Nonsteroideal Anti-inflammatory Drugs (NSAIDs) in clinical practice: managing gastric and cardiovascular risks

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Abstract. For many years, non-steroidal inflammatory drugs (NSAIDs) were commonly used in the treatment of acute pain due to inflammation. With the arrival on the market of NSAIDs with selective action on COX-2 there was a reduction of side effects in the stomach, but not eliminating the possible cardiovascular complications. The availability of NSAIDs such self-medication can aggravate this type of problem, it is therefore the clinician a fair and accurate assessment of the risk \ benefit based on the characteristics of the individual patient.

Key words: Nonsteroideal anti-Inflammatory Drugs (NSAIDs), gastrintestinal risk, cardiovascular risk

Due to their efficacy as anti-inflammatory and analgesic agents, non-steroidal anti-inflammaory drugs (NSAIDs) play a relevant role in the treatment of patients suffering from acute pain whose pathogenesis includes inflammatory processes.

NSAIDs are effective as anti-inflammatory agents as well as analgesic and anti-pyretic drugs. In fact, they act through the inhibition of the cyclo-oxygenase (COX) enzyme, which is involved in prostanoids synthesis from arachidonic acid (1). Three isoforms of cyclo-oxygenase have been isolated in humans, called COX-1, COX-2 and COX-3. The former is a constitutive enzyme, responsible for the synthesis of protective prostaglandins, which regulate platelet aggregation, gastric mucus production and renal perfusion. COX-2 is instead an inducible isoform, specially produced in sites of inflammation, due to cytokins stimulation. COX-3 is a splice-variant of COX-1 (2).

All NSAIDs are not selective for the inhibition of COX isoforms. COX-1 inhibition causes the well-known side effects of NSAIDs, both at the level of the gastric mucosa and of the kidneys, while COX-2 inhibition reduces pain response to tissue damages, attenuating peripheral and central nociceptor sensitisation. Some NSAIDs inhibit reversibly cyclo-oxygenase, while others, such as acetil salicilic acid, exert an irreversible effect or, as indomethacin, a time-dependent effect.

New non-steroidal anti-inflammatory molecules have been recently developed, looking for a selective inhibition of isoenzyme COX-2 (3). The selectivity of action of these new drugs determines a reduction of gastric side effects. Nevertheless, possible cardiovascular adverse events are not prevented: COX-2 selective inhibitors are therefore contraindicated in patients known for (or at risk for) ischemic cardiovascular disease. In fact, COX-2 inhibition leads to a reduced synthesis of prostacyclins, which counteract platelet aggregation during endothelial damage and act as vasodilators. Prostacyclin inhibition induces therefore a potential pro-thrombotic state which may increase the cardiovascular risk (4).

Although NSAIDs related cardiovascular risk has already led to rofecoxib and valdecoxib withdrawal from the market, it is still clinically underestimated for many other molecules and considered as less frequent than the gastro-intestinal risk. Moreover, observational studies and meta-analysis have recently shown that an increased cardiovascular risk may be also associated to the administration of non-selective NSAIDs such as diclofenac and ibuprofen, specially when prescribed for long terms and at high dosages (5-7).

Diclofenac is among the most prescribed NSAIDs due to its favourable gastro-intestinal safety profile and efficacy for pain relief. It has been also recently evaluated by the European Medicines Agency (EMA), showing a dose-related cardiovascular effect, which increases for the higher doses and becomes comparable to the COX-2 selective drugs' (8-9).

In general, to obtain a reliable anti-inflammatory effect, the COX-2 enzyme has to be inhibited at the 80% of its activity (10). NSAIDs are nevertheless often overdosed in daily practice, which represents a determinant factor when examining NSAIDs cardiotoxicity. In fact, the inhibition of COX-2 above the 80% of its activity does not improve efficacy, while increases the cardiovascular risk (11). In a recent study by Dietrich et al, the subcutaneous administration of 25 and 50 mg of diclofenac proved to be more effective for acute postoperative pain relief than placebo and equally effective to 75 mg (12).

Many NSAIDs have been registered in Italy. The majority of them are available without the physician's prescription. In fact, NSAIDs are often considered as self-prescribed medications by patients: the reasons for these phenomenon are their realiable efficacy as pain relievers for many pathologies and their large diffusion.

