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NON-STEROIDAL ANTI-INFLAMMATORY DRUGS: A REVIEW ARTICLE

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ABSTRACT

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) in thousands of years when man used natural sources of these agents in a lot of pain and inflammatory conditions. In the modern day discovery and use of NSAIDs was set with the discovery of "aspirin". Today in addition to aspirin, a host of other NSAIDs of varying potency and efficacy is employed in the management of pain and inflammatory conditions. The nonsteroidal anti-inflammatory drugs have Analgesic, antipyretic, and anti-inflammatory actions and it gives a better understanding of molecular mechanisms of interaction of many nonsteroidal anti-inflammatory drugs of agents (NSAIDs) such as aspirin, ibuprofen, naproxen, nimesulide, ketoprofen oxican and several agents, This chapter looks with key interest in the existing and evolving role of NSAIDs in therapeutics with emphasis on the current insights into their classification, mechanisms of action, newly research drugs of NSAIDs by FDA approval and side effects and associated with its uses in pain and inflammation, adverse effects, pharmacokinetics..

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are form of heterogeneous group of organic acids that have analgesic, antipyretic, and anti-inflammatory actions. Nonsteroidal anti-inflammatory drugs are medications that relieve or reduce pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) also come under the wider definition of Non opioid analgesics. This mean which posses antipyretic or anti-inflammatory action and they are separate type of painkiller from opioid drugs. (such as morphine) that are typically used for more several types of pain. All drugs grouped in this class have analgesic, antipyretic and anti-inflammatory actions in different measures. In contrast to morphine they do not produce physical dependence have no abuse liability and are weaker analgesics (except for inflammatory pain). They are also called non narcotic, non opioid or aspirin-like analgesics. They act primarily on peripheral pain mechanisms, but also in the commonly employed and many are over the counter drugs. Nonsteroidal anti-inflammatory drugs are a wide group of Cyclo-oxygenase (COX) inhibitors also called as aspirin like drugs due to their similar therapeutic activity. They are chemically heterogeneous group of compounds, often chemically unrelated, and can be classified in several groups.

The COX enzyme exist in at least two forms a primary constitutive isoforms COX-1 an inducible forms COX-2. Most NSAIDs inhibits both COX-1 and COX-2 with little selectivity and have serious side effects such as stomach irritation, ulcer, and renal toxicity which are mainly related to the inhibitory activity of COX-1. Cyclo-oxygenase an enzyme that catalyzes the conversion of arachidonic acid to prostaglandins and that has two isoforms of which one is involved in the creation of prostaglandins which produce inflammation and pain. NSAIDs are primarily used in the treatment of inflammatory arthropathies, however their use has also been extended to many non-rheumatologic problems (for example dysmenorrheal pain of different origin, neoplastic fever, migraine thromboembolic disease and patent ductus arteriosus, they are also used for tocolysis and in some neoplastic disease. Several clinical, epidemiological and animal studies have suggested that NSAIDs can reduce the occurrence or progression of colorectal cancer polyps and perhaps other gastrointestinal tumors. Reports and epidemiological studies have shown that NSAIDs can protect the risk of Alzheimer's disease. NSAIDs are used locally in the eye to prevent and treat postoperative cystoids macular edema to control postoperative ocular inflammation and pain for example

after radial keratotomy or photorefractive keratectomy and for non-surgically induced inflammatory disorders such as allergic conjunctivitis.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most common pharmacological treatment for rheumatic disease. Although highly effective in the relief of pain and inflammation, the use of NSAIDs is restricted by the high incidence of associated side effects, particularly in the gastrointestinal (GI) tract and kidney. The economic burden of treatment with NSAIDs is considerable, both in relation to direct costs of the treatment of rheumatic disease and directed and indirect costs of the treatment of NSAID-associated side effects. The increase in the elderly population, the most common sufferers of rheumatic disease, will aggravate this burden in future years.

