CONSENSUS STATEMENT

Non-steroidal anti-inflammatory drug induced upper gastrointestinal haemorrhage and bleeding

(see also pages 728, 797 and 801)

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Non-steroidal anti-inflammatory drugs (NSAIDs) are very widely used in our community. There has been much concern recently about the risks of NSAID-induced upper gastrointestinal haemorrhage and perforation. Many patients taking these drugs have become concerned about these matters and confused by contradictory statements in the media. Consequently, a meeting sponsored by The Arthritis Foundation, The Australian Gastroenterology Institute and The Australian Rheumatology Association was held at St Vincent's Private Hospital, Sydney, in 1991. What follows is a summary of the main issues that were discussed.

NSAIDs and peptic ulcers

Single doses of aspirin and NSAIDs cause reproducible damage to the upper gastrointestinal mucosa, but recovery is fast even in the face of continued exposure to these drugs. The prevalence of peptic ulcer in patients with rheumatic diseases who are taking NSAIDs, as determined by surveys using endoscopy, is approximately 15%–20%, with most ulcers occurring in the stomach. A substantial proportion will be asymptomatic, particularly as the patients get older, and the true clinical significance of these findings is still unclear.

There are few data on the effects of NSAID formulation, dosage or route of administration on the incidence of peptic ulceration and complications. Most data refer to acute injury and are difficult to relate to the chronic peptic ulceration seen in patients who are taking these drugs and are admitted with upper gastrointestinal complications. Plain aspirin is clearly associated with dyspeptic symptoms but these are reduced by employing enteric-coated or slow-release formulations. Similarly, suppositories may reduce dyspepsia associated with NSAIDs, but their impact on the risks for peptic ulcer and complications is uncertain.

Peptic ulcers in patients taking NSAIDs heal at a normal rate if the NSAID is withdrawn and standard ulcer-healing drugs are used. However, the rate of healing is slower if NSAID therapy is continued. Many peptic ulcers "come and go" during the course of NSAID therapy without being formally diagnosed or treated.

Levels of use of NSAIDs in the Australian community

Approximately 11 million prescriptions for NSAIDs per annum are written for around 17 million Australians which indicates a high level of use in our community. Indeed, the total sales in Australia are higher per capita than in any other country for which published data are available. At any time more than 20% of subjects aged 65 years and over are taking NSAIDs by prescription. The use of aspirin and "over the counter" analgesics in this group is probably similar to other age groups, that is 10%–15%. In the 55–65 year age group, use of NSAIDs is lower, being approximately 17% at any time.

Relative risk of upper gastrointestinal haemorrhage and perforation

Although there is uncertainty concerning the appropriateness of the extent of use of NSAIDs in our community, it is now well established that these drugs cause upper gastrointestinal haemorrhage and perforation. However, there is still debate about the level of risk involved.

At the meeting, the technique of meta-analysis was used to review 12 case–control and seven cohort studies examining the risk for NSAID-induced bleeding. These analyses indicated a relative risk for haemorrhage or perforation lying between 2 and 4 for the average individual commencing treatment with NSAIDs.

There are fewer recent epidemiological data for aspirin but information from randomised controlled trials indicates that low doses used for prevention of thrombotic events are associated with a relative risk for haemorrhage of around 1.7 which rises to about 2.4 when higher doses (1–2 g daily) are employed. These studies confirm that the relative risk for haemorrhage with higher doses of aspirin are similar to those with other NSAIDs.

Background risk for upper gastrointestinal haemorrhage

Several studies have shown that the background incidence of ulcer-related haemorrhage and perforation rises steeply with age. An important consideration is that the relative risk of NSAID-induced adverse effects has a multiplying effect on this increasing background risk, so that the elderly have a much higher incidence of NSAID-induced gastrointestinal haemorrhage and perforation than younger subjects.

Unfortunately, some media have selectively highlighted studies that have reported an incidence of deaths from NSAID-induced bleeding that is considerably higher than has been experienced in Australia. The studies on which these media projections have been based have come from overseas and have reported exceptionally high background incidences of haemorrhage.

