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Adverse Effects and Drug Interactions of the Non-Steroidal Anti-Inflammatory Drugs

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Abstract

The aim of this chapter is to increase the awareness of health-care professionals concerning potential adverse effects and drug interactions of non-steroidal anti-inflammatory drugs (NSAIDs), which are among the most widely prescribed medicines, globally. They have a variety of clinical applications due to their anti-inflammatory, analgesic, antipyretic, or antithrombotic effect, but these drugs are not entirely innocuous, since they could increase the risk of gastrointestinal and cardiovascular complications. Furthermore, the drugs from this class have the potential of altering the pharmacokinetics of associated drugs, and also pharmacodynamic interactions have been reported. The clinical significance, mechanisms, and epidemiology of the adverse effects and drug interactions of NSAIDs are presented in this chapter. Prevention strategies for particularly high-risk groups of patients are also exposed. Detailed and up-to-date information regarding the adverse effects and drug interactions of NSAIDs are needed for all healthcare professionals in order to maximize efficacy in treating various illnesses while minimizing the risks for the patients.

Keywords: NSAIDs, gastrointestinal, cardiovascular adverse effects, nephropathy, hepatotoxicity, drug interactions

1. Introduction

The non-steroidal anti-inflammatory drugs (NSAIDs) are among the most successful medicines in the world, being used by large numbers of patients, due to their anti-inflammatory, analgesic, and antipyretic effects. Since the discovery of acetylsalicylic acid (aspirin) in the nineteenth century by F. Hoffmann, more than 50 different molecules have been marketed worldwide. NSAIDs are usually prescribed in chronic inflammatory conditions, but they are also extensively used as over-the-counter (OTC) drugs in a variety of inflammatory processes,

mild-to-moderate pain or fever. Other clinical uses (e.g. low-dose aspirin for cardioprotection) are also very popular.

Chemically, NSAIDs are extremely heterogeneous: salicylic acid derivatives (aspirin, diflunisal), indoles (indomethacin), fenamic acid derivatives (mefenamic acid, meclofenamic acid), acetic acid derivatives (diclofenac, ketorolac), propionic acid derivatives (ibuprofen, ketoprofen, naproxen), enolic acid derivatives (piroxicam, meloxicam), or diaryl heterocyclic compounds (celecoxib, etoricoxib) [1]. Most of the NSAIDs are organic acids, with low pKa values, capable of accumulation in the inflamed tissues, characterized by acidic pH.

Pharmacologically, all NSAIDs share a common mechanism of action, discovered by J.R. Vane in 1971: they act as competitive and reversible inhibitors of Prostaglandin G/H synthase (also known as cyclooxygenase or COX), thus reducing the formation of various prostaglandins [2]. The only exception is acetylsalicylic acid (aspirin), which irreversibly acetylates a key amino acid (serine 529) situated in the active site of COX-1, with the formation of a covalent bond, which leads to permanent enzyme inhibition. A series of studies characterized at least two isoforms of COX in humans:

- COX-1, a constitutive enzyme, normally expressed in many cells, which generates prostaglandins directly involved not only in the protection of gastric mucosa but also in platelet and renal homeostasis. The inhibition of this isoform is considered to be responsible for the gastric adverse effects of non-selective NSAIDs.
- COX-2, induced by pro-inflammatory cytokines or aggression of the tissues, which generates prostaglandins involved in pain, fever, and inflammation. Also, COX-2 can be responsible for some physiological functions.

Depending on the relative selectivity for COX isoforms, two types of NSAIDs have been developed:

- Non-selective (traditional) NSAIDs (ibuprofen, diclofenac, indomethacin, etc.), which inhibit both isoforms of COX, with high potential of inducing gastric irritation.
- COX-2 selective drugs (coxibs, nimesulide, meloxicam), which selectively inhibit COX-2, better tolerated by the gastric mucosa, but with different safety issues.

A key feature of NSAID class is that, partially, both beneficial and adverse effects are caused by the same mechanism of action: inhibition of prostaglandin biosynthesis [1, 3].

2. Adverse effects of NSAIDs

The adverse drug reactions (ADRs) are a major health issue worldwide, causing frequent hospital admissions and being one of the leading causes of mortality [4]. Although adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs) affect a limited percentage of users, the widespread use of these medicines can cause significant health problems. The probability of suffering severe adverse effects is correlated with the dose and the age of the patients, the elderly being more vulnerable. Lower starting doses and reduction of doses in

patients at risk are good preventive strategies, but further studies are necessary in order to develop genetic or biochemical markers of NSAID toxicity, in order to better anticipate the advent of an unwanted drug-induced adverse effect [5].

