Non-steroidal anti-inflammatory drugs: is the balance shifting?

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) have been subject to repeated warnings about their adverse drug reaction profile. The emphasis is usually on upper gastrointestinal tract complications [1-3] but, with concern about the lower gut [4, 5] and other organ systems [6], a view has been advanced that NSAIDs can be bad for patients and that the prescription rate should be reduced [7]. In particular, caution was counselled when the therapeutic indication for use was osteoarthritis since benefits were perceived as borderline when compared with simple analgesics. However, recent developments suggest that unintended effects of NSAIDs may not be uniformly adverse. Benefits to individuals and populations at risk of disease as diverse as ischaemic heart disease, bowel cancer and Alzheimer's disease have been identified and, if confirmed, these findings may alter the risk/benefit ratio.

NSAIDs: the bad news—unwanted adverse effects

The gastrointestinal tract

A substantial proportion of adverse drug reactions reported to the UK's Committee on the Safety of Medicines relate to NSAIDs. Many of these involve elderly patients with upper gastrointestinal problems secondary to unwanted effects mediated by prostaglandin pathways, although direct irritant effects may also occur [8]. There is consistent evidence from many cohort and case control studies that NSAIDs increase the risk of peptic ulcer perforation and upper gastrointestinal haemorrhage about three-fold in comparison with controls [1, 3, 8-10].

The risks to any individual elderly user are small. In the UK it is the extensive use of these agents, with over one non-aspirin NSAID (NANSAID) prescription for each person aged over 65 years in addition to over the counter use, which has produced the perception that upper gastrointestinal bleeding (UGIB) is a major problem with anti-inflammatory drugs. In an average week one patient will be admitted to hospital with UGIB out of 20 000 elderly people taking NANSAIDs [10]. As in each week about 1.5 million older people will take one or more NANSAID doses, the result is about 4000 UGIB admissions each year [10]. Death from such bleeding is unusual in younger patients, but about 600 of those aged 60 years or older will die either as a result of the gastrointestinal bleed or other co-morbidity. Inclusion of aspirin use increases these figures to 5000 UGIB episodes from NSAIDs with about 800 deaths per year. Estimates of attributable risk suggest that NSAIDs are responsible for between one-quarter and one-third of admissions for UGIB in older people [10].

Ulcer perforation is less frequent than haemorrhage, with around 2000 cases per year in those over 60 years [11], but is associated with a higher case fatality rate of up to 33% [12]. Although estimates of relative risk of perforation associated with NSAIDs may be higher than for bleeding peptic ulcers, confidence limits are wide. NSAID use could be associated with 1000 peptic ulcer perforations in older people each year in the UK, with over 300 deaths [12, 13].

Elsewhere in the gastrointestinal tract, the burden of morbidity and mortality from bowel disease remains undetermined. Asymptomatic enteropathy may be more common than previously identified, and occult...
bleeding and protein loss may be of importance in frail elderly people in the presence of other disease states [9, 14]. Clinical disease of large and small bowel with perforation, overt bleeding or stenosis (diaphragmatic narrowing) is described, but has been uncommon [4, 9, 14].

While quantification of the total number of patients with gastrointestinal problems is difficult, it seems possible that around 1000 people each year die from NSAID-associated gastrointestinal complications in the UK and that most of these deaths are of elderly people, many of whom have pre-existing co-morbidity.

Adverse effects on other organ systems

Adverse drug reactions to NSAIDs occur uncommonly in many other organ systems. Unwanted renal effects from NSAIDs are well described but poorly quantified [13, 15], although the chances of admission to hospital with acute renal failure appear doubled in NSAID users [14]. NSAIDs may decrease renal prostaglandin synthesis which alters renal blood flow, glomerular filtration and electrolyte and water excretion. Thus, renal function, often impaired with ageing, may deteriorate further [13]. Long-term use of NSAIDs has been shown to produce subclinical renal dysfunction with reduced renal concentration capacity, lower osmolar clearance and altered free water clearance that appears dose-duration-related and on occasions the co-use of diuretics can exacerbate the renal impairment [16]. Idiosyncratic interstitial nephritis has been described [14].

Poor control of hypertension [17], worsening of heart failure [18], acceleration of osteoarthritic changes [15], bone marrow suppression [19], asthma [20], hepatic disorders [21] and platelet dysfunction [22] have been reported, with severity ranging from subclinical to life-threatening. The impact of these unwanted drug effects on morbidity and the chances of dying appear low but are difficult to estimate since non-recognition and under-reporting of adverse effects are common [19, 23].

Risk profiles appear to differ between different NSAIDs: this may relate to dose prescribed, individual potency and efficacy as well as a general class-related adverse effect [3, 13, 17].

