Review

Non-selective non-steroidal anti-inflammatory drugs (NSAIDs) and cardiovascular risk

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Abstract. NSAIDs are largely used for the treatment of a huge variety of clinical conditions in order to relieve symptoms related to inflammation. The use of NSAIDs is associated with a potential increased risk of gastrointestinal and cardiovascular complications. The cardiovascular risk related to NSAIDs administration is often underestimated and it is frequently believed to be less important than the gastrointestinal risk. Adverse effects of NSAIDs are specifically related to their underlying mechanisms of action. The most plausible mechanism underlying the cardiovascular risk of NSAIDs has been identified in the profound inhibition of COX-2-dependent PGI2 in the presence of incomplete and intermittent inhibition of platelet COX-1. Nevertheless, the cardiovascular risk related to the use of NSAIDs is not only due to the COX-2 selectivity. An important determinant of the clinical effects of NSAIDs depends on the pharmacokinetic features of the different drugs such as half-life, and type of formulations, which can influence the extent and duration of patient exposure to COXisozyme inhibition. The aim of this review is to analyse the mechanisms behind the cardiovascular risk of different NSAIDs. (www.actabiomedica.it)

Key words: non-selective NSAIDs, COX-2 inhibitors, cardiovascular risk, gastrointestinal risk.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used since they are indicated in the treatment of several grades of acute pain and inflammation in a large variety of clinical conditions. They have been available on the market for many years and many compounds in the NSAID class have been registered in the European Union.

The use of NSAIDs is associated with a potential increased risk of gastrointestinal (GI) and cardiovascular (CV) effects (1-2), with variability between different drugs. GI toxicity of NSAIDs is the most studied and recent data show that the relative risk of upper gastrointestinal complications is the lowest for celecoxib and nimesulide, in the medium-high range for naproxen, ibuprofen, diclofenac, etoricoxib, and the highest for ketoprofen, piroxicam and ketorolac (3). Others drug-related adverse events include skin reactions, renal complications and allergic reactions (4-5). Hepatic adverse events associated with NSAIDs, although previously described (5), are quite uncommon when compared with other pharmacological classes (5-7).

Adverse effects of NSAIDs are well understood as specifically related to their underlying mechanisms of action (8). Both therapeutic and adverse effects of NSAIDs are mainly due to the inhibition of

prostanoid synthesis (9). NSAIDs act by blocking cyclo-oxygenase (COX), the enzyme that catalyses the formation of prostanoids from arachidonic acid (AA). It exists in three main isoforms: COX-1, COX-2, and COX-3. COX-3 is a splice variant of COX-1 that shares all of the catalytic features of COX-1 and COX-2 (10).

NSAIDs vary in their selectivity for COX-1 and COX-2 and are generally described as either non-selective COX inhibitors or selective COX-2 inhibitors, according to their relative selectivity (11).

Prostanoids are mainly derived via COX-1. They are responsible for cytoprotection of the gastric mucosa and contribute to normal platelet function with the production of thromboxane (TXA2). Inhibition of the COX-1 isoform is therefore associated with adverse gastrointestinal effects and impaired platelet function.

COX-2 is instead predominantly induced in the presence of inflammation or cell injury and it catalyses the production of prostacyclin (PGI2). During endothelial injury, PGI2 counterbalance the results of platelet activation and acts as a vasodilator. Originally, inhibition of the COX-2 isoform was thought to be responsible for the anti-inflammatory, anti-pyretic and analgesic properties of NSAIDs. However, due to prostacyclin production inhibition, it is also possible that blockade of COX-2 can impair endothelial health, cause a prothrombotic state and increase cardiovascular risk (8). The cardiovascular risk related to NSAIDs administration is often underestimated and it is frequently believed to be less important than the gastrointestinal risk.

The aim of this review is to analyse the mechanisms behind the cardiovascular risk of different NSAIDs optimising the risk-to-benefit ratio during the drug selection.