The adverse effects of NSAIDs can be manifested at different levels.

2.1. Gastrointestinal

The gastrointestinal (GI) adverse effects of NSAIDs are considered to be a hallmark of this pharmacological class, affecting 10–60% of patients [6]. They can include an array of symptoms and manifestations varying in severity from simple dyspepsia with pyrosis to fully developed gastric or intestinal ulcer. The ulcerations can become complicated with acute bleeding and perforation, a life-threatening situation. The most frequent adverse effects of NSAIDs at gastrointestinal level together with the additional risk factors are presented in **Table 1**.

The propensity of NSAIDs to induce gastrointestinal adverse effects depends on the molecule and mode of action. The non-selective NSAIDs frequently cause gastrointestinal damage, while the COX-2 selective NSAIDs have a dramatically improved gastric tolerability. The mechanism of NSAID-induced gastrointestinal damage has been extensively studied [5, 6].

The non-selective NSAIDs can induce lesions of the gastrointestinal mucosa by a topical erosive effect combined with a systemic effect characterized by depletion of prostaglandins synthesized by COX-1 (**Figure 1**). Normally, these “good” prostanoids stimulate the synthesis and secretion of mucus and bicarbonate, increase the blood flow, and promote epithelial proliferation. By removing these beneficial effects, non-selective NSAIDs create a gastric environment more susceptible to topical erosion by exogenous and endogenous factors. Thus, the acidic properties of most NSAIDs initiate mucosal damage because the drug molecules remain in a non-ionized lipophilic form in the acid environment of the stomach, entering into surface epithelial cells where they dissociate, trapping hydrogen ions and inducing lesions. The NSAID molecules additionally reduce the hydrophobicity of gastric mucus, allowing the hydrochloric acid and pepsin to attack the surface epithelium [5, 6].

Also, the decrease of TXA₂, process which can subsequently favor bleeding, is an additional mechanism of NSAID-induced gastric damage.

Affected organ system	Symptoms and manifestations	Additional risk factors
Gastrointestinal tract	Dyspepsia with pyrosis, Abdominal pain, Nausea, Anorexia, Gastric erosions, Ulcers, Perforation, Gastrointestinal hemorrhage, Anemia	History of GI ulcer, <i>Helicobacter pylori</i> , Age above 60, High doses of NSAIDs, Use of anticoagulants and corticosteroids, Use of multiple NSAIDs

Adapted from Refs. [1, 6].

Table 1. Adverse effects of NSAIDs at gastrointestinal level and additional risk factors.

