Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env.Pharmacol. Life Sci., Vol 11[2] January 2022 : 177-181

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

REVIEW ARTICLE **OPEN ACCESS**

Classification, Action, Pharmacology of Non-steroidal anti-inflammatory drugs (NSAIDs) Agents: A Mini Review

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ABSTRACT
NSAIDs are among the most widely used of all therapeutic agents. They are the group of chemically dissimilar agents that differ in their antipyretic, analgesic and anti inflammatory activities. The most important mechanism of their anti-inflammatory action is considered to be inhibition prostaglandin (PG) synthesis at the site of injury. NSAIDs have an ability of block cyclooxygenase (cox) involved in the first step of the arachidonic acid cascade. In addition of the recently used NSAIDs (celecoxib, Rofecoxib, Nabumetone, Nimesulide), a large number of compound which possessed patent inflammatory activity are mentioned in chemical literature. Hence, this present review is intended to give some useful insight into NSAIDs as anti-inflammatory drugs for the treatment of various inflammation disorders.
Keywords: *NSAIDs, anti-inflammatory, prostaglandin*

Received 01 .12.2021 Revised 09.01.2022 Accepted 22.01.2022

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs), nonselective non-steroidal anti-inflammatory drugs (nsNSAIDs) and selective cyclo-oxygenase 2 NSAIDs (COXIBs) are some of the most widely prescribed drugs in the world, and are commonly used to treat fever, pain and inflammation in diseases such as rheumatoid arthritis (RA) and osteoarthritis (OA). They have both beneficial and adverse effects due to the inhibition of prostanoids, derivates of arachidonic acid (AA), which is transformed into prostaglandin G2 (PGG2) and H2 (PGH2) as a result of the activity of cyclo-oxygenase (COX), and PGH2 is subsequently metabolised by terminal synthases into biologically active prostanoids (1). These chemical molecules are composed of hydrophilic groups like carboxylic or enolic group as well as lipophilic ones which contain aromatic ring and halogen atoms. These compounds usually occur in the gastric juice in the protonated (lipophilic) form due to their acidic nature which favors there absorption in small intestine as there is favorable condition for absorption of weak acids. Although NSAID are found in plasma in highly ionized form but still there distribution is poor in extra vascular system because of lower value ranging from 0.1 to 1.0. They areamiliphilic properties which increase their efficacy around >97% for binding with plasma proteins due to which they replace other drugs from protein binding of NSAIDs. However, NSAIDs are oxidized in the liver to form inactive metabolites which are excreted through urine some are partially excreted in bile but due to some abnormal or diseased conditions they might get accumulated even in prescribed dosages (2, 3). In the latent phase of 1980s two isoforms of COX has been discovered produced by different gene. The COX-1 is produced by gene located on chromosome 9 which has a housekeeping role and also regulate different cell functions together with protecting GI mucosal membrane from ulceration using complex series of reactions. The chromosome 1 has the functional gene to produce COX-2 responsible for variety of inflammatory cytokines and injury. The prostaglandins which are accountable for cytoprotection of GI tract and platelet function is produced by COX-1 whereas COX-2 enzyme produces those responsible for pain perception and inflammation (1, 4, 5). As compared with traditional NS-NSAIDs, coxibs the COX-2 selective inhibitors were developed having budding analgesic and anti-inflammatory activity having lesser extent of GI tract injury. Double blind randomized endoscopic trials and studies outcomes showed that these agents not only minimize the risk of developing gastroduodenal ulcers (6, 7) but also reduce the complications of upper GI tract (8). The relative risk of coxibs as compared with NS-NSAIDs for lower GI tract injury is much less well characterized than is the risk in the upper GI tract (9). Recently, many studies evident that NSAIDs may be used as a potential anti-cancer agent with possible application in the treatment of several neurodegenerative conditions. However,

newly discovered anti-inflammatory agents seems to offer significant advantages over non-selectives and COX-2 selective NSAIDs.

