Non-steroidal anti-inflammatory drugs: who should receive prophylaxis?

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SUMMARY
Non-steroidal anti-inflammatory drugs (NSAIDs) are the major recognized cause of iatrogenic disease, and may cause 100 000 deaths per annum through peptic ulcer complications. A number of risk factors can be identified that indicate patients at high risk. These patients can be managed by substitution of a COX-2 inhibitor or by prophylaxis with a proton pump inhibitor (PPI). Because risk factors that render patients at high risk of ulcer complications also act in the absence of NSAID use, PPI prophylaxis (or Helicobacter pylori eradication where H. pylori is the risk factor) have much to offer and controlled studies show that the incidence of recurrent peptic ulcer bleeding can be reduced substantially by PPI co-administration. Substitution of COX-2 inhibitors also has much to offer, arguably most in those without risk factors (although regulatory authorities do not accept this argument). Recent data show that PPI and COX-2 inhibitors can play complementary roles in the management of patients with moderate to severe dyspepsia and at high risk of ulcer complications.

THE PROBLEM
Non-steroidal anti-inflammatory drugs (NSAIDs) are a well-recognized cause of iatrogenic disease, principally because of their ability to cause gastro-duodenal ulcers and complications.1 These cause significant morbidity and mortality, although some estimates of extent are unrealistically high.1 Thus the often-quoted rate of 16 500 deaths to NSAID-associated peptic ulcer complications per annum in the USA2 seems unlikely, representing as it does 110% of all registered peptic ulcer deaths. Realistic estimates from the UK suggest that about 1000 patients per annum die from the effects of NSAID or aspirin (including low-dose aspirin).3 Because NSAID are used widely it is possible that these figures could imply 100 000 deaths per annum worldwide.

Dyspepsia
While dyspepsia seems less serious than ulcer bleeding or perforation, it is more common. An estimated 15% of patients are unable to take NSAID because of dyspepsia and a prevalence of (presumably lower level) dyspepsia among chronic users is in the range of 10–25%, representing an approximate doubling compared to non-users.4

Thrombotic complications of cardiovascular disease
In theory NSAID could increase, have no effect on or reduce the incidence of cardiovascular thrombosis via inhibition of prostacyclin, thromboxane or both. In practice there is little effect of NSAID as a group (see...
although some studies suggest that naproxen, by exerting a profound and prolonged inhibition of platelet thromboxane, might mimic the effects of aspirin and reduce the incidence of myocardial infarction. In the VIGOR study patients on naproxen had fewer thrombotic events than those on rofecoxib. At present it is still unclear whether this represents an antithrombotic effect of naproxen, a prothrombotic effect of selective COX-2 inhibition or a combination of the two.

Other side-effects

Recently, there has been increasing recognition of the effects of NSAIDs on renal function and of the ability of both NSAIDs and selective COX-2 inhibitors to cause elevation of blood pressure. If untreated it is possible that this might ultimately provoke as many cardiovascular events as gastrointestinal events. Direct study of the effects of NSAID on myocardial infarction has not suggested an overall increase. However, hypertension might influence myocardial infarction only after a prolonged period and the relationship between duration of NSAID use and myocardial infarction has not been investigated systematically. Whether patients on NSAID have an increased instance of stroke is not clear, but two studies have shown that heart failure is more common.

MECHANISMS

Gastro duodenal ulcers

Human and animal data support a notion that there are two main components to NSAID ulcer development. Inhibition of prostaglandin synthesis leads to development of micro-erosions early on. These then become evident erosions and deepen to form peptic ulcers. Acid suppression can diminish progression to erosions and ulcers, but only if intragastric pH is maintained at a relatively high level, typically over 4. Human studies support this notion in that normal doses of proton pump inhibitors (PPIs) or supratherapeutic doses of H2 antagonists reduce development of gastric ulcers in contrast to normal doses of H2 antagonists, which do not.

