Role of NSAID's In Periodontics

Dr Varsha Sharma
PG Student

Dr Ashish Kumar
Professor

Dr Komal Puri
Assitant Professor

Dr Manish Khatri
Professor & HOD

Dr Mansi Bansal
Reader

Dr Geeti Gupta
Reader
Department of periodontology
Institute of Dental Studies and Technologies,
Kadrabad, Modinagar, (U.P.)-201201, India

Abstract

Periodontitis is a multifactorial disease where bacteria and host both plays an important role. Non-Steroidal Anti-inflammatory Drugs have shown to be potent anti-inflammatory and host modulating agents (in low doses). This article is an attempt to review the role of NSAIDs in treatment of periodontal diseases.

The damage to the tissues results in release of arachidonic acid from phospholipids of plasma membranes, which is metabolized via the cyclooxygenase (COX-1 or Cox-2) or lipoxygenase pathways. Bacteria present in dental plaque triggers the inflammatory and immunological reactions of the host resulting in periodontal diseases.[1]The final products of cyclooxygenase (CO) pathway includes prostaglandins, prostacyclin's and thromboxane, whereas that of lipoxygenase (LO) pathway include leukotrienes and 5-HETE.[2,3] Host derived enzymes known as matrix metalloproteinase (MMPs), cytokines, prostaglandins (PGs), leukotrienes (LTs), histamines, bradykinin and more recently platelet activating factor (PAF) and leukotriene-1 are responsible for most periodontal tissue destruction. These powerful enzymes destroy the periodontal matrix leading to periodontal diseases.[4]

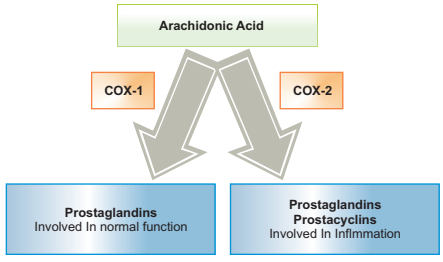

Figure 1: Oxygenation of arachidonic acid by COX-1 and COX-2

Two isoforms of cyclooxygenase are recognized as COX-1 and COX-2. COX-1 is constitutively expressed and is important for physiologic functions including gastric cytoprotection, COX-2 is inducible, upregulated by proinflammatory cytokines, and thought to be involved in inflammation.[5](Figure 1)

The metabolites produced by cyclooxygenase enzyme and lipoxygenase enzyme (eicosanoids) are capable of causing vasodilation, vascular permeability, edema, collagen degradation and bone resorption.[6]

Non-selective NSAIDs, inhibits both the enzymes COX-1 and COX-2 but in addition to providing effective therapeutic activity may exert adverse side effects, largely in gastrointestinal (GI) system and kidney, COX-2 selective NSAIDs collectively denominated as COXIBs e.g. celecoxib, rofecoxib etc. are known to have anti-inflammatory effects comparable to conventional NSAIDs, but with less GI toxicity.[7] Over the time with growing experiments it was known that it is not possible to clearly separate the functions of PGs produced by COX-1 and COX-2, as COX-1 also appears to play a significant role in the inflammatory process. Prolonged use of selective COX-2 inhibitors caused a

significant increase in the incidence of thrombosis and myocardial infarcts.[8-10]

A number of drugs like Indomethacin,[11-14] Flurbiprofen,[11,15] Ibuprofen,[16] Meclofenamic,[17] Piroxicam,[18] Aspirin[19] and Naproxen[20] have been therapeutically used in periodontal diseases.

The host immune reaction when gets activated by matrix metalloproteins (MMPs), cytokines and prostanoids, can be reduced by therapeutic applications of anticollagenase drugs (such as synthetic matrix metallo-proteinase inhibitors), sub antibacterial-dose doxycycline (SSD) and chemically modified tetracycline's (CMTs), anti-cytokine therapy using anti-IL-1 or anti-tumor necrosis factor-α monoclonal antibodies and soluble tumor necrosis factor receptors and bisphos-phonates.

NSAID's are the drugs that inhibit the formation of prostaglandins by blocking the cyclo-oxygenase pathway of arachidonic acid (proinflammatory mediators) metabolism. NSAID's inhibit the formation of prostag-landins, 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.[2,3]

NSAID's role in periodontics

Inflammation in periodontium provoke a characteristic pattern of response which leads to the familiar clinical signs of redness, swelling, tenderness, and pain and which in chronic phase may lead to bone resorption.

Goldhaber and co-workers[21] reported that human gingival tissues could produce a factor which could stimulate bone resorption of mouse calvaria in tissue culture. At about the same time, Klein and Raisz[22] reported that prostaglandins have been identified as potent stimulators of bone resorption in tissue culture. Goldhaber and co-workers then began to add indomethacin, a known inhibitor of cyclooxygenase and prostaglandin production, to their culture media and observed a decrease in bone résorption by up to 50% in their tissue culture system.[118] other researchers confirmed these findings using other tissue culture systems such as dental cysts and mouse fibrosarcoma cells as well as synovial fluid from individuals suffering from arthritis. The role of prostaglandins in the pathogenesis of periodontal disease was further confirmed in studies which examined the levels of arachidonic acid metabolites in inflamed gingiva.[15] Offenbacher[25] and various other researchers also found that the crevicular fluid levels of PGE2 were increased in adult patients with periodontal disease. The other metabolites of the arachidonic pathway, thromboxane, prostacyclin, and the leukotrienes have all been shown to be increased in diseased states.[26]

Prostacyclin is able to release previously incorporated ^{45}Ca from fetal rat bone in vitro, they could be a direct stimulator of bone resorption. Prostacyclin increases vascular permeability and enhances the vascular permeability induced by other inflammatory mediators.[26] All of these observations and the fact that prostacyclin inhibits chemotaxis of human polymorphonuclear leukocytes without inhibiting phagocytosis suggested that prostacyclin might be important in the genesis and maintenance of an inflammatory reaction and that it could contribute to bone resorption in chronic inflammatory periodontal disease. It has been shown that 6-keto-PGF1α is synthesized by inflamed tissue in larger amounts than any other cyclooxygenase product.[27] The synthesis by inflamed gingival tissue was significantly greater than that by normal gingival tissue.

