# Non steroidal anti inflammatory drugs (nsaid): effects

Non steroidal anti inflammatory drugs or NSAIDs are inhibitors of prostaglandin, they have several key therapeutic effects, anti-inflammatory, antipyretic (reduces fevers) and analgesic. NSAIDs prevent the synthesis of prostaglandins; theses are made from the enzyme cyclo-oxygenase (COX) which supports inflammation, pain and fever, there are two cyclo-oxgenase COX-1 and COX-2. NSAIDs block the enzyme COX thus reducing the amount of prostaglandins and therefore reducing inflammation, pain and fevers.

The main mechanism of action of NSAIDs is the inhibition of enzyme cyclo-oxygenase (COX). COX converts the fatty acid arachidonic acid into endoperoxide, prostaglandins and thromoxanes. The prostanoids have many physiological functions such as protecting the gastrointestinal tract, renal, homeostasis responses, platelet aggregation, contraction of uterine smooth muscle etc. There are two isoforms of COX, COX-1 and COX-2. COX-1 produces prostaglandin that support platelets and protect the stomach therefore has the most adverse side effects. COX-2 is inducible and found is inflammatory conditions and some types of carcinoma. Some drugs only inhibit COX-2 which reduces adverse effects that are associated with COX-1, such as the irritation of the stomach lining. Prostaglandins have numerous tasks to play as mediators of inflammation. They enhance the action of histamine and other natural compounds causing vasodilatation and increasing vascular permeability to fluids. These two factors result in the symptoms of inflammation. As well prostaglandins they relay pain messages to the brain.

This journal article supports my essay on NSAIDs[i]“ Salicylic acid and salicylates, obtained from natural sources, have long been used as

medicaments. Salicylic acid was chemically synthesized in 1860 and was used as an antiseptic, an antipyretic, and an antirheumatic. Twenty-five years ago, it was proposed that the mechanism of action of NSAIDs was through their inhibition of prostaglandin biosynthesis. Since then, there has been general acceptance of the concept that these drugs work by inhibition of the enzyme cyclo-oxygenase (COX), which we now know to have at least two distinct isoforms: the constitutive isoform, COX-1, and the inducible isoform, COX-2. COX-1 has clear physiologic functions.

Its activation leads, for instance, to the production of prostacyclin, which when released by the endothelium is antithrombogenic and when released by the gastric mucosa is cytoprotective. COX-2, discovered 6 years ago, is induced by inflammatory stimuli and cytokines in migratory and other cells. It is therefore attractive to suggest that the anti-inflammatory actions of NSAIDs are due to inhibition of COX-2, whereas the unwanted side-effects, such as irritation of the stomach lining, are due to inhibition of COX-1. Drugs that have the highest COX-2 activity and a more favourable COX-2: COX-1 activity ratio will have a potent anti-inflammatory activity with fewer side-effects than drugs with a less favourable COX-2: COX-1 activity ratio. The identification of selective inhibitors of COX-2 will therefore lead to advances in therapy.”

NSAIDs are highly lipophilic substances, adsorption occurs through the gastrointestinal tract, as NSAIDs are weak acids they are less ionised in the gastric juices and therefore are absorbed by the mechanism of ionic or diffusion tapping. Most NSAIDs are given as oral tablets or capsules; others are given by injection to avoid gastric irritation.

The main use of anti-inflammatory drugs is in the treatment of pain resulting from rheumatoid arthritis and osteoarthritis. Rheumatoid arthritis is an inflammatory condition of connective tissue especially within the joint capsule; it may be described as an autoimmune disease, whereby the body’s own immune system starts to destroy the synovial membrane. This may lead a complete destruction of the joint. Osteoarthritis is due to a mechanical damage to the joint which leads to degeneration of the articular cartilage the hip joint is commonly affected. Prostaglandins are found in the hypothalamus are involved in raising the temperature of the body during infection, therefore NSAIDs are useful in inhibiting prostaglandins and reducing body temperature, this is called antipyretic . Most prostaglandin inhibitors are acidic drugs that can directly irritate the gastric mucosa. Prostaglandins in the stomach lead to a decrease in gastric secretions; therefore, inhibiting the synthesis of prostaglandins leads to an increase in sections which may lead to ulcers.