Dyspepsia

Much NSAID dyspepsia is responsive to acid suppression. There appears to be a high level of gastro-oesophageal reflux, although how NSAIDs could predispose to this is not clear. Similarly, mechanisms underlying nerve sensitization are somewhat cryptic, given that inhibition of prostaglandin synthesis reduces, rather than increases, pain in other situations.

ASSESSING STRATEGIES

There is controversy about how strategies to prevent NSAID associated GI side effects should be assessed. A rather simplistic argument about studying ‘real’ ulcers has led some regulatory authorities to demand ‘outcomes’ studies of ‘clinically significant events’, based on a mistrust of endoscopic surrogates. As detailed below, outcomes studies have disadvantages as well as advantages.

Outcomes studies

In these studies, a large number of patients (up to 18 500) are studied on drug comparison and the rate of the development of clinically significant events is measured. An apparent advantage of this approach is that an unselected population is studied, making widespread generalization reasonable. However, the life expectancy seen in such studies without active treatment is lower than would be expected for the age group studied, suggesting that fitter-than-average patients are studied and/or that the drugs used prolong life (for which there is no supportive evidence). The fact that these trials attempt to study unselected patients and if anything select those with a good outlook actually means that relatively few of the patients that concern regulatory authorities are studied, meaning their decisions are often not evidence-based. There are several other difficulties with outcome studies. They are incredibly large and expensive to run and because endpoints are relatively rare they are easy to under-power. This may have contributed to the failure of at least one study (CLASS) to achieve a statistically significant endpoint. Moreover, the appealing logic of studying ‘real clinical events’ is more apparent than real. Because of the numbers involved, successful studies have settled for an endpoint described as PUBS (perforations, ulcers and bleeds). The majority of these are uncomplicated ulcers and consequently their incidence maybe confounded by differences in the instance of dyspepsia. Another disadvantage of outcome studies is not only that soft endpoints are used but endpoint
assessment is imprecise, because it is not carried out according to protocol and monitoring committees have to make a judgement about imperfectly reported endpoints.

Of the two outcome studies of COX-2 inhibitors, CLASS failed to show a statistical significant difference between celecoxib and non-selective NSAIDs, at least in part because of inadequate size. VIGOR, the study of rofecoxib, showed a reduction of 50–60% in selected endpoints compared to naproxen. This fell short of the 75% reduction that might have been expected from epidemiological and endoscopic studies, if rofecoxib were equivalent to placebo in its effects on the development of ulcers and their complications. Whether this is a real difference and, if so, whether it reflects inadequacies of outcomes or endoscopic studies is not known. A recent outcome study of lumiracoxib has studied 18,500 patients with ulcer complications as its primary endpoint and it will be interesting to see. Whether this larger and arguably more precise study finds bigger differences.

Rightly or wrongly, regulatory authorities are not prepared to recommend safer strategies such as the use of COX-2 inhibitors or PPI prophylaxis in low-risk groups, even though it can be argued that this may, in fact, represent the most appropriate target for use of COX-2 inhibitors when indirect costs are taken into account.3 Given this situation, conventional outcome studies thus study a large number of patients containing a relatively small proportion of those for whom safer prescribing is considered appropriate. Moreover, residual risk when high-risk patients take selective COX-2 inhibitors vs. non-selective NSAIDs remains high.20 This is not surprising, given that most factors that render patients using non-selective NSAIDs at high risk are risk factors even in the absence of NSAID use. In the VIGOR study there were high levels of residual risk in patients with a past history of ulcer disease vs. those without, and in those infected with H. pylori vs. those who were H. pylori-negative.7

Recurrence of ulcers and ulcer complications

The limitations of selective COX-2 inhibitors, and of conventional outcome studies mentioned above, suggest that a different treatment for high-risk patients and a different approach to its assessment may be more appropriate. PPIs have been studied using a different type of outcomes study (although the term is not applied conventionally in these circumstances). In this approach, patients who present to hospital with a life-threatening ulcer complication (principally ulcer bleeding) are entered into a trial of treatment designed to prevent recurrence over the next 6 months. The merit of this approach is that high-risk patients who are pragmatically a target of prophylaxis are studied. However, because mechanisms may differ, data may not generalize to the whole population.