Nevertheless, self-prescription and self-medication in general expose patients to higher risks of potential side effects. A recent observational study has shown that one every eight patients, among those at high risk for drug-related adverse events, takes NSAIDs as self-prescription drugs, usually to treat musculoskeletal pain. Among these patients, more than the 30% takes them for more than 7 days and the 3% exceeds the maximum daily recommended dose (13).

NSAIDs undergo fast absorption after oral intake and present a high protein binding (between 90 and 99%). They are metabolised in the liver and excreted through the kidneys. All NSAIDs present a ceiling effect: over a specific dose, the effect does not improve, while side effects significantly increase. NSAIDs are effective in treating ostheoarticular mild pain and reduce opioid consumption when coadministered for moderate to severe pain. Among NSAIDs, diclofenac, nimesulide and ketoprofen are the most commonly used molecules for these indications (14). In 73% of cases, NSAIDs are prescribed as anti-inflammatory and analgesic drugs in patients with symptomatic ostheoarthritis (15). To reduce NSAIDs related side effects, they should be administered at the lowest effective dose and for the shortest possible period. If prescribed for pain relief, NSAIDs administration should be interrupted in cases of lack of efficacy after 7 days of continuous therapy and other pharmacological analgesic classes should be considered. On the other hand, NSAIDs anti-inflammatory properties require up to three weeks to reach full effect. In general, in cases of effective treatment, the physician should adequately stratify the cardiovascular and the gastro-intestinal risks for each patient and each selected molecule. Prescribing the right drug for the right patient is even more important for long term therapies, in order to reduce the patient exposure to the risk of side effects and to early diagnose eventual adverse events (8).

When there is not a higher risk for cardiovascualr events, the administration of NSAIDs with a favourable gastro-intestinal profile is suggested: etoricoxib, celecoxib, diclofenac, ibuprofen e nimesulide are all suitable molecules while ketorolac and ketoprofen are less indicated in this setting. In patients known for gastro-intestinal risk, the association of a protonic pump inhibitor to the NSAID therapy is always suggested. If the patient presents instead a cardiovascular risk, COX-2 selective inhibitors, as well as high doses of diclofenac and ibuprofen, are contraindicated. If the patient already takes low doses of acetil salicilic acid for secondary cardiovascular prophylaxis, naproxen is considered the best choice for coadministration: it will be admnistered 2 hours after the aspirin intake in order to not interfere with its mechanism of action (4) (Table 1).

Table 1. Prevention of NSAIDs related gastrointestinal and cardiovascular risk

• Use the lowest effettive dose for the shortest period of time • If prescribe as analgesie drug. STOP administration after 7 days if NO benefit was reported • If prescribe as anti-inflamatory drug, STOP administration after 3 weeks if NO benefit was reported • If it is possible avoid concomitant therapy with corticosteroids, anticoagulants, low-dose asplrin or antiplatelet agents
Prevention of NSAIDs related Gastrointestinal (GI) & Cardiovascular (CV) risks
NO CV Risk: NO GI risk factors: Coxib, Diclofenac, lbuprofen or Nimesulide (avoid Ketorolac and Ketoprofen) One or more GI risk factors: Coxib or Diclofenac-Ibuprofen-Nimesulide + Proton Pump Inhibitor (PPI) History of ulcer bleeding: Coxib-Diclofenac + PPI
CV risk factors + NO GI risk factors: *CV risk < 3%:* Avoid Coxib Diclofenac ≤ 100 mg/die - lbuprofen ≤ 1200 mg/die -Nimesulide *If concomitant administration of Aspirin:* Avoid co-administration of Ibuprofen Administration of Aspirin 2 h before Naproxen + PPI
CV risk > 3%: Administration of Aspirin 2 h before Naproxen + PPI
CV risk factors + One or more GI risk factors: *CV risk < 3%:* Avoid Coxib Diclofenac ≤ 100 mg/die -Ibuprofen ≤ 1200 mg/die -Nimesulide + IPP *If concomitant administration of Aspirin:* Avoid co-administration al Ibuprofen Adminisuation of Aspirin 2 h before Naproxen + PPI *QI risk > 3%:* Administration of Aspirin 2 h before Naproxen + PPI
CV risk factors + History of ulcer bleeding If it is possible avoid NSAIDs and Coxib If strictly necessary and CV risk < 3%: Celecoxib -Diclofenac ≤ 100 mg/die -Ibuprofen ≤ 1200 mg/die -Nimesulide + PPI

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