Factors increasing the risk of NSAID-induced bleeding

A previous history of ulcer complications or uncomplicated peptic ulceration in the absence of use of NSAIDs increases the risk of ulcer complications to a substantial degree. Gastrointestinal bleeding is five times as likely to occur in those who have experienced an uncomplicated peptic ulcer previously compared with those who have not. A previous history of a complicated ulcer is associated with a relative risk of gastrointestinal bleeding of 15–20 compared with individuals who have not had such a history. Therefore, it is not surprising that in epidemiological studies, the risk for NSAID-

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induced bleeding is increased in those with a previous peptic ulcer, and even more so in those with a previous complicated peptic ulcer.

Other risk factors for NSAID-induced upper gastrointestinal haemorrhage have not been identified clearly. Combined use of aspirin and other NSAIDs probably increases the risk as will heavy intermittent alcohol consumption, but cigarette smoking and lower doses of alcohol have not been shown to be important. There are now good data that suggest that increasing the dose of NSAIDs increases the risk. It also appears that the duration of treatment may be an important factor, since the maximum incidence of bleeding occurs within a few weeks of starting therapy. Indeed, from a number of sources there is evidence that the stomach adapts to NSAID exposure, reducing the likelihood of haemorrhage and perforation. The relevance of this to the advice which is often given, namely to use NSAIDs intermittently according to need, was discussed at length at the meeting. It was felt that the advocated approach to management of musculoskeletal disease should probably stand until further data are available.

Contrasting individual and population risk

To illustrate this issue, an example was presented of a woman aged 65 years who is taking an NSAID. This patient has an annual background risk for hospitalisation due to ulcer complications of 100–200 per 100 000 and this rises to 300–600 per 100 000 on treatment with NSAIDs.

Although this excess risk for the individual is low, the prevalence of use of NSAIDs in our community is so high that the proportion of total cases of haemorrhage which can be attributed directly to NSAIDs is substantial — around 20%–30%. As 6%–12% of elderly patients who develop complications are likely to die from them, the data can be taken to indicate that around 100–200 patients may be dying from NSAID-induced upper gastrointestinal adverse effects annually in Australia. Although this estimate is considerably lower than some figures quoted in the media, it is still cause for great concern from a public health point of view.

It was emphasised at the meeting that the risk to the individual is not extreme, and is comparable to other risks in life. The risk is probably acceptable so long as the indications for, and the response to, NSAIDs are deemed worthwhile by the individual for whom they were prescribed.

The role of prophylaxis

Used concurrently with NSAIDs over treatment periods of 3–12 months, the prostaglandin analogue misoprostol decreases the incidence of gastric ulcers by 50%–90%. H_2-receptor antagonists such as cimetidine or ranitidine and the surface active agent, sucralfate, are not efficacious in preventing NSAID-induced gastric ulcers, indicating that the widespread use of these drugs for this purpose is not rational. H_2-receptor antagonists are useful in preventing duodenal ulcers, but most NSAID-induced ulcers are in the stomach.

Most importantly, does reducing the incidence of NSAID-induced peptic ulcers with concurrent misoprostol reduce the risk for haemorrhage or perforation? The evidence for such an effect in the average patient taking NSAIDs is not yet available. Some cost–benefit studies which have suggested that it would be economic to use misoprostol widely have possibly relied on an overestimate of the efficacy of prostaglandins in preventing peptic ulcers. Age alone was not thought to be sufficient justification for co-prescription of prostaglandins. A large number of people would need to be exposed to misoprostol with its own potential for adverse effects, notably diarrhoea. It was felt that as patients got older (for example, over 75 years) and had other risk factors, in particular previous ulceration, then the potential benefits for misoprostol became clearer.