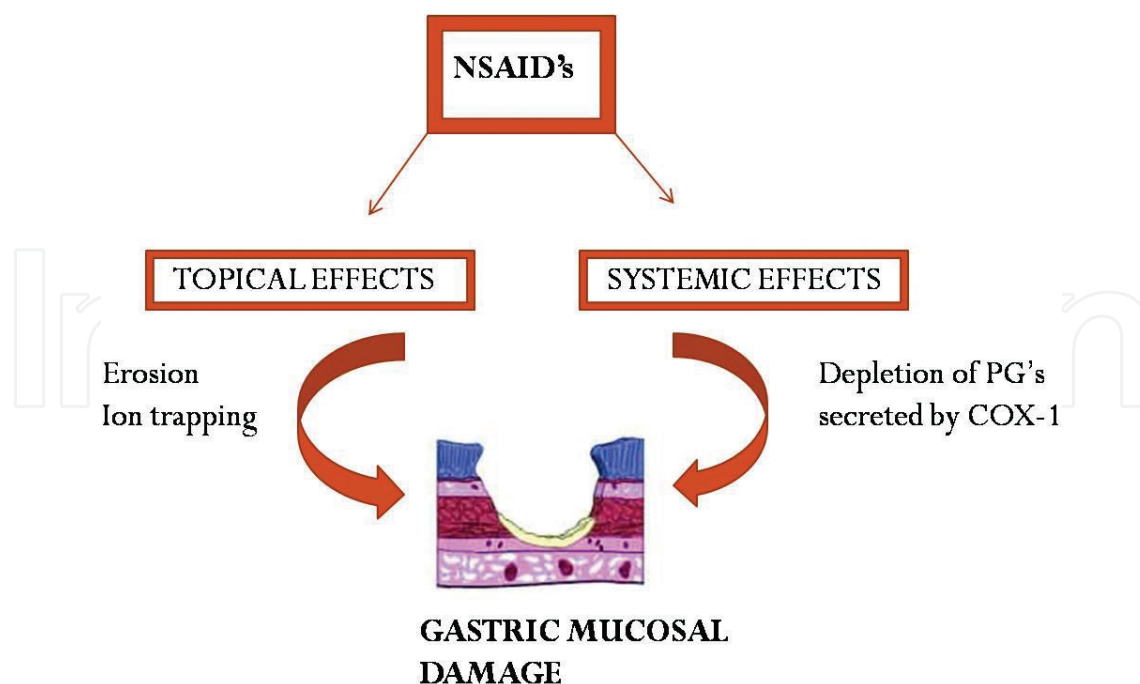


Figure 1. Mechanisms of NSAID-induced gastrointestinal damage.

Whether the direct, topical erosive effect of non-selective NSAIDs or the systemic depletion of “good” prostaglandins is the key factor responsible for the apparition of gastrointestinal damage, is still a matter of controversy.

Several large-scale epidemiological studies have been performed to gather valuable information regarding the gastrointestinal (GI) safety profile of the NSAID class.

For the non-selective NSAIDs, the Arthritis, Rheumatism, and Ageing Medical Information Systems (ARAMIS) study reported that the rate of gastrointestinal events was six times higher in patients taking NSAIDs than in non-users [7]. The meta-analysis of Gabriel et al. indicated that the relative risk (RR) of the first gastrointestinal event is 2.4 (CI 95%: 2.2–2.7) but becomes 4.8 (CI 95%: 4.0–5.6) if a previous history of ulcer exists [8]. Also, another study identified that the relative risk for adverse GI events increased with age, from 1.8 in younger patients to 3.5 in patients between 60 and 75 years old [9].

Furthermore, the Paracetamol, Aspirin, and Ibuprofen New Tolerability (PAIN) study demonstrated that ibuprofen (<1200 mg/day) was similar to acetaminophen (<3000 mg/day) in terms of the incidence of significant GI adverse effects and that statistically significant fewer events were associated with ibuprofen in comparison with aspirin (<3000 mg/day) during 1–7 days of treatment [10].

For the COX-2 selective NSAIDs, the Celecoxib Long-Term Arthritis Safety Study (CLASS) trial randomized patients with rheumatoid arthritis to either celecoxib 400 mg twice daily, ibuprofen 800 mg three times daily, or diclofenac 75 mg twice daily. After 6 months, significantly lower GI events were seen in celecoxib group (RR 0.59; 95% CI: 0.38–0.94) [11].

For etoricoxib, gastrointestinal adverse events were evaluated by combined analysis of 10 clinical trials enrolling 3142 patients. According to this study, etoricoxib halves both perforation and confirmed and unconfirmed bleeding, compared to non-selective NSAIDs [12].

Finally, a meta-analysis of 112 large-scale randomized clinical trials revealed that the risk of ulcer and serious GI complications associated with coxibs were lower than non-selective NSAIDs (RR 0.49; 95% CI: 0.38–0.62 vs. RR 0.55; 95% CI: 0.38–0.80) [13].

The management of patients receiving NSAIDs regarding gastrointestinal toxicity should take into consideration several key facts [5, 14]:

- The lowest dose should be used for the shortest period of time.
- Simultaneous administration of anticoagulants and corticosteroids should be avoided.
- *Helicobacter pylori* infection should be eradicated if present.
- NSAIDs with high GI toxicity (piroxicam, ketoprofen, ketorolac) should be avoided.
- The gastric damage can be reduced by associating NSAIDs with misoprostol or proton pump inhibitors (PPIs).
- If no gastrointestinal risk factors are present, non-selective NSAIDs are preferred.
- If one or more GI risk factors are present, coxibs should be used or non-selective NSAIDs + proton pump inhibitors (PPIs).

2.2. Cardiovascular

Based on currently available data, regulatory agencies from EU (EMA) and USA (FDA) have concluded that an increased risk for unwanted cardiovascular (CV) events has been demonstrated for all the COX-2 selective NSAIDs. The cardiovascular events have a thrombotic nature, being either acute myocardial infarctions (AMI) or strokes. Also, non-selective NSAIDs have a potential of causing unwanted CV events, especially when used in high doses and for longer periods of time.

