INTERNATIONAL JOURNAL OF DRUG DISCOVERY AND HERBAL RESEARCH (IJDDHR)
12(1): Jan .-March.: (2022), 1-4
ISSN: 2231-6078

A review on Anti-Inflammatory Activity

Research Article

Ramakant kabirpanthi[1] , Sapna Avinash Kondalkar[2] , Shailesh Gupta [1]
1.Millennium College of Pharmacy, Bhopal, Madhya Pradesh, India.
2.Regional Ayurveda Research Institute for Drug Development, Gwalior, M. P

Abstract

The non–steroidal anti-inflammatory drugs (NSAIDs) is a drug class that groups together drugs that provide analgesic (pain-killing) and antipyretic (fever-reducing) effects, and, in higher doses, anti-inflammatory effects. The analgesic and anti-inflammatory properties acts by inhibiting two recognized isoenzymes of prostaglandin G/H synthase also known as cycl-oxygenase (COX), which are COX 1 and COX 2.The pharmacodynamic action of these drugs is mostly mediated by inhibition of COX2, while the adverse reactions are largely due to COX1 inhibition.. The NSAID selectively inhibiting COX2 were developed in the 90s to reduce the risk of gastrointestinal toxicity. NSAID use has been found to be associated with an increased risk of heart failure in several randomized clinical trials and observational studies. Nevertheless, there is still limited information on the risk of heart failure associated with the use of individual NSAIDs (both COX 2 inhibitors and traditional NSAIDs) in clinical practice in resource poor communities, and especially on their doseresponse associations. The most prominent members of this group of drugs, are aspirin, ibuprofen, naproxen, that are all available over the counter in most countries. Paracetamol (acetaminophen) is generally not considered an NSAID because it has only little antiinflammatory activity. It treats pain mainly by blocking COX-2 mostly in the central nervous system, but not much in the rest of the body. Most NSAIDs inhibit the activity of (COX-1) and COX2, and thereby the synthesis of prostalglandin and thromboxanes. It is thought that inhibiting COX-2 leads to the anti-inflammatory, analgesic and antipyretic effects and that those NSAIDs also inhibiting COX-1, particularly aspirin, may cause gastrointestinal bleeding and ulcers. This review attempts to give a comprehensive view of NSAIDs pharmacological activities, the drug class, mode of action and usage in a low income economy.

Keywords: non-steroidal anti-inflammatory, drug low income economy, prostaglandin, thromboxane, low income economy.

Introduction:

Non-steroidal anti-inflammatory drugs (NSAIDs) belong to a wide class of therapeutic agents with analgesic and anti-inflammatory properties that inhibit the two recognized isoenzymes of prostaglandin G/H synthase (also known as cyclo-oxygenase (COX)) known as, COX 1 and COX 2.1,2 Since the therapeutic action of these drugs is highly mediated by inhibition of COX 2, and their gastrointestinal adverse reactions are largely due to COX 1 inhibition. The NSAIDs selectively inhibiting COX 2 was developed in the 1990s to reduce the risk of gastrointestinal toxicity in the clinical settings.3 Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely prescribed drugs for the treatment of pain and inflammation in many conditions, including osteoarthritis and rheumatoid arthritis.3,4 The COX-2 selective drugs are the newer drugs that have recently been made available in the drug market, and some examples include nimesulide, nabumatone, meloxicam, etodolac, celecoxib, and rofecoxib.5,6 The last two have become popular amongst clinicians as they are generally considered to be more safe and tolerable, and at least equally efficacious with maximum therapeutic output. There are however many issues that need to be addressed before the COX-2 widespread usage can be recommended in situations where conventional NSAIDs are helpful.

The need for newer NSAIDs has led to the understanding that the inhibition of the COX-1 isoform is responsible for the side effects of the conventional NSAIDs and the COX-2 is responsible for the beneficial effects such as the anti-inflammatory effects and analgesia.8,9 The COX-2 is an inducible isoform and its synthesis is increased at the sites of inflammation. However, there are many concerns that have been discussed regarding these drugs. There is evidence that the COX-2 is already becoming popular drugs in many countries despite of being expensive.10 Some important guidelines have been developed to support clinicians in selecting NSAIDs for usage.

