugs*

| | Patients | | Controls | | Relative risk | | 95% Confidence interval |
|---|---|---|---|---|---|---|---|
| | No taking drugs | No not taking drugs | No taking drugs | No not taking drugs | Quoted | Derived | |
| Somerville *et al* (1986)[17] | 80 | 150 | 34 | 173 | 2·7 | | 1·7 to 4·4 |
| Levy *et al* (1988)[21] | 5 | 52 | 25 | 2392 | 9·1 | | 2·7 to 31·0 |
| Griffin *et al* (1988)[23] | 15 | 42 | 429 | 3468 | 3·6 | | 1·9 to 6·8 |
| Smedley *et al* (1988)[25] | 23 | 93 | 7 | 109 | | 3·85 | 1·66 to 8·96 |
| Adjusted relative risk | 3·09 (2·26 to 4·24) | | | | | | |
| $\chi^2$ | 48·19 (p<0·0001) | | | | | | |
| Homogeneity $\chi^2$ | 5·62 (p>0·05) | | | | | | |

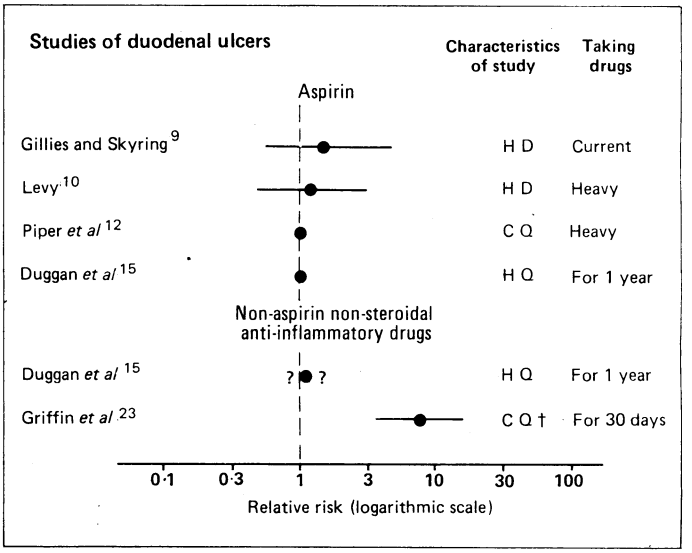


FIG 5—*Relative risks of duodenal ulceration for patients taking aspirin or non-aspirin non-steroidal anti-inflammatory drugs. H=comparison with hospital controls; C=comparison with community controls; Q=quoted values; D=derived values[35]; †=death attributable to ulceration*

TABLE V—*Studies of ulcer perforations and non-aspirin non-steroidal anti-inflammatory drugs*

| | Patients | | Controls | | Relative risk | | 95% Confidence interval |
|---|---|---|---|---|---|---|---|
| | No taking drugs | No not taking drugs | No taking drugs | No not taking drugs | Quoted | Derived | |
| Thompson (1980)[26] | 11 | 78 | 5 | 217 | | 6·12 | 2·31 to 16·21 |
| Collier and Pain (1985)[27] | 92 | 177 | 18 | 251 | | 7·25 | 4·44 to 11·84 |
| Smedley *et al* (1985)[25] | 16 | 116 | 6 | 126 | | 2·90 | 1·14 to 7·39 |
| Adjusted relative risk | 5·93 (4·00 to 8·81) | | | | | | |
| $\chi^2$ | 76·32 (p<0·0001) | | | | | | |
| Homogeneity $\chi^2$ | 2·70 (p>0·1) | | | | | | |

TABLE VI—*Studies of death related to ulcer and non-aspirin non-steroidal anti-inflammatory drugs*

| | Patients | | Controls | | Relative risk | | 95% Confidence interval |
|---|---|---|---|---|---|---|---|
| | No taking drugs | No not taking drugs | No taking drugs | No not taking drugs | Quoted | Derived | |
| Armstrong and Blower (1987)[18] | 141 | 94 | 123 | 1123 | | 13·7 | 10·4 to 18·1 |
| Griffin *et al* (1988)[23] | 34 | 88 | 429 | 3469 | 4·70 | | 3·1 to 7·2 |
| Quader and Logan (1988)[24] | 28 | 20 | 17 | 68 | 2·9 | | 1·4 to 6·3 |
| Adjusted relative risk | 7·62 (6·17 to 9·41) | | | | | | |
| $\chi^2$ | 354·11 (p<0·0001) | | | | | | |
| Homogeneity $\chi^2$ | 32·92 (p<0·0001) | | | | | | |

lesions other than ulcers is increased.[10 21] Secondly, half of those presenting with bleeding who are taking non-aspirin non-steroidal anti-inflammatory drugs have been having the drugs for three months or less.[17] Thirdly, the maximum risk occurs after only four prescriptions.[19] Fourthly, the sporadic use of aspirin is at least as dangerous as regular use.[16] And, finally, there is substantial decline in the risk within one week after stopping treatment.[17 21]

