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Review Article

GASTROPROTECTIVE NSAIDs

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ABSTRACT

NSAIDs suffer from a serious drawback of GI-SEs caused particularly after chronic use. There is evidence concerning the participation of ROS in the etiology & pathophysiology of digestive system disorders like GI-inflammation & gastro ulcer. With the aim to retard the adverse effects of GI-Origin, conjugates of NSAIDs (especially the carboxylic acid derivatives) with some antioxidants can be synthesized by esterification with various antioxidants of natural origin. The conjugates that show the retention or potentiating of anti-inflammatory activity with reduced ulcerogenic side effect could be potential gastroprotective co-drugs of NSAIDs.

Keyboards: NSAIDs, Gastroprotective, ROS, Natural antioxidants, Conjugates, Ulcerogenic

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INTRODUCTION

Inflammation is defined as the changes occurring in response to tissue injury, infection or presence of foreign substance and it is a part of host defense mechanism characterized by redness, pain & swelling at the site. Inflammation leads to damage of cell membrane, which causes leukocytes to release lysosome enzymes & cause several events called Arachidonic acid cascade¹. There are various cells like neutrophils, basophils, macrophages, monocytes, mast cell, platelets, lymphocytes, monocytes etc. Which release various inflammatory mediators and modulators like Arachidonic

Acid metabolites, leukotrienes, Thromboxane, Platelet activating factors lysosomal enzymes, histamine, serotonin as well as various reactive oxygen species¹. The release of chemical compounds and compression of the nerves (due to swelling/oedema) in the vicinity of the inflammation causes pain¹. Inflammation is mediated by several families of mediators among these the Eicosanoids i.e. the lipid mediators produced from

Arachidonic acid cascade are most studied. The eicosanoids include

- (1) prostanoids i.e. Prostaglandins formed through cyclooxygenase pathway,
- (2) Lipoxygenase pathway products like Leukotrienes, lipoxins, hepxillins .
- (3) Cyt.P450 pathway products like epoxy fatty acids and dihydroxyl fatty acids
- (4) The mediators released no enzymatically like isoprostanesisoleukotrienes².

ANTI-INFLAMMATORY DRUGS

The substances that inhibit the important sign of inflammation like redness, pain & swelling are called anti-inflammatory drugs. These may be either steroidal or non-steroidal anti-inflammatory drugs. Steroidal anti-inflammatory act by inhibit the synthesis of both eicosanoids and PAF while NSAIDs act by inhibiting the synthesis of mainly eicosanoids².

The NSAIDs are the drugs used most commonly for their analgesic, antipyretic, anti-inflammatory &

antithrombogenic effects. Their specific use includes the treatment of headache, toothache, body ache, arthritis, ankylosing spondylitis, sports injuries, etc. It is the most widely used class of drugs world over for example in U.S alone out of approximately \$30 billion per year drug costs 25% i.e. \$56.11 is on NSAIDs. But the NSAIDs are called silent epidemic as around 107,000 hospitalizations and MT 16,500 deaths annually are reported in UK alone due to complications due to GI side effects of NSAIDs. The NSAIDs showed increased risk of renal & CV complications but the most common & dangerous of these side effects are related to GI disturbance and occurrence of these GI-SEs may sometimes be such great that it leads to patient non-compliance and even discontinuation of therapy. The fact that both the pharmacological action (i.e. analgesic, anti-inflammatory) and the side effects of NSAIDs are linked to their property of inhibition of synthesis of prostaglandins. It is confirmed that prostaglandins have both beneficial action and inflammatory mediator actions.