Importance in selecting the right NSAID in a clinical setting

The question arises as to why it is necessary to choose a particular NSAID when all have similar pharmacological profile? The answer is that their safety, tolerability, and efficacy differ in clinical situations. Aspirin has dominated the pharmaceutical market for more than 50 years ever since its synthesis in 1899 and physicians have no other choice but to go for it.11,12 The scenario had only started changing in the early 1950s when other NSAIDs started hitting the drug stores and the question of choosing a particular drug started getting importance. NSAIDs presently are the most widely used drugs in medicine and their annual sales in the world are more than 6billion dollars.13 Presently, more than 100 NSAIDs have been tested clinically and more than 50 are there in the world market.13,14 Nearly 35 million people are taking them on daily basis and FDA has ranked the most frequent cause of adverse drug reactions.15 Unfortunately, they also cause most frequently lethal drug toxicity such as gastrointestinal haemorrhage. Importantly, nonprescription use, that is often ignored, is considered to be seven folds higher than the prescription use.16 The advent of newer drugs in the market makes the question of NSAID choice all the more important as exemplified by the fact that 2.5 million prescriptions were written for celecoxib alone under 3 months of its release.16,17 The decision of using NSAIDs in most therapeutic situation is empirical, but certain principles can help clinicians prescribing them safely and effectively. These principles can be reviewed as follows;

Choosing an NSAID: Choosing an NSAID for its analgesic and antipyretic effect in indications like fever, common cold, dental pain, minor soft tissue injuries, musculo-skeletal pain, and non-specific body aches is not difficult as in most circumstances the

drug is to be used for a short duration only.17–19 Both newer drugs, e.g., celecoxib and rofecoxib have now been approved by FDA for short-term relief of pain and inflammation.

Clinicians need to acquaint themselves with minimal number of drugs: for instance most rheumatologists are of the opinion that clinicians should familiarize themselves with a dozen of NSAIDs and try to get full information about them.7,20 Under most circumstances, this list should not generally exceed 20 drugs so that safe and effective use of the drugs can be achieved.

Choice of NSAID: Choice of NSAID for chronic and disabling inflammatory joint diseases like rheumatoid arthritis and osteoarthritis is governed by age, diagnosis, degree of severity, relative gastrointestinal safety, tolerability, and relative efficacy in the given clinical situation.21 It is a common misconception that all NSAIDs are equally therapeutically efficacious and any one of them could be used for the given indication. However, the use of multiple NSAIDs should be strongly discouraged as an agent with comparatively less GI side effects like ibuprofen and diclofenac should be preferred in place of indomethacin, piroxicam, or naproxan, which are more gastrotoxic.5,22 In situations, e.g., osteoarthritis where inflammation of joints is minimal, analgesics like paracetamol should be preferred over antiinflammatory drugs like ibuprofen. The American Rheumatological Association recommends the use of 1gm of paracetamol every 6 hours for pain relief in osteoarthritis.13,23 In situations where diagnosis is uncertain, the drug should be empirically chosen and given for a week or so and if the response is adequate it should be continued until side effects mandate its withdrawal. Ankylosing spondylitis, for unknown reasons, responds better to a particular NSAID like indomethacin. It is probably related to its stronger inhibition of prostaglandin synthesis.9,12 Under some situations, choice of NSAIDs is very obvious. Stroke prevention, post-myocardial infarction prophylaxis, and patient with atrial fibrillation are therapeutic situations where aspirin is the drug of choice because of its unique antiplatelet property of acetylating and causing irreversible inactivation of cyclooxygenase–1 isoform membrane enzyme fatty acid amide hydrolase (FAAD).17 The effect of drug interaction has been illustrated in Table 1 where for example the class of drugs lead to some particular results.

Drugs	Result
Diuretics	Decrease diuresis
Beta-blockers	Decrease antihypertensive effect
ACE inhibitors	Decrease antihypertensive effect
Anticoagulants	Increase of GI bleeding
Sulfonylurea	Increase hypoglycemic risk
Cyclosporine	Increase nephrotoxicity
Alcohol	Increase of GI bleeding

Mechanism of action

NSAIDs Most NSAIDs act as nonselective inhibitors of the enzyme carboxylase (COX), inhibiting both the cyclooxygenase-1 (COX1) and cyclooxygenase-2 (COX-2) isoenzymes. This inhibition is competitively reversible as opposed to the mechanism of aspirin, which is irreversible in the platelets.1,24 Other NSAIDs inactivate this enzyme reversibly and therefore do not cause sustained antiplatelet effects. Aspirin has also been adequately studied in the chemoprevention of colon cancer.10,25 Mefenamic acid is supposed to relieve the pain of dysmenorrhoea better than other NSAIDs, although GI side effects often limit its use.12