Because many of the studies with gastric or duodenal ulcer as an end point include those patients presenting with upper gastrointestinal bleeding the risks associated with ulceration might reflect a primary association with bleeding. If non-steroidal anti-inflammatory drugs provoke gastroduodenal bleeding then acetylation of platelet cyclo-oxygenase might well be the mechanism. One study in rats discounted the importance of platelet mechanisms in gastrointestinal bleeding[38] but studies in humans are needed. Interestingly, smoking—which enhances platelet reactivity and thromboxane production[39 40]—seems to have an opposite effect to non-steroidal anti-inflammatory drugs, reducing the risk that an ulcer will present with bleeding.[37]

Case-control studies—especially the large number of early studies using retrospective data collection—may overestimate risk because a drug history is likely to be sought more vigorously in cases than controls. When uncomplicated duodenal or gastric ulcer is the end point selection bias is also likely as doctors are probably more ready to use endoscopy on patients who are taking non-steroidal anti-inflammatory drugs. Such selection bias is reduced if presentation is largely involuntary—because of bleeding, perforation, or death—but if non-steroidal anti-inflammatory drugs enhance the complication rate of established ulcers these studies too will overestimate how ulcerogenic these drugs are.

TABLE VII—*Studies of duodenal ulcer and aspirin*

| | Patients | | Controls | | Relative risk | | 95% Confidence interval |
|---|---|---|---|---|---|---|---|
| | No taking drugs | No not taking drugs | No taking drugs | No not taking drugs | Quoted | Derived | |
| Gillies and Skyring (1968)[9] | 9 | 41 | 6 | 44 | | 1·61 | 0·53 to 4·89 |
| Levy (1974)[10] | 5 | 58 | 1015 | 14 813 | | 1·26 | 0·50 to 3·14 |
| Piper *et al* (1981)[12] | 7 | 60 | 7 | 60 | 1·00 | | |
| Duggan *et al* (1986)[15] | 7 | 58 | 7 | 58 | 1·00 | | |
| Adjusted relative risk | 1·17 (0·69 to 1·98) | | | | | | |
| $\chi^2$ | 0·21 (p>0·1) | | | | | | |
| Homogeneity $\chi^2$ | 0·47 (p>0·>1) | | | | | | |

TABLE VIII—*Studies of duodenal ulcer and non-aspirin non-steroidal anti-inflammatory drugs*

| | Patients | | Controls | | Relative risk | | 95% Confidence interval |
|---|---|---|---|---|---|---|---|
| | No taking drugs | No not taking drugs | No taking drugs | No not taking drugs | Quoted | Derived | |
| Duggan *et al* (1986)[15] | 15 | 70 | 10 | 75 | 1·1 | | 0·4 to 3·7 |
| Griffin *et al* (1988)[23] | 15 | 16 | 13 | 109 | 7·9 | | 3·7 to 16·8 |
| Adjusted relative risk | 3·16 (1·78 to 5·61) | | | | | | |
| $\chi^2$ | 14·13 (p<0·001) | | | | | | |
| Homogeneity $\chi^2$ | 6·38 (p≈0·01) | | | | | | |

COHORT STUDIES

Suspicions that case-control studies exaggerate the problem are reinforced by the results of four cohort studies, which have all made lower estimates of risk. An early study monitoring events in a cohort of patients receiving five novel non-steroidal anti-inflammatory drugs may be criticised for using insufficiently precise data on drug consumption and on end points and for being too small to detect other than large differences.[41] Three recent studies of intensively monitored populations using group insurance schemes in North America are less open to such criticism.[19 20 28] All three found the relative risk of presentation with upper gastrointestinal bleeding or perforation to be about 1·5. In two studies the increase in risk was not significant, perhaps because of insufficient power. Taken together the three studies suggest there probably is a risk but that it is lower than suggested by case-control studies.

