Accounting for cardiovascular risk when prescribing NSAIDs

DAVID LAIGHT

It is now recognised that oral NSAIDs can increase the risk of cardiovascular events, including myocardial infarction and stroke. This article discusses the potential mechanisms involved and how the risk can be minimised.

Dual cyclo-oxygenase (COX-1 and COX-2) inhibition, using traditional NSAIDs such as naproxen and ibuprofen, is the go-to therapeutic option for the acute and chronic relief of pain, with or without a background of inflammation. However, traditional NSAIDs have long been associated with many gastrointestinal side-effects, including dyspepsia and gastric or duodenal ulceration.

The more recently developed selective COX-2 inhibitor (COXIB) class, which includes celecoxib and etoricoxib, initially promised much in the way of targeting pain and inflammation without hitting the beneficial 'housekeeping' jobs associated with COX-1 activity such as gastric cytoprotection. While this clinical promise was in part realised in the form of reduced gastroduodenal ulceration, COXIBs were also found to be associated with increased cardiovascular risk, including myocardial infarction, ischaemic stroke and hypertension. This led to product withdrawals for two selective COX-2 inhibitors early to the market, valdecoxib and rofecoxib.

Traditional NSAIDs and cardiovascular risk
However, cardiovascular side-effects are not limited to COX-2 selective agents. On top of the continuing concerns over COXIBs, cardiovascular toxicity is now also recognised as a complication of commonly used oral traditional NSAIDs such as diclofenac and high-dose ibuprofen, including myocardial infarction, ischaemic stroke and also heart failure (see Table 1). Indeed, diclofenac is considered to pose an equivalent cardiovascular risk to COXIBs. This is besides the well-established oral NSAID-related problems, such as raised blood pressure and renal impairment, in individuals with hypertension and heart failure.

These fresh safety concerns considerably extend the traditional patient populations at higher risk of NSAID adverse events to include individuals at high, chiefly atherothrombotic cardiovascular risk and patients with established ischaemic heart disease, peripheral arterial disease and cerebrovascular disease. This added vulnerability to cardiovascular harms is made worse by a number of clinical indications for NSAIDs, such
as forms of arthritis that already show a higher baseline risk due to advancing age and/or cardiovascular risk factors. Higher rates of NSAID use in patients with established cardiovascular disease bring further risk exposure.\textsuperscript{12}

A recent meta-analysis by Bally et al.\textsuperscript{13} provides new insights into the time course of COX inhibitor-related cardiovascular risk, illustrated by the incidence of acute myocardial infarction with either oral COXIBs or traditional NSAIDs, including high-dose ibuprofen and naproxen. The cardiovascular ‘safe period’ is minimal, with heart attack risk emerging both quickly (within the first week in a dose-dependent manner) and peaking early (within the first month in most cases). Such database-sourced studies are of course not without limitations, including the reliance on drug dispensing/prescribing data as a surrogate for drug intake and an inability to capture over-the-counter NSAID use. Patient susceptibility to cardiovascular events as a result of an underlying condition also complicates the interpretation of NSAID risk against a background of disease.

Other recent evidence suggests, perhaps surprisingly, that oral NSAID-related prothrombotic cardiovascular risk persists in the presence of antithrombotic therapy, while this combination is associated with a less surprising increase in bleeding risk.\textsuperscript{13,14} Although the absolute increase in cardiovascular risk posed by traditional NSAIDs is very low, the widespread prescription and over-the-counter use of these drugs could translate into significant numbers of additional atherothrombotic events.

### Prostanoid production in health and disease

Prostanoids, which include prostaglandins (PGs) and thromboxane (TX), are lipid-based, locally produced and locally acting cellular messengers (autacoids). They are typically derived from the 20-carbon, polyunsaturated, n-6 fatty acid eicosatetraenoic acid (arachidonic acid), which is abundantly available incorporated as phospholipid in cell membranes, by the activities of isoenzymes COX-1 and COX-2.\textsuperscript{15,16} Arachidonic acid as substrate gives rise to the 2-series of prostanoids: PGD\textsubscript{2}, PGE\textsubscript{2}, PGF\textsubscript{2α}, PGJ\textsubscript{2} (also known as prostacyclin), and TxA\textsubscript{2} (see Figure 1).

While the products of COX-1, constitutively expressed in most tissues, are thought to play essential roles in, for example, cytoprotection of the gastric mucosa, renal blood flow and platelet function, some of the same lipid products when originating from the inducible expression of COX-2 activity in inflammatory cells (particularly PGE\textsubscript{2}), are commonly regarded as hyperalgesic, proproliferative and proallergenic as well as proinflammatory.\textsuperscript{17} Hence, this readily provides a pharmacological rationale for the selective inhibition of the COX-2 isoenzyme in inflammatory disease, providing symptomatic relief of pain and swelling without typical systemic NSAID side-effects. This clinical model also accounts for the origins of side-effects, such as gastrointestinal toxicity, along with a mechanism for the clinical efficacy of NSAIDs, ie as consequences of indiscriminate COX blockade.