Avoid using multiple NSAIDS and consider ulcer prophylaxis in high-risk groups: Some physicians consider combination of NSAIDs in the treatment of inflammatory joint diseases. There is little evidence to support this practice because therapeutic benefits do not add but side effects do. Moreover there is no evidence that fixed dose combinations of NSAIDs are superior to individual drugs in the long-term management of arthritis. Similarly, use of concomitant gastrotoxic drugs should be avoided, e.g., corticosteroids and NSAIDs.6,26 NSAID use in children: Choice of NSAIDs in children is generally restricted to paracetamol, aspirin, naproxan, and now nimesulide.12,27 Although nimesulide has been shown to be superior to the existing drugs in childhood febrile illnesses like upper respiratory infections, but it is more costly than the conventional NSAIDs. Aspirin is not recommended as a routine analgesic and antipyretic drug in childhood viral illness because of fear of Reyes syndrome.27 However, it enjoys its reputation as an anti-inflammatory agent in the management of rheumatic fever and childhood arthropathies.

Drug interactions

NSAIDs reduce renal blood flow and thereby decrease the efficacy of diuretics, and inhibit the elimination of lithium and methotrexate.32 NSAIDs cause hypocoagulability, which may be serious when combined with other drugs that also decrease blood clotting, such as warfarin. NSAIDs may aggravate hypertension and thereby antagonize the effect of antihypertensive drugs such as the ACEinhibitors.18 NSAIDs may also interfere and reduce efficiency some antidepressants. Most wisely used NSAIDs are known to enhance endocannabinoid signaling by blocking the anandamide-degrading

For example diuretics will result in decreased diuresis and beta blocker can result to decrease antihypertensive effect.

inhibition.10,13 COX catalyzes the formation of prostaglandin and thromboxane and thromboxane from arachidonic acid that is itself derived from the cellular phospholipid bilayer by phospholipase A Prostaglandins act as messenger molecules in the process of inflammation. COX-1 is a constitutively expressed enzyme with a "house-keeping" role in regulating many normal physiological processes. One of these is in the stomach lining, where prostaglandins serve a protective role, preventing the stomach mucosal from being eroded by its own acid. COX-2 is an enzyme facultative expressed in inflammation, and it is inhibition of COX-2 that produces the desirable effects of NSAIDs. The mechanism of action of NSAID is illustrated in Figure 1

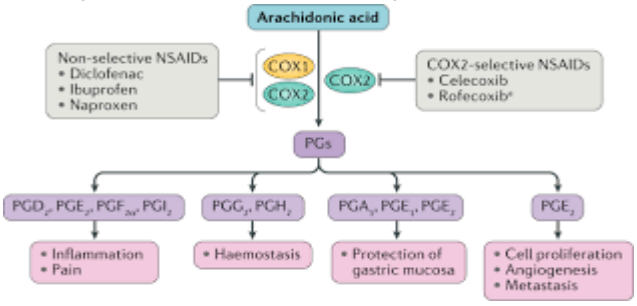
Pharmacokinetics Most nonsteroidal anti-inflammatory drugs are weak acids, with a pKa of 3-5. They are absorbed well from the stomach and intestinal mucosa. They are highly protein-bound in plasma (typically >95%), usually to albumin, so that their volume of distribution typically approximates to plasma

volume.30 Most NSAIDs are metabolized in the liver by

Inflammatory disease	Inflammatory cell infiltrate
Acute respiratory distress syndrome	Neutrophil
Sarcoidosis	T cell, monocyte
Atherosclerosis	T cell, monocyte
Osteoarthritis	Monocyte, neutrophil
Inflammatory bowel disease	Monocyte, neutrophil, T cell, Eosinophil
Bronchial asthma	Eosinophil, T cell, monocyte, basophil
Sarcoidosis	T cell, monocyte
Psoriasis	T cell, neutrophil
Rheumatoid arthritis	Monocyte, neutrophil
Glomerulonephritis	Monocyte, neutrophil

oxidation and conjugation to inactive metabolites that typically are excreted in the urine, though some drugs are partially excreted in bile. Metabolism may be abnormal in certain disease states, and accumulation may occur even with normal dosage. Ibuprofen and diclofenac have short half-lives (2-3 hours).30 Some NSAIDs (typically oxicams) have very long half-lives (e.g. 20-60 hours).The pharmacokinetics profile of NSAIDs is illustrated in Figure 3, and as indicated for oral administration eosinophils, basophils, mast cells, monocytes, and lymphocytes, although not all cell types need be involved in an inflammatory episode. The cells migrate to the area of tissue damage from the systemic circulation and become activated.9,10 Diseases with a chronic inflammatory component Some diseases with their inflammatory cell infiltration has been describe as shown for acute respiratory distress syndrome, sarcoidosis, atherosclerosis, and many others as describe in Table 2. Most of these diseases infiltrate the neutrophils, T-cell monocytes, eosinophils or the basophils.15