Use of NSAIDs in musculoskeletal diseases

NSAIDs are indicated when inflammation is significant, as in active rheumatoid arthritis, seronegative arthropathies and acute gout. However, much musculoskeletal disease is not primarily or intensely inflammatory in nature, for example osteoarthritis, soft tissue rheumatic complaints, back and neck pain and some sports injuries. There are few clinical trial data to indicate the optimal management of these conditions yet they are the commonest reasons for prescribing NSAIDs. With respect to sports injuries, it was noted that there were few good controlled data showing superior efficacy of NSAIDs versus placebo.

It was emphasised that NSAIDs do not decrease the progression of any rheumatic disease, and with chronic use may even enhance the rate of destruction of joints. This point is quite contentious, with counter claims that some NSAIDs protect joint cartilage. However, there are no substantive data to support either view with respect to NSAID use in humans at present.

The modern approach to management of osteoarthritis, which affects 5%–6% of the population, is to carefully assess the patient and to individualise management. A management plan should emphasise patient knowledge of the condition, weight loss if indicated and simple physical measures such as an exercise program and adjustments to methods of performing activities of daily living. If drug therapy is necessary, then the use of paracetamol should be the first step, followed by NSAIDs if lack of symptom control by other means suggests their use.

Recent well-controlled, short-term studies in osteoarthritis indicate that, on average, there is no difference in efficacy between low-dose NSAID, high-dose NSAID and paracetamol. This very important work needs to be confirmed and extended over longer periods of treatment. The dose and duration of all drug therapy ought to be reviewed regularly to minimise unnecessary exposure of patients to these drugs. It was noted that there was no evidence that paracetamol caused upper gastrointestinal adverse effects, particularly ulceration and haemorrhage or perforation, and therefore this drug deserved more attention as an option for the treatment of common musculoskeletal conditions.

The value of education of prescribers concerning proper evaluation of patients, consideration of simple alternatives to immediate prescription of continuous NSAID therapy and regular review of therapy was emphasised strongly.

In summary, much musculoskeletal disease is not or only mildly inflammatory and non-pharmacological measures can be very helpful. Individualisation of therapy is important. Flexibility in dosage and duration of therapy when using paracetamol or NSAIDs is appropriate.

Conclusions

The major points pertaining to use of NSAIDs for the management of musculoskeletal diseases, the risks for upper gastrointestinal haemorrhage and the measures that might be taken to address this problem have been summarised in this joint position statement for the Australian Gastroenterology Institute, the Arthritis Foundation of Australia and the Australian Rheumatology Association.

1. NSAIDs are widely used in Australia, at a rate significantly higher than most other comparable countries.
2. Most use is for non-inflammatory rheumatic conditions, the care of which is managed by general practitioners.
3. Careful assessment of a patient's musculoskeletal problems followed by an examination of a range of management options from simple lifestyle and physical interventions to the use of paracetamol and then NSAIDs is an appropriate approach to an individual with one of these conditions. The value of regular reassessments of the need for continued prescription of NSAID in individuals is emphasised.
4. The relative risk for an individual for NSAID-induced haemorrhage or perforation is about 2–4.
5. The risk increases considerably with age because of the age-dependent increase in background risk for peptic ulceration.
6. The combination of two risk factors, for example age plus previous peptic ulceration (particularly complicated peptic ulcer), further multiplies the risk for individuals.
7. In elderly patients with a further risk factor such as previous peptic ulceration, co-

prescription with the prostaglandin analogue misoprostol becomes an option — there is evidence that it reduces the frequency of ulcers but not yet evidence to indicate that it prevents haemorrhage or perforation.

8. There is no justification available in the literature for the routine use of sucralfate or H_2-receptor antagonists in patients taking NSAIDs to prevent NSAID-induced gastric ulceration or its complications. (H_2-receptor antagonists do protect against duodenal ulceration and their use is reasonable in those who have had a previous duodenal ulcer.)

Acknowledgements

The authors would like to thank Mr G Sandhu for recording the discussion leading to this statement, Mr Alan Watkinson of The Arthritis Foundation for facilitating the meeting and The Australian Gastroenterology Institute and The Arthritis Foundation of Australia for supporting the meeting.