Available online on 15.02.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Non-steroidal anti-inflammatory drugs: an overview

Jahnavi Kasturi, Pavani Reddy Palla, Vasudha Bakshi, Narender Boggula*

Department of Pharmaceutical Chemistry, School of Pharmacy, Anurag Group of Institutions, Venkatapur, Ghatkesar, Telangana, India.

ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) including both traditional non-selective NSAIDs and the selective cyclooxygenase (COX)-2 inhibitors, are widely used for their anti-inflammatory and analgesic effects. NSAIDs are a necessary choice in pain management because of the integrated role of the COX path way in the generation of inflammation and in the biochemical recognition of pain. NSAIDs are the competitive inhibitors of cyclooxygenase (COX), the enzyme which mediates the bioconversion of arachidonic acid to inflammatory prostaglandins (PGs). Their use is associated with the side effects such as gastrointestinal and renal toxicity. They are the most commonly employed first line drugs for all these conditions and many others-like musculoskeletal trauma, minor aches and pains, and dysmenorrhoea. The therapeutic anti-inflammatory action of NSAIDs is produced by the inhibition of COX-2, while the undesired side effects arise from inhibition of COX-1 activity. Thus, it was though those more selective COX-2 inhibitors would have reduced side effects. Based upon a number of selective COX-2 inhibitors (Rofecoxib, Celecoxib etc.) were developed as safer NSAIDs with improved gastric safety profile. Several newer applications like prophylaxis of stroke with aspirin are now common place. Use of these drugs for the prophylaxis of conditions like Alzheimer's disease and colorectal cancer is being evaluated. Unfortunately, they have several toxicities ranging from minor heartburn to severe gastrointestinal haemorrhage and perforation. Therefore, newer NSAIDs have been introduced in recent years to circumvent this problem. In preliminary studies, these have shown better safety, efficacy, and tolerability but the full spectrum of adverse reactions of these drugs is yet to be fully known. This review can be used for further research as well as clinical purpose.

Keywords: Non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase inhibitors, prostaglandins, aspirin.

Article Info: Received 05 Jan 2019; Review Completed 29 Jan 2019; Accepted 01 Feb 2019; Available online 15 Feb 2019

Cite this article as:

Jahnavi K, Pavani Reddy P, Vasudha B, Narender B, Non-steroidal anti-inflammatory drugs: an overview, Journal of Drug Delivery and Therapeutics. 2019; 9(1-s):442-448 http://dx.doi.org/10.22270/jddt.v9i1-s.2287

***Address for Correspondence:**

Narender Boggula, Assoc. Professor, Department of Pharmaceutical Chemistry, School of Pharmacy, Anurag Group of Institutions, Venkatapur, Ghatkesar, Telangana, INDIA-500088.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are a diverse group of compounds with similar biological capabilities: all NSAIDs reduce or eliminate the erythema, swelling, elevated temperature and pain caused by a variety of inflammatory stimuli. The mechanisms of action of NSAIDs have not yet been fully elucidated, but evidence suggests that their anti- inflammatory effects are primarily achieved through inhibiting prostaglandin production. This mode of action is common to all NSAIDs[1]. The cyclooxygenase enzyme was first identified as the therapeutic target of NSAIDs by Vane in 1971, showing that these anti-inflammatory substances block the biosynthesis of prostaglandins (PGs) that contribute to a variety of physiological and pathophysiological functions[2]. The most prominent NSAIDs are aspirin, and naproxen, all available over the countries in most countries. Paracetamol (acetaminophen) is generally not considered an NSAID because it has only little anti-inflammatory activity. It treats pain mainly by blocking COX-2 mostly in the central nervous system, but not much in the rest of the body. Cyclooxygenase (COX) inhibitors, commonly called non steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, diclofenac, and naproxen, have anti-inflammatory and analgesic/ antipyretic properties across a wide range of dosing regimens. Prescription-strength NSAIDs are effective for relief of chronic musculoskeletal pain and inflammation in conditions such as rheumatoid arthritis (RA) or osteoarthritis (OA). Lower, Over-The-Counter (OTC) doses of NSAIDs are effective for short-term (e.g. ≤10 days) relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, common cold, muscular aches, and arthritis. NSAIDs taken at OTC doses can also be effective at relieving painful episodes in patients with chronic diseases such as OA. Ibuprofen is an NSAID with a long history of safe and effective use at both prescription (maximum 2,400–3,200 mg/d) and OTC (<1,200 mg/d) doses[3]. Single-dose studies using OTC doses have confirmed that ibuprofen (400 mg) provides superior analgesic efficacy to acetaminophen (1,000 mg).