Conclusion It is clear that the COX-2 inhibitors are safer, better tolerated, and equally efficacious, but many clinical issues need to be fully resolved. The fact that NSAIDs in developing economy has been shown to be readily available as over the

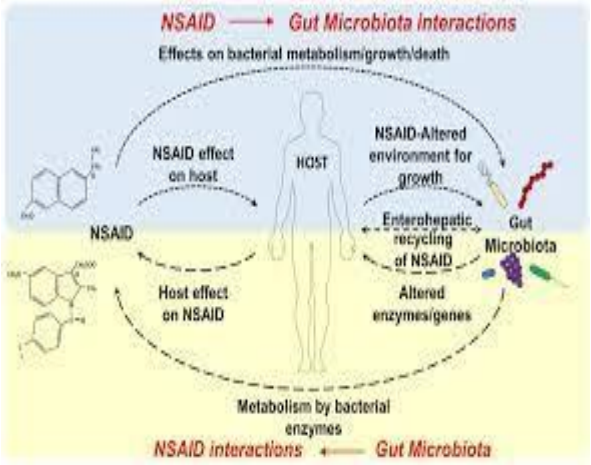


counter medication predisposes the drug to heavy abuses and the side effect as in the case of paracetamol overdose leads to frequent hospitalization of victims or in some cases the effects are not noticed till disaster occurs. The non–steroidal antiinflammatory drugs (NSAIDs) belong to a drug class that groups together drugs that provide analgesic (pain-killing) and antipyretic (fever-reducing) effects. In higher doses these drugs produce antiinflammatory effects. The analgesic and anti-inflammatory properties acts by inhibiting two recognized

of NSAIDs most NSAIDs are weak acids and absorbs well in the stomach and intestinal mucosa. They are also metabolized in the liver by oxidation and conjugation, and 95%. bound to plasma protein, with high bioavailability.

Analgesic, antipyretic, anti-inflammatory and antiplatelet

The clinical features of inflammation have been recognized since ancient times as swelling, redness, pain, and heat. The underlying mechanisms which produce these symptoms are complex, involving many different cells and cell products. A normal inflammatory response is essential to fight infections and is part of the repair mechanism and removal of debris following tissue damage. Inflammation can also cause disease, due to damage of healthy tissue. This may occur if the response is over-vigorous, or persists longer than is necessary. Additionally, some conditions have a previously unrecognized inflammatory component, e.g. atherosclerosis. The inflammatory response occurs in vascularzsed tissues in response to injury. It is part of the innate nonspecific immune response. Inflammatory responses require activation of leukocytes: neutrophils,



isoenzymes of prostaglandin cycl-oxygenase (COX), which are subgroups COX 1 and COX 2.The pharmacodynamic action of these drugs is mostly base on the inhibition of COX2, while the adverse reactions are largely due to COX1 inhibition.. Currently, there are still information gaps on the risk of heart failure associated with the use of individual NSAIDs

Reference:

1. Grosser T, Fries S, FitzGerald GA. Biological basis for the cardiovascular consequences of Cox 2 inhibition: therapeutic challenges and opportunities. J Clin Invest. 2006;116(1):4–15.
2. Hernandez–Dıaz S, Lorenzo V, Rodrıguez GL. Non–steroidal anti– inflammatory drugs and the risk of acute myocardial infarction. Basic Clin Pharmacol Toxicol. 2006;98(3):266–274.
3. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclo–oxygenase. JAMA. 2006;296(13):1633–1644.
4. McGettigan P, Henry D. Cardiovascular risk with non–steroidal anti– inflammatory drugs: systematic review of population–based controlled observational studies. PLoS Med. 2011;8(9):e1001098.