European Medicine Agency (EMA) and cardiovascular safety of NSAIDs

Since the anti-inflammatory effects of NSAIDs were believed to be mediated by inhibition of COX-2 and their gastrointestinal side effects by inhibition of COX-1, it was hypothesised that selective COX-2 inhibitors would provide a safer alternative to traditional NSAIDs. In fact, some studies have reported a lower incidence of upper gastrointestinal complications with selective COX-2 inhibitors than with traditional NSAIDs (12). Nevertheless, concerns about the cardiovascular safety of selective COX-2 inhibitors have limited their use (13).

As a consequence, the Agency's Committee for Medicinal Products for Human Use (CHMP) reviewed the cardiovascular safety of COX-2 inhibitors. This review of the cardiovascular, gastrointestinal and skin safety of non-selective NSAIDs started in June 2005 at the request of the European Commission. The CHMP compared COX-2 inhibitors to non-selective NSAIDs, thus collecting safety information about both pharmacological classes. The review was finalised in June 2005 and had led to different prescribing recommendations, which still remain valid. It identified in fact an increased thrombotic risk with selective COX-2 inhibitors, especially for cardiovascular reactions such as heart attack or stroke. It also concluded that a small increased risk of thrombotic events associated with non-selective NSAIDs could not be excluded, particularly when NSAIDs are used at high doses for long-term treatment. Although the level of risk may vary between drugs within the NSAID class, there was not enough evidence to confirm these differences. The CHMP advised that, although the benefits of NSAIDs outweighed the risks, they should be used at the lowest effective dose for the shortest possible treatment duration (14).

New epidemiological evidence and updated clinical trial data continue to suggest an increased thrombotic risk with COX-2 inhibitors if compared with placebo. Although for the majority of patients the potential increase in thrombotic risk is small, the risk may be higher in patient populations with pre-existing risk factors for, or a history of, cardiovascular disease (15-17).

In 2010 the Medicines and Healthcare products Regulatory Agency (MHRA), a government agency responsible for regulating medicines and medical devices in the UK, published a final report related to the issue of cardiovascular risks associated with NSAIDs and the results of two epidemiological studies published after 2006 (6, 18, 19). These two studies sug-

gested that some increased cardiovascular risk may apply to all NSAIDs users, irrespective of their baseline risk and duration of use and not only to chronic users or those with risk factors, although the greatest concern still relates to chronic use of high doses in patients at risk (20).

The CHMP started a new review in October 2011 at the request of the UK drug regulatory agency, focusing on the newly available evidence since its previous conclusions and providing an updated view on the evidence of cardiovascular risk with non-selective NSAIDs (20).

In October 2012 the European Medicines Agency (EMA) has finalised the review started a year before on the cardiovascular safety of non-steroidal anti-inflammatory drugs. The CHMP concluded that evidence from newly available published data on the cardiovascular safety of this class confirm findings from previous reviews, conducted in 2005 and 2006 (21-22). In relation to naproxen and ibuprofen, the CHMP was of the opinion that the current treatment advice adequately reflects the knowledge regarding the safety and efficacy of these medicines. On the other hand, concerning diclofenac, the latest evidence appears to show a consistent but small increase in the risk of cardiovascular side effects compared with other NSAIDs, similar to the risks of COX-2 inhibitors (23). Most of the data analysed from the CHMP was related to the three most widely used NSAIDs worldwide – diclofenac, ibuprofen and naproxen. In Italy, the most commonly prescribed NSAIDs are diclofenac, nimesulide and ketoprofen (24). In the 73% of the cases the NSAIDs are prescribed both as anti-inflammatory or analgesic drugs for osteoarthritis related diseases (25).

The last Health Search Report conducted by the Italian Society of General Practitioners showed that among those patients using NSAIDs for more than 90 days/year, the 3% - 4% is at high gastrointestinal risk, while the 2% - 3% is at high cardiovascular risk and 1% -2% of patients shows advanced hepatic diseases (26). To minimise complications related to NSAIDs in patients at high risk, the knowledge of the safety profile of different molecules is essential.

