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A Review of Non-Steroidal Anti-Inflammatory Drugs

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Abstract

A number of non steroidal anti-inflammatory drugs (NSAIDs) are present in market and many are adding in the list after certain time. These are worldwide used for their anti-inflammatory and analgesic property and effect. Out of that some are established long back (traditional) and some are non selective. The main role of NSAIDs is in pain relief or decrease to some extent and it is due to Cyclooxygenase-2 (COX) pathway. This class of drugs came under critical observation due to their various side effects such as gastrointestinal, renal and cardiovascular. Still traditional NSAIDs are widely used. This review will give information on their efficacy and their side effects.

Keywords*: NSAIDs, Analgesic, pain, cardiovascular, Gastrointestinal, renal effect.*

1. Introduction

Generally, NSAIDs are used primarily to treat inflammation, mild to moderate pain[1], and fever. There are three general classes of drugs commonly used in the treatment of rheumatic arthritis: non-steroidal anti-inflammatory agent (NSAIs) such as celecoxib[2], diclofenac sodium, and ibuprofen etc., Glucocorticoids[3] such as betamethasone, prednisone etc. and disease modifying anti-rheumatic drugs[4] (DMARs) such as hydroxychloroquine, leflunomide, methotrexate, sulfasalazine etc. Specific uses include the treatment of headache, arthritis, rheumatism, spondylitis, muscle strain, sprains, tendonitis and menstrual cramps etc. Some of the commonly used NSAIDs in the market are aspirin, celecoxib, diclofenac, ibuprofen, diflunisal, indomethacin, etodolac, piroxicam, Naproxen, fenoprofen, ketoprofen etc. NSAIDs also are included in many cold and allergy preparations.

Common side effects of NSAIDs are Nausea, Vomiting, fatigue, pruritus, dizziness, rashes, headache, diarrhoea, decreased appetite, constipation and drowsiness. The side effects vary among NSAIDs. Apart from these side effects, kidney failure, liver failure, ulcers and prolonged bleeding after surgery also there. Asthamatic patient experiencing serious allergic reactions with NSAIDs which may leads to shortness of breath. Consumers and health professionals are recommended that the Therapeutic good administration (TGA) has completed a recent safety review of the known association between the use of non-steroidal anti-inflammatory drugs (NSAIDs) and the increased risk of miscarriage. Also in 2007, American Heart association also warns bout the use of NSAIDs using by cardiac patients. By using aspirin (also an NSAID) is used to inhibit the clotting of blood and prevent strokes and heart attacks in individuals at high risk for strokes and heart attacks but suffers with ringing in ears, seizure, hallucinations, fever etc. As per the European Medical agencies Diclofenac identified as high risk NSAIDs as its effect on heart[5]. The degree of risk varies from drug to drug and dose dependent. As compare to Diclofenac, Naproxen and lower doses of ibuprofen shows lower cardiac risk. Indomethacin also shows cardiovascular risk profile similar to Diclofenac and shows gastrointestinal and CNS side effects.[6] Ketorolac is only used for short-term treatment of moderately severe acute pain that otherwise would be treated with narcotics.

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2. Cardiovascular effects:

After introduction of NSAIDs in early 70's some of the side effects are observed. Out of that one of the major is cardiovascular abnormalities noated along with hypertension, congestive heart failure etc. Among the non selective NSAIDs ibuprofen, indomethacin increases the blood pressure in patients with hypertension.[7]After Meta analysis, it gives evidences that NSAIDs significantly increases blood pressure. In elder patients, it leads to chronic illness, including musculoskeletal disorders and hypertension. Such an effect may be associated with increase in morbidity and mortality associated with community. So caution to be taken while taking short term NSAIDs.[8]This high blood pressure changes the renal prostaglandin levels. Further, the normal endothelial reactivity becomes abnormal with an increase in the basal arterial peripheral resistance. NSAIDs and COX-2 selective inhibitors shows increase in blood pressure specifically patients having controlled hypertension.[9]Clinicians already warn long back that uses of NSAIDs increases the risk of congestive heart failure. Also increasing death rate was associated with use of NSAIDs.[10]When NSAIDs are frequently used the balance between risk and benefits to be taken in consideration in heart patients.

