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CLINICAL PRACTICE

Non-steroidal anti-inflammatory drugs and cardiovascular risk

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Medications to relieve pain and inflammation are among the most commonly used drugs in our society today. The traditional non-selective non-steroidal anti-inflammatory drugs (NSAIDs) and the selective cyclooxygenase-2 (COX-2) inhibitors are effective anti-inflammatory and analgesic agents used in a wide range of acute and chronic medical conditions. The gastrointestinal adverse effects are well recognised. There is now strong evidence to suggest that both the traditional NSAIDs (excluding aspirin) and the COX-2 inhibitors are associated with an increased risk of thrombotic events (including myocardial infarction (MI) and stroke) and excess mortality both in patients with and without pre-existing cardiovascular disease.

Although their benefits in terms of symptomatic relief when used appropriately are unquestioned, there is concern that the NSAIDs and COX-2 inhibitors are prescribed or recommended by doctors and pharmacists (many of these drugs are available without prescription) for trivial or inappropriate indications without due consideration regarding their potential adverse effects. The traditional NSAIDs, freely available in public sector facilities, are often requested by patients and perceived by doctors as a 'cheap' and convenient way to keep patients happy and terminate a consultation. Some practitioners seem unaware of the magnitude of the problem or of the number needed to treat to cause harm. Many patients receive these drugs before other pharmacological or non-pharmacological treatments have been attempted. This has led to over-prescribing of these agents, particularly in an elderly population, in whom associated cardiovascular disease is the leading cause of death.

We aim to highlight the importance of these cardiovascular effects, and will summarise the clinical data on cardiovascular events, provide an overview of the basic science underlying the cardiovascular side-effects, and provide suggestions for prescribing COX-2 inhibitors and NSAIDs in patients with or at risk of developing vascular disease.

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Background

The traditional non-selective NSAIDs (naproxen, ibuprofen, diclofenac), which inhibit both forms of the COX isoenzyme (COX-1 and COX-2), are associated with significant gastrointestinal side-effects. As these side-effects were believed to be mediated primarily by COX-1 inhibition, newer selective NSAIDs or COX-2 inhibitors (rofecoxib, celecoxib, parecoxib, valdecoxib) were developed from the late 1990s to primarily inhibit the COX-2 isoenzyme. Subsequent studies reporting a lower incidence of gastrointestinal side-effects with COX-2 inhibitors, and heavy promotion, with direct-to-consumer advertising, led to an explosion in the use of the COX-2 inhibitors worldwide.

The first sign that COX-2 inhibitors might increase cardiovascular risk was from the VIGOR (Vioxx Gastrointestinal Outcomes Research) trial.[1] This randomised controlled trial reported a 50% reduction in serious gastrointestinal side-effects, but a 5-fold increase in thromboembolic cardiovascular events (primarily acute MI) in patients taking rofecoxib 50 mg daily compared with naproxen 1 000 mg daily at 9 months. Having naproxen as a comparator complicated the interpretation, which led to the false notion that naproxen was cardioprotective. The increase in cardiovascular risk with rofecoxib was later confirmed by the APPROVe (Adenomatous Polyp Prevention on Vioxx) trial, which showed a 2-fold increase in cardiovascular events with 25 mg/d of rofecoxib compared with placebo in patients with a prior adenomatous polyp.[2]

These data led to the withdrawal of rofecoxib from the world market in September 2004. Subsequently, the APC (Adenoma Prevention with Celecoxib) trial, which compared celecoxib with placebo, reported a 3-fold increase in cardiovascular risk in patients taking celecoxib 400 mg twice daily.[3] Another meta-analysis of two trials in high-risk patients taking valdecoxib who had recently undergone coronary artery bypass surgery, showed a significant 3-fold increase in cardiovascular events.[4] This led to the withdrawal of valdecoxib in April 2005.

With two COX-2 inhibitors withdrawn from the world market, attention then turned to the cardiovascular safety of the traditional non-selective NSAIDs with conflicting studies implicating higher doses of ibuprofen and diclofenac with increased cardiovascular events.

Against this backdrop in February 2005, the US Food and Drug Administration requires that all COX-2 inhibitors and non-selective NSAIDs carry a warning highlighting the potential for increased risk of cardiovascular events.[5] Similarly, the Medicines Control Council of South Africa has required labelling of all COX-2 inhibitors, but has made no recommendation about the cardiovascular safety of the traditional NSAIDs.[6]

Data on risk of cardiovascular events

Drawing conclusions from the numerous data on the COX-2 inhibitors and NSAIDs is not straightforward, as most of the data were obtained from post-hoc and non-prespecified analyses of randomised trials with many trials lacking a placebo arm. Although the current data have their limitations, it is possible to draw a number of conclusions.