Cardiovascular risk of the NSAIDs in clinical practice

NSAIDs are largely used for the treatment of a huge variety of clinical conditions in order to relieve pain and other symptoms related to inflammation and the beneficial effects are perceived by most patients as greatly superior to hypothetic and not always easily understandable side effects. However, the use of these drugs in patients with previous cardiovascular events or with a significantly high cardiovascular risk implies the need for careful evaluation of the possible unfavourable effects on cardiovascular system.

A recent nationwide study of a post-myocardial infarction (MI) cohort performed in Denmark (27) provides evidence of increased cardiovascular risk associated with NSAIDs treatment in post-MI patients and advocates caution with any use of NSAIDs in such patients. In the meanwhile it shows that the individual drugs are associated with different cardiovascular risk. In particular the use of the nonselective NSAID diclofenac and of the selective COX-2 inhibitor rofecoxib was associated with a dose dependent increased risk of cardiovascular death (HR 1.96 and 1.66, respectively); ibuprofen and naproxen increased cardiovascular risk to a smaller extent (HR 1.34 and 1.27, respectively).

The comparative risk with the individual NSAIDs at typical doses in community settings had been previously evaluated (21) in a systematic review of community-based controlled observational studies, suggesting that among the most widely used NSAIDs, diclofenac raises risk by a remarkable level whereas naproxen and low-dose ibuprofen present a lower increase of cardiovascular risk. The data for etoricoxib were sparse, but this drug implied a significantly higher HR than naproxen or ibuprofen. In the meanwhile, the evidence on cardiovascular risk casts relevant doubts on the use of indomethacin.

The increase in risk was reported after a short-term use whereas it worsens with prolonged use, even in people with no or few risk factors for cardiovascular disease.

This means that every NSAIDs user is exposed to an increase in cardiovascular risk and that the problem is not confined to those with previous risk factors or to chronic users.

In clinical practice doctors should always consider if the prescription of NSAIDs is mandatory in a specific situation and patients should always use the lowest effective dose for the strict period of time necessary to relieve symptoms. The need for any longer treatment should be carefully periodically reconsidered by the general practitioner or by any specialist involved in the care of patients, especially when a high preexisting cardiovascular risk is present.

Mechanism of cardiovascular increased risk of NSAIDs

Prostanoids are second messengers, which can cross the cell membrane and interact with high-affinity G-protein-coupled receptors. Prostanoids play important roles in many cellular responses and pathophysiologic processes, such as modulation of the inflammatory reaction, erosion of cartilage and juxtaarticular bone, GI cytoprotection and ulceration, angiogenesis and cancer, haemostasis and thrombosis, renal haemodynamics and progression of kidney disease, as well as atheroprotection and progression of atherosclerosis (28). Prostanoids are generated intracellularly from arachidonic acid (AA) mainly through the activity of phospholipase A2. Once released, intracellular free AA is transformed to prostaglandin (PG) H2 by the cyclooxygenase. Then, PGH2 is metabolised to the prostanoids by different synthases expressed in a tissue-specific way.

The importance of prostanoids in maintaining CV homeostasis was primarily highlighted by the evidence that low-doses of aspirin reduces the secondary incidence of myocardial infarction (MI) and stroke by approximately 25%. Aspirin at low doses is the only NSAID able to irreversibly inactivates platelet COX-1 activity, which translates into an almost complete suppression (> 95%) of platelet capacity to produce TXA2 throughout the 24-hour dosing interval (29). This complete and permanent suppression of platelet COX-1 activity by aspirin is necessary to translate into cardioprotection because even tiny concentrations of TXA2 may cause platelet activation.