As with any therapeutic area, it is hoped that a greater understanding of the mechanism of action of NSAIDs will help in the development of improved agents. Exciting findings in pharmacological research are now producing one of the few real advances in the rheumatology field seen in recent years. We have known for 25 years that NSAIDs inhibit prostaglandin biosyntheses, via inhibition of the Cyclo-oxygenase (COX) enzyme, and that this explains both the anti-inflammatory and side effects of this class of drug. It has only recently been discovered that there are two forms of the COX enzyme. The constitutive form, COX-1, performs a “housekeeping” function and is responsible for physiological prostaglandins production, particularly in the gastric mucosa and kidney. It is now believed that it is inhibition of this isoforms which produces the characteristics side effects of NSAIDs. The other isoforms, COX-2, is induced by inflammatory mediators and has a path physiological role in inflammation. Inhibition of this isoforms is responsible for the therapeutic effects of NSAIDs.

This knowledge has led to the suggestion that NSAIDs which selectively inhibit COX-2 relative to COX-1 will retain the anti-inflammatory action of their class, whilst minimizing the harmful side effects. Pharmacological researchers have shown that there are large differences between established NSAIDs with respect to their relative potencies against COX-1 and COX-2. How does this relate to the clinical situation? Comparison of data from these pharmacological studies and epidemiological studies supports the view that NSAIDs with a higher activity against COX-2 than COX-1 have improved GI safety profiles. Such results have stimulated the research-based pharmaceutical industry to see selective COX-2 inhibition as the way forward in NSAIDs development and several non-steroidal COX-2

inhibitors are currently under research. Improved safety profiles will allow more sustained and widespread use of these agents, but the challenge to the practising physician will be in developing their most appropriate use, alone or in conjunction with other rheumatic therapies. This symposium brings together epidemiology, pharmacology, and clinical practice in a multidisciplinary, approach to NSAID-related adverse events and the role of COX. Firstly, an epidemiological view from the ARAMIS databanks (covering 17000 arthritis patients) confirms that there is significant morbidity and mortality associated with arthritis. There are clear difference between the toxicity of NSAIDs and that of disease modifying drugs. The pharmacology and mechanism of action of NSAIDs is considered, with special reference to the effects of NSAIDs on COX-1 and COX-2. This work highlights the availability of numerous test systems for the measurement of COX selectivity and stresses the need to obtain a consistent overall picture from several data sources before clinically meaningful conclusions can be drawn. When this is achieved, there is a clear link between COX-2 selectivity and improved GI safety profile. Also discussed are the potential benefits of COX-2 inhibitors to arthritis patients and new ways in which these agents can be used in the clinic. Finally, clinical data are presented on meloxicam, a new non-steroidal COX-2 inhibitor.

NSAIDs have following group of drugs

1. Analgesic
2. Antipyretic
3. Anti-inflammatory

1) Analgesic effects-

- a) The analgesic effects of NSAIDs is thought to be related to the peripheral inhibition of prostaglandins production and may also be due to the inhibition of pain stimuli at a subcortical site.
- b) NSAIDs prevent the potentiating action of prostaglandins on endogenous mediators of peripheral nerve stimulation (eg. Bradykinin).

2) Antipyretics-

The antipyretic effect of NSAIDs is believed to be related to

a) Inhibition of production of prostaglandins induced by interleukin-1 (IL-1) and interleukin-6 (IL-6) in the hypothalamus.

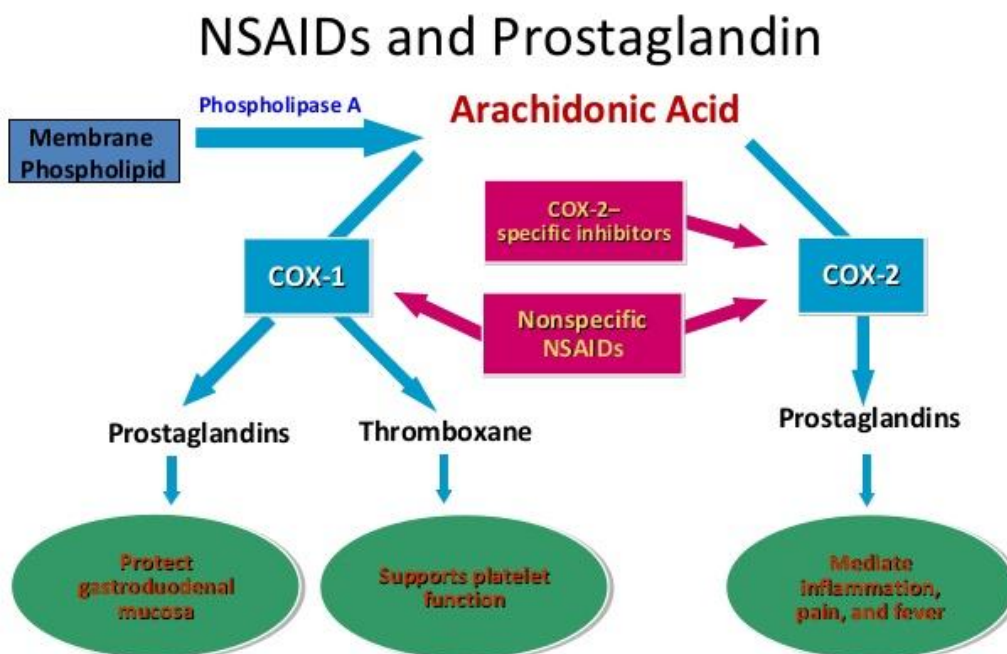
b) The resetting of the thermoregulatory system leading to vasodilation and increase heat loss.