This approach has been applied both to PPIs2, 21 and COX-2 inhibitors.23 With PPIs, two studies have investigated such secondary prophylaxis in patients hospitalized initially because of an NSAID-associated bleeding gastric ulcer. In patients continuing to take NSAIDs, PPI prophylaxis reduced 4-fold the risk of a further similar episode over the next 6 months, compared to a strategy of H. pylori eradication. A third study has compared directly a PPI prophylaxis strategy in this group with a switch to COX-2 inhibitors.23 Results were similar in each group. However, a strategy of H. pylori eradication may have enhanced the effectiveness of COX-2 inhibitors and diminished the effectiveness of PPIs.

For aspirin, data are less clear cut.24 One study showed a very low rate of recurrent problems with H. pylori eradication alone (there was no non-eradication group to determine whether this was a beneficial consequence of eradication21). This low rate made it impossible to determine whether PPIs were effective. In a second study there was a higher rate of recurrent ulcer complications (although in some patients this was associated with failed eradication22). There was a very substantial and significant fall in ulcer complications with PPIs.

Medium duration patient endoscopy studies

Endoscopy has been used traditionally to evaluate therapeutic strategies for ulcers that are not associated with NSAIDs. There are no good reasons to believe that endoscopy studies are any less valid in patients taking NSAIDs than they are in patients with ulcers who do not. It may be that traditional outcome studies are of no additional value, because their results can be predicted from patient endoscopy studies.1

Moderately large endoscopy studies in patients over 6 weeks to 6 months have shown a 3- to 4-fold reduction in the development of ulcers with PPI prophylaxis or with switching to a COX-2 inhibitor.1, 3
Interestingly, these are larger differences than are seen in outcome studies. Whether endoscopy studies over-estimate the reduction in risk, or outcome studies (because of endpoint imprecision) underestimate it, are interesting questions for which answers have not yet been forthcoming. The Therapeutic Arthritis Research into Gastrointestinal Endpoint Trial (TARGET) by contrast found a five fold difference in ulcer complications (defined in ways that were as close as possible to those used in clinical practice) between lumiracoxib and the NSAIDs naproxen and ibuprofen. Whether this reflects chance, endpoints selections, trial design or drug choice remains to be seen.

**Short-term volunteer studies**

These are even less popular as a means of evaluating strategies than are medium-term patient endoscopy studies. Erosions are often declared to be of no clinical significance, although it is not self-evident that they have less significance than ulcers detected endoscopically (with which they are often confused). In fact, erosions are of intrinsic significance in clinical practice, as few would discount their importance when discovered as the sole lesion in patients presenting with a haematemesis. Moreover, as evidence has accrued it has become clear that erosions are strongly predictive in individual patients at risk and in populations of the effectiveness-of-the-individual strategies.

Thus, in a study of 1506 patients undergoing endoscopy prior to a study of rofecoxib vs. NSAID over 6 months, those who had erosions at baseline were approximately five times more likely to develop an ulcer in the study. Perhaps even more significantly, they were five times more likely to develop a spontaneous PUB than those without erosions. This influence was stronger than being infected with *H. pylori*.

Moreover, strategies developed from the acute study of erosions in volunteers have been, without exception, predictive of results in patient endoscopy and outcome studies. For example, volunteer studies predicted correctly that only PPIs or high doses of H$_2$ antagonists would prevent NSAID-associated gastric ulcers, that misoprostol would be effective protection, that use of COX-2 inhibitors would reduce ulcer disease and that any effects of NO donating NSAID would be limited.