SYNOPSIS

Those case-control studies using prospective data collection and an involuntary end point (complications or death) are probably least open to bias if the possibility that non-steroidal anti-inflammatory drugs might specifically enhance the complication rate is discounted. Individual studies with these characteristics suggest an overall relative risk between 3·0 and 5·0 for the association of both aspirin and non-aspirin non-steroidal anti-inflammatory drugs with gastrointestinal bleeding. Cohort studies make a lower estimate of risk—about a 50% increase. If these figures are correct the problem with non-steroidal anti-inflammatory drugs is not that they are particularly dangerous but that they are so widely used.

## Estimates of risk: endoscopic monitoring

Another way of estimating the ulcerogenicity of non-steroidal anti-inflammatory drugs is to measure the prevalence or incidence of ulcers by endoscopic surveillance. To avoid bias in such studies patients taking non-steroidal anti-inflammatory drugs should be compared with a comparable control group of patients not taking anti-steroidal anti-inflammatory drugs and endoscopy should be done by someone blind to the patients' drug consumption. None of the studies reviewed below has done this.

The results of prevalence studies in which a cross section of reportedly consecutive or unselected patients taking non-steroidal anti-inflammatory drugs were studied are shown in table IX. These studies show a remarkably high prevalence of

TABLE IX—*Studies of prevalence of ulcers in patients taking non-steroidal anti-inflammatory drugs*

| | | Patients | | | Gastric ulcer | | Duodenal ulcer | |
|---|---|---|---|---|---|---|---|---|
| | Other drugs taken | Type of arthritis | No | Definition of ulcer | % Of patients taking non-steroidal anti-inflammatory drugs | Implied relative risks* | % Of patients taking non-steroidal anti-inflammatory drugs | Implied relative risks* |
| Sun *et al* (1974)[36] | Aspirin | Rheumatoid arthritis | 140 | Barium (endoscopy) | 9 | 30 | 19 | 13·6 |
| Silvoso *et al* (1980)[30] | Aspirin | Mixed | 82 | Three dimensional | 17 | 57·7 | 1 | 0·7 |
| Collins and du Toit (1987)[31] | Non-aspirin non-steroidal anti-inflammatory drugs | Mainly rheumatoid arthritis | 108 | Not defined | 22 | 73·3 | 6 | 4·3 |
| Larkai *et al* (1987)[32] | Non-aspirin non-steroidal anti-inflammatory drugs | Rheumatoid arthritis or osteoarthritis | 65 | ≥5 mm diameter | 11 | 36·7 | 5 | 3·3 |
| Farah *et al* (1988)[33] | Non aspirin non-steroidal anti-inflammatory drugs | Rheumatoid arthritis | 185 | Not defined | 20 | 66·7 | 19 | 13·6 |
| | | Without rheumatoid arthritis | 45 | Not defined | 11 | 36·7 | 22 | 15·7 |

*Calculated by reference to Ihamake *et al*,[42] data on controls without symptoms.

gastric ulcer, ranging between 9% and 22%, with rather less consistency for duodenal ulcer.

Incidence studies take patients shown not to have a peptic ulcer at initial endoscopy and record the number developing ulcers by the time of a further endoscopy or accumulating over a given time period. Included in table X are the control data from the two recent studies of prophylaxis with ranitidine or misoprostol.[1,2] The rates are high but there are major and opposite discrepancies between the European study on ranitidine[1] and that from the United States on misoprostol[2] in the incidence of gastric ulceration (6% by two months in the European study *v* 22% by three months in the American study) and duodenal ulceration (8% by two months in the European study *v* 3·5% by three months in the American study). These differences cannot easily be attributed to differences in age, sex, underlying disease, inclusion criteria, or specific drugs used (naproxen, piroxicam, diclofenac, and indomethacin in the European study; naproxen, piroxicam, and ibuprofen in the American study). In the European study it seemed possible that duodenal ulceration might be more likely with piroxicam,[1] but this was not seen in the United States study.[2] Although an undue susceptibility of patients with rheumatoid arthritis to gastric ulceration has been proposed, the American study that found a very high incidence of gastric ulceration included only patients with osteoarthritis. The age and sex distribution of the patients was broadly similar in the two studies. There are no good grounds for a belief in national differences. The discrepancies between the two studies must raise the possibility that they were dealing with different phenomena. There is some concrete evidence that this is so: in the American study smaller lesions were classified as gastric ulcers than in the European study (minimum 3 mm diameter *v* 5 mm).