3) Anti-inflammatory effects-

a) Due to inhibition of the enzymes that produce prostaglandin H synthase (cyclooxygenase, or COX), which converts arachidonic acid to prostaglandins and to TXA₂ and prostacyclin

b) Aspirin irreversibly inactivates COX-1 and COX-2 by acetylation of a specific serine residue.

c) This distinguishes it from other NSAIDs which reversibly inhibit COX-1 and COX-2.



Mechanism of action NSAIDs

The inhibition of Cyclo-oxygenase enzyme as the main mechanism of NSAID's analgesic, antipyretic and anti-inflammatory properties. Since the characterization of this mechanism by Vane for aspirin, and other drugs in this class have proven consistent this mechanism. Aspirin and some NSAIDs blocked prostaglandin(PG) generation. This is now considered to be the major mechanism of action of NSAIDs. Prostaglandins, prostacyclin(PGI₂) and thromboxane A₂ (TXA₂) are produced from arachidonic acid by the enzyme Cyclo-oxygenase which

exists in a constitutive (COX-1) and an inducible (COX-2) isoforms, the former serves physiological 'housekeeping' functions, while the latter, normally present in minute quantities, as induced by cytokines and other signal molecules at the site of inflammation generation of PGs locally which mediate many of the inflammatory changes. However, COX-2 is constitutively present at some sites in brain and in juxtaglomerular cells may serve physiological role at these sites. Most NSAIDs inhibit COX-1 and COX-2 non selectively, but now some selective COX-2 inhibitors have been produced. Features of nonselective COX-1/COX-2 inhibitors traditional NSAIDs and selective COX-2 inhibitors are compared Aspirin inhibits COX irreversibly by acetylating one of its serine residues; return of COX activity depends on synthesis of fresh enzyme. Other NSAIDs are competitive and reversible inhibitors of COX, return of activity depends on their dissociation from the enzyme which in turns governed by the pharmacokinetic characteristics of the compound.

Analgesia- PGs induce hyper analgesia affecting the transducing properties of free nerve endings stimuli that normally do not elicit pain are able to do so. NSAIDs do not affect the tenderness induced by direct application of PGs, but block the pain densitizing mechanism induced by Bradykinin, TNF, interleukins (ILs) and other analgesic substances. They are, therefore, more effective against inflammation associated pain.

Antipyretics- NSAIDs reduce body temperature in fever, but do not cause hypothermia in normothermic individuals. Fever during infection is produced through the generation of pyrogens including, ILs, TNF, interferon's which induce PGE₂ injected into the hypothalamus. The isoforms present at this site appears to be COX-2 (possibly COX-3 also). However, fever can occur through non-PG mediated mechanisms as well.

Anti-inflammatory – The most important mechanism of anti-inflammatory action of NSAIDs is considered to be inhibition of PG synthesis at the site of injury. The anti-inflammatory potency of different compound roughly corresponds with their potency to inhibit COX. However, nimesulide is a potent anti-inflammatory but relatively weak COX inhibitor. PGs are only one of the mediators of inflammation; inhibition of COX does not depress the production of other mediators like LTs, PAF, cytokines, etc. Inflammation is the result of concerted participation of a large number of vasoactive, chemo tactic and proliferative factors at different stages, and there are many targets for anti-inflammatory action.