Ideally the NSAIDs should inhibit PG-synthesis at the sites of inflammation only hence produce the desired anti-inflammatory analgesic / or antipyretic action. In fact the NSAIDs start their action in GIT also, their most common route of administration. But in GIT the Prostaglandins play an important role of maintaining the homeostasis i.e. has a beneficial effect. The examples of beneficial effects of prostaglandins in GIT are:

1) Bicarbonate secretion

HCO₃ are formed from the surface epithelial cells of gastroduodenal epithelium and are secreted into the mucus layer which covers it. PGE₂ is the major eicosanoid which stimulates the gastric bicarbonate secretion but NSAIDs are potential inhibitors of PGE₂ synthesis especially in GI-epithelium as NSAIDs stay longer in GI-epithelial cells due to the NSAIDs- ionic trapping phenomenon causing prolonged inhibition of PG-production in the digestive tract. The mucus bicarbonate layer is an important line of defense in GIT against the damaging effects of gastric acid, pepsin or other aggressive factors like proteases, H.pylori oxidative stress etc. and thereby provides the apical membrane of the surface epithelial cells with a near neutral pH milieu².

2) Mucus Secretion

Gastric mucus, a viscous gel that coats the entire gastric mucosa is produced by & secreted from the surface epithelial cells. Topical prostaglandins, dimethylPGE₂, PGF₂& carbenoxolone have been observed to increase the mucus gel thickness³.

3) Hydrophobicity

GMSH i.e. gastric mucosal surface hydrophobicity is essential component of mucosal defense system that is decreased by NSAIDs².

4) Back-diffusion of H+

The removal of back-diffused H⁺ ions through the microcirculatory flow is an important aspect of GI-defense against the gastric acid. This microcirculation in

GIT is also regulated by prostaglandins secreted locally. NSAIDs by PG-synthesis inhibition action breaks this mucosal protection defense further adding to ulcerogenic side effect of NSAIDs.

5) Generation of reactive oxygen species

Oxidative stress plays an important role in tissue injury. It has been observed that if the prooxidant conditions predominates due to increased generation of reactive oxygen species or due to poor or weakened antioxidant inbuilt mechanism leading to oxidative stress in the tissue and there are experimental evidences supporting the fact that the ulcerogenic effect of NSAIDs are mediated by reactive oxygen species⁴.

Thus NSAIDs produce lesions in the GIT by

- 1) Direct inhibition action, a physicochemical phenomenon, due to their acidic nature (i.e. naked carboxylic acid group)
- 2) Prostaglandin synthesis inhibition action by inhibiting cyclooxygenases, a pharmacological phenomenon, hence inhibiting the local synthesis and secretion & protective mucus as well as bicarbonate ions in GIT.
- 3) By prolonged stay inside the GI-epithelial cells, a biochemical phenomenon, by 'NSAIDs-ionic trapping'.
- 4) By causing thrombosis in microcirculation & vasoconstriction of arterioles of submucosa.
- 5) By delayed ulcer healing, an indirect phenomenon as the prostaglandins play a key role in ulcer healing, while inhibition of endogenous PG-synthesis in GIT by NSAIDs results in delayed ulcer healing.
- 6) By generation of ROS which have direct damaging effect.

GI-DISEASE AND ROLE OF ROS

There is enough experimental and clinical evidence which shows the role of various ROS in NSAIDs induced GI-ulceration⁵ NSAIDs produce the prooxidant environment i.e. oxidative stress in GIT.

NSAIDs and generation of ROS-oxidative stress

Oxidative stress plays an important role in tissue injury. It has been observed that if the prooxidant conditions predominate either due increased generation of ROS or due to poor, weakened antioxidant inbuilt mechanism it leads to oxidative stress in the tissue.

The various ROS generated in vivo include superoxide ions (O₂⁻), hydroxyl (OH⁻), alkoxy (RO⁻), peroxy (ROO⁻), and nitric oxide (NO⁻). These ROS are the free radicals which are extremely short lived, highly reactive moiety carrying an unpaired electron, always in attempt to attack other molecule to acquire an electron to pair its unpaired electron. These other molecules may be lipids, proteins, nucleic acids resulting in damages to biomolecules constituting cell membranes, organelles, DNA, RNA etc.