### MAGNITUDE OF RISK

One problem with studies using endoscopic monitoring is that there is no comparable control group of patients not taking non-steroidal anti-inflammatory drugs. Moreover, not all the studies define what they mean by a gastric or duodenal ulcer or give their criteria for distinguishing ulceration from erosion. The absence of a control group makes it impossible to measure the magnitude of risk from such studies. The best that can be done is to compare estimates of prevalence with other studies that included comparable unselected patients not taking non-steroidal anti-inflammatory drugs. An endoscopic survey of 346 Finns without symptoms found a point prevalence of 0·3% for gastric ulceration and 1·4% for duodenal ulceration.[42] In Leiden when Kreuning examined 50 colleagues without symptoms endoscopically she found no gastric or duodenal ulcers.[43] Cancer screening programmes in Japan have detected gastric ulceration in up to 2% of those examined,[44,45] but mortality statistics suggest that gastric ulceration is more common in Japan than in the populations in which the effects of non-steroidal anti-inflammatory drugs have been investigated.[46] Moreover, screening programmes may include an increased proportion of patients with dyspepsia.[47]

Population studies of the incidence of peptic ulceration generally relate to patients who have symptoms. Early population studies, when detection was generally by barium meal, suggested an average incidence rate of 1·9 per 1000 for duodenal ulcer and 0·4 per 1000 for gastric ulcer.[48] These relate to patients with symptoms.

If such figures are used as the basis for comparison with the prevalence and incidence rates found in endoscopic studies of patients taking non-steroidal anti-inflammatory drugs they imply an enormous enhancement of risk, particularly for gastric ulceration (tables IX, X). Values relating to the incidence of ulcers (table X) are likely to be an overestimate because the control group would have contained few silent ulcers, but this is unlikely to account entirely for the discrepancy between the results of endoscopic surveillance and case-control studies. Even the Japanese prevalence data of 2% for gastric ulceration, which generate the most conservative estimates of risk based on endoscopy, suggest that non-steroidal anti-inflammatory drugs enhance the risk of gastric ulceration by an order of magnitude.

## Are ulcers related to non-steroidal anti-inflammatory drugs odd?

The size of these discrepancies raises the possibility that the ulcers seen in patients taking non-steroidal anti-inflammatory drugs are fundamentally different from those found in other patients. Four characteristics are worth emphasising: their symptoms, their size, the underlying disease, and adaptation.

### SYMPTOMS

Ulcers in patients taking non-steroidal anti-inflammatory drugs are more likely to be silent than are ulcers found in the general population.[49] A recent study suggests that this is not due to confounding by age.[50] The explanation might be that non-steroidal anti-inflammatory drugs, being analgesics, suppress production of prostaglandins and so conceal ulcer pain; or that patients with silent ulcers may be selected because doctors are reluctant to prescribe non-steroidal anti-inflammatory drugs for patients with dyspepsia; or that patients with ulcers due to a non-steroidal anti-inflammatory drug present early because the drug promotes a complication; or that the lesions regarded as ulcers that are detected by endoscopic monitoring in patients taking non-steroidal anti-inflammatory drugs may in some sense be less serious than those regarded as ulcers in others.

Of these possibilities, only the last could explain the differences in the results of epidemiological and endoscopic studies. The first three would lead case-control studies of

TABLE X—*Studies of incidence of new ulcers*

| | | Patients | | | | Gastric ulcer | | Duodenal ulcer | |
|---|---|---|---|---|---|---|---|---|---|
| | Drugs taken | Type of arthritis | No | Definition of ulcer | Length of study (months) | % Of patients taking non-steroidal anti-inflammatory drugs | Implied relative risks* | % Of patients taking non-steroidal anti-inflammatory drugs | Implied relative risks* |
| Caruso and Porro (1980)[14] | Aspirin, non-aspirin non-steroidal anti-inflammatory drugs | Mixed | 249 | No | 12 | 0·8 | 20 | | |
| Ehsannulah *et al* (1980)[1] | Non-aspirin, non-steroidal anti-inflammatory drugs | Mainly rheumatoid arthritis | 126 | Gastric ulcer >0·5 cm; duodenal ulcer not defined | 2 | 6 | 900 | 8 | 256 |
| Graham *et al* (1988)[2] | Non-aspirin, non-steroidal anti-inflammatory drugs | Osteoarthritis | 138 | >3 mm | 3 | 21·7 | 2170 | 3·5 | 74 |

*Calculated with reference to average annual incidence figures quoted in Langman.[48]

patients presenting with complications to exaggerate risks either by allowing the ulcer to progress silently to the point where complications develop or by accelerating this development.

