NSAIDs – should every prescription carry a Government Health Warning?

Non-steroidal anti-inflammatory drugs (NSAIDs) excite quite different emotions on the one hand from pathologists, surgeons, and to a lesser extent gastroenterologists, and on the other from rheumatologists and general practitioners. The former group sees NSAIDs as dangerous and potentially lethal irritants of the gastrointestinal tract, while the latter insists that they are extremely valuable and generally well tolerated drugs for first line use in arthritis and musculoskeletal disorders. These seemingly irreconcilable opinions are readily explained by personal experience, rather than by careful consideration of statistics. The pathologist sees only the fatal end result if perforation or haemorrhage causes death, the surgeon sees only those with perforation or continued haemorrhage, whilst the rheumatologist and general practitioner issue immense numbers of prescriptions for NSAIDs with only infrequently observed major problems. The precise incidence of serious gastrointestinal adverse effects amongst NSAID users is not known, but estimates suggest a rate of one episode of bleeding for 6000 prescriptions issued.1 Nevertheless, because of the large number of prescriptions written annually for these drugs (approximately 22 million in 19832) some thousands of patients will develop problems constituting a sizeable proportion of all cases with haemorrhage or perforation. Thus despite the faint impression made on the individual prescriber, the cumulative morbidity and mortality is unacceptably high. The report of two surgeons, C P Armstrong and A L Blower, on page 527 in this issue of Gut presents details of all patients during a three year period needing emergency surgery for bleeding or perforation of peptic ulcer, and of all patients dying from these conditions whether in hospital or at home in the South Cheshire Health District. This report clearly shows the magnitude of the problem – almost 80% of those dying from ulcer complications had received NSAIDs. The only other investigation which has tried to identify all cases of death from peptic ulcer and relate these to use of NSAIDs was the Confidential enquiry into deaths from peptic ulcer in Hampshire between 1981–3.3 Information was sought by questionnaire about all those whose death certificates indicated peptic ulcer, but because of various organisational difficulties replies were incomplete. Nevertheless where information was available about those dying in hospital, approximately 50% had been on NSAIDs.

The number of deaths associated with the ingestion of NSAIDs nationally is not known, but if the figures from South Cheshire are representative then extrapolation suggests that perhaps more than 4000 people die annually in the United Kingdom from these gastrointestinal complications. To put this into perspective, the annual death rate from self-poisoning, one of the epidemics of our time, amounts also to about 4000, of which less than one fifth occur in hospital.4
Exactly why NSAIDs should injure the intestinal tract is far from clear. The hypothesis has been proposed that as these drugs inhibit prostaglandin synthesis (by action on cyclo-oxygenase) this is the common factor between their anti-inflammatory effect on the joints and their ability to impair gastrointestinal mucosal resistance; decreasing mucosal prostaglandin concentrations facilitates acid-peptic aggression, with resultant gastritis, erosion and ulceration with its attendant complications. While this hypothesis has many attractions it does not explain why the ability of different drugs to inhibit prostaglandin synthesis in experimental situations bears little direct relationship to their clinical anti-inflammatory effect nor to their propensity to cause mucosal damage. Equally puzzling is the unpredictable occurrence of adverse events. Drug induced enzyme changes are usually dose related, although in many situations the reaction may be regarded as ‘idiosyncratic’. Sometimes adverse reactions are caused by an inherited enzyme abnormality or deficiency. In the case of NSAIDs no inherited or other identifiable cause predisposing to adverse reactions has yet emerged to identify susceptible patients, nor to explain the unpredictability of side effects.

Why the elderly should be so seriously affected by the adverse effects of NSAIDs is also perplexing. Large numbers of prescriptions are written for this age group, because of the increasing incidence of osteoarthrosis with age, while those with rheumatoid arthritis are on the whole younger. About half of the NSAIDs prescribed are for the over 60s. Not only is the incidence of gastrointestinal complications high in the elderly, but the outcome in terms of mortality is much worse, the case fatality rate being three times greater in the over 70s in Armstrong and Blower’s series. It seems probable that most prescriptions are given to those most at risk from complications of treatment. Considerable debate has taken place (and continues) about the differing likelihood of various NSAIDs of causing gastrointestinal side effects. The simple conclusion seems to be that all have the capacity to cause trouble; none can safely be exonerated. From time to time claims have been made that certain drugs (either new compounds, prodrugs or new formulations) are less irritant, yet in most instances increasing experience has shown such views to be ill founded. Few formal clinical trials have the power (are large enough) either to establish, or to refute a difference in incidence of side effects: if serious bleeding occurs only once in 6000 cases, useful data can only be gleaned from postmarketing surveillance by the pharmaceutical industry, or by notifications to the Committee on Safety of Medicines – ‘pharmacoepidemiology’.

