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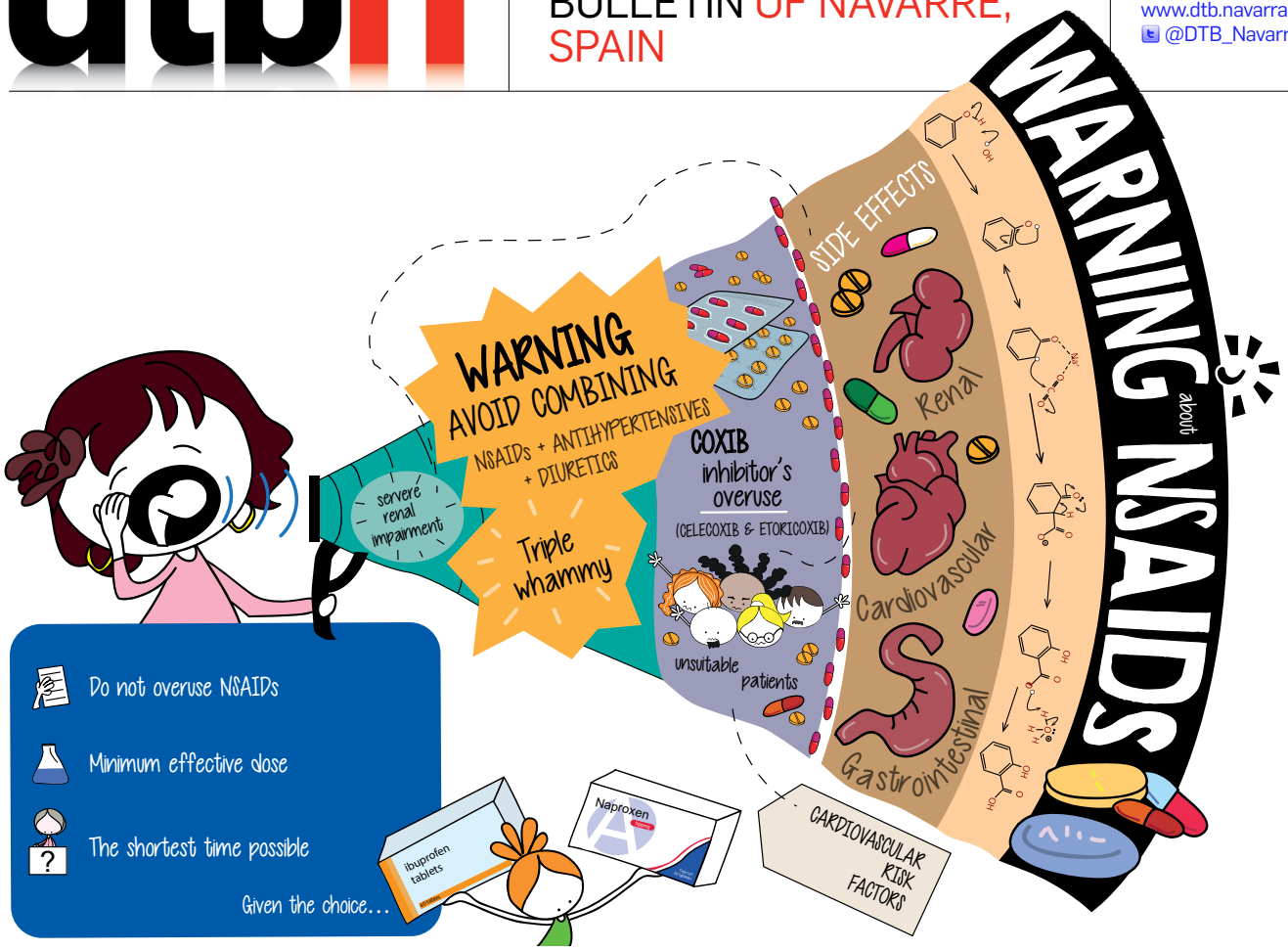

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abstract

Objective: To review current evidence and guidelines concerning the cardiovascular, gastrointestinal, and renal risks of nonsteroidal anti-inflammatory drugs (NSAIDs). **Materials and methods:** A PubMed search to identify reviews and meta-analyses on risks associated with NSAIDs was performed on 30 June 2016. Safety alerts on the use of NSAIDs issued by the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) were also reviewed. The use of NSAIDs in Navarre was evaluated based on prescriptions and prescribed medicine billing data from the database of the Navarre Health System, Spain. **Results and conclusions:** The gastrointestinal, cardiovascular, and renal adverse effects of NSAIDs are related to the total daily dose and may appear less than 15 days from the start of treatment. The safest NSAIDs are ibuprofen and naproxen, whether used alone or in combination with a gastric protector in accordance with the patient's gastrointestinal risk factors. Selective COX-2 inhibitors diclofenac, aceclofenac, ibuprofen (at a dose ≥ 2400mg/d) and dexibuprofen (at a dose ≥ 1200mg/d) are contraindicated in patients with severe heart disease such as heart failure, ischemic heart disease (NYHA II-IV), peripheral artery disease and cerebrovascular disease. Additionally, in patients with cardiovascular risk, the benefit/risk balance of this drug class must be weighed. Although gastrointestinal risk can be countered using gastric protectors, there is no concomitant drug therapy for cardiovascular risk. The results of this review reveal an overuse of celecoxib and etoricoxib in Navarre. NSAIDs in combination with proton pump inhibitors (PPIs) should be used with caution, since PPIs are not indicated for all patients requiring NSAIDs. Furthermore, the combination of these drugs may result in incorrect dosages.