SIZE

A simple indication that ulcers found in patients taking non-steroidal anti-inflammatory drugs were different from those found in the general population would be a difference in size, but this has not been reported in most studies. One case-control study of perforation reported that giant gastric ulcers were more common in those taking non-steroidal anti-inflammatory drugs[11] whereas in another endoscopic study of patients taking aspirin or non-aspirin non-steroidal anti-inflammatory drugs most of the gastric ulcers were 5 mm or less in diameter.[2 30]

UNDERLYING DISEASE

The possibility that patients with rheumatoid arthritis are specifically prone to gastric ulceration has been much discussed but is not clearly supported by the evidence. Some studies in such patients have found an excess of patients with gastric ulcers[30 31 33] but others have not,[29] and some—notably the American misoprostol study—have found a large excess of gastric ulcers in the control group of patients with osteoarthritis taking non-steroidal anti-inflammatory drugs,[2] suggesting that the drugs rather than disease are of principal importance.

ADAPTATION

An important clue comes from the observation that the gastric mucosa adapts to continued ingestion of aspirin[51] or indomethacin.[52] Acute lesions (erosions or petechiae) become fewer after two to eight weeks of taking the drug than during the first week. A challenging epidemiological parallel is provided by a study showing that the relative risk of presentation with haematemesis and melaena rises to a maximum in patients who have received four prescriptions for a non-steroidal anti-inflammatory drug before it falls to 1·0 (that is, no increased risks) in those who have received 10 prescriptions.[19]

## Non-steroidal anti-inflammatory drug gastropathy?

One approach to these observations has been to redefine terms. It has been argued that the ulcers associated with non-steroidal anti-inflammatory drugs are different from "ordinary" ulcers and are part of a spectrum of disease that includes erosions and petechiae. The term non-steroidal anti-inflammatory gastropathy has been advanced for this disease.[53 54] This approach may ultimately be valuable, particularly in elucidating different underlying mechanisms and emphasising the difficulty of distinguishing small ulcers and erosions, but at present it begs more questions than it answers. It does not alter epidemiological estimates of the risk of serious complications. Because non-steroidal anti-inflammatory drug gastropathy is so common in patients taking the drugs it must be a fairly benign condition, and the important issue remains the size of the risk of serious complications.

## Synopsis of risks

Non-steroidal anti-inflammatory drugs cause gastric ulcers and probably duodenal ulcers. The size of this risk is not clear, but the increased chance of involuntary presentation with haematemesis and melaena or perforation probably lies between a 50% and a fivefold increase. Short term endoscopic monitoring, however, suggests a much higher incidence. This may be because at least some of the (silent) lesions detected in this way are intrinsically less dangerous and resolve spontaneously by a process of adaptation. Although the evidence is fragmentary, several studies suggest that the first few months of taking a non-steroidal anti-inflammatory drug may be particularly dangerous.[17 19]

Even the simplest questions are, however, unresolved. Ulcer morphometry with digitised information obtained by video endoscopy may help to determine whether ulcers caused by non-steroidal anti-inflammatory drugs are different from others in terms of size, shape, depth, or colour.[55] Interpreting endoscopic data requires comparisons with a control group—at best patients with arthritis not taking non-steroidal anti-inflammatory drugs, at worst concurrent patients without arthritis. Blinding of the endoscopist to drug taking is probably an unrealistic ideal, but a blinded retrospective review of video images may be an adequate substitute.