All NSAIDs inhibit COX, an enzyme that converts arachidonic acid to prostaglandins, thereby mediating pain,

inflammation, and fever. In the process, prostaglandin H_2 is converted to five primary prostaglandins, including thromboxane A_2 (which stimulates platelet aggregation and blood clot formation) in platelets and prostacyclin (a vasodilator that inhibits platelet aggregation) in the endothelium. Two COX isoenzymes (COX-1 and COX-2) are commonly recognized. In general, COX-1 is constitutively expressed and is involved in gastroprotection from stomach acid and in thromboxane formation by platelets. COX-2 is inducible by inflammatory mediators in a wide range of tissues and has been associated with inflammation; however, it may also be constitutively expressed, where it contributes to renal physiology, reproductive function, bone resorption, and neurotransmission.

Classification

- Non-selective COX inhibitors:
- Salisylates : Aspirin, sodium salisylate
- Propionic acid derivatives: Ibuprofen, naproxen, ketoprofen, flubiprofen
- Anthranilic acid derivatives: Mephanamic acid, meclofenamic acid
- Aryl-acetic derivatives: Diclofenac, aceclofenac
- Oxicams: Piroxicam, tenoxicam
- Pyrolo-pyrol derivatives: Ketorolac
- Indole derivatives: Indomethacin
- Pyrozolone derivatives: Phenylbutazone, oxyphenbutazone
- Preferentical COX-2 inhibitiors: Nimesulide, meloxicam, nabumetone
- Selective COX-2 inhibitors: Celecoxib, rofecoxib, etoricoxib, parecoxib
- Analgesics-anti-pyretics:
- Paraminophenol: Paracetamol
- Pyrozolone derivative: Metamizol, propiphenazone

Biological roles of prostaglandins

Prostaglandins (PGs) are hormone-like bioactive substances mediating autocrine and paracrine signaling over the short distances and are involved in many physiological and pathological processes. They act via high-affinity G-protein-coupled receptors: four EP receptors for PGE2 termed EP1-EP4, IP receptor for prostacycline, DP receptor for PGD2, FP receptor for PGF2α. These receptors are linked to the different signal transduction pathways[3]. Once a prostanoid is formed, it exits the cell and then interacts with G protein-coupled receptors, either on the parent cell or on closely neighboring cells to modulate the second messenger levels[4]. Although their tissue distribution depends on the cellular enzymatic material, prostanoids are involved in a very broad range of physiological and pathophysiological responses[5].

Enzymatic structure

The COX isoenzymes are membrane-bound enzymes in the endoplasmic reticulum (ER). The three dimensional structure of the ovine COX-1 was first reported in 1994 and the crystal structures of human and murine COX-2 quickly followed. COX functions as a homodimer and attempts to create monomeric species which have yielded only inactive enzyme. The crystal structures of the COX isoforms are quite structurally homologous and consistent with a high sequence identity (ca. 60%); the overall structures of COX-1 and COX-2 are highly conserved. The COX monomer consists of three structural domains: an N-terminal epidermal growth factor (EGF)-like domain, a membrane binding domain (MBD) of about 48 amino acids in length which anchors the protein to one leaflet of the lipid bilayer, and a large C-terminal globular catalytic domain with the COX active site which accommodates the substrate or the inhibitors and the peroxidase one which contains the heme cofactor. These sites are distinct but functionally and structurally interconnected[6].