Safety considerations for NSAIDs

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are medications with analgesic, inflammatory and antipyretic effects that are widely used, both as prescription and as over-the-counter medicines.[1] Although NSAIDs are effective for a variety of symptoms, they can also cause severe adverse effects of which regular users may not be aware. Table 1 shows the usual dosage and maximum daily dose for various drug classifications.[2]

Data on self-administered NSAIDs are scarcer than on prescribed NSAIDs. There is evidence that more than 40% of patients take over-the-counter NSAIDs, mostly (84%) for headache, musculoskeletal or menstrual pain, although users may be unaware of their adverse effects.[4,5]

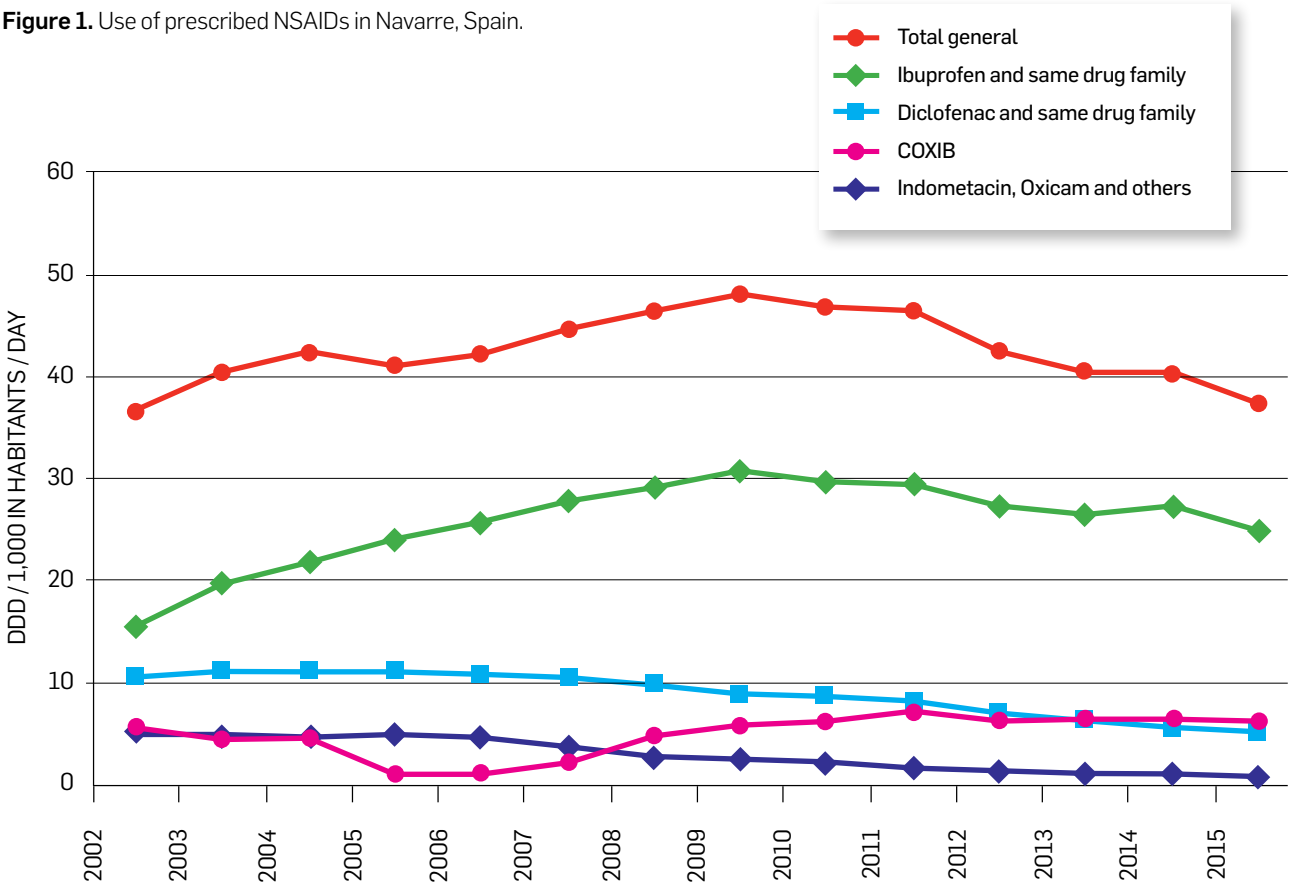
A study conducted in Portugal in 2015 revealed that the most widely used over-the-counter drugs were ibuprofen and diclofenac and that the duration of treatment was less than a week in 80% of cases.[6]

In 2014, the Spanish Medicines Agency (AEMPS) published a report on the use of prescription NSAIDs in Spain between 2000 and 2012.[7] The AEMPS reported a 26.5% increase in the use of NSAIDs in the study period. The most widely used NSAID was ibuprofen, followed by diclofenac. According to the AEMPS, the use of ibuprofen and other drugs of the same family increased by 143.7% in Spain in 12 years and accounted for 65.1% of the total NSAIDs used in 2012.