As a consequence, the Food and Drug Administration (FDA) has requested that all COX-2 selective NSAIDs should be labeled with a boxed warning regarding increased risk of serious CV thrombotic events and a contraindication for patients who have recently undergone a CABG procedure. For non-selective NSAIDs, FDA has concluded that short-term use is not associated with increased CV risk, but the labeling should mention the potential risk [14].

COX-2 selective NSAIDs, especially the coxibs (rofecoxib-removed from market, celecoxib, etoricoxib), inhibit the synthesis of vascular prostacyclin (PGI₂), a natural inhibitor of platelet aggregation with vasodilator properties. PGI₂ is a protective mediator for cardiovascular system, acting via its receptor IP, expressed in different cell types. The increased risk of vascular events caused by the reduction of PGI₂ formation might be mitigated by a simultaneous suppression of COX-1 in the platelets. Unfortunately, COX-2 selective drugs, having no affinity for COX-1, do not reduce the platelet production of thromboxane A₂ (TXA₂) (**Figure 2**).

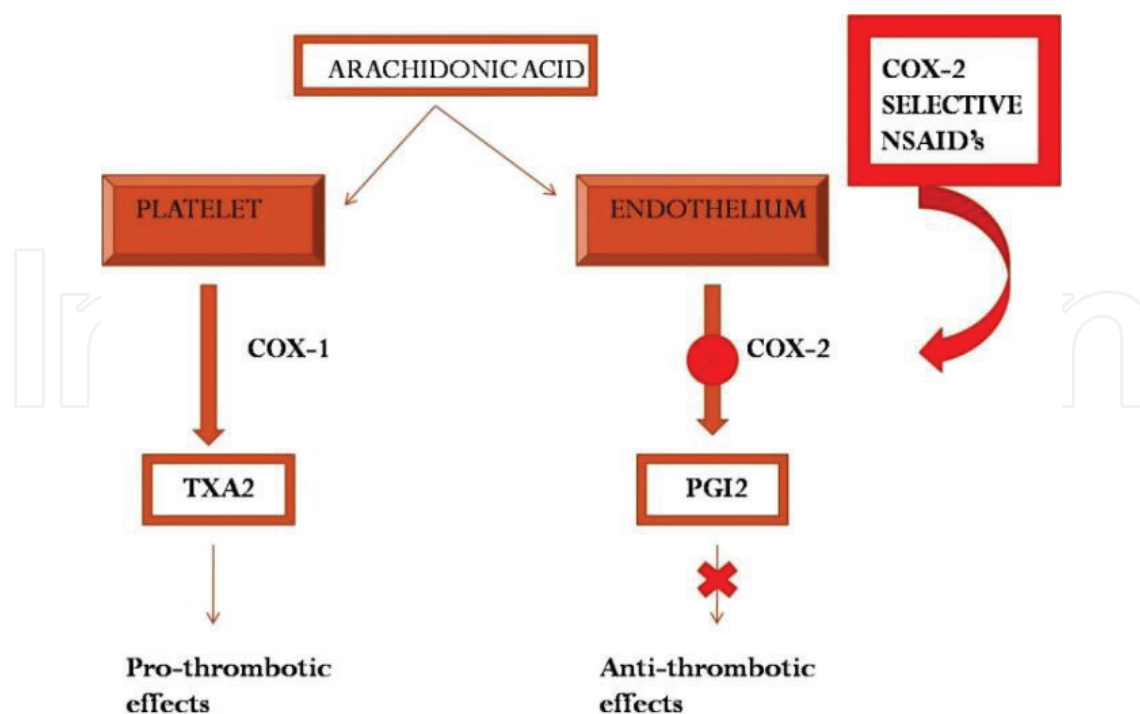


Figure 2. Mechanism of COX-2 selective NSAIDs-induced thrombosis.

Combined, these two effects may lead to a “pro-thrombotic state” with a significant risk of developing myocardial infarction or stroke [5]. However, with the exception of naproxen, neither of the non-selective NSAIDs (apart from aspirin) could affect platelet COX-1 in such a significant manner necessary for a platelet inhibitory effect [15].