5. Scheiman JM, Hindley CE. Strategies to optimize treatment with NSAIDs in patients at risk for gastrointestinal and cardiovascular adverse events. Clin Ther. 2010;32(4):667–677.
6. Rostom A, Muir K, Dube C, et al. Prevention of NSAID–related upper gastrointestinal toxicity: a meta–analysis of traditional NSAIDs with gastroprotection and cox–2 inhibitors. Drug Healthcare Patient Safety. 2009;1:47–71.
7. Strand V. Are COX–2 inhibitors preferable to non–selective non– steroidal anti–inflammatory drugs in patients with risk of cardiovascular events taking low dose aspirin? Lancet. 2007;370(9605):2138–2151.
8. Garcia Rodriguez L, Tacconelli S, Patrignani P. Role of dose potency in the prediction of risk of myocardial infarction associated with non– steroidal anti–inflammatory drugs in the general population. J Am Coll Cardiol. 2008;52(20):1628–1636.
9. http://whqlibdoc.who.int/hq/2011/a95053_eng.pdf
10. Essential medicines selection. Geneva: World Health Organization; 2012.
11. Fosbol EL, Folke F, Jacobsen S, et al. Cause specific cardiovascular risk associated with nonsteroidal anti–inflammatory drugs among healthy individuals. Circ Cardiovasc Qual Outcomes. 2010;3(4):395–405.
12. Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for the treatment of osteoarthritis and rheumatoid arthritis: a systematic review of randomised controlled trials. BMJ. 2002;325(7365):619–623.
13. Buttgereti F, Burwester R, Simon LS. Gastrointestinal toxic side effects of non–steroidal anti–inflammatory drugs and cyclooxygenase inhibition. Am J Med. 2001;110(3A):13S–19S.
14. Walton A. Renal aspects of treatment with conventional nonsteroidal anti–inflammatory drugs versus cyclooxygenase–2–specific inhibitors. Am J Med. 2001;110(3A):33S–42S
15. Emery P. Cyclooxygensase–2:A major therapeutic advance? Am J Med. 2001;110(1A):42S–45S.
16. Schnitzer TJ. Cycloxygense–2– specific–inhibitors: Are they safe? Am J Med. 2001;110(1A):46S–49S.
17. Buer JK. Origins and impact of the term 'NSAID. Inflammopharmacology. 2014;22(5):263–267.
18. Warden SJ. Prophylactic Use of NSAIDs by Athletes: A Risk/Benefit Assessment. Phys Sportsmed. 2010;38(1):132–138.
19. Hinz B, Cheremina O, Brune K. Acetaminophen (paracetamol) is a selective cyclooxygenase–2 inhibitor in man. FASEB J. 2008;22(2):383– 390.
20. Pattanittum P, Turner T, Green S, et al. Non–steroidal anti–inflammatory drugs (NSAIDs) for treating lateral elbow pain in adults. Cochrane Database Syst Rev. 2013;31(5):CD003686.
21. Lim BX, Lim CH, Lim DK, et al. Prophylactic non–steroidal anti– inflammatory drugs for the prevention of macular oedema after cataract surgery. Cochrane Database Syst Rev. 2016;11:CD006683.
22. Danelich IM, Wright SS, Lose JM, et al. Safety of nonsteroidal anti inflammatory drugs in patients with cardiovascular disease". Pharmacotherapy. 2015;35(5):520–535.
23. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. New England Journal of Medicine. 2000;343(21):1520–1528.
24. Shiri R, Koskimäki J, Häkkinen J, et al. Effect of Nonsteroidal Anti– Inflammatory Drug Use on the Incidence of Erectile Dysfunction. Journal of Urology. 2006;175(5):1812–1816.
25. Gleason JM, Slezak JM, Jung H, et al. Regular Nonsteroidal Anti–Inflammatory Drug Use and Erectile Dysfunction. J Urol. 2011;185(4):1388–1393.
26. Higuchi K, Umegaki E, Watanabe T, et al. Present status and strategy of NSAIDs–induced small bowel injury. Journal of Gastroenterology. 2009;44(9):879–888.
27. Nakhai–Pour HR, Broy P, Sheehy O, et al. Use of non aspirin nonsteroidal anti–inflammatory drugs during pregnancy and the risk of spontaneous abortion. CMAJ. 2011;183(15):1713–1720.
28. Kowalski ML, Makowska JS. Seven steps to the diagnosis of NSAIDs hypersensitivity: how to apply a new classification in real practice? Allergy Asthma Immunol Res. 2015;7(4):312–320.
29. Auriel E, Regev K, Korczyn AD. Nonsteroidal anti–inflammatory drugs exposure and the central nervous system. Handb Clin Neurol. 2014;119:577–584.
30. Woessner KM, Castells M. NSAID single–drug–induced reactions". Immunol Allergy Clin North Am. 2013;33(2):237–249.
31. Rainsford KD. Ibuprofen: pharmacology, efficacy and safety". Inflammopharmacology. 2009;17(6):275–342.
32. Fung M, Thornton A, Mybeck K, et al. Evaluation of the Characteristics of Safety Withdrawal of Prescription Drugs from Worldwide Pharmaceutical Markets–1960 to 1999. Therapeutic Innovation & Regulatory Science. 2001;35(1):293–317.
33. Viljoen A, Mncwangi N, Vermaak I. Anti–inflammatory iridoids of botanical origin. Curr Med Chem. 2012;19(14):2104–2127.