The enzymes that produce prostaglandins are called cyclooxygenase (COX). There are two types of COX enzymes namely COX-1 and COX-2 and are found in the blood vessels, stomach and kidneys. Both the enzymes that form prostaglandin, but the normal action of COX-1 include the physiological production and regulation of the prostanoids.

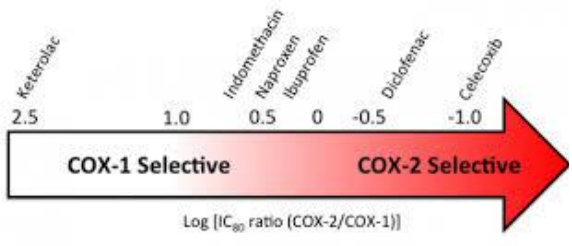

Fig.1 Relative COX-1 and COX-2 selectivity for commonly used non aspirin NSAIDs. Celecoxib is the only COX-2 selective NSAID on the market in the U.S. (Source Pharmwiki)

COX-1 is responsible for the synthesis of Prostaglandins and thromboxane in many cells and are important in gastric protection. NSAID-induced COX-1 inhibition is associated with gastrointestinal toxicity while drugs that selectively inhibit COX-2 have less GI side effects, but higher incidence of cardiovascular toxicity by altering the normal balance in production of prostacyclin vs thromboxane by different cell types in the cardiovascular system. This accounts increased in stroke and death that has been associated with the use of NSAIDs & selective COX-2 inhibitors. Drugs that block either COX-1 or COX-2 can also interfere with the production of prostaglandins that play an important role in maintaining renal blood flow in patients with compromised renal function. COX-2 is detected in endothelial cells. Celecoxib is a Cox-2 selective drug.

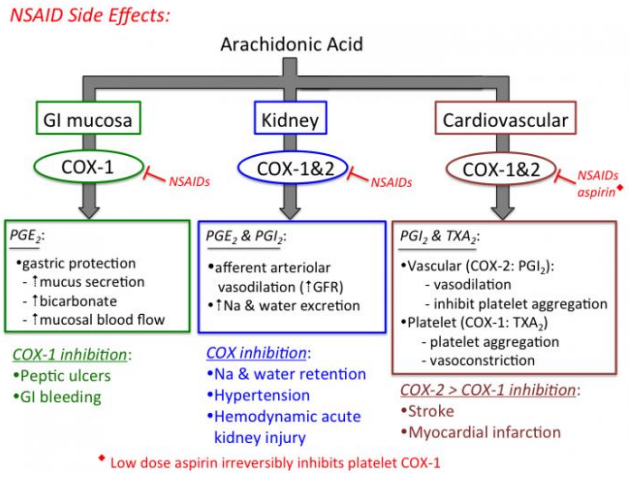

Figure 2. Major physiological roles for COX-1 & COX-2, and mechanisms underlying drug-induced side effects. PGI_2: prostacyclin, TXA_2: thromboxane.

COX-1 produces and regulates prostanoids and that maintains GI mucosa, Platelet aggregation, and renal prostaglandin synthesis. COX-1 inhibits peptic ulcer and GI bleeding while COX-2 inhibits stroke and myocardial infarction. As discussed earlier that Naproxen is safer as compare to other NSAIDs with

respect to cardiac risk profile, diabetes mellitus, and high blood pressure.[11]

As anti-inflammatory and analgesic effect of NSAIDs and COX-2 inhibitors are similar. Here increase in GI tolerability with low-dose aspirin with COX-2 inhibitors is preferential to non-selective NSAIDs. In the California Medicare study, there is reduction in cardiovascular risk with low dose of aspirin with rofecoxib and reduction in risk with indomethacin, sulindac but not with ibuprofen.

3. Gastrointestinal effects (GI)

In the stomach, COX-1 mediated production of prostaglandins PGE_2 & PGI_2 plays an important role in regulating the production of bicarbonate and mucus, as well as regulating normal blood flow. Each of these effects helps to protect the cells lining the wall of the stomach from the erosive effects of stomach acid.[12]Many new approaches to treat GI sparing NSAIDs have been developed and shows promising result and reduced toxicity. The use of NSAIDs limited as they induce erosion and ulcers in gastrointestinal (GI) track. It is important to identify the factors which increases the risk of GI circumstances (Such as advance age, history of ulcer, combination of doses of NSAIDs, uses of corticosteroids etc) and method to reduce it.[13]The development of ulcers after administration of NSAIDs gives the hints in new designing of anti-inflammatory drugs with reduced side effects and toxicity.