The Cyclo-oxygenase (COX) enzyme also known as prostaglandin end peroxide H synthase (PGHS) exists in two isoforms PGHS-1 or COX-1 and PGHS-2 or COX-2. There is a

significant structural distinction between the two, with only 60% homology. Although encoded by different genes, both isoforms are membrane-bound glycoprotein's that catalyze the formation of prostanoid from arachidonic acid.

COX-1- is expressed constitutively in most mammalian cells and tissues such as seminal vesicle, platelets, and endothelium. In quiescent condition, it performs ongoing regulatory function referred to as "housekeeping duties". Prostaglandins produced by COX-1 activity perform functions such as gastro and renal protection, macrophage differentiation, platelet aggregation, and mucus production. In inflammatory conditions, molecular studies have demonstrated that COX-1 mRNA and protein expression do not change, confirming their limited role in the inflammatory process. COX-1, however, remains both experimentally and clinically relevant due to the adverse effects triggered by the nonselective inhibition of cyclooxygenase enzymes by some NSAIDs.

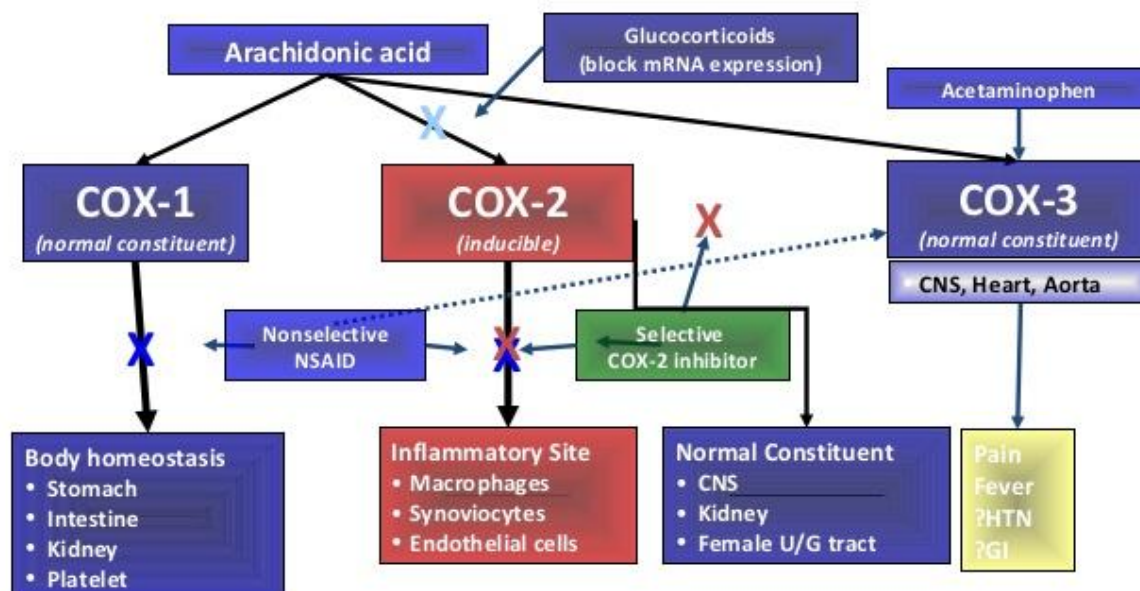
COX-2- is an inducible enzyme called upon by tissue injury and other stimuli such as lipopolysaccharide (LPS), interleukin-1, and tumor necrosis factor alpha (TNF) .it is active at injury sites and in a variety of tissues such as the vascular endothelium, and rheumatoid synovial endothelial cells mediating inflammatory, pain, fever, and carcinogenic responses. A manifold increase in COX-2 levels occurs in inflammatory process triggering an increased synthesis of pro-inflammatory prostaglandins. Initially thought of as exclusively inducible in nature, studies have shown COX-2 has some constitutive or regulatory roles. Housekeeping duties in reproduction, renal physiology, bone resorption, and neurotransmission have been documented.

The arachidonic acid pathway is central to inflammatory responses and consequently the mechanism of action of NSAIDs. Prostanoid, the end product of this pathway, performs a wide range of physiological functions.