Oxygen is vital for aerobic life processes and approximately 5% of the inhaled O₂ is converted to various ROS by univalent reduction of O₂⁶. In fact all reactive oxygen species are generated from oxygen. ROS is a collective term that includes both radicals and non-radical species participating in initiation or propagation reactions. These free radicals are generated continuously from the oxygen consumed in respiration; cell mediated inflammatory and immune processes. Normally there is a balance between the number of free radicals/ROS generated in our body and the number of defensive scavengers for these reactive oxygen species thus protecting us from the deterrent effects of these reactive species. These reactive species in search of pairing their unpaired electron attack the vital biomolecules like DNA, proteins etc. Thus damaging bio membranes like those of mitochondria, eventually causing cells to lose their structure and/or function and ultimately in cell death. Various necrotic factors, protease and ROS from the damaged cells also attack the surrounding cells, resulting ultimately in tissue & organ injury. When the balance between the number of ROS generated and the number of ROS-scavengers/antioxidants in biological system in towards more generation than neutralization then this state is called "Oxidant stress" which results in tissue injury and subsequent diseases. In case of prolonged therapy with NSAIDs as in case of treatment of rheumatoid arthritis, osteoarthritis and other chronic inflammatory conditions etc. There is strong evidence that NSAIDs induced GI ulcerations, lesions are due to excessive oxidant stress. NSAIDs like indomethacin induce micro vascular injury in gastric mucosa and the reports suggest that the inhibition of prostaglandin synthesis was unlikely to be the sole mechanism responsible for gastric injuries induced by NSAIDs induced gastric ulceration is well studied where it reported that the excessive generation of oxygen radicals in extracellular spaces and depletion of GSH in conjunction with inhibition of glutathione peroxidase activity⁸ is responsible for oxidative tissue damage of gastric mucosa after prolonged administration of NSAIDs (indomethacin, Ibuprofen, Aspirin etc.). The vulnerability of various bio membranes to various ROS is due to presence of PUFAs, like arachidonic acid, linoleic acid, linolenic acids in the form of esters with cholesterols, phospholipids or triglycerides. The proteins, nucleic acids and carbohydrates are less responsible to free radical attacks induced membrane injuries.

Defenses against ROS-Antioxidant defenses

An antioxidant is a substance which reduces or delays oxidation of oxidizable substrate by themselves getting oxidized in comparison to the substrates. Human body has endogenously produced antioxidants which protect the body from damaging ROS/ free radicals produced by various biochemical reactions, environmental pollutants, irradiations, or in this case produced by chronic use of NSAIDs as in cases of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis etc. The various endogenous sources of antioxidant can be following:

1. Enzymatic for example superoxide dismutase (SOD), catalases (CAT), glutathione peroxidase (GPx)⁹, cytochrome C oxidase etc.
2. No enzymatic antioxidants for example the low molecular weight non-enzymatic agents synthesized in the body acting as free radical scavenger like bilirubin, α -keto acid, sex hormones, melatonin, lipoic acid, coenzymes, uric acid, histidine containing peptides, etc.
3. Dietary sources like vitamin C, vitamin E, various categories of natural colored pigments (like yellow, orange, red pigments as in mangoes, carrot, tomatoes, turmeric, etc.), plant phenols as flavonoids, anthocyanidins, phenylpropanoids. These endogenously produced antioxidants protect the body from damaging oxidation reactions. But these endogenous antioxidant supply is limited and there is a need to replenish antioxidant resources either endogenously or through supplementation especially in situation of oxidative stress in the tissues for example in gastric ulcers happening most commonly after chronic use of NSAIDs¹¹

The NSAIDs induced GI side effects include nausea, vomiting, abdominal pain, mucosal lesions, serious complications like bleeding, perforation etc. It is clear that GI-discomfort and hence the poor patient compliance are the major limitations of NSAIDs therapy. Hence some gastro protective NSAIDs should be designed for which various strategies can be adopted as:

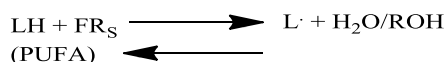
- 1) Mask the naked acid (carboxylic acid) group of NSAIDs so that the local irritant action is removed i.e. covert the acid into ester or amides.
- 2) The acid/amide formed should be such that it does not release the NSAID inside GIT or get trapped in the GI-epithelial cells but carries it to the desired site of action col inflammation where it releases the free NSAID.
- 3) Co-administration of NSAIDs and antioxidants

Based on the above facts it is suggested that to prevent gesture-ulceration, etc. caused due to chronic/acute use of NSAIDs, the co-administration of NSAIDs with antioxidants will be suitable. There are various classes of antioxidants.

