International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 10; Issue 09 (B); September 2021; Page No.25153-25155
DOI: http://dx.doi.org/10.24327/ijcar.2021.25155.5019

Research Article

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN PERIODONTOLOGY

Aditya Kumar., Mayur Kaushik., Nitin Tomar and Shilpa Sharma

Department of Periodontology, Subharti Dental College and Hospital, Meerut, Uttar Pradesh (250005), India

A R T I C L E I N F O

Article History:
Received 12th June, 2021
Received in revised form 23rd July, 2021
Accepted 7th August, 2021
Published online 28th September, 2021

Key words:
NSAIDS, Anti-inflammatory, Arachidonic acid metabolites, Selective COX-2 inhibitors, Bone Morphogenetic Protein.

A B S T R A C T

The periodontal disease is primarily a bacterial infection which lead to inflammatory changes along with host response, the chemical agents released by bacteria as well as the host response results in periodontal destruction. The host immune reaction when gets activated by matrix metalloproteins (MMPs), cytokines and prostanoids, can be reduced by therapeutic applications of anti-collagenase drugs (such as synthetic matrix metalloproteinase inhibitors), sub antibacterial-dose doxycycline (SSD) and chemically modified tetracycline's (CMTs), anti-cytokine therapy using antiIL-1 or anti-tumor necrosis factor-α monoclonal antibodies and soluble tumor necrosis factor receptors and bisphosphonates. NSAIDs are the drugs that inhibit the formation of prostaglandins by blocking the cyclo-oxygenase pathway of arachidonic acid (proinflammatory mediators) metabolism.

INTRODUCTION

Periodontal disease is a chronic infection of the periodontium affecting soft and mineralized tissues surrounding the teeth. It is a highly prevalent infectious injury caused by specific bacterial species.[1] The periodontal disease progression is associated with subgingival bacterial colonization and biofilm formation that provokes chronic inflammation of soft tissues, degradation of collagen fibres supporting the tooth to the gingiva and alveolar bone, as well as resorption of the alveolar bone itself. Gram negative, anaerobic or microaerophilic bacteria within the biofilm are often associated with disease initiation and progression.[1]

The periodontal disease is primarily a bacterial infection which lead inflammatory changes along with host response, the chemical agents released by bacteria as well as the host response results in periodontal destruction.[2] The damage to the tissues results in release of arachidonic acid from phospholipids of plasma membranes, which is metabolized via the cyclooxygenase or lipoxygenase pathways.[3] Most of the tissue breakdown is indirectly caused by toxic bacterial products that trigger the host response.[4]

NSAIDs are the drugs that inhibit the formation of prostaglandins by blocking the cyclo-oxygenase pathway of arachidonic acid (proinflammatory mediators) metabolism.[5] NSAIDs inhibit the formation of prostaglandins, including prostaglandin E2, which is produced by resident and infiltrating cell types in the periodontium (including neutrophils, macrophages, fibroblasts and epithelial cells) in response to LPS.[6]

Corresponding author:* **Aditya Kumar
Department of Periodontology, Subharti Dental College and Hospital, Meerut, Uttar Pradesh (250005), India

Thus, the aim of this article is to review the current understanding of non-steroidal anti-inflammatory drugs and their potential applications in periodontal therapy.

History

Anti-inflammatory drugs originated serendipitously from certain plants and their extracts, which were being applied for the relief of pain, fever and inflammation. in the 17th century, the active ingredient of willow bark salicin was identified in Europe. The Kolbe Company in Germany started mass producing salicylic acid in 1860.

Non-steroidal anti-inflammatory drugs (NSAIDs) are some of the most commonly used pharmaceuticals world-wide. They are used for prevention and treatment of inflammatory diseases, arthritis, collagen diseases, pain, fever, and ischemic cerebrovascular disorders because of their anti-inflammatory, analgesic, antipyretic, and antiplatelet functions. In recent years, it has also been reported that they are effective for the prevention of colorectal cancer.[7]

General Structure and Properties of The Nsaids

- NSAIDs structurally consist of an acidic moiety (carboxylic acid, enols) attached to a planar, aromatic functionality.
- All are relatively strong organic acids with pKas in the 3-5 range. Most, but not all, are carboxylic acids.
- The NSAIDs differ in their lipophilicities based on the lipophilic character of their aryl groups and additional lipophilic moieties and substituents.

- The acidic group in these compounds serves as major binding group (ionic binding) with plasma proteins. Thus, all NSAIDs are highly bound by plasma proteins.
- The acidic group also serves as a major site of metabolism by conjugation. Thus a major pathway of clearance for many NSAIDs is glucuronidation (and inactivation) followed by renal elimination.