CLASSIFICATION OF NSAIDS-

1. NSAIDs (good anti-inflammatory action)
2. NSAIDs (poor anti-inflammatory action)

Proposed Mechanism: COX-1, COX-2, & COX-3



1) NSAIDs (good anti-inflammatory action)

A) Nonselective COX inhibitors

- 1) Salicylates: Aspirin, diflunisal.
- 2) Propionic acid derivatives: Ibuprofen, Naproxen, Keroprofen, Flurbiprofen.
- 3) Anthranilic acid derivatives: Mephenamic acid, meclofenamic acid.
- 4) Aryl-acetic acid derivatives: Diclofenac, Aceclofenac.
- 5) Oxicam derivatives: Piroxicam, Tenoxicam.
- 6) Pyrrolo-pyrrole derivatives: Ketorolac.
- 7) Indole derivatives: Indomethacin.
- 8) Pyrazolone derivatives: Phenylbutazon, oxyphenbutazonem, azapropazone.

B) Preferential COX-2 inhibitors

Nimesulide, Meloxicam, Nabumetone, Etodolac.

C) Selective COX-2 inhibitors

Celecoxib, Etoricoxib, Parecoxib, Rofecoxib, Valdecoxib.

2) NSAIDs (poor anti-inflammatory action)

A) Para-aminophenol derivatives (possible COX-3 inhibitor):

Paracetamol (Acetaminophen)

B) Pyrazoline derivatives:

Metamizol, Propiphenazone.

C) Benzoxazocine derivative:

Nefopam

Medical uses:

NSAIDs are usually used for the treatment of acute or chronic conditions where pain and inflammation are present.

NSAIDs are generally used for the symptomatic relief of the following conditions

- Osteoarthritis
- Rheumatoid arthritis
- Mild-to-moderate pain due to inflammation and tissue injury
- Low back pain
- Inflammatory arthropathies (eg. Ankylosing, spondylitis, psoriatic arthritis, reactive arthritis)
- Tennis elbow
- Headache
- Migraine
- Acute gout
- Dysmenorrhoea (menstrual pain)
- Metastatic bone pain
- Postoperative pain
- Muscle stiffness and pain due to parkinson's disease
- Pyrexia (fever)
- Ileus
- Renal colic
- Macular edema
- Traumatic injury

Aspirin, the only NSAIDs able to irreversibly inhibit COX-1, is also indicated for antithrombosis through inhibition of platelet aggregation. This is useful for the management of arterial thrombosis and prevention of adverse cardiovascular events like heart attacks. Aspirin inhibits platelet aggregation by inhibiting the action of thromboxane A₂.

In a more specific application, the reduction in prostaglandins is used to close a patent ductus arteriosus in neonates if it has not done so physiologically after 24 hours.

NSAIDs are useful in the management of post-operative dental pain following invasive dental procedures such as dental extraction. When not contra-indicated they are favoured over the use of paracetamol alone due to the anti-inflammatory effect they provide. When used in combination with paracetamol the analgesic effect has been proven to be improved. There is weak evidence suggesting that taking pre-operative analgesic can reduce the length of post operative pain associated with placing orthodontic spacers under local anaesthetic.

Pharmacokinetics:

Most non steroidal anti-inflammatory drugs are weak acids, with 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. Most NSAIDs are metabolized in the liver by 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). Some NSAIDs (typically oxicams) have very long half-lives (eg. 20-60 hours)

Contraindications:

NSAIDs may be used with caution by people with the following conditions.

1. •Irritable bowel syndrome
2. •Persons who are over age 50, and who have a family history of GI(gastrointestinal) problems.
3. •Persons who have had past GI problem from NSAIDs use.
4. NSAIDs should usually be avoided by people with the following conditions.
5. •Peptic ulcer or stomach bleeding
6. •Uncontrolled hypertension

7. •Kidney disease
8. •People that suffer with inflammatory bowel disease (crohn's disease or ulcerative colitis)
9. •Past transient ischemic attack (excluding aspirin)
10. Past stroke (excluding aspirin)
11. Past myocardial infraction (excluding aspirin)
12. Coronary artery disease (excluding aspirin)
13. Undergoing coronary artery bypass surgery
14. Congestive heart failure (excluding low-dose aspirin)
15. In third trimester of pregnancy
16. Persons who have undergone gastric bypass surgery
17. Persons who have a history of allergic or allergic-type NSAID hypersensitivity reactions, eg. Aspirin-induced asthma

Most common side/adverse effects of NSAIDs:

1. The most common side effects of non-steroidal anti-inflammatory drugs include: stomach problems, including pain, constipation, diarrhea, gas, nausea, and stomach ulcers
2. Kidney problems
3. Anemia
4. Dizziness
5. Swelling in the legs
6. Abnormal liver tests (blood tests)
7. Headaches
8. Easy bruising
9. Ringing in the ears
10. Rash

The widespread use of NSAIDs has meant that the adverse effects of these drugs have become increasingly common. Use of NSAIDs increases risk of a range of gastrointestinal (GI) problems, kidney disease and adverse cardiovascular events. As commonly used for post-operative pain, there is evidence of increased risk of kidney complications. Their use

following gastrointestinal surgery remains controversial, given mixed evidence of increased risk of leakage from any bowel anastomosis created.

An estimated 10-20% of NSAID patients experience dyspepsia. In the high doses of prescription NSAIDs were associated with serious upper gastrointestinal adverse events, including bleeding have declined.

NSAIDs, like all drugs, may interact with other medication. For example, concurrent use of NSAIDs and quinolones may increase the risk of quinolones' adverse central nervous system effects, including seizure.

There is an argument over the benefits and risks of NSAIDs for treating chronic musculoskeletal pain. Each drug has a benefit-risk profile and balancing the risk of no treatment with the competing potential risks of various therapies is the clinician's responsibility.

1. Combinational risk
2. Cardiovascular
3. Possible erectile dysfunction risk
4. Gastrointestinal
5. Inflammatory bowel disease
6. Renal
7. Photosensitivity
8. During pregnancy
9. Allergy like hypersensitivity reactions

NEW DRUGS OF NSAIDs-

1. Etodolac (Ultradol)
2. Nabumetone (Relafen)
3. Piroxicam (feldene)
4. Misoprostol (cytotec)
5. Diclofenac (voltaren)

ETODOLAC:

Etodolac is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic properties. Its therapeutic effects are due to its ability to inhibit prostaglandin synthesis. It is indicated for relief of signs and symptoms of rheumatoid arthritis and osteoarthritis.

Pharmacodynamic-

Etodolac is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic activity. Like other NSAIDs, Etodolac is an inhibitor of prostaglandin synthesis at the cyclooxygenase level. The analgesic effect of full doses of Etodolac is longer than that of aspirin, lasting up to 8 hours.

Mechanism of action of Etodolac –

Etodolac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities. The mechanism of action like that of other NSAIDs, is not completely understood, but may be related to prostaglandin synthetase inhibition

Uses of Etodolac-

Etodolac is used to relieve pain from various conditions. It also reduces pain, swelling, and joint stiffness from arthritis. This medication is known as a nonsteroidal anti-inflammatory drug (NSAID). It works by blocking your body's production of certain natural substances that cause inflammation.

If you are treating a chronic condition such as arthritis, ask your doctor about non-drug treatments and /of using other medications to treat your pain. See also warning section.

Take this medication by mouth as directed by your doctor, usually 2 or 3 times a day with a full glass of water (8 ounces/240 milliliters). Do not lie down for at least 10 minutes after taking this drug. To prevent stomach upset, take this medication with food, milk, or an antacid.

The dosage is based on your medical condition and response to treatment. To reduce your risk of stomach bleeding and other side effects, take this medication at the lowest effective dose for the shortest possible time. Do not increase your dose or take it more often than directed. For ongoing conditions such as arthritis, continue taking this medication as directed by your doctor.

Side effects –

Upset stomach, nausea, diarrhea, drowsiness, or dizziness may occur. If any of these effects persist or worsen, tell your doctor or pharmacist promptly.

This medication may raise your blood pressure.

Serious side effects, including : easy bruising/bleeding, difficult /painful swallowing, hearing changes such as ringing in the ears, mental /mood changes, signs of kidney problems such as change in the amount of urine, unexplained stiff neck, vision changes, symptoms of heart failure such as swelling ankles/feet, unusual tiredness, unusual /sudden weight gain. This drug may rarely cause serious liver disease. And serious allergic reaction of this drugs is rare.

Precautions:

Before taking Etodolac, tell your doctor or pharmacist if you are allergic to it, or to aspirin or other NSAIDs (such as ibuprofen, naproxen, Celecoxib); or if you have any other allergies.

