At our mother’s knee – an occasional review

Non-steroidal anti-inflammatory agents and the gastrointestinal tract

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Non-steroidal anti-inflammatory drugs (NSAIDs) have had a bad press recently. The proliferation of these widely used agents has attracted the derogatory appellation ‘me too’. Some, such as benoxaprofen, zomepirac, indoprofen and a controlled delivery indomethacin formulation (‘Osmosin’), have been withdrawn because of concern about adverse drug effects including gastrointestinal bleeding (benoxaprofen) (Editorial, 1982) and bowel perforation (‘Osmosin’) (Day, 1983). Concern has been expressed for as long as NSAIDs have been available and there is little doubt that acute administration of many of them causes gastric erosions in animals and provokes microscopic bleeding in man. What remains controversial is whether there is a causative link between NSAID ingestion and peptic ulceration or important upper gastrointestinal haemorrhage.

During the last two decades admissions to hospital and mortality rates for peptic ulcer have fallen in the UK (Coggon et al., 1981). This is mostly accounted for by changes among the young with little change in the mortality rate for women over 75 years of age. Aspirin consumption and smoking have declined and this may be a partial explanation of the overall trend but the elderly are major users of other NSAIDs and this might explain the differential ulcer mortality rate between old and young. However, the situation is complex. The elderly often have other diseases and take other drugs, more prescriptions are issued for NSAIDs to those under 65 years of age than those over 65 and the number of prescriptions written has been steadily increasing in all age groups. There is therefore a need to question our fundamental assumptions about NSAIDs.

Do NSAIDs damage the gastro-duodenal mucosa?

Aspirin causes gastric mucosal damage and microbleeding. Studies in animals show a consistent pattern with gastritis, mucosal erosions and/or occult bleeding (Roth et al., 1963; Hurley & Crandall, 1964). Similar changes are seen in some animals given high doses of other NSAIDs but there is wide interspecies variation: unlike rats, domestic pigs have minimal duodenal mucosal changes after 15 mg/kg indomethacin (Rainsford & Willis, 1982).

Acute gastro-duodenal changes are described in man with many NSAIDs and aspirin in particular. For example Caruso & Bianchi Porro (1980) compared 10 NSAIDs plus corticosteroids given to 249 patients with arthritis; 78 (31%) developed lesions in the upper gastrointestinal tract identified at gastroscopy during a 12 month follow-up, more with multiple (51%) than single (23%) drug treatment. However, deciding on the relative merits of the NSAIDs used is difficult; despite long-term treatment with these agents, apparently none of the 249 had mucosal lesions at the start of the study and the allocation was not random.

And is it damage or impaired defence?

What is the precise effect of NSAIDs upon the gastric mucosa? In many instances, significant damage (gastric erosions and petechiae) only occurs when the gastric mucosa of NSAID-treated animals is exposed to topically injurious or irritant agents such as bile, ethanol, chillis, or salicylates (Whittle, 1977; Robert et al., 1983). In the absence of NSAIDs such agents cause mucosal reddening, vasodilatation and shedding of surface epithelial cells, but few overt breaks in the mucosa. These studies suggest the NSAIDs do not necessarily inflict mucosal damage themselves but rather impair mucosal defence mechanisms. An interesting example of this phenomenon is the development of gastric antral erosions in indomethacin-treated rats after feeding solid food (Satoh et al., 1982). The extent of the damage is directly proportional to the amount of food eaten. Damage does not occur with isocaloric liquid feeds (which may even be protective) suggesting that indomethacin blocks a mechanism capable of protect-
ing the mucosa against direct physical trauma.

It is, of course, widely assumed that this defence mechanism is prostaglandin mediated, and there is critical evidence in favour of this proposition. NSAIDs inhibit gastric mucosal prostaglandin synthesis and the enhancement of damage caused by injurious stimuli in their presence is mirrored by a greater resistance to damage when prostaglandin levels are increased (whether from endogenous or exogenous sources) (Robert et al., 1983).

**Salicylates: a special case?**

Salicylates are different from many other NSAIDs in acting as topical irritants to the gastric mucosa. The basis of this property is ill understood but it is separate from the ability to inhibit prostaglandin synthesis (Ligumsky et al., 1982). Sodium salicylate is not an inhibitor of prostaglandin synthesis in gastric mucosa but is a topical irritant: this normally results in trivial mucosal damage followed by beneficial adaptive changes which enhance resistance to further gastric damage (Robert, 1981). However, where prostaglandin synthesis is inhibited (as with aspirin, or when sodium salicylate is given after pretreatment with indomethacin) greater damage results than with either inhibitors of prostaglandin synthesis or topical irritants alone (Ligumsky et al., 1982; Steele & Whittle, 1984). Indomethacin probably also has topical irritant properties (Chvasta & Cooke, 1972) but the extent to which this is true of other NSAIDs and whether topical irritancy amounts to the same as electro-physiological breakdown of the gastric mucosal 'barrier' is not known.