Selective COX-2 inhibitors with better GI safety have to consider. Blocking COX-1 mediated production of prostaglandins in the stomach by aspirin and other non-selective NSAIDs (e.g. ibuprofen, naproxen) is expected to increase the incidence of peptic ulcers (and associated symptoms including bleeding & pain). The spectrum of peptic ulceration caused by NSAIDs can range from superficial to large, with acute bleeding being relatively common. Varieties of medical treatments are reported to damage one or more segments of GI tract. Sometimes it is due to prolonged uses of the drugs.[14]

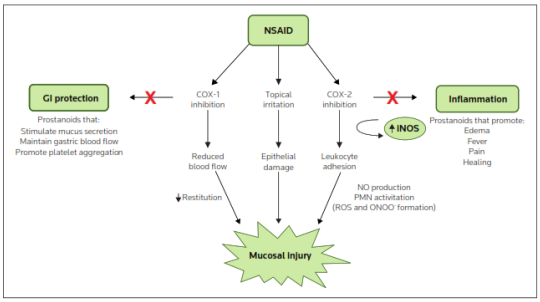

Figure 3. Pathogenesis of gastric damage induced by NSAIDs[12]

The use of NSAIDs causes topical irritation associated with more acidic drugs such as aspirin followed by epithelial damage leads to ulceration. Similarly COX-1 inhibition leads to reduction in blood flow cause mucosal injury. The inhibition of COX-2 leads to neutrophil adherence when administered NSAIDs, it may spares prostaglandin through mucosa.[12] When comparing traditional NSAIDs and coxibs, celecoxib is known to cause less harm to the gastrointestinal tract because of the mechanism by which this drug selectively inhibits COX-2.[15] The common side effects observed due to uses of NSAIDs are dyspepsia, nausea, heartburn[16]

For the reduction of ulcer we can give another non NSAIDs analgesic, but it can't solve the purpose specifically patient having severe arthritis. In long term therapy alternative treatment has to be considered. The dose should be controlled for limited period. In long term use of NSAIDs cardiovascular risk profile along with GI, laboratory investigation has to be done. If patient have high cardiovascular and GI profile avoid NSAIDs.

4. Renal effect

There are two kidney injuries caused due to NSAIDs. Haemodynamically mediated and immune mediated. This acute kidney injury described by rapid fall in glomerular filtration rate (GFR) leads to acute and chronic renal failure and death as well.[15,17]After presystemic metabolism the NSAID excretes parent compounds and their metabolites through renal mechanisms through glomular filtration, tubular reabsorption, and active secretion. Also it excretes through biliary, pulmonary and mammary.[17]Renal events reported with COX-2 and COX-2 specific NSAIDs are increased BUN, dysuria, hematuria,

interstitial nephritis etc. NSAIDs increase the negative effect of cyclosporine on kidney function. There are no specific symptoms for kidney injury due to NSAIDs but leg swelling, nausea, fatigue and breathing problem can be seen.

Due to acute renal failure (ARF), normal function of the kidney get disturbed and that leads to accumulation of waste products. ARF happens via their inhibition of the production of prostaglandins, and the resultant decrease in blood flow to the kidneys. The natural use of angiotensin-receptor blockers, angiotensin-converting enzyme inhibitors, the amino glycosides and diuretics increases risk for the development of ARF. NSAIDs can cause CRF owing to interstitial nephritis or papillary necrosis. The patients who suffered from ARF have higher risk of development of chronic renal failure (CFR).

Renal papillary necrosis (RPN) is the kidney disorder arises due to excess dose of NSAIDs. NSAID-induced RPN is caused by the resultant lack of blood flow to the renal papillae; with the result that hypoxia occurs in these structures. Celecoxib can cause RPN.

5. Conclusion:

Generally NSAIDs are used for arthritis patients, reduce inflammation and pain. While their uses, their mechanism of action, adverse drug reaction, and effects has to be considered. These medications should be prescribed for the shortest duration only with the lowest effective dose, and has to take care of GI, renal, and cardiovascular toxicity. NSAIDs can also increase the risk of stroke, high blood pressure, the risk of falls. Thus, these risks and benefits should be balanced carefully in individual patients to optimize overall outcomes, especially in the elderly.

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