Interactions:

Drug interactions may change how your medications work or increase your risk for serious side effects. This document does not contain all possible drug interactions. Keep a list of all the products you use. Products that may interact with this drug include: aliskiren, ACE inhibitors (such as captopril, lisinopril), angiotensin2 receptor blockers (such as lasartan, valsartan), cidofovir, corticosteroids (suchas prednisone), lithium water pills diuretic such as furosemide.

Overdose: If someone has overdosed and has serious symptoms such as passing out or trouble breathing, call 911. Otherwise, call a poison control center right away. Symptoms of overdose may include: severe stomach pain, trouble breathing, extreme drowsiness.

PIROXICAM:

A cyclooxygenase inhibiting, non-steroidal anti-inflammatory agent (NSAID) that is well established in rheumatoid arthritis and osteoarthritis and used for musculoskeletal disorders, dysmenorrhea, and postoperative pain. Its long half-life enables it to be administered once daily.

Indication –For treatment of osteoarthritis and rheumatoid arthritis.

Pharmacodynamics-

Piroxicam is in a class of drugs called nonsteroidal anti-inflammatorydrugs (NSAIDs). Piroxicam works by reducing hormones that cause inflammation and pain in the body. Piroxicam is used to reduce the pain, inflammation, and stiffness caused by rheumatoid arthritis and osteoarthritis.

Mechanism of action –

The anti-inflammatory effect of Piroxicam may result from the reversible inhibition of cyclooxygenase, causing the peripheral inhibitions of prostaglandin synthesis. The prostaglandins are produced by an enzyme called cox-1. Piroxicam blocks the cox-1 enzyme, resulting into the disruption of production of prostaglandins. Piroxicam also inhibits the migration of leukocytes into sites of inflammatory and prevents the formation of thromboxane A₂, an aggregating agent, by the platelets.

Uses of Piroxicam-

Piroxicam is used to reduce pain, swelling, and joint stiffness from arthritis. Reducing these symptoms helps you do more of your normal daily activities. This medication is known as a nonsteroidal anti-inflammatory drug (NSAID). It works by blocking your body's production of certain natural substances that cause inflammation.

If you are treating a chronic condition such as arthritis, ask your doctor about non-drug treatments and / or using other medications to treat your pain. See also warning section.

Side effects of Piroxicam-

1. Indigestion
2. Upper respiratory infection
3. Headache
4. Diarrhea
5. Nausea
6. Abdominal pain
7. Swelling
8. Anemia
9. Dizziness
10. Fever
11. Chest pain
12. Heart failure
13. GI infection
14. Hepatitis

Precaution –

Cardiovascular risk- risk may increase with duration of use, patients with risk factors for or existing cardiovascular disease may be at greater risk.

Gastrointestinal risk-GI adverse events may occurs at any time during use and without warning symptoms

Interaction –

Drug interactions may change how your medications work or increase risk for serious side effects.

Overdose –

If someone has overdosed and has serious symptoms such as passing out or trouble breathing, symptoms of overdose may include severe stomach pain, trouble breathing, extreme drowsiness.

CONCLUSION:

The therapeutic importance or NSAIDs in the management of acute and chronic pain and inflammation cannot be overemphasized. Also with the emergence of their therapeutic benefits, it is worth chronicling its pharmacological profile, specifically their established and expected mechanistic pathways of eliciting their activity. With promising outcomes in the experimental studies with improved gastrointestinal effects associated with modified NSAIDs and potential activity of NSAIDs, this chapter will henceforth given an insight into what is known and what could be possibly done in advancing the therapeutic potentials of NSAIDs beyond the management of pain and inflammation as we know.

REFERENCE:

1. Dr. Madan kaushik a book of pharmacology-II published by PV. Publication page no. 219.
2. <https://www.sciencedirect.com/NSAIDs>.
3. <https://www.slideshare.net/abdulwaheed45/NSAIDs>
4. <https://www.tandfonline.com> NSAIDs
5. <https://www.intchopen.commechacnismofactionofNSAIDs>
6. K.D.Tripathi essential book of pharmacology 6th edition page no.184-201
7. <https://www.drugbank.ca/drugsofetodolac/piroxicam>
8. <https://www.webmd.com/etodolac/piroxicam>
9. <https://www.wikipedia.orgforNSAIDS>