### Vascular wall thromboxane/prostacyclin balance theory

This simple view of COX isoenzymes having separate roles in health and disease has lately come into question, with an awareness that COX-2 is not exclusive to inflammatory cells. For example, at least some COX-2 products, particularly vascular endothelium-derived prostacyclin (a vasodilator and antiplatelet agent) are important, along with some endothelial COX-1-derived prostacyclin, for haemostasis.\textsuperscript{18} COX-2 activity also seems important in wound healing. Indeed, a continuum of blood clotting risk may be proposed based on the ability of an oral NSAID to differentially inhibit the generation of antiplatelet prostacyclin and the production of vasoconstrictor and proaggregatory TxA\textsubscript{2}.\textsuperscript{19} This reflects the balance between vascular endothelial COX-1 and COX-2 inhibition and platelet COX-1 inhibition. According to this vascular wall thromboxane/prostacyclin balance theory, cardiovascular risk is therefore highly anticipated for selective COX-2 (and thereby vascular endothelial) inhibition, which leaves platelet function intact (owing to the absence of COX-2 expression in mature platelets).

Conversely, some combination of COX-1 and COX-2 blockade, as is usually provided by a traditional, non-selective NSAID, is predicted to moderate the prothrombotic risk associated with COX-2 blockade alone, by redressing at least some of the endothelial/platelet

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**Table 1.** Oral traditional NSAID cardiovascular risk summary

| 2-series of prostanoids: PGD\textsubscript{2}, PGE\textsubscript{2}, PGF\textsubscript{2α}, PGJ\textsubscript{2} (also known as prostacyclin) and TxA\textsubscript{2} (see Figure 1). |
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functional prothrombotic imbalance (through the introduction of COX-1-dependent platelet inhibition). For the majority of traditional, non-aspirin NSAIDs, COX-1 inhibition/antiplatelet effects are not sufficient to eliminate the prothrombotic cardiovascular risk due to vascular COX-2 inhibition. Furthermore, an increased COX-1 inhibitory/antiplatelet profile is likely to increase the risk of gastroduodenal ulceration/bleeding, emphasising the likely trade-offs between cardiovascular and gastrointestinal safety profiles with traditional NSAIDs (see Table 2).

However, not all NSAIDs are the same and a notable exception to this general pattern of weak effects on platelets of non-aspirin NSAIDs is naproxen, which is capable of sustained COX-1 inhibition associated with a long plasma half-life and subsequent extended duration of antiplatelet action. In further contrast, the profound antiplatelet effect of low-dose aspirin, which is associated with selective, irreversible COX-1 blockade from which platelets cannot recover, appears to confirm the paradigm by actively conferring cardioprotective properties in the setting of the prevention of cardiovascular disease. Interestingly, the antiplatelet effects of aspirin can be blocked by other traditional NSAIDs which naturally raises concerns about the long-term potential of oral NSAIDs to undermine low-dose aspirin-derived cardioprotection. Indeed, interruption to this cardioprotection, in the form of discontinuation of low-dose aspirin, leads to a swift rebound elevation in cardiovascular risk in both primary and secondary prevention.

**COX selectivity and cardiovascular risk**

While most traditional NSAIDs are generally considered to be non-selective agents, some inhibitory preference may still be exhibited. This pharmacological spectrum of relative COX selectivities could clinically translate into a spectrum of cardiovascular as well as (inversely related) gastrointestinal risk profiles (see Table 2). In the cases of etodolac, diclofenac and meloxicam, this inhibitory preference amounts to an appreciable

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### Table 2. Gastrointestinal/cardiovascular ‘risk matrix’ and clinical pattern/nature of systemic COX inhibition, based on the vascular thromboxane/prostacyclin balance theory

<table>
<thead>
<tr>
<th>Lower gastrointestinal risk</th>
<th>Higher gastrointestinal risk</th>
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<tbody>
<tr>
<td><strong>Higher cardiovascular risk</strong></td>
<td>Selective COX-2 inhibition (eg celecoxib)</td>
</tr>
<tr>
<td><strong>Lower cardiovascular risk</strong></td>
<td>Non-selective COX inhibition (eg naproxen) plus antiulcer drug</td>
</tr>
<tr>
<td><strong>Cardioprotective</strong></td>
<td>Sustained, selective COX-1/platelet inhibition (eg low-dose aspirin) plus antiulcer drug</td>
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**Clinical patterns of COX inhibition**

In addition to the intrinsic drug characteristic of COX selectivity, pharmacokinetic factors play an important part in the nature and also dynamics of the clinical risk/benefit profile of individual oral NSAIDs. Hence, clinical aspects such as dose, dosing interval and NSAID plasma half-life help determine, for example, both the extent and duration of COX-2 inhibition and concomitant COX-1 inhibition. This is well demonstrated in the case of diclofenac, where the need for initially high plasma levels in order to maintain concentrations in the therapeutic range over the dosing interval (necessitated by a relatively short plasma half-life), produces a transient non-selective COX inhibition until falling plasma levels re-assert a relative COX-2 selectivity (and presumably peak cardiovascular risk) for

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**Figure 1.** The COX-mediated prostanoid pathway from arachidonic acid

COX-2 selectivity, and this conceivably raises cardiovascular concerns akin to COXIBs. However, with respect to specific cardiovascular harms, Bally et al’s meta-analysis of acute myocardial infarction risk with oral NSAIDs in real-world use suggests that the risk posed by celecoxib is no greater than that associated with traditional NSAIDs, all of which pose a risk.