**NSAIDs: the good news—unintended beneficial effects**

Colorectal polyps and cancer

Animal and human data are consistent with the hypothesis that aspirin and NANSAsIDs reduce the likelihood of developing colorectal neoplasia. In rodents NSAIDs inhibit the growth of experimentally-induced colonic tumours [24-26]. As some prostaglandins appear to increase cellular proliferation and tumour growth [27], so inhibition of prostaglandin synthesis may be an important mechanism in the anti-tumour effect of NSAIDs. A potential anti-cancer action of these agents is reinforced by observations in familial multiple polyposis coli that the NSAID sulindac causes regression of rectal polyps following ileorectal anastomosis [28].

Case-control and cohort observational studies indicate that the risks of colonic neoplasia are reduced following exposure to NSAIDs. A case-control study of individuals participating in a faecal occult blood screening programme suggests a halving of the risk of colorectal adenoma following the previous use of NSAIDs [29]. Furthermore, there appeared to be a dose-response relationship, with longer and more frequent use of NSAIDs associated with lower risk of adenoma. The lowest risk (relative risk 0.21 (95% confidence interval 0.1-0.8)) was associated with prescribed use of NSAIDs for longer than 5 years [29]. Could confounding factors or bias have substantially influence the perceived effect? Influences such as diet and lifestyle may be important confounding factors, but risks were reduced even when cases were compared with controls who did not have colorectal adenomas but who were positive for faecal occult blood [29]. What is surprising are the modest doses of anti-inflammatory drugs that appear to have a protective effect. Other studies have shown reduced risk of colorectal cancer (in addition to adenomas) following the use of NSAIDs [30-32], although not all studies show risk reduction [33]. Cancer elsewhere in the gastrointestinal tract (stomach, oesophagus) may be reduced by regular aspirin use [34], and cancers of the lung and breast appear less common in aspirin users [35], although these findings need confirmation.

What are the potential implications of this? In England and Wales there are approximately 27 000 new cases (with 17 000 deaths) of colorectal cancer each year; of these, 23 000 cases (15 000 deaths) are in those aged 60 years and over. If NSAIDs are truly protective and reduce the risk by one-third, then 5000 lives could be saved and 9000 new cases of colorectal cancer prevented each year by the universal use of these agents, albeit potentially at the cost of a rise in UGIB and perforation. At present about 20-25% of people aged 60 years and over take an NSAID each week, with about 30% exposed to an NSAID each month [10]. While a chemoprotective effect (if it exists) may differ between old and young people, and the dose-duration nature of the effect has yet to be ascertained, up to 2000 less new cases of colorectal cancer might be occurring as a result of this frequency of use of NSAIDs in the community, with about 1000 fewer deaths.

**Ischaemic heart disease**

Aspirin has a role in the secondary prevention of
cardiovascular complications in patients who have had a myocardial infarction [36, 37]. The use of aspirin in the primary prevention of coronary artery disease has also been suggested in one prospective study, although the outcome benefits were balanced by a slightly increased risk of stroke with a relatively high aspirin dose [38]. Attention has focused on thrombotic mechanisms and platelet function [39]; a large population study has demonstrated a positive relationship between ischaemic heart disease and platelet aggregation [40]. Aspirin inhibits platelet aggregation by reducing the activity of the enzyme cyclo-oxygenase that is necessary for the production of prostaglandins [41, 42]. Other NSAIDs also inhibit cyclo-oxygenase activity and platelet aggregation and, like aspirin, may be expected to have a beneficial role in the prevention of myocardial infarction. Substantive direct evidence of this is lacking. Prescription event monitoring suggests a reduction in the frequency of myocardial infarction in patients prescribed NSAIDs [43]. Surprisingly this has not been further investigated.

Alzheimer's disease

Recent reports suggest a reduced risk of Alzheimer's disease in people who take NANSAsIDs. This was first shown in studies of twin-pairs, with a lower rate of Alzheimer's disease in those exposed to anti-inflammatory agents [44]. Subsequently another report has reinforced this observation, with a halving of risk by NSAIDs (odds ratio 0.38; 95% confidence interval 0.15–0.95) [45]. Furthermore there are data that indicate a protective effect on the rate of progression of the disease and that longer duration of NSAID use has an enhanced protective effect [46]. The mechanism(s) for any such effect is uncertain, although anti-inflammatory agents may inhibit the inflammation associated with the deposition of amyloid that is important in the pathogenesis of Alzheimer's disease [47]. These are preliminary results and the evidence is currently inconclusive but, if substantiated, this could represent an important advance in therapy.