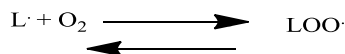
Mechanism of action of ROS, free radicals-lipid peroxidation

When free radicals like OH[•], ROO[•], RO[•], or others ROS extract a hydrogen atom from a PUFA (of bio membranes) a carbon centered lipid radical is produced. This is followed by the addition of oxygen to lipid radical to form lipid derived free radicals for example lipid peroxy radicals, lipids hydroperoxyl radicals, conjugated dienes.) These propagate the chain reaction by extracting H-atom from nearby PUFA. The resulting lipid hydroperoxide easily decomposes to form lipid alkoxy radicals (LO[•]) as shown in figure:

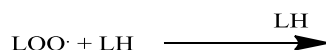
Initiation:



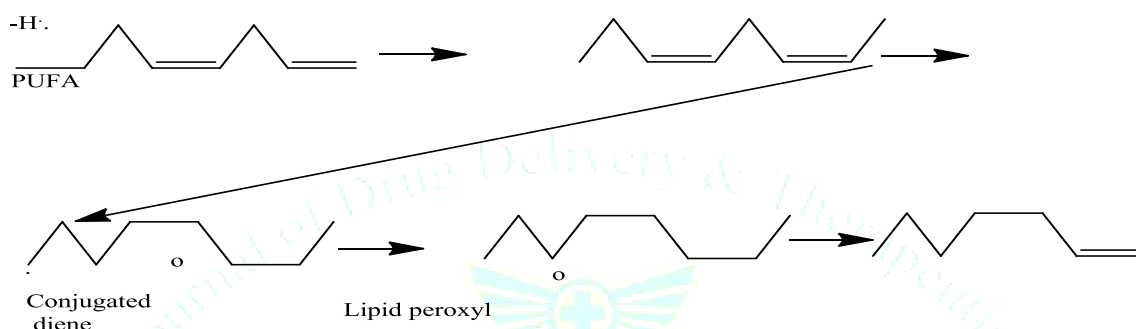
Propagation:



Termination:



The chain reaction continues (damaging the cell membrane) till some antioxidant interrupts it through scavenging the radicals i.e. the termination steps [Schafer 2000, July P-994].



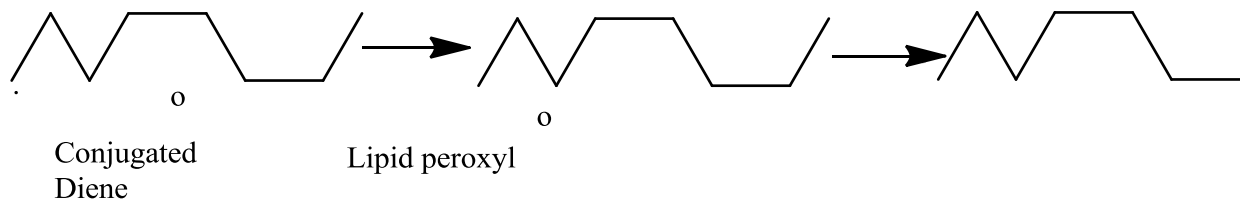
CONCLUSION

Hence some gastroprotective NSAIDs should be designed for which various strategies can be there:

- 1) Mask the naked acid (carboxylic acid) group of NSAIDs. so that the local irritant action is removed i.e. convert the acid into ester or amides.

- 2) The acid/amide formed should be such that it does not release the NSAIDs inside GIT or get trapped in the GI-epithelial cells but carries to the desired site of action. Col inflammation where releases the free NSAIDs.

- 3) Co-administration of NSAIDs and antioxidants.



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