Aspirin is an irreversible inhibitor of COX-1 but has adverse side an effect, most side effects of NSAIDs is related to their action on the gastrointestinal tract. In the stomach prostaglandins are normally involved in the protection of the gastric mucosa (lining of the stomach) against the corrosive actions of the gastric acid; prevention of prostaglandin synthesis by NSAIDs therefore remove this protection and make the stomach open to irritation and ulceration. NSAIDs themselves are irritant chemicals which have a direct effect on the gastric mucosa. Other Problems of NSAIDs such as aspirin have an effect the kidneys, because the role of prostaglandins in the maintenance

of blood flow to the kidneys, NSAIDs often cause kidney damage and disorders of salt and fluid balance.

This article shows the adverse effects and mechanism of NSAIDs on the gastrointestinal tract.

### Mechanisms of gastrointestinal (GI) injury

NSAIDs injure the gut by causing topical injury to the mucosa and systemic effects associated with mucosal prostaglandin depletion derived from COX-1. The systemic effects of NSAIDs appear to have the predominant role. Because of that the use of enteric-coated aspirin preparations and parenteral or rectal administration of NSAIDs in order to prevent topical mucosal injury has failed to prevent the development of ulcers.

### Topical injury

The acidic properties of most NSAIDs (included ASA) initiate mucosal damage. These weak acids remain in their non ionised lipophilic form in the highly acidic gastric environment. These conditions favour migration into surface epithelial cell, where NSAIDs are dissociated into the ionised form that traps hydrogen ions, inducing mucosal injury.

## Systemic effects

NSAIDs inhibit cyclooxygenase (COX), a key in the biosynthesis of prostaglandins. There are two isoforms, COX 1 and COX 2. Traditional NSAIDs (tNSAIDs) and ASA inhibit both isoforms. Selective NSAIDs (COXIBs) spare COX 1 and primarily inhibit COX 2. COX 1 isoform is expressed in most tissues, producing prostaglandins that play an important protective role in the gut by stimulating the synthesis and secretion of mucus and bicarbonate,

increasing mucosal blood flow and promoting epithelial proliferation. When NSAIDs inhibit this enzyme create a gastric environment that is more susceptible to topical attack by endogenous and exogenous factors. Besides, the inhibition of the COX 1 blocks platelet production of thromboxane, which increases bleeding when an active GI bleeding site is present . On the other hand, COX2 isoform is induced inmost tissues in response to inflammatory stimuli. Prostaglandins derived from COX-2 can be generated at the ulcer margin and appear to play an important role in ulcer healing through triggering the cell proliferation, promotion of angiogenesis and restoration of mucosal integrity . This isoform is the primary target for anti-inflammatory drugs. Therefore selective COX-2 NSAIDs while having little to no effect on COX-1 should result in effective pain relief with reduced adverse GI effects. This ‘ COX2 hypothesis’ has been challenged by data from animal studies. Wallace et al reported that inhibition of both COX-1 and COX-2 is required for NSAID-induced gastric injury in the rat.”

Aspirin (acetylsalicylic acid) was first isolated in 1829 by Leroux from willow bark. It can cause irreversible inactivation of cyclo-oxygenase, acting on both COX-1 and COX-2. Aspirin has many pharmacologic effects for example it has antipyretic action it reduces fevers and is rapidly effective in febrile patients, yet has little effect on normal body temperature. It has many effects on the body; prostaglandin PGE2 is produced in the brain and causes the temperature regulatory centre in the hypothalamus to raise the body temperature, Aspirin inhibits PGE2 production so body temperature falls.

Aspirin also has anti-inflammatory action, during inflammation, prostaglandin and other arachidonic acid are produced and contribute to the pain, swelling

and tissue damage, and aspirin inhibits the production of arachidonic acid thus reducing inflammation. It is a very good anti-inflammatory effects it helps in condition for example the treatment of musculoskeletal disorders, such as rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.