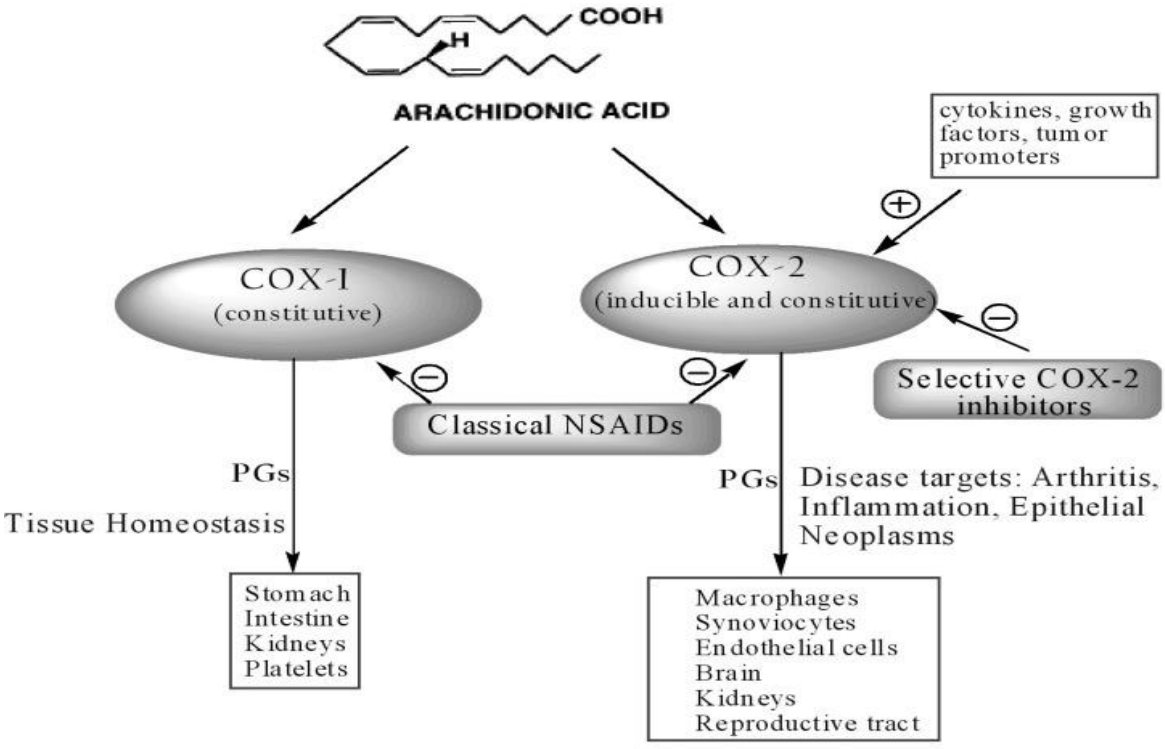

Figure 1: General mechanism of NSAIDs

Mechanism of action

COX enzymes (i.e., COX-1 and COX-2) catalyze the conversion of arachidonic acid into prostaglandin (PG) G2, an unstable intermediate that is rapidly converted to PGH2. Subsequently, PGH2 is metabolized into different structurally-related PGs, including PGE2, PGD2, PGF2, PGI2 and thromboxane (TX)A2[7]. COX-1 is constitutively expressed in mammalian tissues, and COX-1-derived PGs are essential for physiological functions, although studies in experimental models of CRC have suggested that COX-1 could exert tumor-promoting effects[8]. In contrast, COX-2 is inducible by inflammatory cytokines, growth factors and tumor promoters in several cell types. Upregulation of COX-2 expression is seen in 40–50% of human colorectal adenomas and in 80–90% of carcinomas and results in enhanced PG production[9]. COX-2 plays a pivotal role in tumor initiation, promotion and progression by increasing the production of (1) reactive oxygen species, (2) PGE2 and other PGs that promote cell proliferation, (3) vascular endothelial growth factor and platelet-derived growth factor and (4) matrix metalloproteinases. COX-2 also controls the expression of both pro- and anti-apoptotic proteins and restrains the proliferation of immune cells with anti-neoplastic activity. Among the NSAIDs, aspirin is the only drug that is able to permanently inhibit COX-1 and COX-2 activity. At anti-platelet therapeutic doses (75–100 mg daily), aspirin is up to 100-fold more potent in inhibiting platelet COX-1 than monocyte COX-2[10].

The analgesic and anti-inflammatory actions of NSAIDs including COX-2 selective inhibitors are due to their effective inhibition of prostaglandin synthesis catalysed by the COX-2 isoenzyme (Figure 2). This isoenzyme is massively up-regulated in inflammatory states such as rheumatoid arthritis, so inhibiting it reduces inflammation. Aspirin and the non-selective NSAIDs inhibit COX-1 and COX-2 isoenzyme. The COX-1 isoenzyme is involved in the synthesis of prostaglandins. These prostaglandins protect the gastric mucosa from ulceration and participate in platelet aggregation via the prostaglandin derivative, thromboxane A_2. Inhibition of COX-1 has been strongly implicated in the gastric ulceration and bleeding induced by the non-selective NSAIDs.