Table 1. Classification of the most common NSAIDs, usual dose and maximum daily dose.

Non-steroid antiinflammatory drugs		Usual dose[3]	Maximum daily dose[3]
Salicylates	Acetylsalicylic acid	500mg/4-6h	4g
Propionic	Naproxen	550-1,100mg/d	1,100mg
	Ibuprofen	400-600mg/6-8h	2,400mg
	Ketoprofen	50mg/12-6h	200mg
	Flurbiprofen	8.75mg/3-6 h	43.75mg
	Dexibuprofen	600-900mg/d	1,200mg
	Dexketoprofen	12.5mg/4-6 h 25mg/8h	75mg
Acetics	Aceclofenac	100mg/12h	200mg
	Diclofenac	50mg/8-12h	150mg
	Ketorolac	10mg/4-6h	40mg
	Indomethacin	25mg/6-12h 75mg/12-24h	200mg
Oxicams	Meloxicam	7.5-15mg/d	15mg
	Piroxicam	10-20mg/d	20mg
	Lornoxicam	8-16mg/d	16mg
	Tenoxicam	20mg/d	40mg
Anthranilic	Mefenamic acid	500mg/8h	1,500mg
Selective COX-2 inhibitors	Celecoxib	200mg/24 h	400mg
	Etoricoxib	30-120mg/24h	60-120mg
	Parecoxib	40mg followed by 20-40mg/6-12h	80mg

Figure 1. Use of prescribed NSAIDs in Navarre, Spain.



Between 2002 and 2009, the use of prescribed NSAIDs increased by 31%. Since then, it has decreased to a percentage similar to that of 2002. Consistent with data on the use of NSAIDs across Spain, ibuprofen and other NSAIDs of the same family were the most widely used drugs in Navarre in the period studied. Between 2002 and 2015, the use of these NSAIDs increased by 61%, and in 2015 accounted for 67% of the total amount of NSAIDs used. The generalized decrease in the use of prescribed NSAIDs is probably due to safety warnings on NSAIDs published by regulatory agencies.

In Navarre, about 14% of the general population and 19% of adults older than 64 years received NSAID therapy at some point during the first three months of 2016. Of these patients, it is estimated that 4% of the general population and more than 10% of adults older than 64 years received continuous NSAID therapy in this period. Table 2 shows the most commonly used drugs among patients who received the same NSAID during the three months.

Celecoxib is the most widely used NSAID for long-term or chronic therapy, followed by naproxen and ibuprofen, both in the general population and in patients older than 64 years. The percentage of patients treated with COXIB was higher in older adults than in the general population, whereas the use of ibuprofen and naproxen was less frequent. Although ibuprofen is the most common NSAID in non-chronic therapies, celecoxib is more usual in chronic therapies.

A review of primary care prescribing data in Navarre until 31 May 2016 was performed. In total, 72.4% of chronic therapies in older patients were for the treatment of musculoskeletal diseases, 3.1% were for central nervous system diseases, and the remaining were for other diseases or general problems.

By specific drug, between 76.8% and 84.1% of prescriptions for diclofenac, aceclofenac, naproxen, esomeprazole and COXIB were for the treatment of a musculoskeletal disease. Of note, ibuprofen and naproxen NOT in combination with a PPI were prescribed for a wider variety of diseases than other NSAIDs, as follows: 60.6% to 67.1% were prescribed for musculoskeletal disease and 4.4%-9.1% for central nervous system disease. In other words, the data demonstrate that ibuprofen and naproxen are widely prescribed not only for musculoskeletal diseases, but also for CNS diseases such as migraine and other conditions and symptoms.

Table 2. Most common continuous NSAID therapies in Navarre, Spain.