Is there any way in which adverse effects can be avoided? A major change in prescribing patterns avoiding NSAIDs and substituting simple analgesics would lessen problems, but undoubtedly symptomatic control of rheumatic diseases would be much less good. Nevertheless, in terms of cost/benefit analysis the remote chance to the individual of drug induced death must be balanced against symptomatic control of mainly non-fatal disease; there is little evidence that NSAIDs influence the outcome of any of the diseases treated. Obviously NSAIDs must not be used for trivial musculoskeletal problems where safer alternatives might suffice. In the report of Armstrong and Blower it is disconcerting that in over 10% of those for whom NSAIDs had been prescribed, the indication could not be identified.

The role of over the counter (OTC) NSAID medication has not yet been assessed. Ibuprofen 200 mg (Nurofen) has recently become available
without prescription in the United Kingdom (according to the packet: ‘gentler than aspirin on the stomach and as well tolerated as paracetamol’). Traditionally ibuprofen has attained a reputation for being ‘gentle’, yet as the recommended dose has been increased adverse effects seem to have become more troublesome, and it certainly features prominently in Armstrong and Blower’s statistics. Nevertheless as they point out, there is no information about the relative frequency with which differing drugs were prescribed in their district, or the extent of OTC usage, although they have ascertained the pattern of NSAID intake in a hospital control group. In many countries several NSAIDs are available without prescription and so beyond the direct control of doctors; licensing authorities have a major responsibility here.

Prediction of serious complications is hardly realistic on the basis of premonitory symptoms, as in almost 60% of the patients reported by Armstrong and Blower the first evidence of an ulcer was the complication. Nevertheless, the occurrence of dyspepsia is very common and must not be ignored, and stopping the NSAID treatment must be seriously considered. Sometimes taking the drug with meals may lessen abdominal discomfort, but there is no evidence to suggest that this does, or does not prevent ulceration. Changing the NSAID may improve abdominal symptoms. The cause of this sort of dyspepsia, often in the absence of recognisable gastrointestinal lesions and its variations between NSAIDs, is unexplained. Endoscopic examination has a role, but it is not feasible to examine everyone who develops abdominal symptoms during NSAID therapy, nor is it reasonable to precede treatment with a screening endoscopy to ensure absence of disease at the outset.

Can adverse effects be prevented by the simultaneous administration of anti-ulcer drugs? Much interest is at present being shown in this area by the pharmaceutical industry. So far the histamine H2 receptor antagonists have proved disappointing. While some studies have shown healing of ulcers with continuing NSAID treatment, others have reported bleeding or perforation during simultaneous administration of a NSAID and an H2 antagonist. In the present state of knowledge co-administration of an H2 antagonist cannot be recommended as a safe approach. Will mucosal protective drugs such as sucralfate, compound bismuth (De-Nol) or prostaglandins be any more successful? Results of trials in progress are awaited with interest. It might be possible to incorporate a safety device into the formulation of NSAIDs, but this possibility must await the results of much more research.

Besides the problems with gastroduodenal bleeding and perforation, other serious gastrointestinal side effects of NSAIDs must be remembered. Langman and coworkers have provided evidence that ingestion of these drugs may be implicated in many instances of bleeding, or perforation of the small intestine or colon, although the precise source and pathology was not always shown. Small intestinal perforation has occurred with certain preparations and especially with slow release formulations. Heller and colleagues reported that 22 of 70 patients with oesophageal strictures were using NSAIDs, twice the incidence in an age and sex-matched control group.

What then are the recommendations for decreasing the incidence of adverse gastrointestinal complications from NSAIDs? (1) Exercise extreme care in the elderly – is a NSAID really indicated? (2) Avoid NSAIDs in
trivial, minor or self-limiting disorders at any age. (3) Avoid prescribing NSAIDs for those with pre-existing abdominal symptoms, or those with a known history of peptic ulceration. Perhaps preliminary endoscopic screening may be justified in some of these patients to clarify the situation. (4) Consider using a simple analgesic as an alternative, or in rheumatoid arthritis a second line drug (although these of course have their own potential problems) with a simple analgesic. (5) Perhaps reconsider the place of salicylates which lately have lost favour with many rheumatologists. Whilst aspirin is well known to be associated with gastrointestinal bleeding, the incidence may well be lower (perhaps one episode of bleeding in a quarter million doses) than with NSAIDs. (6) In the future perhaps consider coadministration of a ‘protective’ drug.

Should every prescription carry a government health warning? Probably not, but prescribers must be ever cognisant of the potential hazards of their recommendations, even if such events only occur every few years in an individual’s experience. All doctors carry the responsibility to their patients of weighing carefully the pros and cons before prescribing an NSAID.

The place of over-the-counter NSAIDs should be examined carefully, certainly before any further agents are made available. All packets should carry a prominent warning as to the possible hazards. It is essential that medical practitioners and the pharmaceutical industry pay careful attention to all risks of drug administration and give appropriate warnings. Unlike smoking and alcohol abuse, this is no area for governments, the responsibilities are entirely professional.

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References