The ability of aspirin to control pain occurs both through a peripheral and central action when aspirin inhibits the synthesis of prostaglandins in inflamed tissue, and it prevents the prostaglandin from sensitising the nociceptors, by inhibiting prostaglandin synthesis in the brain. Aspirin is also thought to also modify transmissions in the pain conducting pathways. Aspirin has other analgesic effects which is usually effective for low- to moderate-intensity pain. Integument pain is relieved better than the pain from hollow visceral areas. Relief of pain occurs through both peripheral and central mechanisms. In the peripherally, it inhibits the synthesis of PGs in inflamed tissues, thus preventing the sensitisation of pain receptors to both mechanical and chemical stimuli. Also in the centrally, the analgesic site exists in close proximity to the antipyretic region in the hypothalamus. Its analgesia action is not associated with mental alterations, such as hypnosis or changes in sensation other than pain.

## EFFECTS OF ASPIRIN ON PROSTAGLANDIN SYNTHESIS

Both COX-1 and COX-2 enzymes are inhibited by aspirin, but not by opioids, acetaminophen, or tramadol. The active site of both enzymes appears to be at the end of a long, tubular channel in the molecule. Aspirin block arachidonate’s entrance to this channel (as seen in picture below). Aspirin does this by irreversibly acetylating a specific serine molecule (serine 530 for

COX-1 and serine 516 for COX-2) When blocked by aspirin, COX-1 becomes completely inactive. COX-2, on the other hand, converts arachidonate to 15-R-hydroxyeicosatetraenoic acid (15-R-HETE). Neither enzyme is capable of producing prostaglandin H2, the necessary precursor of prostaglandin and thromboxane synthesis.

Aspirin causes damage to the gastric mucosa partly by inhibiting the formulation of prostaglandins that protect stomach wall from gastric acids. Aspirin in addition has Gastrointestinal effects such as It can cause epigastric distress, nausea, and vomiting by irritating the gastric mucosal lining and stimulating the chemoreceptor trigger zone in the CNS. It may cause a dose-related gastric ulceration, bleeding, and erosive gastritis because of inhibiting the formation of PGE2, which inhibits gastric acid secretion and has a cytoprotective effect. Salicylates-induced gastric bleeding is painless and may lead to an iron deficiency anemia. Aspirin is used in restricted situation for the symptomatic relief of fever. Because of an increased incidence of Reye’s syndrome in children who previously were given aspirin for the relief of viral fevers, it is now recommended that a child with any fever be given paracetamol instead, if medication is required. It is useful as analgesics for certain categories of pain, such as headache, arthritis, and dysmenorrhea. It remains the standard, first-line drug in the therapy of rheumatoid arthritis, and can provide relief of symptoms in acute rheumatic fever. Some clinicians recommend small daily doses of aspirin for prophylaxis of thromboembolism, stroke, or myocardial infarction because of its antiplatelet activity.

Some adverse effects of aspirin when uses in large repeated dosages are headache, mental confusion, lassitude, and drowsiness, tinnitus and difficulty

in hearing, hyperthermia, sweating, thirst, hyperventilation, vomiting, and diarrhea.

## Contraindications

Aspirin, non-steroidal anti-inflammatory drugs and anticoagulants should be avoided in all patients with liver disease because of the risk of altering platelet function, causing gastric ulceration and bleeding. NSAIDs have also been implicated in precipitating renal dysfunction and vericeal bleeding in patients with end-stage liver disease. Although COX-2 inhibitors may cause a lower incidence of bleeding complication, currently they are avoided in patients with liver disease as their still pose a risk.

Paracetamol is an analgesic agent. It does not have ant-inflammatory or anti-platelet activities, but it is a useful analgesic in febrile illnesses such as influenza. As paracetamol has no anti-inflammatory properties it does not inhibit prostaglandin thus have no affect on the gastric mucosa. As an analgesic, paracetamol is best taken on an empty stomach for fast action, as it gets absorbed faster. As it is not associated with Reyes’s syndrome, it is the preferred analgesic in the symptomatic treatment of children with viral infections.

The mechanism of action of paracetamol is now thought to be via COX-3 inhibition. This enzyme is present in the brain and spinal cord and is selectively inhibited by paracetamol. Paracetamol has no action on COX-1 and COX-2, thus does not have any gastric side effects. The central action of paracetamol explains it antipyretic effects and its lack of other peripheral adverse effects associated with NSAIDs. Paracetamol has few adverse side

effects as it is tolerated by the stomach because inhibition of prostaglandin in the periphery is weak; allergic reactions and skin rash sometimes occur. Heavy, long term daily use may predispose chronic renal disease.