Whether the dyspepsia experienced by some patients taking some NSAIDs might relate to topical irritancy, or some other property, is also unknown but there seems no reason necessarily to attribute it to inhibition of prostaglandin synthesis. For NSAIDs which are topical irritants gastro-duodenal mucosal damage may be reduced by altering the formulation or mode of administration. This mucosal change assessed endoscopically may be obviated by enteric coating of aspirin but not by buffering (Lanza et al., 1980).

**Does acute gastric mucosal damage matter?**

Most animal studies involve acute administration of NSAIDs and observe the development of gastric erosions. This begs two questions: (1) Do NSAIDs remain injurious to the gastric mucosa (human or animal) with continued ingestion or does adaptation occur? (2) Is the relatively trivial damage of a gastric erosion the first step in the development of chronic ulcers or are these separable phenomena?

**Continued ingestion**

In both man and laboratory animals mucosal changes can be detected within an hour of a single dose of aspirin (O’Laughlin et al., 1981). As judged endoscopically and by bleeding into the lumen there is greater damage when further doses are given over 24 and 48 hours (O’Laughlin et al., 1981; Graham et al., 1983; Hunt & Franz, 1981). Subsequently, the mucosa seems to adapt and the pattern of injury changes and its extent probably declines: dogs given aspirin over 10 days initially developed erosions but these disappeared with continued ingestion (Hurley & Crandall, 1964). At this stage the mucosa remains resistant to further aspirin challenge for 48 hours after cessation of chronic dosing. In man two endoscopic studies have agreed that adaptation occurs with continued aspirin ingestion though the results have been less dramatic than in the dog. In one study, there were fewer petechiae (though no fewer erosions) after 7 days than after one day of aspirin ingestion (O’Laughlin et al., 1981). More recently, the number of erosions has also been reported to diminish with continued ingestion (Graham et al., 1983).

**Do erosions become chronic ulcers?**

It is sometimes assumed that erosions represent ulcers at an early stage. There is no evidence that this is so. The evidence of adaptation to aspirin suggests that such a progression is at least unusual. It is also assumed that acute gastric mucosal damage assessed by microbleeding correlates with the chronic ulcerogenicity of the drug. This too is unproven. In their endoscopic survey, Caruso & Bianchi Porro (1980) found only two new ulcers and 46% (11/24) had an ulcer recurrence, results little different from those expected in such patients not given NSAIDs. This contrasts with the 31% (78/249) who developed other more trivial 'gastric lesions'.

**Is there a NSAID – chronic ulcer association?**

Most data come from case-control studies. Given that the association may be weak, the patients are usually taking other drugs and have other illnesses and that the widely believed NSAID-ulcer link may provide impetus for referral and investigation of a dyspeptic patient, these studies are often bedevilled by confounding, spurious associations and bias (Kurata et al., 1982).

Corticosteroids perhaps are a good example of this difficulty. Cooke (1967) reviewed the available data and concluded that there was no evidence of an association with peptic ulcer. In a widely quoted study Conn & Blitzer (1976) reached the same conclusion
after collating 42 prospective trials of steroid therapy but Messer et al. (1983), after reviewing 71 controlled studies in 3061 patients, found an excess of peptic ulcers in patients treated with corticosteroids (relative risk 2.3).

For NSAIDs the most consistent association is between chronic gastric ulcer and aspirin particularly in Australia, where analgesic intake is high, particularly in women (Gillies & Skyring, 1969; Piper et al., 1981). This has been corroborated by data from the Boston Collaborative Drug Surveillance Program which showed a link between heavy (but not light) aspirin intake and gastric ulcer but no demonstrable associations between aspirin and duodenal ulcer or between other NSAIDs and chronic ulcer (Jick, 1981).

Indomethacin has been available for over a decade and yet data are sparse. Studies of individual drugs continue to be small and, if prospective, often lack suitable control groups. Case report series may be misleading as there is usually no reference to overall prescribing habits and may merely reflect increased awareness of a potential problem. Attention has moved toward studying NSAIDs as a group thereby ignoring possible differences between them despite manufacturers claims, often based on microbleeding data, to the contrary. A recent study from Bolton, for example, found that at least 34% of elderly ulcer patients took NSAIDs compared with 10% of those with normal findings at endoscopy (Clinch et al., 1983). In common with many studies, however, drug history was determined retrospectively and controls were not matched for age, sex or method of presentation. Despite these difficulties, the relative risk of about 3 calculated from this data set is similar to that suggested for corticosteroids and ulcer.

Do NSAIDs retard healing?