These findings, supported by others, contest the view that different levels of cardiovascular risk can be attributed solely according to COX selectivity profile. Furthermore, they challenge the notion that a traditional NSAID can be cardiovascular ‘risk neutral’, specifically in relation to naproxen. The exact mechanism(s) of either traditional NSAID- or COXIB-related prothrombotic profiles and the centrality of the role of COX-2 inhibition evidently remain to be fully explained.
Replace
Substitute alternative analgesic medication for an NSAID or use topical NSAID for regional pain relief

Reduce
Use the lowest dose over the shortest treatment course, consistent with obtaining therapeutic outcomes

Refine
Closely monitor patient responses and regularly review the therapeutic rationale for NSAID use along with the clinical choice of agent (with naproxen and ibuprofen being preferred)
Consider conventional patient safety profile, for example likelihood of gastrointestinal harm and its management as well as cardiovascular safety profile
Consider how patient safety profiles may be affected by oral NSAID interactions with concomitant medications, particularly aspirin

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Balancing risks when prescribing traditional NSAIDs
Given the prothrombotic consequences of systemic non-selective COX inhibition, medicines optimisation now supports the evaluation of individual NSAID ‘global’ risk profiles together with patient medical history, including gastrointestinal, renovascular and cardiovascular safety profiles. Furthermore, NICE advises use of the lowest effective dose of oral NSAID and the shortest treatment duration necessary to control symptoms. In addition, the continuing therapeutic need for treatment with any oral NSAID should be regularly reviewed, while closely monitoring patient clinical responses and circumstances.

As for the clinical choice of oral NSAID, according to NICE, ibuprofen (1200mg daily or less) or naproxen (1000mg daily or less) are the preferred options, and here therapeutic ‘like-for-like’ substitution is made easier by the fact that at least analgesic efficacy is very similar for the majority of traditional NSAIDs. By the same token, there may be grounds to avoid the use of oral diclofenac altogether, with its undesirable combination of intermediate gastrointestinal risk profile and relatively high prothrombotic risk profile (see Table 2).

Combination of a traditional oral NSAID with an antiulcer drug, such as esomeprazole, misoprostol or ranitidine, represents a simple expedient for managing anticipated gastrointestinal complications, in effect emulating the COX-2 selectivity advantage provided by COXIBs. Furthermore, paracetamol and codeine-containing preparations might be considered over an NSAID for analgesia, and a topical NSAID may substitute for a systemic NSAID for local pain relief. Taken together, these prescribing responses to managing systemic NSAID cardiovascular risk amounts to a ‘replace, reduce, refine’ or ‘3 Rs’ approach (see Table 3).

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Conclusion
The inhibition of prostanoid production is central to both the therapeutic and gastrointestinal/renal adverse event profile of NSAIDs. Attempting to divorce this conventional risk from analgesic/anti-inflammatory benefit with COX-2 selective agents has uncovered or possibly actively promoted a shift in risk to prothrombotic cardiovascular complications. This is a risk that is shared by traditional oral NSAIDs, particularly at high-dose and even after short-term exposure.

Despite clinical reservations about rating the relative cardiovascular safety of oral NSAIDs, naproxen on balance poses a somewhat lower cardiovascular risk than other traditional NSAIDs, as well as COXIBs. Naproxen (perhaps consistent with its potential to provide a sustained inhibition of platelet COX-1), along with ibuprofen (not high-dose), are suggested as ‘safer’, oral non-aspirin NSAIDs of choice in this regard if NSAID use is necessary. However, the cardioprotective, antiplatelet actions of low-dose aspirin, especially in the context of secondary prevention, may be subverted by oral traditional NSAIDs.

Future oral NSAID prescribing can address these emerging concerns by taking a holistic account of both NSAID adverse event profiles/drug interactions and patient safety profiles in order to maximise clinical benefit over integrated risk for individual patients. Furthermore, clinically selecting for relative cardiovascular safety may come at the expense of gastrointestinal complications, unless these can be suitably managed with gastroprotective therapies. However, overall the oral traditional NSAID-related absolute increase in cardiovascular risk is very low, and those without heart problems who are under 65 years, only take occasional courses of NSAIDs and do not exceed recommended doses (‘healthy users’), are expected to be only minimally affected.

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