NSAIDs- Their Classification

The NSAIDs were classified in different group on the basis of their chemical, pharmacological properties, and COX selectivity (1). The classification of NSAIDs on the basis of their chemical structure is summarized in the Table-1 (10). NSAIDs can be classified into four groups based on the relative selectivity of COX-1 and COX-2 (Table 2) (11).

NSAIDs- Pharmacodynamics and Pharmacokinetics

NSAIDs showed their therapeutic actions because of their ability to restrict some kind of prostaglandins (PGs) synthesis through the cyclooxygenase enzymes (COX-1 and COX-2) inhibition. Thromboxanes A2 ans prostaglandins (PGs) were synthesized by COX-1 having different physiological functions like controling mucosal barrier in GI-tract, renal homeostasis and platelet aggregation whereas PGs which are produced by COX-2 were related to inflammation, pain and fever. The normal cells use to contain COX-1 however COX-2 is expressed in inflammatory cells (12-14). The desired effect of NSAIDs is due to the COX-2 inhibition while COX-1 play major role in side effects (15). GI tract showed high absorption rate towards mostly know NSAIDs. Some of them showed hepatic first-pass metabolism such as diclofenac reducing its bioavailability while drugs like sulindac and parecoxib are prodrugs and need hepatic metabolism to become their active metabolites (sulindac sulfide and valdecoxib, respectively). The half-life of common NSAIDs drug can be anywhere from 0.25-0.3 hours as in case of aspirin whereas in piroxicam it was found around 45-50 hours (16, 17).

NSAIDs-Mechanism of Action

Vane discovered the NSAIDs mechanism of action however it was fully explained by Simmons after the presence of COX-2. All the NSAIDs inhibit the COX despite being structurally different (5, 18, 19). The fatty acid metabolism give rise to the Prostaglandins (PGs) as end products produced via COX pathway and these PGs play key role in a number of therapeutic areas including inflammation, pain, pyrexia, cancer and neurological diseases (20). Arachidonic acid (AA) is embedded in cell membranes as a phospholipid ester which is precursor of PG synthesis via the COX pathway and lipoxygenase (LOX) enzyme catalysis to lipid mediators collectively known as eicosanoids. Initially AA was converted to prostaglandin G2 (PGG2) which was further reduced to prostaglandin H2 (PGH2) by peroxidase reaction. There are total five biologically active primary PGs: prostaglandin D2 (PGD2), prostaglandin E2 (PGE2), prostaglandin F2□ (PGF2□), prostacyclin (PGI2) and thromboxane A2 (TxA2). They all interac with prostanoid G protein coupled with other receptors (21). Most of the tissues contain COX-1 which perform different functionality like cytoprotection of the gastric mucosa, platelet aggregation, regulation of renal blood flow, while cell differentiation and angiogenesis are also induced (22) however, COX-1 is only found in platelets (23, 24). Another highly inducible enzyme i.e., COX-2 is expressed in brain, spinal cord (25) and kidney (26). Inflammatory sites are greatly under the influence of COX-2 expression which is increased in response to cytokines and also been observed in neoplastic and endothelial cells of many different tumours (27-35). Chandrasekharan has discovered the third isoform of COX (36) named as COX-3 which is a variant of COX-1 and it is different from COX-1 as in COX-3 mRNA contain intron-1. Rat COX-3 has been fully expressed and found to have no COX-activity (37).

NSAIDs- Current guideline and Uses

The World Health Organization (WHO) in the year 1986 release a hierarchy for treating the pain related to cancer with three-step sequential approach based on the severity of pain and in this NSAIDs are categorized as group-1 therapeutics giving to treat the mild pain as well as acute pain like acute musculoskeletal injury (38). NSAIDs were recommend by different professional societies like American Geriatric Society, American College of Rheumatology, and the European League against Rheumatism although but with some vigilance like they should be used in least effective dose and for a short period of time only because upon their administration some common side effects related to gastrointestinal, renal and cardiovascular systems may get arises and should monitored on regular basis (39, 40, 41). Some of the studies showed that the inappropriate use of NSAIDs is a growing concern. A study conducted on 3,050 patients suffering from chronic pain deduced the results that 97% of these subjects took NSAIDs for more than 21 consecutive days (42). The American Geriatric Society recommended that chronic use of NSADIs should be restricted because medicine like aspirin may cause gastrointestinal bleeding. These kind of symptoms become more serious is high risk groups in which patients above 75 years, using corticosteroid or using anticoagulants or antiplatelet agents are included (15, 43).