In contrast to aspirin, non-selective NSAIDs and COX-2 inhibitors are associated with an increased CV risk. The most plausible mechanism of the CV risk associated with NSAIDs is that they cause a profound inhibition of PGI2, which is generated by COX-2 (30). Since PGI2 is an anti-thrombotic and antiplatelet hormone, it functions as a protective mediator for the CV system, and reductions in its formation could increase platelet reactivity. The increased risk of vascular events caused by the inhibition of COX-2-dependent PGI2 might be mitigated by a concomitant suppression of platelet COX-1 activity and the generation of the pro-aggregatory mediator TXA2 (6). However, most non-selective NSAIDs and coxibs do not affect platelet COX-1 activity at a degree (> 95%) necessary to translate into inhibition of platelet function.

Cardiovascular risk and non-selective NSAIDs

The CV toxicity associated with the use of NSAIDs is an important clinical issue, which led to the withdrawal from the market of the coxibs, rofecoxib and valdecoxib. However, both observational studies and meta-analyses of data derived from randomised clinical trials showed that also some non-selective NSAIDs, such as diclofenac, were associated with an increased CV risk (22, 31).

The most plausible mechanism underlying the CV risk of NSAIDs has been identified, that is, the profound inhibition of COX-2-dependent PGI2 in the presence of incomplete and intermittent inhibition of platelet COX-1. The higher the level of COX-2 inhibition and the lower the level of COX-1 inhibition, the greater appears to be the risk of thrombotic cardiovascular events like fatal or non-fatal myocardial infarct and stroke (8). The extent of patient exposure (dose and duration) is an important determinant of enhanced risk of nonfatal MI. Since a linear relationship exists between the degree of inhibition of COX-2 and the degree of inhibition of PGI2 in vivo, reduction of the dose should translate into a reduction of the CV risk (6, 32).

Importantly, it has been shown that it is necessary to block COX-2 by 80% in whole blood to translate into an antinflammatory effect in vivo (33). However, in the clinical practice the NSAIDs are usually ad-

ministered at supratherapeutic doses (i.e. diclofenac). This may represent an important determinant, which explains the differences in CV toxicity among NSAIDs. In fact, whole blood COX-2 inhibition by NSAIDs higher than that necessary for a therapeutic effect (>80%) seems associated with a CV risk (6).

Nonsteroidal anti-inflammatory drugs are grouped on the basis of their pharmacodynamic features – that is COX-1/COX-2 selectivity. The degree of COX selectivity of an NSAID, defined by its potency to inhibit COX-1 and COX-2 activities by 50% in vitro, is a chemical feature of the different drugs. We can group NSAIDs as being more selective in vitro for COX-1, such as naproxen and ibuprofen, and those more selective for COX-2, which are the majority of NSAIDs. When comparing the potencies of NSAIDs against COX-1 and COX-2, IC50 values are often used. However, there are assumptions underlying such an approach that are not necessarily correct. NSAIDs are used therapeutically at doses that produce more than a 50% reduction in prostanoid formation. Comparison of the potencies of the NSAIDs against COX-1 and COX-2 at the IC80 value, therefore, appears more appropriate. The analysis of IC80 provides the data related to the amount of COX-1 inhibition when NSAIDs are used at levels sufficient to inhibit COX-2 by 80%, that is the inhibition needed to produce some therapeutic effects. Warner et al in 1999 conducted a full and careful in vitro analysis of COX-1 and 2 selectivities for a large range of NSAIDs and COX-2-selective compounds (11). They showed that, even for a drug such as diclofenac, which is > 4-fold selective for COX-2 in terms of IC80 values, therapeutically relevant selectivity will be very difficult to achieve; the concentration of diclofenac necessary to produce 80% inhibition of COX-2 will produce almost 70% inhibition of COX-1. However, most non-selective NSAIDs at therapeutic dose do not affect platelet COX-1 activity at a degree (>95%) necessary to translate into inhibition of platelet function and balance the COX-2 effect (11).