Multiple large-scale epidemiological studies have been performed to gather data regarding the cardiovascular (CV) safety profile of the NSAID class.

A comparative analysis of patients with arthritis receiving celecoxib 400 mg twice daily and patients receiving placebo in an aspirin primary prevention meta-analysis showed that the annualized rate for acute myocardial infarction (AMI) was higher in patients receiving celecoxib compared to placebo (0.80 vs. 0.50) [16].

In a meta-analysis of three large observational studies, etoricoxib was associated with a significant 97% increase risk of AMI [17].

For the non-selective drugs, several epidemiological studies have provided conflicting results. For ibuprofen, studies evaluating potential risk for CV events ranged from showing no risk (RR 0.96; 95% CI: 0.81–1.14) to a significantly increased risk (HR 1.84; 95% CI: 1.62–2.08) [18].

For naproxen, studies ranged from showing a decreased risk (RR 0.75; 95% CI: 0.62–0.92) to significantly increased risk (OR 1.27; 95% CI: 1.01–1.60) [19].

More recently, a large meta-analysis of 754 RCTs (350,000 patients) concluded that diclofenac (150 mg daily) presents similar risks to COX-2 selective drugs for mortality (RR 1.02; 95%

CI: 0.84–1.24) but naproxen (1000 mg daily) is associated with fewer CV events and lower mortality [20].

On the basis of evidence gathered so far, several strategies for NSAID treatment and CV prevention have been suggested [5, 14]:

- Patients with low CV risk (under 1%/year) can be administered either a non-selective NSAID or a coxib, the choice between the two depending on the GI risk.
- In patients with intermediate CV risk (1–3%/year), the choice should be ibuprofen or naproxen (+PPI).
- In patients with high CV risk (above 3%/year), the choice is naproxen +PPI and aspirin, given 2 hours before.
- In Europe, EMEA contraindicates coxibs if cardiovascular risk factors are present.

2.3. Renal

In normal human subjects, NSAIDs do not have a significant influence on renal function. Nevertheless, prostaglandins are important mediators at the kidney level. They are involved in maintaining the volume control and electrolyte balance, they also control the release of renin and contribute to renal vasodilation. All NSAIDs can alter renal function by inhibiting COX-1 (which regulates renal hemodynamics and glomerular filtration) and/or COX-2 (which mediates salt and water excretion) expressed in the kidneys [21].

Usually, NSAIDs are associated with salt and water retention, due to the loss of PG-induced action on ADH. This hydro-saline retention has the potential of triggering arterial hypertension, but the effect varies greatly among the different molecules. Apparently, indomethacin and naproxen may increase the mean arterial pressure with 3–4 mm Hg [22].

Rarely, NSAIDs can cause a nephropathy, favored by high doses of multiple drugs but also in patients with congestive heart failure, chronic kidney disease, hypovolemia, disorders of the RAAS system. The manifestations of nephropathy may vary (e.g. interstitial nephritis, nephrotic syndrome, and papillary necrosis), and, unfortunately, it can progress to acute renal failure [23]. Of the available NSAIDs, indomethacin is the most potent inhibitor of renal prostaglandins, therefore being associated with more cases of renal failure. Drugs with an intermediate risk include ibuprofen, naproxen, diclofenac, sulindac, and piroxicam [24]. The nephrotoxic potential of COX-2 selective drugs is less clear.

2.4. Hepatic

Hepatotoxicity is a rare adverse effect of NSAIDs, but with potential serious consequences. A series of clinical trials have reported transient elevations of liver transaminases during the treatment with NSAIDs, but the values have usually normalized in time. Only in a minority of patients, a significant liver injury was observed, with symptoms which included nausea, vomiting, upper abdominal pain, fatigue, and jaundice. The injuries were primarily cholestatic, but hepatocellular or mixed cases were also documented [25].

Two large cohort studies pinpointed a 9/100,000 patients ratio of developing NSAID-associated hepatotoxicity. In the first study, out of 228,392 patients taking diclofenac, indomethacin, naproxen, sulindac, or piroxicam, 34 cases of acute liver injury were identified. The relative risk of developing liver injuries increased in patients with rheumatic diseases (RR 10.9; 95% CI: 2.4–50.2). Age and gender did not increase the relative risk [26]. The second study involved 625,307 patients from England and Wales, only 23 cases of acute liver injury being identified. Only sulindac was associated with a significant risk [27].