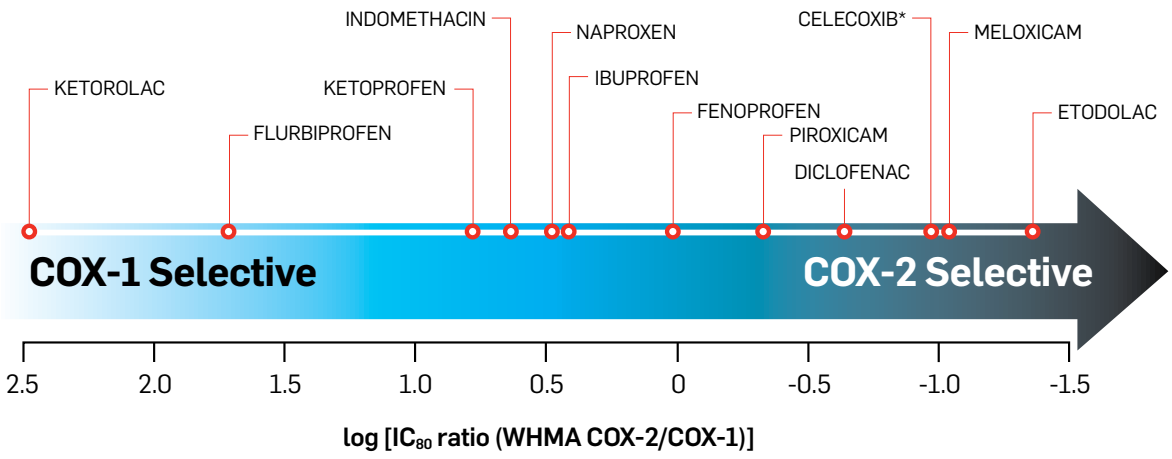
	% of patients treated with continuous NSAID therapy in the first 3 months of 2016	
	GENERAL POPULATION	> 64 YEARS OLD
Celecoxib	32.1%	41.8%
Naproxeno	27.3%	21.9%
Ibuprofen	17.3%	13.0%
Etoricoxib	10.4%	10.8%
Diclofenac	7.2%	6.5%
Aceclofenac	1.6%	2.5%

Mechanism of action

NSAIDs inhibit the conversion of arachidonic acid into prostaglandins via the inhibition of cyclooxygenase enzymes (COX). The inhibition of these enzymes affects gastrointestinal, physiological, gastrointestinal, cardiovascular and renal function, which means that the same mechanism of action simultaneously has beneficial and deleterious effects.

The two main isoforms of COX are COX-1, present in most tissues, gastric mucus, and platelets[8,9] and COX-2, found in tissues such as the vascular endothelium or in the joints during inflammation. Analgesia is primarily achieved by the inhibition of COX-2. However, as COX-2 produces prostaglandin I2 (PGI2), which has cardioprotective vasodilation and antiplatelet activity, its inhibition also increases cardiovascular risk. Additionally, COX-1 produces thromboxanes - with vasoconstrictor and platelet aggregating activity - and its inhibition is linked to a decrease in platelet aggregation and to a higher GI toxicity.[10] The section below includes a description of the risks and safety warnings on NSAIDs from regulatory agencies.

Selective inhibition by COX isoforms attributed to NSAIDs has been represented in a variety of figures like the one below:[11]



IC80 = NSAID concentration needed to inhibit COX enzymatic activity by 80%.
WHMA = "William Harvey human modified whole blood assay".
*COX-2 selective inhibitor.

Adverse effects of NSAIDs

The most important and widely known adverse effects of NSAIDs are gastrointestinal, cardiovascular, and renal risk. Additionally, they can cause other problems such as hepatotoxicity[12] or severe hypersensitivity reactions.[13]

Gastrointestinal risk

There is extensive evidence of the gastrointestinal toxicity of NSAIDs,[14] with upper gastrointestinal bleeding (UGIB) being the most serious adverse effect reported so far.[15] Gastrointestinal risk is dose-dependent and a study performed in Spain and Italy[16] in 2004 revealed that the incidence of UGIB was 4 per 10,000 persons. The study also concluded that 38% of UGIB episodes reported were attributable to the use of NSAIDs. Ketorolac, piroxicam, indomethacin, ketoprofen, naproxen and aspirin have been found to be associated with a high risk of UGIB even at low doses.

Other NSAIDs such as dexketoprofen, meloxicam, and rofecoxib (withdrawn) present a moderate risk, whereas low doses of aceclofenac, ibuprofen and diclofenac have been associated with a low risk of UGIB. A study reported that the use of celecoxib carries a low risk of UGIB. However, this finding should be taken with caution, as the sample of patients receiving this drug was very small.

COXIBs seem to present a low gastrointestinal risk, as long as treatment does not exceed six months. This is supported by a trial with celecoxib, which revealed that the gastrointestinal risk of this drug at 12 months of treatment was similar to that of ibuprofen or diclofenac.[17] This trial also showed that the use of COXIB or diclofenac in combination with omeprazole in patients with arthritis and a history of gastrointestinal ulcer had similar preventive effects for recurrent gastric bleeding.[18]

Prophylaxis for gastropathy is indicated in the presence of the following gastrointestinal risk factors:[15]

- Age >60 years (increases from 70 years on)
- A history of peptic ulcer or gastrointestinal bleeding
- Concomitant use of anticoagulants or corticosteroids
- Use of a high dose of NSAID (more than double the usual dose)
- Dual therapy with acetylsalicylic acid (ASA) and clopidogrel and presence of dyspepsia or gastroesophageal reflux disease.

