Viewpoint

Management of NSAID induced gastrointestinal disturbance

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The value of treatment with non-steroidal anti-inflammatory drugs (NSAIDs) is suggested by their widespread use. over 22 million prescriptions being issued each year. Patients commonly suffer from adverse gastrointestinal effects, however. Avoidance of these would be eased if we had a fuller understanding of basic mechanisms and predisposing factors. Assessment is further hindered because peptic ulcer is common in the elderly even without NSAID treatment. there are no characteristic symptom patterns, patients with connective tissue diseases may be inherently more prone to gastrointestinal damage. there is a wide range of disorders for which NSAIDs are indicated, be it long term (rheumatoid arthritis, osteoarthritis) or acutely (soft tissue injuries), and there are at least 18 available generic NSAIDs.

Ulcer frequency

Duodenal ulcer has been accepted as a disease of the young or middle aged, but recent data suggest that the incidence of both gastric and duodenal ulcer, at least as judged by perforation rates, has increased markedly in the United Kingdom in the elderly over the past 25 years, whereas it has fallen substantially in younger people. The reasons for this change are not clear, and we are left with the impression that there are specific factors which have made elderly people more prone to peptic ulceration and its complications. Altered smoking habits in the elderly seem unlikely to account for the change, but increased use of NSAIDs may be partially responsible.

The prevalence of peptic ulcer has been reported to be 29% and 32% in osteoarthritis and rheumatoid arthritis respectively. In a random sample of patients with rheumatoid arthritis who were receiving NSAIDs, 36% were found to have peptic ulcer with gastric ulcer and duodenal ulcer of equal prevalence (Sturrock and Russell, in preparation). The prevalence of gastrointestinal lesions is higher in patients receiving more than one NSAID, suggesting a cumulative risk.

Symptom patterns

Patients taking NSAIDs may suffer from dyspeptic symptoms without having ulcers, or have an ulcer with or without dyspeptic symptoms, and they may suffer the ulcer complications of bleeding or perforation, often without any premonitory symptoms. All these patterns of disease, however, can be found in otherwise healthy people. A high prevalence of asymptomatic gastric ulcer (43%, women: 18% men) and duodenal ulcer (41%, women: 29% men) has been reported. Asymptomatic recurrence of duodenal ulcer was reported to be almost as frequent as symptomatic recurrence, and two thirds of patients with a recurrence of gastric ulcer had a complete lack of symptoms. There is evidence that the incidence of asymptomatic ulceration may be higher in patients with arthritis or those receiving NSAIDs, or both. In a series of rheumatoid patients.
with gastric ulcer, 56% were asymptomatic (Sturrock and Russell, in preparation).

If ulcer complications were to be observed to occur frequently in NSAID takers in the absence of premonitory dyspeptic symptoms it would be difficult to determine whether NSAID users were indeed prone to painless ulceration, or whether the proportion of patients with dyspepsia was reduced because those who complained of gastrointestinal symptoms would have had NSAID treatment withdrawn, thus averting ulcer complications. It is also possible that the analgesic properties of NSAIDs mask the symptoms of dyspepsia, or that patients with arthritis are used to pain and their disease expectation includes gastrointestinal upset. In these circumstances it is difficult to interpret data suggesting that a high proportion of patients taking NSAIDs have ulcers without dyspeptic symptoms unless the sample of NSAID takers is a random cross section of all those given treatment.

Coincident disease in arthritis

It is difficult to determine whether patients suffering from one disease are at risk of another. Postmarketing surveillance has shown that the greater intensity of clinical surveillance, which is an inevitable consequence of disease, will increase the chances of a second disease being recognised. Secondly, if an association between arthritis and ulcer is sought by examining the prevalence of ulcer in arthritis, and of arthritis in ulcer patients, the chances of detecting associations will be increased, but a spuriously high level of association by comparison with a reference value will also be noted.

There have nevertheless been repeated suggestions that the patient with arthritis, particularly rheumatoid disease, is inherently susceptible to peptic ulceration, though whether any increase represents a special property of the rheumatoid process, or is a general feature to be expected in those who are, say, marginally malnourished, is not clear. Platelet activating factor has been proposed as a mediator in the production of stress ulceration of the gastrointestinal tract and may explain the prevalence of gastrointestinal disturbance in chronic painful diseases such as rheumatoid arthritis.

Ulcer and dyspepsia in NSAID takers

Dyspeptic symptoms commonly complicate NSAID treatment, the prevalence varying with the intensity of treatment and probably with NSAID potency. NSAIDs have been referred to as blocking the prostaglandin-buttressed defences of the gastric mucosa. Prostaglandins are known to increase gastric mucosal blood flow, bicarbonate secretion, mucus thickness, and to enhance restitution of mucosal damage. Experimentally NSAIDs have been shown to increase acid output, decrease mucus biosynthesis, and diminish bicarbonate production. In addition, NSAID treatment in animals predisposes to experimental ulceration. Persuasive as these data may be they do not necessarily imply that treatment with NSAIDs causes ulcer or ulcer complications in man. A significant proportion of patients with ulcer bleeding or perforation has nevertheless been found to have taken NSAIDs. This proportion was found to be larger than in inpatient or community controls matched by age and sex, with an approximately threefold increase in risk for both gastric and duodenal ulcer in individuals aged 60 and over. Confounding seems unlikely to explain the differences, but the studies do not allow us to conclude whether NSAID ingestion predisposes to ulceration per se, or to complications in those with established ulcer. Caruso and Bianchi Porro, however, in a prospective endoscopic study noted that gastric erosions increased markedly in NSAID takers when endoscopic findings before and after treatment were compared. There was an increased proportion of NSAID takers in patients with bleeding ulcer compared with controls, in contrast with the relative lack of ulcer complications in short term controlled trials of NSAID treatment. Furthermore, when groups of 6000 to 12 000 patients taking particular NSAIDs were followed up in postmarketing surveillance studies no differences in ulcer complication rates were noted in those given any of five different NSAIDs nor between rates in the absence or presence of treatment with these individual agents.