Mechanism of action of NSAIDs: The mechanism of action of NSAIDs can be divided into their effects on inflammation, pain, and fever.[8]

- **Anti-inflammatory effect** through inhibition of prostaglandin G/H synthase, or cyclooxygenase, which is the enzyme catalyzing the transformation of arachidonic acid to prostaglandins and thromboxanes.
- **Analgesic effect** on pain resulting from the increased peripheral sensitization that occurs during inflammation and leads nociceptors to respond to stimuli that are normally painless.
- **Antipyretic effect** by inhibition of prostaglandin E2 (PGE2) synthesis, which is responsible for triggering the hypothalamus to increase body temperature during inflammation.[9]

Uses of NSAIDs in Periodontology

- NSAIDs are the mainstay of therapy for the management of acute dental pain.
- To minimize edema following surgical procedures, and for endodontic pain**.** For example, for analgesia Ibuprofen in a dose of 400 mg, Aspirin 650 mg and Acetaminophen 600 to 1000 mg have been used.
- Post-operative administration of flurbiprofen over the dose range of 50 to 150 mg results in a linear increase in analgesia in the oral surgery model.
- Ketorolac 30 mg provides pain relief comparable with that from meperidine 100 mg or morphine 10 mg but ketorolac causes less drowsiness, nausea, and vomiting than morphine 12 mg.
- Meclofenamate acts simultaneously to inhibit both the cyclooxygenase and lipoxygenase pathways, resulting in reduced formation of prostaglandins and leukocytes.

Adverse effects

Among aspirin, other nonselective NSAIDs, and the newer selective cox-2 inhibitors. Although these three classes of drugs for the most part product qualitatively similar adverse effects, they differ quantitatively in the risks that they pose.[10]

- Gastrointestinal toxicity
- Effects on platelets
- Hypertension:
- Cardiovascular effects
- Central Nervous System
- Acid-Base
- Reye's syndrome

Non-Steroidal Anti-Inflammatory Drugs and Their Effect on Periodontal Disease

Periodontitis is multifactorial infectious disease of the supporting structures of the teeth, characterized by destruction of the bone and connective tissue with specific periodontopathic bacteria and their virulence factors being the primary etiologic agents. Recognition that host response is a component of the etiology of the periodontal diseases has provided a rationale for adjunctively treating the host with medicaments in addition to conventional treatment aimed at suppression of the bacterial infection.[11]

- **Modulation of arachidonic acid metabolites:** The basic rationale behind the use of nonsteroidal anti-inflammatory drugs is to block the arachidonic acid metabolites that are pro-inflammatory mediators implicated in a variety of bone resorptive and tissue degrading processes. These compounds block platelet activity through thromboxane inhibition, inhibit cyclooxygenase, and prevent the production of arachidonic acid metabolites.
- **Pro-inflammatory cytokine inhibition:** The catabolic activities of these cytokines are controlled by endogenous inhibitors that include IL-1 and TNF receptor antagonists. When administered for therapeutic purposes, these antagonists can reduce inflammation.
- **Modulation of matrix metalloproteinase's:** TIMP levels increase in pathologic conditions, this increase may not compensate for elevated concentration of activated MMPs. Cell culture studies have demonstrated that recombinant TIMP can reduce stimulated bone resorption therefore administration of recombinant TIMP might be an effective treatment modality.[12]

Effects of NSAIDs on PG levels

- Steroids inhibit PLA2, stabilize lysosomal membranes, and inhibit cellular degranulation, all serving to reduce the availability of free arachidonic for CO enzymatic activity. Steroids also cause degradation of preexisting mRNAs for IL-lß and TNFa there by dampening the secondary PGE2 response.
- Use of antioxidants which serve to prevent the oxidation of arachidonic acid by molecular oxygen and the subsequent hydrolysis to form PGE2.
- The third approach is directed towards inhibiting the cyclooxygenase directly by NSAIDs; i.e., flurbiprofen and Ibuprofen, as an attempt to control periodontal diseases.

Effect of NSAIDs on the relationship between surface roughness and osseointegration

It is widely accepted that implants with a rough surface show better biological behavior. The higher success rate is attributed to increased adhesion of cells to the implant surface and to increased levels of cytokine and growth factor production, implying a phenotype with increased differentiation.[13]

Effects of NSAIDs on Bone Morphogenetic Protein (BMP):

Experimental in vitro studies have shown negative effects of NSAIDs on growth factors that encourage osteogenesis primarily BMPs. It was also observed that simultaneous treatment of human periodontal ligament cells with BMP-2 and interleukin- 1β (IL-1β) enhanced the activity of alkaline phosphatase (ALP) and production of PGE2, and promoted the differentiation of osteoblasts. Some researchers have observed that in the

presence of inflammation, NSAIDs restore the levels of growth factors that promote bone healing when growth factors were added exogenously.[14]

Effect of NSAIDs and duration of their use

It was observed that when selective COX-2 inhibitors like rofecoxib was used for longer durations like 6 weeks there was less bone in growth in the inner core of a BHC (bone harvest chamber) but this effect vanished if the drug is given for only two weeks. The effect of short-term administration of low therapeutic doses of indomethacin, meloxicam or rofecoxib, a minor negative effect on bone healing was seen with refecoxib.