In patients with and without cardiovascular disease, there is good evidence to suggest that the COX-2 inhibitors are associated with an increased incidence of cardiovascular events. There is growing evidence to suggest that these adverse effects appear to be a 'class effect' of the COX-2 inhibitors with a dose-dependent increase in risk. There are numerous studies that indicate different degrees of risk associated with different COX-2 inhibitors, but to date there have been no head-to-head comparisons of the various COX-2 inhibitors.[7] Cardiovascular risk seems to increase from the start of therapy and continues throughout the duration of treatment.[8]

A recently published meta-analysis of 121 randomised trials that assessed the effects of COX-2 inhibitors compared with placebo on the risk of cardiovascular events, reported a 42% relative increase in the incidence of serious vascular events (mainly myocardial infarction) – incidence 1.2%/year taking COX-2 inhibitors v. 0.9%/year taking placebo. No significant difference was observed between the COX-2 inhibitors studied (rofecoxib, celecoxib). In absolute terms, 3 extra people will have a vascular event per 1 000 per year.[9]

A recently published systematic review of 23 observational studies found similar results.[10] Rofecoxib was associated with a 35% relative increase in cardiovascular events compared to placebo with a 2-fold increase in risk with doses in excess of 25 mg/day. The risk was shown to increase early in therapy, probably with the first dose.[8] The data on celecoxib have been inconsistent. A meta-analysis and a case-control study suggest that celecoxib is associated with increased cardiovascular events at a dose > 400 mg/day.[3,11,12] Another meta-analysis failed to demonstrate an increase in cardiovascular risk in patients with predominantly rheumatological disorders and Alzheimer's disease. However, many of these studies were not originally designed to assess cardiovascular risk and many were of short duration.[13]

Larger trials are needed to accurately determine the magnitude of risk of the individual COX-2 inhibitors at varying doses. The PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety v. Ibuprofen or Naproxen) trial is planned to investigate the relative safety of these drugs in 21 000 patients.[14]

Studies of the traditional, non-selective NSAIDs have been more difficult to interpret. As NSAIDs were originally developed for the relief of pain, long-term placebo-controlled trials evaluating cardiovascular events have not been conducted. Nevertheless, conflicting available data suggest that the cardiovascular risks may be significant but lower than with the COX-2 inhibitors.

A meta-analysis of 91 trials that compared a COX-2 inhibitor to a non-selective NSAID in patients without cardiovascular disease, demonstrated a similar incidence of serious vascular events in patients taking high-dose (ibuprofen 800 mg 3 times a day, diclofenac 75 mg 2 times a day) non-selective NSAIDs (1.0%/year v. 0.9%/year). This meta-analysis was unable to conclude whether lower doses of NSAIDs would have the same effect.[9]

In a systematic review, diclofenac and indomethacin carried the highest risk, with a 40% relative increase in cardiovascular events, but dose-effects could not be assessed.[10] Although there is agreement between randomised and non-randomised studies that naproxen appears to be neutral for MI risk, investigators recently halted the ADAPT (Alzheimer's Disease Prevention Trial) because of an excess of cardiovascular events in participants randomised to naproxen.[9,15]

Another meta-analysis of 13 randomised trials in patients with joint disease and Alzheimer's disease showed a non-significant trend towards increased cardiovascular risk in Alzheimer's disease trials, but not in trials of joint disease.[16]

The most convincing evidence that cardiovascular risk is dose-dependent comes from an analysis of the Nurses' Health study that suggests that frequent use (> 22 days/month or > or = 15 tablets per week) of non-selective NSAIDs (73% used ibuprofen, 14% used naproxen) in healthy women without cardiovascular disease resulted in a 44 - 86% relative increase in cardiovascular events compared with non-users.[17] This effect of NSAIDs did not differ according to the presence or absence of chronic conditions. This study also demonstrated that paracetamol led to a 35% relative increase in cardiovascular events in patients consuming paracetamol tablets > 22 days per month.

While all the above data concern patients without known cardiovascular disease, the limited data in patients with established cardiovascular disease are of particular concern. A large Danish registry of 58 432 post-MI patients demonstrated that both COX-2 inhibitors (rofecoxib, celecoxib) and non-selective NSAIDs (ibuprofen, diclofenac) were associated with a 2 - 3-fold increase in mortality and a trend for an increased risk of rehospitalisation for MI.[18] These adverse effects were dose-related and most patients were receiving treatment for a short

time (1 month on average). In absolute numbers, 14 patients treated with a celecoxib, 24 patients treated with diclofenac, and 45 patients treated with ibuprofen for 1 year will result in 1 additional death. These data confirm that these drugs should be used with particular caution in high-risk patients and should preferably be avoided unless absolutely essential.