Among the NSAIDs more potent at inhibiting COX-2 than COX-1 in vitro, it has been shown that COX-2 selectivity is a continuous variable and some non-selective NSAIDs show comparable experimental COX-2 selectivity to some coxibs (e.g., diclofenac and celecoxib). However, it has to be noted that the degree of COX-isozyme selectivity found in vivo depends on the dose administered. Finally, an important determinant of the clinical effects of drugs in vivo (both therapeutic and toxic effects) depends on the pharmacokinetic features of the different drugs such as half-life, and type of formulations such as slow-release or plain, which can influence the extent and duration of patient exposure to COXisozyme inhibition.

The idea that the higher cardiovascular risk related to the use of NSAIDs is not only due to the COX-2 selectivity is well represented by nimesulide. Nimesulide is a preferential COX-2 inhibitor, since it also exhibits some degrees of COX-1 inhibition. In addition to COX inhibition, nimesulide displays different antinflammatory pharmacological effects (34). In contrast to coxibs, known to increase the risk for cardiovascular diseases, nimesulide seems to exhibit no significant cardiovascular toxicity (35). In particular, spontaneous adverse drug reaction reports revealed that nimesulide shows a low risk of cardiovascular events such as myocardial infarction or congestive heart failure (36-38); however, controlled clinical trials are needed to confirm the cardiovascular safety profile of this drug (36-38). Moreover, preclinical studies suggest that nimesulide is able to inhibit some pathways of neuroinflammatory processes following cerebral ischemia and to improve related neurological deficits (39). These data suggest a potential neuroprotective role of this drug in the cerebrovascular diseases.

Conclusion

NSAIDs are extensively prescribed in patients with osteoarthritis and several other painful conditions.

The prescription of these drugs is based both on well-established clinical experience and published data, confirming their efficacy and fast onset for acute articular and extra-articular pain.

During the last decades, the attention for adverse effects related to NSAIDs administration has increased, especially for subjects at high cardiovascular and gastro-intestinal risk.

In particular information on cardiovascular risk with NSAIDs have been available since 2006 and cur-

rent evidence suggests that there are significant differences among commonly used members of the class. A recent review conducted by EMA on the cardiovascular risk associated with non-selective NSAIDs concluded that the possibility of a small increased risk of thrombotic events cannot be excluded, particularly when these medicines are used at high doses and for long-term treatment. For diclofenac, the currently available data consistently indicated that cardiovascular risk is higher than other widely used non-selective NSAIDs. Although the risk seen with diclofenac is only slightly higher than with other non-selective NSAIDs, the Agency's Pharmacovigilance Risk Assessment Committee started an assessment, as formally requested by the United Kingdom on the 17th of October 2012, to determine whether the existing recommendations and warnings on cardiovascular risk for diclofenac-containing medicines are appropriate. However, NSAIDs with a high risk of cardiovascular complications are widely used. In fact, diclofenac and etoricoxib together account for approximately one-third of all sales of NSAIDs in the 15 countries included in the examination recently published on PLOS by McGettigan and Henry (40).

If clinical circumstances require a NSAIDs prescription to patients at increased risk of thrombotic events and/or gastrointestinal damage, we should select the NSAID with the most advantageous risk to benefit profile, and it can be useful to monitor the patient for increases in blood pressure, development of edema, deterioration of renal function, or development of gastrointestinal bleeding. If the Gastrointestinal damage NSAIDs related can be reduced by co-prescription of proton pump inhibitors, there is no convincing evidence that low dose aspirin mitigates the cardiovascular risk of NSAIDs or how we can prevent it.

In conclusion, available evidence indicates that NSAIDs have different safety profile and the cardiovascular risk is not always correlated exclusively with COX selectivity. In patients at high cardiovascular risk the treatment should be directed towards a non-selective NSAID, safer then coxib when a cardiovascular event is present in the clinical history. Moreover, recent findings suggest that cardiovascular risk profile of different non-selective NSAIDs is variable, and the choice should be directed towards specific molecules with a lower increase of risk for the patient. Even without previous events and/or in acute treatment it is important to evaluate the prescription in terms of safety and it is mandatory to minimise the dose and the period of treatment with NSAIDs.

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