CONCLUSION

Ever since NSAIDs have been discovered they are being used for relief of pain, fever and inflammation. NSAIDs are the one which block the arachidonic acid metabolites thus suppressing the host responses. NSAIDs like indomethacin, flurbiprofen, ibuprofen, naproxen, piroxicam have been shown to suppress the magnitude of the acute inflammation, delay the onset of the acute inflammatory reaction, and reduce alveolar bone resorption but the effect of NSAIDs greatly enhanced with oral hygiene and plaque control in both animal and human models.

Selective COX-2 inhibitors have also been studied in periodontics. They exhibit a better clinical risk/benefit ratio than classical NSAIDs. Studies have shown that meloxicam a selective COX-2 inhibitor, prevents alveolar bone loss in animal model. In future there is a need for development of newer low dose NSAIDs for long term use as that of low dose sub-antimicrobial doxycycline therapy or topically delivered NSAIDs which has more retentive and long term effect without the known side effects that NSAIDs have.

References

Sockransky SS, Haffajee AD. Evidence of bacterial etiology: a historical perspective. *Periodontol 2000* 1994;5:7-25.

Ivanyi L, Lehner T. Stimulation of lymphocyte transformation by bacterial antigens in patients with periodontal disease. Arch Oral Biol 1970;15: 1089-1096.

Ivanyi L, Lehner T. Lymphocyte transformation by sonicates of dental plaque in human periodontal disease. Arch Oral Biol 1971;16:1117-1121.

Ivanyi L, Wilton JM, Lehner T. Cell mediated immunity in periodontal disease; cytotoxicity, migration inhibition and lymphocyte transformation studies. Immunology 1972;22:141-145.

Goldhaber P, Roth SI, Cirulis G. The Effect of parathyroid and other human tumors and tissues on bone resorption in tissue culture. Cancer Res 1964;24:254-256.

Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature New Biol 1971;231:232-235.

Moriyama T, Higashi T, Togashi K, Iida T, Segi E, Sugimoto Y, *et al*. Sensitization of TRPV1 by EP1 and IP reveals peripheral nociceptive mechanism of prostaglandins. Molecular pain. 2005 Jan 17;1:1744-8069.

Portanova JP, Zhang Y, Anderson GD, Hauser SD, Masferrer JL, Seibert K, *et al*. Selective neutralization of prostaglandin E2 blocks inflammation, hyperalgesia, and interleukin 6 production in vivo. J Exp Med 1996;184:883–891.

Matsuoka T, Hirata M, Tanaka H, Takahashi Y, Murata T, Kabashima K, *et al*. Prostaglandin D2 as a mediator of allergic asthma. Science 2000;287:2013–2017.

Harris SG, Padilla J, Koumas L, Ray D, Phipps RP. Prostaglandins as modulators of immunity. Trends Immunol 2002; 3:144-150.

Haines KA, Giedd KN, Rich AB, Korchak HM, Weissmann G. The leukotriene B4 paradox: neutrophils can, but will not, respond to ligand-receptor interactions by forming leukotriene B4 or its co-metabolites. J Biochem 1987; 241:55-62.

Wright SD, Ramos RA, Tobias PS, Ulevitch RJ, Mathison JC. CD14, a receptor for complexes of lipopolysaccharide (LPS) and LPS binding protein. Science 1990;249:1431-1443.

Stevens RH, Gatewood C, Hammond BF. Cytotoxicity of the bacterium actinobacillusactinomycetemcomitans extracts in human gingival fibroblasts. Arch Oral Biol 1983;28:981-987.

Felder CC, Kanterman RY, Ma AL, Axelrod J. Serotonin stimulates phospholipase A2 and the release of arachidonic acid in hippocampal neurons by a type 2 serotonin receptor that is independent of inositolphospholipid hydrolysis. Proc Natl Acad Sci 1990;87:2187-2191

How to cite this article:

Aditya Kumar *et al* (2021) 'Non-Steroidal Anti-Inflammatory Drugs in Periodontology', *International Journal of Current Advanced Research*, 10(9), pp. 25153-25155. DOI: http://dx.doi.org/10.24327/ijcar.2021. 25155.5019

*****