Nimesulide, a COX-2 selective NSAID marketed in Europe, was also associated with an increased risk of liver toxicity, but the European Medicines Agency (EMA) concluded in 2011 that the benefit/risk ratio remains positive for patients with acute pain or primary dysmenorrhea [28, 29].

2.5. Blood

Non-steroidal anti-inflammatory drugs (NSAIDs) can affect platelet aggregation and bleeding time due to inhibition of PG and TXA₂ synthesis. Aspirin is the most potent compound in this respect, due to the irreversible inhibition of COX-1 from the platelets, which translates into an increase in bleeding time. For aspirin, prolongation of bleeding time is about twice that of baseline in healthy subjects after a single dose of 325 mg. The effect begins 12 hours after a dose, and lasts between 24 and 48 hours. The other drugs from the class can also increase bleeding time, but the values are situated in the upper limit of the normal [30].

2.6. Hypersensitivity

Non-steroidal anti-inflammatory drugs (NSAIDs) have been reported as the second most common cause of drug-induced hypersensitivity reactions, hypersensitivity to aspirin affecting from 0.5 to 1.9% of the general population, with greater prevalence in asthmatics or patients with chronic urticaria [31, 32]. The NSAID-induced hypersensitivity has a wide range of clinical manifestations from anaphylaxis or severe bronchospasm developed within minutes to delayed-type responses, appearing after days or weeks. Bronchial asthma, aspirin-exacerbated respiratory disease (AERD), rhinosinusitis, urticaria are frequently encountered. The delayed-type skin or systemic reactions are very rare and include Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS).

The pathogenetic mechanism of NSAID-induced asthma and AERD is represented by the inhibition of COX-1 (by aspirin and other non-selective NSAIDs), which triggers a mechanism leading to an asthmatic attack or nasal symptoms. Apparently, deprivation of PGE₂ may lead to activation of inflammatory pathways and a local and systemic generation of cysteinyl leucotrienes, the most potent bronchoconstrictors.

Beside aspirin, hypersensitivity reactions have been documented especially in NSAIDs with heteroaryl acid group (naproxen, diclofenac, ibuprofen), newer COX-2 selective compounds having a very low incidence of this adverse effect [33].

3. Drug interactions of NSAIDs

Drug interactions are increasingly becoming a major concern for healthcare providers due to the necessity of using multiple drugs for the treatment of complex pathologies [34]. NSAIDs are frequently involved in drug-drug interactions, leading to increased hospitalization and health care cost [35].

3.1. Antihypertensives

In normotensive and untreated hypertensive patients, NSAIDs are probably having a weak effect on blood pressure. The addition of a NSAID to antihypertensive drugs could reduce the efficacy of antihypertensives, with a poor control of blood pressure. Several classes of antihypertensives are more prone to suffer this interaction: renin-angiotensin-aldosterone inhibitors, diuretics, and beta-blockers. Calcium channel blockers and centrally acting sympatholytic drugs are not affected. Elderly patients with hypertension may suffer significant changes in blood pressure control [36].

In addition to effects on blood pressure, there is concern that the interaction NSAID-Antihypertensives could increase the risk of acute kidney injury, since both classes have renal effects [37].

The pathogenetic mechanisms of these interactions are variable. NSAIDs interfere with the angiotensin converting enzyme (ACE) inhibitors directly and indirectly by decreasing renal prostaglandin synthesis and by reducing ACE inhibitors-induced prostaglandin synthesis. Also, NSAIDs decrease the efficacy of diuretics by reducing their natriuretic effect. The beta-blockers are influenced by the reduction of prostaglandin synthesis and a reduction in plasma renin, but their antihypertensive effects are marginally modified [38].

A comprehensive review of clinical data from the USA highlighted that indomethacin, naproxen, and piroxicam were associated with clinically significant increases in blood pressure, especially in patients treated with enalapril [38, 39]. Another US study of hypertensive patients, treated with ACEIs, and also receiving ibuprofen (2400 mg/day), nabumetone (2000 mg/day), or celecoxib (400 mg/day), found that ibuprofen, but not nabumetone or celecoxib, increased the mean arterial pressure with 6.5 ± 1.4 mm Hg [40].

Also, considering that aldosterone antagonists (spironolactone) may increase the risk of GI bleeding, patients should be informed that the long-term use of a NSAID could increase the probability of GI adverse effects [37].