In platelets, inhibition of COX-1 leads to inhibition of thromboxane A_2 synthesis. This very effectively inhibits platelet aggregation. Low-dose aspirin irreversibly inhibits platelet aggregation via this mechanism and is therefore widely employed as prophylaxis against thrombotic cardiovascular disease. At therapeutic doses, COX-2 selective inhibitors have little effect on the COX-1 enzyme, so they do not inhibit platelet aggregation.

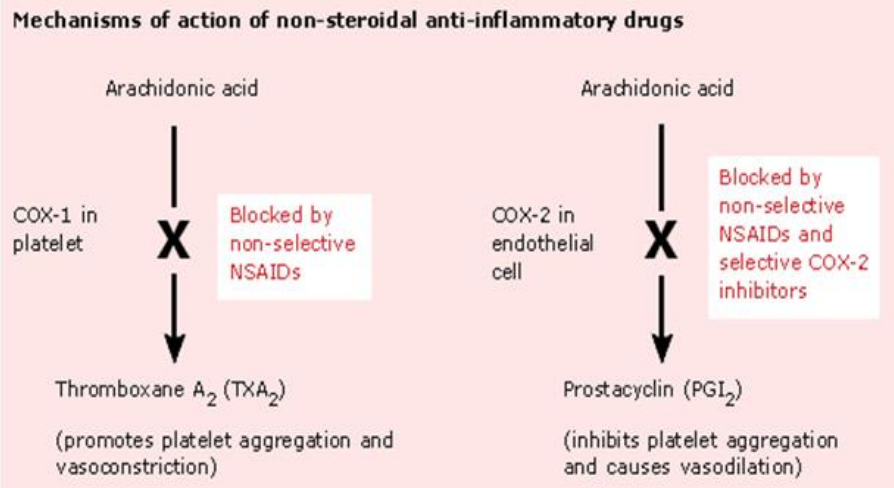

Figure 2: MOA

Naproxen

Naproxen is a non-steroidal anti-inflammatory drug (NSAID). It works by reducing hormones that cause inflammation and pain in the body. Naproxen is used to treat pain or inflammation caused by conditions such as arthritis, ankylosing spondylitis, tendinitis, bursitis, gout or menstrual cramps. Naproxen sodium is an anti-inflammatory agent with analgesic and anti-pyretic properties. Both the acid and its sodium salt are used in the treatment of rheumatoid arthritis and other rheumatic or musculoskeletal disorders, dysmenorrhea, and acute gout. Naproxen Sodium is the sodium salt form of naproxen, a member of the aryl-acetic acid group of non-steroidal anti-inflammatory drugs (NSAIDs) with anti-inflammatory analgesic and antipyretic properties. Naproxen sodium reversibly and competitively inhibits cyclooxygenases (COX), thereby blocking the conversion of arachidonic acid to pro-inflammatory prostaglandins. This inhibits the formation of prostaglandins that are involved in pain, inflammation and fever. The over-the-counter (OTC) use of naproxen is expected to pose minimal cardiovascular risk; however, the benefit–risk ratio and appropriate use should be considered at an individual patient level, particularly to assess underlying conditions that may increase the risk of events. Likewise, regulatory authorities should revisit label information periodically to ensure labeling reflects the current understanding of benefits and risks. Musculoskeletal aches and pains are one of the most common medical complaints around the world, and increasing life expectancies are driving an increased incidence of degenerative joint disease, burdening patients and healthcare systems[11]. Naproxen binds reversibly with COX-1 and COX-2 to exert its effects but has an increased selectivity for COX-1 inhibition, which is fivefold greater than the level of COX-2 inhibition [12]. Naproxen reaches peak plasma concentrations between 2 and 4 h (naproxen sodium C_{max} at 1–2 h) and has a half-life of 12–17 h[13]. Naproxen is a highly effective analgesic, and its long half-life provides consistent blood levels and efficacy, making it a choice comparator in many clinical trials. Naproxen's medical uses are related to its mechanism of action as an anti-inflammatory compound. Naproxen is used to treat a variety of inflammatory conditions and symptoms that are due to excessive inflammation such as pain and fever (naproxen has fever-reducing, or anti-pyretic properties in

addition to its anti-inflammatory activity). Notably, not all medications that reduce fever are anti-inflammatory compound Inflammatory sources of pain that may respond to naproxen's anti-inflammatory activity are conditions such as migraine, osteoarthritis kidney stones, rheumatoid arthritis, psoriatic arthritis, gout, ankylosing spondylitis, menstrual cramps tendinitis and bursitis.