**PRACTICAL PRESCRIBING**

**Reducing ulcer risk**

COX-2 inhibitor substitution or PPI prophylaxis are normally considered for patients who at increased risk of ulcer complication. While superficially attractive, this preconception needs careful analysis. In general, risk factors that render patients at increased risk of ulcer complications on NSAIDs also render them at increased risk of ulcer complications of NSAIDs. In those with no identifiable risk factors other than the drug, switching to a COX-2 inhibitor results in an extremely low incidence of ulcers and their complications. Thus, in the VIGOR study, patients without other risk factors has an annualized PUB rate of 1.9 per 100 patient-years on NSAIDs and 0.2 per 100-patient years on rofecoxib, a fall of 1.7 event per 100 patient-years. For patients with risk factors the comparable rates were 4.6, 2.1 and 2.5. In some groups such as those with a previous ulcer complication the residual rate on rofecoxib was even higher (approximately 10 events per 100 patient-years), although small numbers means that there are wide confidence intervals around this estimate. However, broadly speaking the results of CLASS were very similar. Thus, for patients with risk factors, conceptual analysis and experimental evidence suggest that other strategies such as PPI prophylactics or *H. pylori* eradication should be used as an alternative.

**Dyspepsia**

‘Dyspepsia’ is a word used to describe different symptoms with resulting confusion. This is particularly true with NSAID dyspepsia. There is some evidence that patients with NSAIDs have an increased incidence of dismotility, such as dyspepsia with upper abdominal bloating, as well as ulcer-like dyspepsia and reflux-like dyspepsia. How NSAIDs enhance the risk of reflux and of oesophagitis is unknown, but these symptoms seem to be very common. Acid-suppressing drugs such as PPIs and H$_2$ antagonists have been shown to reduce NSAID dyspepsia, probably via an effect on both ulcer-like and reflux-like dyspepsia.

It is probably true that two scenarios characterize NSAID users: the patient who develops severe and disabling dyspepsia early in use, and then discontinues them. Although it has not been studied formally, a treatment that controls dyspepsia and enables continued use would be very helpful in facilitating analgesic
and anti-inflammatory benefits. Some anecdotal evidence suggests that this can be achieved with acid suppression. Other patients who continue to take NSAIDs also suffer from dyspepsia at a lower level and in an intermittent way. The intermittency of dyspepsia in NSAID users made the study difficult, in giving an apparently high placebo rate. Nevertheless, recent large systematic trials have shown formally that PPIs such as esomeprazole both reduce NSAID dyspepsia with acute treatment and prevent or retard its return with maintenance.27, 28

**COMBINED USE OF COX-2 INHIBITORS AND PPIs**

*Reducing ulcer risk*

NSAID ulcers develop because of aggravation of prostaglandin-mediated mucosal events followed by acid peptic attack. This dual pathogenesis implies a possible benefit from a dual therapy. Recently data with the PPI esomeprazole have suggested that this could be the most effective way to approach the goal of eliminating NSAID-associated ulcers. Ulcer-free patients who were nevertheless at high risk because of age or past history and who were taking either non-selective NSAID or a selective COX-2 inhibitor were randomized to received esomeprazole 20 mg, esomeprazole 40 mg or placebos, and following for up to 6 months. Esomeprazole reduced ulcer development in patients taking NSAID and also did so at least as well in those taking COX-2 inhibitors.29

Conversely, with past history and continuing *H. pylori* infection residual rates are substantial, implying a policy of *H. pylori* eradication and/or the alternative of PPI prophylaxis. The latter is also appropriate for patients taking aspirin alone or with NSAID or COX-2 inhibitors.30

*Dyspepsia*

Interestingly, in analogous studies of patients with dyspepsia, esomeprazole also reduced dyspepsia associated with NSAID and in those using COX-2 inhibitors to a similar extent, and this continued with maintenance treatment for up to 6 months.27, 28 More data are needed but the consistency of these results, together with their biological plausibility, mean that use of selective COX-2 inhibitors and PPIs may be the most effective approach to patients with risk factors for ulcer disease or with disabling NSAID dyspepsia.

**CONCLUSIONS**

Contrary to the pronouncements of advisory and regulatory bodies, the group with the most to gain from switching to a COX-2 inhibitor may be those without risk factors placing them at high risk of ulcer disease. For many of the latter, co-prescription of a PPI may have advantages over use of COX-2 inhibitors alone in dealing with both drug-related and drug-unrelated risk.

**REFERENCES**