The same US study found that small but significant increases in blood pressure occurred when indomethacin, piroxicam, naproxen, or ibuprofen were introduced in patients treated with hydrochlorothiazide or amiloride [38]. Another study examined the effects of ibuprofen (2400 mg/day) and naproxen (750 mg/day) on blood pressure in hypertensive patients treated with hydrochlorothiazide. After 4 weeks, the effects of NSAIDs on blood pressure were considered minor [41].

In conclusion, hypertensive patients under treatment with ACEIs or hydrochlorothiazide should avoid chronic use of NSAIDs [37].

3.2. Antithrombotics

Drug interactions between NSAIDs and antithrombotic medication have been extensively studied, as they can generate serious consequences.

The simultaneous administration of NSAIDs and cardioprotective aspirin can result in a competition for access into the active site of COX-1. Theoretically, this could lead to a reduction of aspirin's irreversible inhibition of platelet COX-1, with a subsequent reduction of clinical efficacy (prevention of an unwanted thrombotic event). A study on 5208 people found that patients taking prophylactic aspirin together with ibuprofen (more than four times per week) showed an almost doubled risk for MI, compared with patients taking ibuprofen infrequently [42]. Other studies showed different results. A retrospective study on 42,611 patients, including 8688 cases of MI, found that patients treated with aspirin and any NSAID had a lower risk for MI than the ones not taking aspirin and NSAIDs [43]. Another study on 22,071 apparently healthy patients showed that regular but not intermittent use of NSAIDs inhibits the clinical benefits of aspirin [44].

Despite the conflicting results of these studies, the avoidance of chronic use of NSAIDs in patients under treatment with cardioprotective aspirin is advisable. FDA recommends taking ibuprofen at least 8 hours before and 30 minutes after aspirin to reduce the likelihood of an interaction [45].

Although NSAIDs do not cause a direct pharmacodynamic interaction with warfarin, concomitant use may increase the probability of GI bleeding [46].

3.3. Antidepressants

In the 1990s, a large number of reports of bleeding disorders associated with selective serotonin reuptake inhibitors (SSRIs) were published, prompting further investigations. Although platelets do not synthesize serotonin, they can uptake it from plasma, and therefore serotonin may be involved in hemostasis and thrombosis. Thus, at the association of SSRIs with NSAIDs, which can also affect platelets, an interaction is possible. Furthermore, a pharmacokinetic interaction is possible, considering that some SSRIs inhibit CYP2C9, an enzyme involved in the metabolism of ibuprofen and diclofenac [47].

A recent review estimated that the risk of GI bleeding with the use of SSRIs relative to the non-use is 2.6 (95% CI: 1.7–3.8) [48]. Another review of the literature synthesized data from four retrospective studies examining the adverse outcomes from the association of SSRIs with NSAIDs. Two of the studies concluded that the risk ratio for an upper GI bleeding after the association was greater than the additive risk of either drug alone [49].

3.4. Alcohol

Alcohol can favor GI bleeding when consumed in large quantities, so that an additive effect with NSAIDs has been documented. A case-control study using 1224 inpatients found

a 2.7- fold increase in the risk for GI bleeding in individuals who regularly took ibuprofen and consumed alcohol (95% CI: 1.6–4.4) [50]. Another study using 1083 hospitalized patients found that the presence of either NSAIDs use or a history of alcohol abuse led to an odds ratio (OR) of 2.9 for severe GI events, while the presence of both risk factors led to an OR of 10.2 [51].

3.5. Methotrexate

Several NSAIDs have been found to reduce renal clearance of methotrexate, which could generate toxic events (renal failure, pancytopenia), especially at high doses [37]. Recently, a Cochrane review stated that using low doses of MTX (under 25 mg weekly, administered sc) and NSAIDs will not produce a clinically significant interaction [52].

4. Conclusions

The non-steroidal anti-inflammatory drugs (NSAIDs) have a variety of clinical applications due to their anti-inflammatory, analgesic, antipyretic, or antithrombotic effects.

The safety profile of NSAIDs remains positive when used in low doses for the temporary relief of pain or fever. In elderly patients, or in those with gastrointestinal or cardiovascular risk factors, more caution is necessary in order to avoid the apparition of serious adverse effects.

Patients chronically treated with ACE inhibitors, hydrochlorothiazide, spironolactone, or aspirin should be informed about the risks of NSAIDs administration.

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