Side effects

Naproxen side effects may include:

- Indigestion, heartburn, stomach pain, nausea;
- Headache, dizziness, drowsiness;
- Bruising, itching, rash;
- Swelling; or
- Ringing in your ears
- Swelling or rapid weight gain;
- The first sign of any skin rash, no matter how mild;
- Signs of stomach bleeding - bloody or tarry stools, coughing up blood or vomit that looks like coffee grounds;
- Liver problems - nausea, upper stomach pain, itching, tired feeling, flu-like symptoms, loss of appetite, dark urine, clay-colored stools, jaundice (yellowing of the skin or eyes);
- Kidney problems - little or no urinating, painful or difficult urination, swelling in your feet or ankles, feeling tired or short of breath;
- Low red blood cells (anemia) - pale skin, feeling light-headed or short of breath, rapid heart rate, trouble concentrating; or
- Severe skin reaction - fever, sore throat, swelling in your face or tongue, burning in your eyes, skin pain followed by a red or purple skin rash that spreads (especially in the face or upper body) and causes blistering and peeling.

Adverse drug reactions of naproxen

Allergic reactions: If you have had a reaction to acetylsalicylic acid (ASA) or other NSAIDs (e.g., ibuprofen, ketoprofen, ketorolac) that included a runny nose, itchy skin rash, nasal polyps, or shortness of breath and wheezing, you should not take this medication. If you experience symptoms of a severe allergic reaction (e.g., hives; difficulty breathing; wheezing; swelling of the face, tongue, or throat).

Aseptic meningitis: This medication can rarely cause symptoms of aseptic meningitis (inflammation or swelling of the membranes around the brain and spinal cord that is not caused by bacteria). If you have an autoimmune condition (e.g., systemic lupus erythematosus, mixed connective tissue disease), Symptoms such as stiff neck, severe headache, nausea, vomiting, fever, or changes in consciousness.

Bladder problems: This medication may cause bladder pain, painful or difficult urination, or increased frequency of urination.

Blood clotting: This medication may reduce the ability of the blood to clot. If you are taking anticoagulants (e.g., warfarin, heparin) or have hemophilia or other blood disorders (e.g., low platelets), discuss with your doctor how this medication may affect your medical condition, how your medical condition may affect the dosing and effectiveness of this medication.

Drowsiness/reduced alertness: As with other NSAIDs, naproxen sodium can cause drowsiness, dizziness, and blurred vision. Avoid driving and other activities that require alertness and concentration until you determine the effect this medication has on you.

Fluid and electrolyte balance: NSAIDs such as naproxen sodium can cause fluid retention and edema (swelling). This can lead to high blood pressure or worsening of heart failure. If you have heart failure or high blood pressure. Naproxen sodium may also cause high blood potassium levels. If you are a senior; have diabetes or kidney failure; or are taking beta-blockers (e.g., metoprolol, atenolol), angiotensin converting enzyme (ACE) inhibitors (e.g., ramipril, enalapril), or some diuretics (e.g., triamterene, amiloride), you are more at risk of high blood potassium.

Heart attack and stroke: This medication may be associated with an increased risk of heart attack and stroke. The risk is increased with higher total daily doses and taking the medication over long periods of time. If you have a history of heart disease (e.g., heart attack, stroke, heart failure) or have risk factors for heart disease (e.g., high blood pressure, high cholesterol, diabetes, smoking, kidney disease) discuss with your doctor how this medication may affect your medical condition, how your medical condition may affect the dosing and effectiveness of this medication, and whether any special monitoring is needed.

Kidney function: Long-term use of naproxen sodium may lead to kidney problems. If you have kidney problems, liver disease, or heart failure; or are dehydrated, on a salt restricted diet, or are a senior, you have an increased risk for kidney problems while taking this medication. If you are taking medications such as diuretics (e.g., hydrochloro thiazide, triamterene, indapamide), ACE inhibitors (e.g., enalapril, ramipril), angiotensin receptor blockers (e.g., valsartan, candesartan), or cyclosporine, you are also at an increased risk.