Mechanism of adverse cardiovascular effects

The reported adverse effects are biologically plausible given our understanding of the role of COX inhibition in vascular pathophysiology. Within the vascular lumen, COX-1 and COX-2 play an important role in the interaction between platelets and endothelial cells and in thrombogenesis. Activated platelets produce COX-1-dependent thromboxane A2, which acts as a platelet agonist and vasoconstrictor (prothrombotic). Endothelial and smooth-muscle cells produce COX-2-dependent prostacyclin, especially after cell damage. Prostacyclin has vasodilatory effects and is a platelet antagonist (inhibits thrombogenesis). COX-2 inhibitors suppress endothelial production of prostacyclin, leaving prothrombotic platelet thromboxane A2 mediated by COX-1 relatively unopposed. With loss of the antiplatelet and vasodilatory effects of prostacyclin, a relative excess of thromboxane A2 would favour vasoconstriction, platelet aggregation and thrombosis. In addition, the COX-2 inhibitors can cause sodium retention, a reduction in glomerular filtration rate and exacerbation of hypertension, which may promote an increased risk of cardiovascular events.

Cell damage, atherosclerotic plaques, and laminar shear forces selectively upregulate the expression of COX-2 by endothelial cells to maintain homeostasis. COX inhibition by any NSAID or COX-2 inhibitor can be expected to upset the thrombotic equilibrium, increasing the risk of cardiovascular events.[19]

How do we explain the variable side-effects between the NSAIDs and COX-2 inhibitors of different drugs of the same class? Not all NSAIDs and COX-2 inhibitors are the same. Owing to important structural, pharmacodynamic and pharmacokinetic differences, the different traditional NSAIDs have variable COX-1 and COX-2 inhibiting properties. Increasing degrees of COX-2 selectivity are associated with augmented cardiovascular risk. The NSAIDs, in increasing order of COX-2 selectivity, are naproxen, ibuprofen and diclofenac. Similarly, different COX-2 inhibitors have varying effects of COX-2 inhibition. The COX-2 inhibitors, with increasing order of COX-2 selectivity, are celecoxib, rofecoxib and etoricoxib.[20] The above properties may partly explain the different gradients of risk associated with different COX-2 inhibitors and NSAIDs.

How do we explain the dose-dependent increase in risk? NSAIDs display temporary and reversible binding to COX and therefore, in theory, will lead to greater inhibition at higher doses. Conversely, the COX-2 inhibitors display irreversible covalent binding to COX, which may partly explain the greater inhibition of COX-2 during intermittent use and at lower doses.

Recommendations for use

COX-2 inhibitors are contraindicated in patients with ischaemic heart disease (including postoperative coronary artery bypass graft patients) or stroke, and these patients should be switched to alternative treatments if possible. NSAIDs are not without risk and should be used with caution, especially in patients with ischaemic heart disease or at high risk thereof because of hypertension, diabetes, smoking or hypercholesterolaemia.

Since NSAIDs and COX-2 inhibitors are mostly used for symptom relief, rather than disease modification, these drugs should be prescribed only when non-pharmacological and other lower-risk pharmacological drugs (aspirin, paracetamol, narcotic analgesics) have failed. A NSAID with a low COX-2 selectivity should be the preferred choice (see above). Health care providers should assess the patient's individualised risk/benefit ratio before prescribing a NSAID or COX-2 inhibitor, and prescribe the lowest dose of these drugs for the shortest possible time necessary to control symptoms.

Patients should be periodically monitored for adverse side-effects and the ongoing need for NSAID or COX-2 inhibitor use. Reflex repeat prescriptions should be avoided. Taking low-dose aspirin with a NSAID or COX-2 inhibitor has not been studied sufficiently adequately to make a firm recommendation, but it is clear that this combination will increase gastrointestinal risk.

Most importantly, perhaps we all need to scrupulously re-examine our prescribing habits. The NSAIDs and paracetamol are among those agents labelled as '*troos medisyne*'. These cheap, supposedly harmless medications are added onto the script at the patient's request along with the laxative, nocturnal sedative or skin cream. The recent revelation of the magnitude of potential harm associated with NSAIDs and paracetamol after several decades of prescribing them to patients with vascular disease, often for tenuous indications, is sobering.

Conclusion

Significant increases in risk of cardiovascular events in NSAID users have been found in clinical trials, especially in patients taking COX-2 inhibitors. Although two COX-2 inhibitors have been taken off the market, other COX-2 inhibitors and NSAIDs are still readily available to doctors and patients. COX-2 inhibition by COX-2 inhibitors and NSAIDs results in a disturbance in the equilibrium of COX-1 and COX-2, which predisposes to a prothrombotic state and increased cardiovascular events. When prescribing NSAIDs and COX-2 inhibitors, doctors should carefully weigh the benefits of treatment against potential gastrointestinal and cardiovascular harm. Patients with established car-

diovascular disease or at risk for cardiovascular events should not be treated with COX-2 inhibitors and NSAIDs unless it is absolutely essential and all other treatment options have been explored. The number of patients one needs to treat with these agents before causing harm is alarmingly small, and perhaps the packaging of the traditional NSAIDs, like the COX-2 inhibitors, should carry a health warning!

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