Cyclo-oxygenase inhibition: COX-1 and COX-2

The mechanism of action of NANSAsIDs and aspirin is mediated by inhibition of prostaglandin synthesis through an interaction with the enzyme cyclo-oxygenase. This bifunctional enzyme exists in two isoforms, COX-1 and COX-2. The COX enzyme initially oxidises arachidonic acid to prostaglandin G₂ through a cyclo-oxygenase process and then peroxidases prostaglandin G₂ to prostaglandin H₂. These two sites for activity are adjacent but spatially distinct. NANSAsIDs probably bind at a number of sites to prevent access for arachidonic acid [48]. For example, aspirin irreversibly inhibits COX-1 by acetylation of the serine at position 530, thereby excluding access for arachidonic acid [49]. The constitutive isoform of COX is COX-1 and is found in gastric mucosa, the kidney and platelets. COX-2 is an isoform inducible by inflammatory stimuli and is encoded by a different gene. Aspirin, indomethacin and piroxicam are much less active against COX-2 than COX-1 [50, 51] and the mediation of gastric and renal damage and reduced platelet aggregation may be proportional to the inhibition of COX-1 [52, 53]. Most NANSAsIDs marketed in the past two decades were developed from COX-1 screening and are selective for COX-1, although diclofenac has a similar inhibitory effect on both isoforms. A number of new compounds are being developed with high potency against COX-2 and these may have potent anti-inflammatory activity with fewer gut side-effects but with reduced action on platelets.

Are the benefits worth the risks?

Although risks to the gut from NSAIDs are substantial, unexpected benefits are being identified. Benefits include a reduction in thrombo-embolic stroke—although with a possible increase of haemorrhagic stroke [33, 37]—and a reduction in myocardial infarction rates with NANSAsIDs (although this has yet to be confirmed in a prospective study). In England and Wales 150 000 people die each year of ischaemic heart disease, of whom 90% are 60 years or over. Thus, even a modest protective effect could translate into a substantial number of lives saved. The potential advantages from chemoprotection of colorectal cancer as well as cancer elsewhere in the gut are noteworthy. Whether the additional use of misoprostol to protect the gastrointestinal tract from peptic ulceration would alter this therapeutic advantage is unknown. There are data suggesting that misoprostol may reduce gut malignancy [54]. Preliminary evidence that cancer of lung and breast is less common in aspirin users needs confirmation [35]. Some of the differences between individual NSAIDs in propensity to damage the upper gut probably relate to COX-1/COX-2 selectivity—whether similar differences might exist with cardiovascular or cancer chemoprotection is unknown.

Upper gastrointestinal disease is by far the most common adverse effect of NSAIDs [23]. Although there may be other unrecognized adverse reactions with an underestimated frequency and severity, if NSAIDs do reduce bowel cancer risk as well as that of other cancers and have a role in ischaemic heart and some other forms of vascular disease as well as in Alzheimer's disease, could the benefits outweigh the risks as far as the chances of dying are concerned? The use of NANSAsIDs with minimal COX-1 inhibition may not require upper gastrointestinal prophylaxis, and may
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have a lower incidence of adverse gastrointestinal effects. More selective COX-2 inhibitors such as meloxicam and others with even greater selectivity currently being developed are likely to have limited use as anti-platelet and cardiovascular agents, although in bowel cancer COX-2 is the predominant isofom [55, 56].

Morbidity is more difficult to assess. Stopping NSAIDs after peptic ulcer bleeding may not always be necessary if anti-ulcer prophylaxis is used, particularly as withdrawing NSAIDs may be associated with a high level of locomotor symptoms—alternative analgesics can be unsatisfactory [57]. Mild reductions in renal function, occult bleeding and protein loss from the gut, and minor changes in organ function produced by NSAIDs in frail old people could contribute substantially to morbidity in ways yet to be fully understood. Overall, however, Alzheimer's disease is a considerable public health issue with much suffering for those afflicted as well as their carers—a reduction in frequency, severity and rate of progression associated with NSAID use indicated in preliminary reports has substantial implications if confirmed.

Conclusion

NSAIDs have had bad publicity for the last 15 years—at one stage it was even suggested they carry a health warning [58]. More recent findings suggest that some unintended NSAID effects are not adverse but beneficial. With the introduction of newer NAMSAs with predominant COX-2 inhibition and the ability to target the action required according to COX-1/COX-2 selectivity, the balance of risks to benefit and outcome appears to be shifting.

Key points

• The incidence of adverse gastrointestinal effects in community NSAID users is lower than is generally appreciated.
• NSAIDs may have beneficial effects in ischaemic heart disease, some tumours and Alzheimer's disease.
• Unintended beneficial effects may offset the socio-economic adverse effects of NSAIDs.
• The development of a new generation of NSAIDs highly selective for cyclo-oxygenase isotype should further improve the therapeutic risk/benefit ratio.

References

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