Patients with several of these risk factors have a 9% higher risk of experiencing a NSAID-induced gastrointestinal event after six months of exposure to NSAIDs.

In 2007, the AEMPS issued a safety warning on the gastrointestinal risk of piroxicam and ketorolac. The AEMPS reported that the use of piroxicam presents a greater risk of gastrointestinal complications and severe skin reactions than other NSAIDs. Consequently, it was concluded that the benefit/risk balance of piroxicam was only favourable in patients with arthrosis, rheumatoid arthritis and ankylosing spondylitis – but never as first-line therapy in patients older than 80 years – for whom gastric prophylaxis should always be considered. Since 1 September 2007, the AEMPS has restricted the prescription of drugs containing piroxicam to hospital diagnosis[19] (except for topical use).

NSAIDs choice depends on the safety profile of the drug and the patient's risk factors

Similarly, ketorolac was restricted to hospital use in 2008 due to evidence of an increased risk of severe complications such as peptic ulcer and acute renal injury.[20] Only the indication of oral and injectable ketorolac for short-term treatment of postoperative pain was maintained.[21] Administration in the form of injectable solution is also acceptable for renal colic pain.[22] The use of this drug for other indications entails unnecessary risks.

Cardiovascular risk

Acute Myocardial Infarction (AMI) and stroke

Except for acetylsalicylic acid, NSAIDs increase cardiovascular risk[14,23,24] and the risk of AMI,[25,26] stroke,[5] heart failure and heart failure decompensation,[25,27] and atrial fibrillation.[26,27,28] Risk increases with the dose and duration of NSAID therapy. NSAIDs do not seem to have a risk latency period,[14] given that risk increases even in short-term therapy.[24,29,30]

In 2004, the AEMPS decided to withdraw rofecoxib[31] based on evidence on an increased incidence of severe cardiovascular episodes (particularly AMI and stroke) associated with this drug. A trial[32] with patients with rheumatoid arthritis comparing rofecoxib with naproxen revealed that the risk of AMI was four times higher when rofecoxib was administered. Subsequent studies revealed that long-term therapy with rofecoxib vs placebo for the prevention of recurrent colorectal neoplastic polyps increased the risk of AMI and stroke.[33]

With respect to celecoxib, a trial on the prevention of adenoma was prematurely suspended after a significant increase was observed in the incidence of cardiovascular events and death in patients receiving either 400mg/d or 800mg/d.[34]

Additionally, the AEMPS issued a safety warning on the occurrence of severe cardiovascular and skin events associated with the use of parecoxib and valdecoxib (active ingredient not marketed in Spain)[35]. Subsequent comparative placebo-controlled studies confirmed the association between COX-2 inhibitors and a significant increase in AMI (Rate Ratio = 1.86; 1.33-2.59) and severe vascular events (AMI, stroke or vascular death), Rate Ratio = 1.42; 1.13-1.78.[36]

A range of studies comparing COXIBs with some traditional NSAIDs report no differences in the incidence of AMI, stroke or vascular death. However, a study of COXIBs vs naproxen revealed a correlation between COXIBs and increased risk of AMI.[36]

A meta-analysis showed that some NSAIDs increase cardiovascular risk (primarily AMI and sudden cardiac death) when compared to taking no NSAID therapy. The increase in the risk ratio (RR) for the different NSAIDs studied was: diclofenac, RR = 1.40 (CI95% 1.19 to 1.65); meloxicam, RR= 1.24 (CI95% 1.06 to 1.45); indomethacin, RR = 1.36 (CI95% 1.15 to 1.61).[30]

A systematic review of vascular and gastrointestinal effects of a range of NSAIDs vs placebo revealed that COXIBs, diclofenac and probably ibuprofen at high doses present similar increased vascular risk. This was mainly due to the increase of severe cardiovascular events (AMI and death due to heart disease). The increase in the risk ratio (RR) of severe vascular events for the different NSAIDs was as follows: COXIBs, RR = 1.37 (CI95% 1.14-1.66); diclofenac, RR = 1.41 (CI95% 1.12-1.78). The results for ibuprofen were not statistically significant, RR = 1.44 (CI95% 0.89-2.33), although an increase in the incidence of severe cardiovascular events was observed, RR = 2.22 (CI95% 1.10-4.48). Notably, the use of naproxen was not observed to be related to an elevated risk of severe vascular events, RR = 0.93 (CI95% 0.69-1.27). The incidence of heart failure-induced death increased significantly with the use of COXIBs and diclofenac. No statistically significant differences were observed regarding the use of ibuprofen and naproxen.[25]

Similar results were obtained in another systematic review.[37] Naproxen seems to have fewer risks even at high doses.[25]