The apparently incompatible results of case control studies suggesting that NSAIDs may cause ulcer complications, and surveillance studies suggesting that they do not, can be reconciled if the likely incidence of ulcer complications is taken into account. Some 30 000 episodes of haematemesis or melaena, or both, occurring each year in the United Kingdom lead to hospital admission, or about 1 in 2000 of the population. About half of these are due to gastric or duodenal ulcer, or about 1 episode of ulcer bleeding for every 4000 population of all ages each year. If we suppose that the average NSAID prescription has a duration of one month then the ordinary expectation of an episode of ulcer bleeding might be about 1 in every 48 000 monthly prescription periods. Thus in a population of all ages a threefold multiplication of risk would not be discernible during surveillance studies. General figures suggest that a tripling of the risk in individuals over 60 years of age would in effect mean that one
episode of ulcer bleeding or perforation might occur in association with every 3000 NSAID prescriptions in that age group (the chances of ulcer complications being greater in the elderly than in the young). If such calculations are correct it suggests we need to scrutinise more closely the need for NSAID treatment in elderly patients who do not have a severe arthopathy. Treatment should not be withheld from those with active rheumatoid disease; and available evidence suggests not that these patients are particularly at risk, but that the elderly with nondescript complaints or with osteoarthritis may be prone, at least, to ulcer complications.26

The total number of NSAID prescriptions issued has increased by over 10 million in the UK in recent years, with the elderly being most likely to receive treatment, but this rise probably accounts for a fifth to a quarter of the increase in total perforations noted.3 Nevertheless the coincidence between an increasing incidence of ulcer perforation in the elderly, and a rising rate of NSAID consumption in the same age group, suggests that it might be wise to keep the NSAID dosage as low as possible.

Investigation

There are no simple guidelines to separate those needing investigation of gastrointestinal symptoms from those who do not. The choice is usually made on symptomatic grounds even though there seems to be a high incidence of asymptomatic ulcer in patients with arthritis. Likewise there are no clear grounds for choosing between endoscopy and double contrast radiology examination, though experience in this age group favours endoscopy, particularly as a means of detecting small mucosal lesions and erosions and in examining the duodenal cap efficiently. Elderly and arthritic patients find endoscopy easier and generally prefer it to a barium meal, which requires considerable mobility on a hard x ray table to obtain optimal films. Modern fibre optic endoscopes are safe even in patients with advanced rheumatoid disease.

Management

When a patient taking a NSAID develops dyspepsia most clinicians will withdraw treatment altogether, or alternatively substitute another NSAID, or prescribe peptic ulcer therapy. The decision between these strategies has no rational basis. If the adverse gastrointestinal effects of NSAIDs, which have been reviewed by Rainsford,28 are associated with their anti-inflammatory properties (whether or not this is due to cyclo-oxygenase inhibition) then substitution of a similar drug should make little difference to symptoms except through changes in placebo effects although tolerance may develop.

Another strategy is to substitute a pro-drug needing hepatic activation or to use suppository treatment; both manoeuvres would be soundly based if NSAID side effects were local rather than systemic, but we do not know if this is true as indomethacin suppositories are associated with gastric mucosal damage.

For the arthritic patient with an ulcer who needs to continue NSAID treatment, most clinicians are likely to choose an H2 receptor antagonist such as cimetidine or ranitidine. Ulcer healing has been shown to occur despite continued NSAID treatment,29 and in one study the average healing time is similar whether an H2 receptor antagonist or sucralfate is used.30

The dilemma remains, however, as to whether prophylactic therapy should be undertaken for patients who require to take NSAIDs long term. The H2 receptor antagonists have been shown to prevent experimentally induced NSAID ulceration in animals31 and salicylate induced erosions32 and NSAID induced blood loss in human volunteers.33 Sucralfate has been claimed to have a protective effect against NSAID induced injury in man,34 and theoretically the new synthetic prostaglandin analogues misoprostol and enprostil would be logical agents to use because of their ability both to inhibit gastric acid secretion and to increase a number of factors shown to be important in the maintenance of gastric mucosal integrity. Limited experimental evidence in human volunteers shows that these prostaglandins can also protect the gastric mucosa from experimental damage,23 but there is as yet no evidence to confirm their role or superiority over established treatments in patients.

Perhaps of more concern is the objective of prophylactic therapy. Is it to prevent the gastrointestinal symptoms associated with NSAID treatment? If so, study design to allow for the tolerance which develops is essential before conclusions are drawn. Is it to prevent gastric erosions observed with treatment? If so, we need to know much more of their natural history, as those seen with salicylate treatment, like symptoms, reduce with time; and whether those that persist will develop into ulcers. Lastly, will prophylactic treatment prevent the development of peptic ulcer in arthritic patients and especially its complications? Very large clinical trials involving many thousands of patients over several years will be necessary to answer this question.

In the meantime those patients receiving long term NSAID therapy who have an ulcer should be treated and NSAIDs may be continued. It would be wise to ascertain ulcer healing by endoscopy and in
this small group prophylactic therapy is justifiable. For the remainder, long term prophylaxis is best reserved for those with troublesome symptoms until the results of further studies are available.

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References