Table 1. Classification of NAIDS on the basis of their chemical structure

Salicylic acid derivates	Acetylsalicylic Acid (Aspirin), Sulfosalazine
Para-aminophenol derivates	Acetaminophen* (Paracetamol)
Indole and indene acetic acids	Indomethacin, Etodolac, Sulindac
Hetero-aryl acetic acids	Diclofenac, Ketorolac, Tolmetin
Aryl-propionic acids	Ibuprofen, Ketoprofen, Flurbiprofen, Naproxen, Fenoprofen, Oxaprozin, Aceclofenac, Fenclofenac
Anthranilic acids (fenamates	Mefenamic Acid, Meclofenanic Acid
Enolic acids (oxicam	Piroxicam, Tenoxicam, Meloxicam
Alkanones	Nabumetone
Pyrazolidinediones	Phynylbutazone, Oxyphenylbutazone
Diarylheterocycles (selective COX-2 inhibitors	Celecoxib, Rofecoxib, Valdecoxib, Lumiracoxib, Parecoxib, Eterocoxib.

Table 2. Classification of NAIDS on the basis of their COX inhibition activity (1)

Group 1	Poorly selective NSAIDs that fully inhibit both COX-1 and COX-2 (<5-fold COX-2 selectivity)	Ibuprofen, diclofenac, aspirin, piroxicam, naproxen
Group 2	NSAIDs capable of inhibiting both COX-1 and COX-2 with a preferential selectivity toward COX-2 (5 to 50 fold COX-2 selectivity)	Celecoxib, meloxicam, nimesulide, etodolac
Group 3	NSAIDs that strongly inhibit COX-2 but only weakly inhibit COX-1 (>50-fold COX-2 selectivity)	Rofecoxib, NS-398
Group 4	NSAIDs that seem to be only weak inhibitors of both COX-1 and COX-2	Sodium salicylate, nabumetone

CONCLUSIONS

NSAIDs are the oldest drugs which have been successfully administered for treating the pain, fever and inflammation by inhibiting prostaglandin synthesis although they impart some kind of serious health complication also. COXIBs, were than introduced with similar efficacy as NS-NSAIDs but having lesser side effects due to the increased GI tract tolerability however prolonged use of aspirin to prevent cardiovascular diseases even in low dosages may degrade its gastro protective effect because of this negative effect some of COXIBs have been discontinued from market. NSAIDs are the commonly prescribed drugs for comprehensive care of elderly peoples. Although, mechanism of action, current guidelines, adverse drug reaction, and the pleiotropic effects of this drug is also important. However, elderly peoples are very susceptible even for the lower doses of NSAIDs and may develop some side effects like GI, renal, and cardiovascular toxicity. Even though, they are some substantial proof that NSAIDs can be used in dementia prevention, improve muscle performance, improve urinary incontinence, and decrease the risk of some specific cancers although it increase the risk of falls, increase geriatric psychiatric events, and increase the risk of stroke. Thus, these risks and benefits should be balanced carefully in individual patients to optimize overall outcomes, especially in the elderly.

ACKNOWLEDGEMENTS

No financial support is availed during this work.

Conflict of Interest

No conflict of interest.

Author's Contribution

Nancy- Write the manuscript, summarized the data, **Archana**- Cross check the data and help in the language structure, **Sanjeev Kumar Bhatt**- Take note of formatting part in the manuscript

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CITATION OF THIS ARTICLE

Nancy, Archana and Sanjeev Kumar Bhatt. Classification, Action, Pharmacology of Non-steroidal anti- inflammatory drugs (NSAIDs) Agents: A Mini Review.Bull. Env. Pharmacol. Life Sci.,Vol11[2] January 2022: 177-181