Liver problems: Rarely, this medication causes liver problems. If you have reduced liver function

Skin reactions: This medication can cause skin reactions, some of which may be severe. If you experience a skin rash, especially where the skin is blistering or peeling, This medication may make your skin more sensitive to sunlight (including sunlamps) and may cause sunburn, skin blisters, and skin redness, itching or discolouration.

Ulcers or bleeding in the stomach or intestines: Naproxen sodium can cause stomach ulcers, perforation (holes), and bleeding from the stomach. These complications can occur at any time without warning and are sometimes severe enough to require immediate medical attention. The risk of ulcers and bleeding are increased if you are taking higher doses of this medication for longer periods of time. Other factors that increase the risk of these complications include drinking excessive amounts of alcohol, increased age, smoking, poor health, *H pylori* infection, and taking certain medications (e.g., warfarin, ASA, clopidogrel, prednisone, citalopram, fluoxetine, paroxetine, sertraline). If you currently have ulcers in the stomach or intestines that are bleeding, or have an inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis) ,

Pregnancy: This medication should not be used during the third trimester (last 3 months) of pregnancy. This medication should not be used during the first and second trimester (first 6 months) of pregnancy unless the benefits

outweigh the risks. This medication may reduce your ability to become pregnant.

Breast-feeding: You should not use this medication if you are breast- feeding.

Adverse drug reactions of NSAIDS

ADRs associated with NSAIDs primarily manifest in gastrointestinal (GI), cardiovascular (CV), and renal sites.

GI effects

GI complications are well-recognized risks of NSAIDs as a class and vary by the respective NSAID used as well as by dose[14]. Like Aspirin increases bleeding risk, even at low cardioprotective doses. In terms of non-selective NSAIDs, a meta-analysis of data from three retrospective case-control studies found that ibuprofen had the lowest odds ratio (OR) for development of GI bleeding versus diclofenac, naproxen, piroxicam, and indomethacin, but that the OR increases with dose level for each agent[15,16]. Ibuprofen was noted to produce significantly fewer overall GI AEs vs acetaminophen. In this study, a significant AE was defined as any event that was serious, severe, or moderate; necessitated a second physician consultation; led to treatment discontinuation; or was of missing intensity. The Paracetamol, Aspirin, and Ibuprofen New Tolerability (PAIN) study (N=8,677) assessed the frequency of significant adverse events (AEs) associated with OTC analgesic dosing in patients with acute pain.

In this study, a significant AE was defined as any event that was serious, severe, or moderate; necessitated a second physician consultation; led to treatment discontinuation; or was of missing intensity. The PAIN study demonstrated that OTC ibuprofen (≤1,200 mg/d) was similar to acetaminophen (≤3,000 mg/d) in terms of the incidence of significant AEs (13.7% vs 14.5%, respectively), but that statistically significantly fewer such events occurred with ibuprofen in comparison with aspirin during 1–7 days of treatment[17]. As expected, rates of GI AEs were significantly lower in patients receiving OTC doses of ibuprofen versus aspirin (4.0% vs 7.1%; P<0.001), and interestingly, ibuprofen was noted to produce significantly fewer overall GI AEs vs acetaminophen (5.3%; P=0.025). The PAIN study also identified numerous factors associated with increased risk of AEs, including female sex, older age, height ≤160 cm, use of the analgesic for musculoskeletal pain (vs menstrual cramps, sore throat, toothache, or fever), concomitant use of prohibited medications, and increasing number of concomitant medications[18]. Concomitant medications also influence the risk of GI events among NSAID users. The risk of upper GI events is increased when non-aspirin NSAIDs are combined with aspirin, but this increase in risk may be ameliorated when NSAIDs are used concurrently with ulcer-healing drugs (i.e., proton pump inhibitors)[19].

CV risk

All non-aspirin NSAIDs may be associated with a potential increase in CV thrombotic risk. The risk of heart attack or stroke may increase if you use more than directed or for longer than directed [20,21]. Hence there is no period of latency for CV thrombotic risk, and therefore, patients should take the lowest dose of NSAIDs for the shortest period of time possible. There are few data on actual CV risk with NSAID use at OTC doses, but risk is likely to be small, especially in younger patients who have few CV risk factors. It has been hypothesized that the increase in CV risk among NSAID users stems from increased blood pressure (BP) due to COX-2 inhibition in the kidneys – an effect that has not been observed with OTC doses [22,23].