In practice few clinicians would continue NSAIDs in patients with peptic ulcers but trials involving large numbers of patients would be needed to confirm or refute this practice. There have been few studies of continuing NSAID intake in patients with proven ulcers and patient numbers have been small since most clinical trials of ulcer healing drugs exclude those taking NSAIDs. The available evidence, however, suggests that it may not be mandatory to discontinue them. O’Laughlin et al. (1982) found that 12 (55%) of 22 gastric ulcers healed after 8 weeks medical treatment despite continued aspirin use. Davies et al. (1978) had similar findings at 4 weeks in their gastric ulcer patients who continued to take NSAIDs: 6 of 12 chronic ulcers healed despite continued use of these ‘ulcerogenic’ drugs.

Are patients with gastrointestinal bleeding more likely to be taking NSAIDs?

Acute upper gastrointestinal bleeding is convenient to study as most patients are admitted to hospital. Studies of aspirin intake before the bleed show a fairly consistent excess of aspirin intake compared with controls but difficulties of recall bias and considerable variation in the proportion of aspirin takers in the control groups has produced variable estimates of the strength of the association. Levy et al. (1974) in a large study of patients admitted to hospitals in the Boston area found that consistent heavy aspirin intake (at least 4 days per week for 12 weeks) was more common in those admitted with acute bleeding particularly from gastric ulcer or gastritis (but not from duodenal ulcer) but that this association was not detectable with lower intakes of aspirin or other NSAIDs. It was estimated that the increased risk of upper gastrointestinal haemorrhage was only 15 per 100,000 regular heavy users per year.

Other difficulties are shown in a Nottingham study of 346 patients admitted for haematemesis and melena (Coggon et al., 1982). Paracetamol intake was more common than in matched controls. Approximately one third of the aspirin consumption before the bleed was accountable by reference to this paracetamol excess as probable analgesic use for gastrointestinal symptoms and a further third by reference to the use of aspirin by the controls. About one third of the aspirin takers amongst the patients could not be accounted for and thus a causal relationship could exist. However, aspirin ingestion is widespread particularly on an infrequent, as required, basis. The Boston and Nottingham studies show little link between casual intake and bleeding. By comparison with the extensive use of aspirin, upper gastrointestinal bleeding induced by this drug must be uncommon.

By contrast, there is no evidence to suggest that patients consuming other NSAIDs are at higher risk of major gastrointestinal haemorrhage*. Reports are mostly anecdotal and uncontrolled with little reference to the total population of NSAID users at risk of complications. Whether some NSAIDs are more likely to cause important upper gastrointestinal bleeding remains speculative. Benoxaprofen was withdrawn mainly because of hepatotoxicity and bleeding peptic ulcers in elderly patients taking the drug yet there is no convincing evidence that this agent is more injurious to the gastric mucosa than indomethacin or naproxen which are widely used (Rainsford, 1982). Possible gastrointestinal adverse events with new drugs are more likely to be reported and published than similar events with older agents. Newer compounds, possibly because of claims of gastrointestinal tolerance, may be more likely to be used in patients with a known peptic
ulcer diathesis. Thus case reports can only suggest that a problem might exist and can provide little information about the magnitude. This is well illustrated by recent discussion in the *British Medical Journal* linking piroxicam with gastrointestinal bleeding (Fok *et al.*, 1985; Beerman, 1985; Innman & Rawson, 1985). Likewise the suggestion that elderly women with gastric ulcers are more likely to be NSAID takers and more likely to require blood transfusion than younger women with ulcers may be a reflection of selection methods for endoscopy (Cooke & Thompson, 1981).

**Do NSAIDs predispose to peptic ulcer perforation?**

There are difficulties in attributing the changes in the pattern in peptic ulcer perforation admissions solely to changes in the pattern of NSAID use. Peptic ulcer perforations have been declining in men during the last 20 years despite increased NSAID use during this time and have also been decreasing in younger women who receive more prescriptions for NSAIDs than women over 65 years of age, in whom peptic ulcer admissions are increasing. Furthermore, not all elderly patients admitted with peptic ulcer perforation are taking NSAIDs. Thus in a recent study Collier & Pain (1985) found that 48% (79/168) of a consecutive series of patients over 65 years of age admitted to the Ipswich Hospital were taking NSAIDs compared with 7% (12/168) of a surgical control group. Although the differences in NSAID use appear large, the method used in this study of case note review of a diagnosis where antecedent suspected NSAID use was likely to be recorded and less likely to be recorded in a control group where there was no such suspicion: the 7% NSAID use by the control group is about half that usually found in community based surveys. Whether increased NSAID use reflects systemic disease and the increased use merely parallels use of other drugs is also unclear. However, these difficulties are unlikely to completely account for the differences observed despite the estimated relative risk of 11 calculated from this data set being almost certainly an overestimate.