Elevated blood pressure

All NSAIDs increase blood pressure (BP), as they cause sodium and water retention.[38] The mean increase is 3/2 mmHg, with substantial variability.[39,40] As a result, the use of COX-2 can contribute to an increased cardiovascular risk.[41] The EMA published a report and a safety warning on risk factors such as elevated blood pressure associated with the use of etoricoxib and contraindicated its use in patients with uncontrolled BP, especially at doses of 90mg and recommended regular BP monitoring.[42] Prior to this warning, the AEMPS had already contraindicated its use in this population of patients.[43] Etoricoxib is associated with more frequent and severe effects on BP than other COXIBs and NSAIDs, especially at high doses.[44]

The minimum effective dose should be administered for the shortest time possible, and need of treatment should be reconsidered regularly

Patients with a history of heart disease

The use of NSAIDs can increase the risk of death and hospitalization for AMI and heart failure between three and five times.[45] In patients with a history of heart failure, diclofenac, ibuprofen and celecoxib have been associated with an increased risk of recurrent AMI and death.[30,46] A study performed in Denmark revealed that 7 to 14 day treatment with most NSAIDs was associated with an elevated risk of recurrent AMI and death in patients with a history of AMI.[47] The American Heart Association (AHA) considers COXIBs to be a last-option treatment in patients with previous heart disease or cardiovascular risk.[48]

In patients with heart failure, European guidelines on heart failure do not recommend the use of NSAIDs, including COXIBs, as they raise the risk of this disease worsening resulting in hospitalization.[49]

There is evidence of an increased risk of stroke associated with the use of diclofenac and aceclofenac, particularly at high doses and in long-term therapies. The concomitant use of acetylsalicylic acid does not counter this effect. In contrast, ibuprofen and naproxen do not increase the risk of stroke.[50]

AEMPS and EMA warnings and recommendations

Between 2004 and 2015, EMA and AEMPS issued several safety notes and warnings on the use of NSAIDs, which are summarized below:

- COXIBs raise atherothrombotic risk[34,43] (AMI, stroke and peripheral arterial vascular problems). Incidence can increase by 3 episodes per 1,000 persons per year of treatment. The absolute risk is even higher in patients with a history of heart disease.[51]

- Diclofenac at 150mg/d has been associated with a risk of atherothrombotic episodes similar to that of COXIBs.[51]

- Aceclofenac converts to diclofenac and has a similar thrombotic risk profile.[52]

- Ibuprofen at a dose of 2,400mg/d (maximum permissible dose) may be linked to an increased risk of atherothrombotic episodes. Conversely, at a dose of 1,200mg/d or lower it has not been found to be related to an increased risk.[51,53]

- Dexibuprofen is the active enantiomer of ibuprofen. A 1,200mg dose of dexibuprofen is equivalent to 2,400mg of ibuprofen, and safety warnings on the cardiovascular risk of dexibuprofen 1,200mg are the same as for ibuprofen 2,400mg.[54]

- Studies on the pharmacodynamics of ibuprofen show that this drug reduces the antiplatelet effect of acetylsalicylic acid (ASA). Although the epidemiological data available do not prove that there is a clinically significant interaction, the cardioprotective effect of ASA decreases with the regular administration of ibuprofen.[54]

- Naproxen at a dose of 1,000mg/d seems to entail a lower risk of atherothrombotic episodes, as compared to COXIBs. In contrast, naproxen involves a higher gastrointestinal risk than diclofenac and ibuprofen.[51,53]

- Other NSAIDs: scant data are available on other NSAIDs, and their relationship with an increased atherothrombotic risk cannot be dismissed.[51,53]

The AEMPS recommendations on ibuprofen at a dose ≥ 2,400mg/d, dexibuprofen at a dose ≥ 1,200mg/d, diclofenac,[55] aceclofenac[52] and COXIBs[43] are:

- Diclofenac should not be used in patients with severe cardiovascular diseases such as heart failure (NYHA II-IV), ischemic heart disease, peripheral artery disease and cerebrovascular disease.

According to EMA and AEMPS safety alerts and warnings on NSAIDs, the benefit/risk balance should be considered in the presence of cardiovascular risk factors (diabetes mellitus, hypertension, hypercholesterolemia, smoking).[51,53-55]

- The overall benefit/risk balance is positive, provided that NSAIDs are used in the appropriate setting.
- NSAIDs must be used at the lowest effective dose and for the shortest time possible.
- Prescribing should be done on the base of the global safety profiles and drug sheet of each drug and according to the cardiovascular and gastrointestinal risk of each patient.
- Patients should not change from one NSAID to another without the physician first considering the drug safety profile and the patient's preferences.