Renal

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. Uncommon, but concerning, renal syndromes caused by nonselective NSAIDs include sodium retention, peripheral edema, increased BP and weight, congestive heart failure (rare), hyperkalemia, and acute renal failure. Risk factors include preexisting severe hepatic or renal dysfunction, nephrotic syndrome with high-level proteinuria, older age, diabetes, hypertension, and congestive heart failure[24]. Furthermore, individuals experiencing renal stress (e.g., dehydration) from exercise in hot environments may be at a small increased risk for acute renal failure with ibuprofen[25]. NSAIDs may lessen response to diuretics and worsen renal insufficiency associated with use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs). However, a study of OTC analgesics in elderly patients with diuretic-treated hypertension and mild renal insufficiency found no significant impact of ibuprofen on creatinine clearance nor on blood urea nitrogen, serum creatinine, sodium, or potassium levels. Aldosterone antagonists (e.g., Spiranolactone) are associated with an increased risk of GI bleeding and possibly impaired healing of gastric or duodenal erosions [26,27]. Thus, risk of GI bleeding in patients taking these agents may be further increased when NSAIDs are used concomitantly. Patients treated long term with aldosterone antagonists should be informed of the risk of upper GI bleeding and perhaps warned of the risk of using OTC NSAIDs long term. It found that prescription of ibuprofen and its administration decreased clearance of furosemide and increased urine sodium excretion. Topical diclofenac had no effect on furosemide pharmacokinetics or pharmacodynamics, and oral diclofenac compared with furosemide alone decreased urine output, but neither formulation was associated with alterations in BP.

Anti-thrombotics

NSAIDs are not prone to a direct pharmacodynamic interaction with anticoagulants such as warfarin; however, concurrent use of NSAIDs and anti-thrombotics may further increase the likelihood of GI bleeding. Metabolism of S-warfarin, the most clinically relevant warfarin isomer, occurs via CYP2C9.Ibuprofen and other NSAIDs are also substrates of CYP2C9and may thus increase anticoagulant activity by delaying S-warfarin metabolism. Therefore, it may be prudent to avoid prescription-strength NSAIDs in patients receiving warfarin[28]. In contrast, one of the metabolites of acetaminophen (N-acetyl-para-benzoquinone-imine) interferes with enzymes involved in the vitamin K cycle, which ultimately can lead to reduction in synthesis of clotting factors and excessive anticoagulation[29]. Even with short-term use, acetaminophen given concurrently with anticoagulants may increase international normalized ratio (INR), implying an increase in bleeding risk and necessitating close INR monitoring and possible warfarin dosage adjustments[30]. Aspirin Co-administration of aspirin and most NSAIDs (other than diclofenac and ketorolac) can lead to pharmacodynamic DDIs resulting from competition for access to the acetylation site of platelet-expressed COX-1. NSAID-driven reversible, transient inhibition of platelet aggregation blocks aspirin's irreversible inhibition, thereby potentially allowing clot formation. This NSAID-driven effect on aspirin is of particular concern in individuals at high CV risk who take low-dose aspirin daily to reduce the risk of a thrombotic event. Ibuprofen should be avoided in patients with known or suspected aspirin-sensitive asthma. Patients should be counseled to limit their use of OTC NSAIDs and to

avoid acetaminophen while on anticoagulant therapy, the former because of the increased risk of GI bleeding with NSAIDs, however small, and the latter because of the direct interaction that would increase the risk of all-site bleeding[31].

Anti-depressants

Anti-depressants are psychiatric medications used to alleviate mood and anxiety disorders. Some antidepressants may be associated with an increased risk for bleeding, which may be additively enhanced by co-administration of NSAIDs. Selective serotonin reuptake inhibitors (SSRIs) increase bleeding risk by inhibiting platelet adhesion and function. Co-administration of NSAIDs in patients taking SSRIs can substantially increase the risk of bleeding[32]. Several mechanisms may account for the interaction between SSRIs and NSAIDs: 1) Both classes inhibit platelet aggregation and function but via different mechanisms;[33]. 2) A pharmacokinetic interaction in which some SSRIs inhibit CYP2C9, an enzyme responsible for the metabolism of some NSAIDs (e.g., ibuprofen and diclofenac); [34], or 3) Independent effects in which SSRIs increase symptoms and bleeding via an independent mechanism without any direct pharmacokinetic interaction (e.g., by increasing gastric acid secretion). Tricyclic anti-depressants (TCAs) do not substantially inhibit CYP2C9. In the Dutch cohort study, in contrast to the tenfold increase in risk when NSAIDs are added to SSRIs, patients receiving TCAs plus an NSAID experienced a more modest increase in GI events[34].