## Prophylaxis

All the ulcer healing drugs have been shown to diminish short term damage caused by non-steroidal anti-inflammatory drugs. On the (unproved but not unreasonable) assumption that reduced short term damage implies a reduced likelihood of ulcer development one could argue in favour of giving ulcer healing drugs with non-steroidal anti-inflammatory drugs. In practice $H_2$ antagonists have been given widely to patients taking non-steroidal anti-inflammatory drugs on an informal basis. Two recent trials that dealt with the issue of prophylaxis specifically, however, showed that the issue is more complex (fig 6). In the United States misoprostol caused a remarkable reduction in the development of gastric ulceration, from 21·7% to 5·6% at dose of 400 μg/day and to 1·4% at 800 μg/day.[2] In this study very few patients had duodenal ulcers, and it is hard to say whether misoprostol made any difference to the incidence. In the European study, by contrast, ranitidine 150 mg twice daily reduced a higher incidence of duodenal ulceration at two months from 8% to 1·5% but had no effect

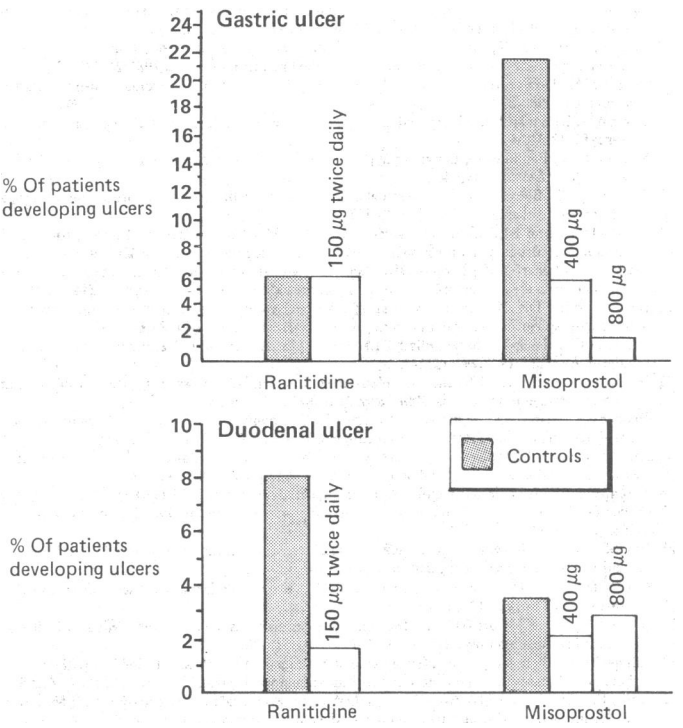


FIG 6—*Prophylaxis of gastric and duodenal ulcers by ranitidine (given for 2 months) and misoprostol (given for 3 months). Reductions in incidence of duodenal ulcers with ranitidine and of gastric ulceration with both doses of misoprostol were significant*

on the incidence of gastric ulceration (6% with or without ranitidine).[1]

It has been calculated that 200 deaths from ulcers attributable to non-steroidal anti-inflammatory drugs occur in Britain each year.[17] In excess of 22 million prescriptions are written each year. Given that each lasts one month, the cost of coprescribing misoprostol or ranitidine with each of them as prophylaxis would be about £600m a year in Britain. Even if the drugs were totally effective in preventing deaths from the non-steroidal anti-inflammatory drugs the cost per life saved, calculated from epidemiological data, would be about £3m.[17] Moreover, the data give the prescriber an untidy message—should doctors use misoprostol to prevent the gastric ulcers, ranitidine to prevent the duodenal ulcers, or both at double the cost? Would such costs or the incidence of adverse drug reactions generated by such massive coprescribing justify the benefits achieved? Would acid inhibiting drugs be as effective as misoprostol if higher doses were used? Before rational prophylactic policies can be formulated we need additional information:

- Groups at particular risk should be identified. Suggestions that old women are especially vulnerable, however, are not well supported by all data
- When acid inhibition is used for protection the optimal degree of suppression needs to be defined. In short term studies more profound acid inhibition, particularly with omeprazole, has been most effective[56]
- A direct comparison of optimal doses of misoprostol and an acid inhibiting drug is needed
- The possibility needs investigation that short term prophylaxis—tiding a patient over a period when an endogenous adaptive process takes place—might have long term value.

Several large well controlled studies will be needed to answer these questions. Fundamental to these issues is whether the ulcers found in patients taking non-steroidal anti-inflammatory drugs are as dangerous as those in other patients or whether they run a more benign course and behave more like erosions than ulcers.

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## Correction

### Prophylactic antibiotics and caesarean section

We regret that the last three references were omitted in this editorial by Professor P W Howie and Dr P G Davey (6 January, p 2). These are

18 Hunt MN, Chan AYC, Karran SJ. Postoperative complications: how much do they cost? *Ann R Coll Surg Engl* 1986;**68**:199-202.
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