**Stomach or intestine?**

The recent notoriety achieved by the slow release indomethacin preparation Omosin serves as a timely reminder that the stomach is not necessarily the major site of NSAID-induced damage. In 1983 two cases of multiple intestinal perforation in patients taking Omosin were reported. Omosin capsules were found free in the peritoneum and impacted in diverticula which were inflamed and had perforated through local ulcerations (Day, 1983). Omosin was withdrawn from the UK market. In the ensuing 9 months there were 10 notifications to the Committee on the Safety of Medicines of intestinal perforations in patients on all forms of indomethacin compared to 6 over the previous 20 years.

As yet it is not clear where the truth lies. Reporting to the Committee on Safety of Medicines is uncontrolled. Inevitably there is under-reporting of side effects which are not generally recognized whilst a period of relative over-reporting follows identification of the new side effects. The issue is further confused because the Omosin capsule delivered potassium bicarbonate in addition to indomethacin. However, Langman *et al.* (1985) have compared anti-inflammatory drug intake ascertained by hospital case note review in 268 patients with intestinal perforation or haemorrhage with control data. There were over twice the number of NSAID takers amongst the patients while there was little difference in the pattern of other drugs used by the two groups and cardiovascular drugs in particular. This suggests that the NSAID-intestinal perforation association may be important.

It has been claimed that indomethacin suppositories may cause proctitis and challenge has been associated with reversible electrophysiological and histological changes (Rampton & Barton, 1984). Similar changes occurred when patients with ulcerative colitis were treated with flurbiprofen (Rampton & Sladen, 1981). Relapse of ulcerative colitis may be associated with the use of NSAIDs though whether NSAIDs cause ulcerative colitis to relapse or whether patients with an impending relapse are more likely to ingest them cannot be determined.

Fenamates have long been known to cause diarrhoea. Recently, a specific entero-colitis occurring in patients taking mefenamic acid has been recognised (Hall *et al.*, 1983). The significance of both the diarrhoea and the entero-colitis occurring with mefenamic acid is difficult to assess. Fenamates appear to have a specific toxicity to enterocytes and erythrocytes and an ability to stimulate intestinal secretion which are not shared by other NSAIDs (Gullikson *et al.*, 1982).

These data are both heterogeneous and limited. Nevertheless the possibility that NSAIDs possess intestinal toxicity deserves to be taken seriously particularly as aspirin- or indomethacin-induced intestinal ulceration in laboratory animals is well recognized. In such experiments intestinal erosions develop within a few hours and gross ulceration within 48 hours (Kent *et al.*, 1969; Robert & Asano, 1977; Satch *et al.*, 1982). The pathogenesis of these lesions is poorly understood but they are associated with mucosal inflammation and can be prevented by fasting, interruption of the enterohepatic circulation and treatment with antibiotics or prostaglandins.

What is particularly striking is the similarity between these lesions and those described in case reports
in man. Recently Bjarnason et al. (1985) have reported abnormal 1111 leucocyte scans in patients with rheumatoid arthritis taking NSAIDs and have suggested that NSAIDs may cause terminal ileal ulcers in man: this awaits systematic confirmation perhaps by colonoscopy. Whether Osmosin has uncovered a significant but previously unrecognized iatrogenic disease in man or whether there are species differences in the susceptibility to NSAID-induced intestinal ulceration and perforation is unknown.

Conclusions and speculation

NSAIDs present a series of paradoxes. Direct observations suggest that enhanced resistance to aspirin occurs with continued ingestion but on epidemiological grounds it is only in those who chronically ingest large amounts of aspirin that there is an increased risk of bleeding or gastric ulceration. Does this suggest that those who bleed or develop ulcers lack the normal mechanisms of adaptation to continued ingestion? Alternatively, significant bleeding and gastric ulceration may develop by mechanisms unrelated to those leading to microbleeding or gastric erosions. However, in terms of erosions and microbleeding aspirin is significantly more toxic than other NSAIDs and it is the only NSAID for which there is convincing evidence for a causal association between ingestion and major bleeding or gastric ulceration.

The mechanism by which NSAIDs reputedly cause dyspepsia is no clearer that it is for compounds which do not affect prostaglandin synthesis. Limited data suggest that there should be concern over the toxicity of such drugs to the intestine and the current trend of the pharmaceutical industry to develop slow release preparations in order to avoid gastric toxicity may be misguided.

Addendum

A recent case control study from Nottingham presented at the autumn meeting of the British Society of Gastroenterology using matched hospital and community controls has shown an association between non steroidal anti inflammatory drug use and bleeding peptic ulcer in patients aged 60 and over (relative risk approximately 3).

Reference

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