In elderly patients, NSAIDs can be contra-indicated or limited due to comorbidites and/or concomitant drugs

NSAID choice based on the patient's baseline clinical situation

The most appropriate NSAIDs in common clinical situations are:

- Cardiovascular risk: ibuprofen (up to 1200mg/d) or naproxen (up to 1000mg /d).[37]
- Gastrointestinal risk: ibuprofen + PPI as first option and diclofenac + PPI or COXIBs with or without PPI as second option.[56]
- Low gastrointestinal risk and high cardiovascular risk: naproxen.[56]
- High gastrointestinal risk and low cardiovascular risk: COXIBs or other NSAID + PPI.[15,56]
- High cardiovascular and gastrointestinal risk: avoid the use of NSAIDs as much as possible.[56,57]

A combination of NSAID + PPI is marketed in Spain at the same dosage. It is a combination of naproxen/esomeprazole (500/20mg) at a usual dose of one tablet every 12 h.[58] It is worth considerating this combination. On the one hand, the use of PPIs in combination with a gastrolesive drug (NSAIDs, anticoagulants, antiplatelet agents, oral corticosteroids) is only recommended for patients with a history of gastrointestinal disease or associated risk factors (advanced age, severe comorbidities, chronic high-dose treatment). On the other hand, the recommended regimen for this combination doubles the usual daily dose of esomeprazole 20mg,[59] which raises the risk of adverse events associated with PPIs. Evidence has been published in recent years on the potentially severe side effects of long-term continuous administration of PPIs, including hypomagnesemia, fracture risk, enteric infections (eg. *C. difficile*), spontaneous bacterial peritonitis, nosocomial and community pneumonia, iron and vitamin B12 deficiency, complications in cirrhotic patients, acute interstitial nephritis, and chronic kidney disease.[60,61]

Renal risk

NSAIDs can alter renal function as a result of the inhibition of COX-1, which regulates glomerular filtration, and COX-2, which is involved in water and salt excretion. NSAID users have a threefold higher risk of acute renal failure than non-users. There seems to be a direct relationship between dose and risk. At high doses, RR = 3.4 (CI 95% 1.6-7.0) whereas at a low dose, RR = 2.5 (CI 95% 1.2-5.4).8 There is evidence that 8% of patients with subacute renal failure develop NSAID-induced renal disease.[64]

Renal problems caused by the use of NSAIDs include sodium retention, edema, increased BP, weight gain, congestive heart failure, hypercalcemia and acute renal failure. Risk factors related to renal abnormalities induced by the use of NSAIDs include: severe hepatic dysfunction, renal dysfunction, nephrotic syndrome, advanced age, diabetes, hypertension and congestive heart failure.[14] The risk of acute renal failure induced by NSAID therapy doubles. RR (rate ratio) = 2.05 (CI 95% 1.61-2.60). RR was 2.42 (CI 95% 1.52-3.85) for naproxen and 1.54 (CI 95% 1.14-2.09)62 for celecoxib. Ibuprofen appears to be associated with low risk at the usual dose and with high risk at higher doses. The OR associated with ibuprofen doses ≤1,200mg/d, 1,200-2,400mg/d and ≥2400mg/d were 0.94 (CI 95% 0.58-1.51); 1.89 (CI 95% 1,34-2.67) and 2.32 (CI 95% 1.45-3.71), respectively (p trend = 0.009).[63]

NSAIDs are contraindicated in patients with renal risk.[64] If needed, the use of ibuprofen 1200mg/day has a lower risk.[14]

Interactions to be considered

NSAIDs are commonly used in the chronic treatment of polymedicated patients with several comorbidities. This may cause drug-to-drug interaction of variable severity. Some drug-to-drug interactions of NSAIDs with other pharmacological groups are detailed below.[14]

Antihypertensive drugs

NSAIDs can increase BP as a result of the inhibition of renal prostaglandins and an increased fluid retention, which reduces the effectiveness of antihypertensive drugs. More specifically, the increase in BP can be greater if NSAIDs are used in combination with angiotensin receptor blockers (ARBs) or angiotensin converting enzyme (ACE) inhibitors.[14] Moreover, the concomitant prescription of an ACE inhibitor or ARB plus a diuretic agent and an NSAID (COX-2 inhibitors included) is known as "triple whammy".[65] This combination of drugs has been proven to increase the risk of renal failure by 30% (RR = 1.31; CI95% 1.12-1.53). The risk rises (82%) in the first 30 days of triple whammy therapy (RR = 1.82; CI95% 1.35-2.46). Therefore, given the widespread use of NSAIDs in the general population, analgesic therapy should be chosen with caution in patients receiving ARBs or ACE inhibitors and diuretic therapy.

Selective serotonin reuptake inhibitors (SSRIs)

SSRIs may increase the risk of bleeding associated with NSAIDs, since they inhibit platelet adhesion and function. Moreover, SSRIs are inhibitors of the cytochrome 2C9 (CYP2C9), which metabolizes some NSAIDs such as ibuprofen and diclofenac. Therefore, the concomitant administration of SSRIs and these NSAIDs can increase NSAID concentrations and cause more intense adverse effects.[14]

Lithium

NSAIDs can reduce lithium excretion. More specifically, there is evidence that lithium concentrations increase with the administration of ibuprofen 1800mg/d or naproxen 750mg/d.[14]

Corticosteroids

The administration of NSAIDs in combination with corticosteroids can increase the gastrointestinal toxicity and bleeding associated with the two drug families.[14]