Anti-rheumatics/chemotherapy

Methotrexate is an anti-metabolite used at high doses as a chemotherapeutic and at low doses for treatment of psoriasis and RA [35]. Several NSAIDs, including prescription ibuprofen and naproxen, have been found to reduce renal clearance of Methotrexate[36], which could lead to toxicity (e.g., renal failure or pancytopenia), at least when Methotrexate is used at high doses. A single-case report speculated that daily use of an OTC ibuprofen product for 4 weeks reduced Methotrexate excretion. Resulting Methotrexate accumulation caused bone marrow depletion, which may have contributed to *Pneumocystis carinii* pneumonia in a patient with Crohn's disease[37,38]. Given that renal effects have also been reported with prescription ibuprofen monotherapy[39]. Patients taking high-dose Methotrexate should avoid NSAID use, even at OTC doses. Additionally, caution should be exercised when NSAIDs are used in patients receiving low-dose Methotrexate. No other reports of clinically relevant DDIs resulting in ADRs in individuals receiving concomitant NSAIDs and chemotherapeutics or rheumatologic therapies were identified[35].

Fertility

NSAIDs (doses not reported) were associated with an 80% increased risk for miscarriage with even higher risks when NSAIDs were taken close to the time of conception or for longer than 1 week. There was a trend toward increased risk with aspirin use but no increase in risk associated with acetaminophen. While data are limited, it has been hypothesized that NSAID use may reduce fertility and increase the risk of miscarriage. It may be prudent for women who are trying to become pregnant to avoid NSAID use around the time of conception[40]. Additionally, prostaglandins play an important role in maintaining the patency of the fetal ductus arteriosus during the third trimester of pregnancy[41].

Corticosteroids

Combined use of oral corticosteroids and NSAIDs may increase the potential for serious GI toxicity. On further analysis, this increased risk was attributed to a 4.4-fold increased risk for peptic ulcer disease in individuals who had also taken NSAIDs (any type or dosage) compared with no elevated risk when NSAID users were excluded. although no specific studies have identified a clear risk for increased GI bleeding when OTC NSAIDs are co-administered with oral corticosteroids, it may be prudent for health care providers to prescribe COX-2-specific NSAIDs or counsel patients to avoid OTC NSAIDs to reduce the potential risk for GI bleeding[42].

Drug interaction of NSAIDs

NSAIDs are one of the most common causes of adverse drug reactions. As patient age and the number of medications increase, NSAIDs in the elderly should be prescribed with caution. NSAIDs concomitantly used with specific medication can alter the risk of gastrointestinal ulceration and/or bleeding. These drugs include selective serotonin reuptake inhibitors (SSRIs), corticosteroids, digitalis glycosides, diuretics, beta blockers, calcium antagonists, angiotensin converting enzyme, warfarin, clopidogrel, aspirin, and other anti-coagulants. Some specific NSAIDs were found to reduce renal clearance of Methotrexate, a commonly used medication for rheumatoid arthritis[43].

Conclusion

Knowing about the mechanism of action, current guidelines, adverse drug reaction, and the pleiotropic effects of common drugs is important. NSAIDs are one of the most commonly prescribed drugs in the elderly. These medications should be prescribed for the shortest duration possible in the lowest effective dose, and with careful surveillance to monitor GI, renal, and cardiovascular toxicity. This is especially true for elderly patients who are very susceptible to the side effect profiles of NSAIDs. There is some evidence to support the role of NSAIDs in dementia prevention, improve muscle performance, improve urinary incontinence, and decrease the risk of some specific cancers.

Acknowledgement

We wish to thank the management of School of Pharmacy, Anurag Group of Institutions, Venkatapur, Ghatkesar, Telangana, India for providing constant encouragement, praiseworthy inspiration, facilities and support.

Authors Contribution

All the authors contributed equally.

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