ASA

The chronic use of ibuprofen in patients with ASA can diminish the capacity of ASA to prevent cardiovascular events, since it interferes with the irreversible acetylation of ASA on platelets.[48] A study revealed that patients hospitalized for cardiovascular disease receiving treatment with ibuprofen in combination with aspirin had a higher risk of all-cause mortality (HR = 1.93; CI 95% 1.30-2.87) and impaired cardiovascular function (HR = 1.73; CI 95% 1.05-2.84) when compared with patients only taking ASA.[66] Some studies with patients treated with antithrombotic therapy have revealed that the use of a NSAIDs elevates the risk of thrombosis (11.2% vs 8.3% in patients not treated with NSAIDs) and bleeding (4.2% vs 2.2% in patients not treated with NSAIDs).[67]

The AEMPS issued a warning in 2015 that although the epidemiological data available did not support the presence of a clinically significant drug-to-drug interaction between ibuprofen and ASA, it cannot be excluded that the cardioprotective effect of ASA decreases with the regular and continuous administration of ibuprofen.54 The FDA recommends taking ibuprofen 8 hours before or 30 minutes after ASA to prevent potential interactions.[68]

Furthermore, the administration of NSAIDs with ASA increases the risk of GI bleeding, which can be countered with antiacids.[14]

Anticoagulants

The use of NSAIDs and paracetamol (acetaminophen) should be limited in patients receiving anticoagulant therapy since it increases the risk of bleeding.[14]

NSAIDs in older patients

NSAIDs should be administered with caution to older patients, since some factors such as comborbidities and the potential for drug-to-drug interaction with baseline therapies may contraindicate or limit their use.

Stopp and Beers criteria consider NSAIDs (except for COXIBs) inappropriate in patients with a history of peptic ulcer or gastrointestinal bleeding, unless they are administered with a PPI or H2 antagonist[69,70] to prevent recurrence.[69] Several studies have reported that such patients have a fivefold increased risk of NSAID-associated gastrointestinal toxicity compared to young adults. Risk factors include direct gastric mucosa damage, inhibition of endogenous protective prostaglandins, longer duration of bleeding and potential impairment of the patient's capacity to excrete these drugs.[71] The use of gastric protectors in these patients reduces the risk of gastroduodenal ulcer.[72,73]

NSAIDs are contraindicated in patients with high blood pressure[70] and severe heart failure[69,70] due to the risk of exacerbation, as well as in routine therapies for osteoarthritis >3 months in duration when paracetamol has not been administered.[69] COXIBs are contraindicated in patients with cardiovascular disease due to the risk of myocardial infarction and stroke.[69] All NSAIDs are contraindicated in patients with renal failure with creatinin excretion < 30 mL/min, as it can increase the risk of acute renal failure and impair renal function.[70] The occurrence of renal abnormalities has been associated with the inhibition of prostaglandins, which can cause alterations in glomerular filtration and BP. Also, in patients with ventricular dysfunction, NSAIDs can increase the risk of congestive heart failure.[58,59]

In elderly patients with liver disease, coagulopathy, concomitant use of anticoagulants or elevated alcohol use, NSAIDs can raise the risk of bleeding significantly due to altered vascular homeostasis.[74]

In reviewing the long-term NSAID therapies prescribed in Navarre, older patients are more frequently prescribed COXIBs (table 2) (52.6% vs 42.5%) than the general population, whereas ibuprofen and naproxen are less common in the older population (34.9% vs 44.6%). This means that older patients, who have a higher cardiovascular risk, are not being prescribed the most appropriate NSAIDs. In light of the data obtained, NSAID prescription protocols should be reviewed. It should be taken into account that gastrointestinal risk can be countered with gastric protectors, but there is no concomitant drug therapy for cardiovascular risk.

Acknowledgements

We are grateful to Douglas Salzwedel of the University of British Columbia, Canada, for reviewing the text.

Conclusions

The gastrointestinal, cardiovascular, and renal adverse effects of NSAIDs are directly related to the total daily dose taken and can appear less than 15 days following the start of treatment.

The safest NSAIDs are ibuprofen and naproxen whether used alone or in combination with a gastric protector in accordance with the patient's gastrointestinal risk factors.

The use of the selective COX-2 inhibitors diclofenac, aceclofenac, ibuprofen (at a dose ≥ 2400mg/d) and dexibuprofen (at a dose ≥ 1200mg/d) is contraindicated in patients with severe heart disease such as heart failure, ischemic heart disease (NYHA II-IV), peripheral artery disease and cerebrovascular disease. Moreover, in patients with cardiovascular risk, the benefits and risks of using these type of drugs must be considered prior to use.

Taking into account the wide number of contraindications of the COX-2 inhibitors, there may be an overuse of celecoxib and etoricoxib in Navarre.

Gastrointestinal risk can be countered with the prescription of gastric protectors. However, there is no concomitant drug therapy for cardiovascular risk.

NSAIDs used in combination with proton-pump inhibitors (PPIs) should be used with caution, since PPIs are not indicated for all patients requiring NSAID therapy. In addition, the combination of these drugs may result in using the incorrect dosage of one of the drugs.

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