PGs of the E group seem to play an important role in the pathogenesis of chronic periodontitis by regulating production of osteoclast-activating factor in activated lymphocytes, inducing an increase in the size or number of osteoclasts and accelerating release of lysosomal enzymes and collagenase from activated macrophages.

Tawfik et al[28] found significant correlation between the E- and F-type PGs in gingival tissues and concluded that PGE is by itself pro-inflammatory and causes increased vascular permeability, while PGF is basically anti-inflammatory and inhibits increased vascular permeability.

Dewhirst et al[29] found elevated levels of PGE2 and TXB2 in inflamed samples and Neither PGE2 nor TXB2 were detected in non-inflamed samples.

It was observed that the inflamed gingival tissue in the experimental system synthesize a significantly higher amount of PGs related to PGE2 (PGE2 and its catabolite PGA2) than the normal gingival tissue. The methods of blocking or moderating the effect of prostaglandins were then researched upon. In the early 1970s, Vane and co-workers[19] discovered that aspirin and other non-steroidal drugs exert their effects primarily by interfering with arachidonic acid meta-bolism.[18] One of the first NSAID's to be studied for inhibition of periodontal bone loss was indomethacin, a specific inhibitor of cyclooxygenase and one of the most potent NSAIDs available in the early 1970s.

In a series of retrospective studies conducted between 1981 and 1990 by Waite et al (1981)[30] and Feldman et al (1983)[31] on human subjects who had rheumatoid arthritis and were taking a variety of NSAID's to control symptoms related to that disease were monitored for their periodontal condition. It is apparent from the combined studies that patients who were taking NSAID's demonstrated overall less bone loss than individuals not taking the drug.

Waite and co-workers[30] studied patients with arthritis or ankylosing spondylitis and found that patients taking NSAID's have lesser bone loss. They stated that an inhibitory effect of indomethacin on bone loss in periodontal disease could result from a reduction in prostaglandin concentration as a result of drug therapy. The prostaglandins are present in the later stages of the inflammatory process and their formation seems to be associated with the migration of mononuclear cells and also with the complement system.[30]

Feldman,[31] in evaluating arthritic patients taking aspirin or aspirin plus indomethacin for at least a 5-year period, found fewer sites with 10% or greater bone loss and the overall bone loss for the dentition was lower.[31] In his cross-sectional study he reported that the patients taking NSAID's had a decreased rate and extent of bone loss and also stated that there is no evidence to suggest that the reduction in the alveolar bone loss noted in arthritic patients was a natural concomitant of the arthritic process; they suggested that this may be due to the long-term ASA or ASA plus indomethacin regimen.[31]

Torbinejad (1979)[32] provided an early report on the effect of indomethacin on bone loss in vivo. Large increases in polymorphonuclear leukocytes and macrophages were seen in association with the inflammatory lesion in both control and NSAID treated animals. However, in spite of the appearance of these cells in the experimental animals, no bone loss was noted, indicating that the NSAID indomethacin could block bone resorption suggesting their effects on PGs.[32]

Similar results were achieved by Nyman et al (1979)[21] on ligature-induced periodontitis in beagle dogs, where they found reduced alveolar bone resorption with indomethacin. It was concluded that when indomethacin is administered during the induction of periodontal disease with ligatures, the inflammatory component is reduced, resulting in less bone loss. They reasoned that indomethacin has suppressive effects on neutrophil accumulation, edema, swelling and vasodilation in acute inflammation. This means that ligatures placed in a subgingival position primarily operate by disrupting the epithelial barrier and denuding the connective tissue, indomethacin treatment suppressed the acute inflammatory reaction, and the ligatures therefore could produce only minute signs of acute gingivitis.

Another interesting finding, which correlated with data presented earlier in a study by Waite,[30] was the effect of plaque on the effectiveness of the drug. When subgingival plaque scores were higher, the effect of indomethacin was not as great as it was at lower plaque levels, suggesting that indomethacin may work better when plaque is well controlled at the gingival margin.[21] Also in 1979, Nichols et al, suggested a transient effect of indomethacin on alveolar bone metabolism in the ligature model.[32]

Weaks-Dybvig et al[23] in 1982, using a ligature induced periodontal disease model in the squirrel monkey, reported that administering indomethacin prior to the ligature placement and throughout the period of ligature-induced disease inhibited significant losses of alveolar bone. They also found that bone mass was greater in indomethacin treated animals than in non-

indomethacin treated animals following ligature placement. Additionally, it was determined that osteoclast density was decreased following 1 week of indomethacin treatment. Authors suggested that indomethacin suppression of bone resorption in the ligature model is primarily through inhibition of PG synthesis at the time of ligature placement. In addition to inhibiting prostaglandin biosynthesis, indomethacin may be altering cellular responses via nonprostaglandin mediated pathways. They also stated that Indomethacin nearly abolished the substantial loss of alveolar bone mass, the Loss of bone height, and the large increase in osteoclast density during the time period of this experiment.[23]

In 1984, Williams and co-workers[15] were the first to demonstrate the effect of an NSAID on naturally occurring bone loss in vivo. Using the NSAID flurbiprofen, a phenylalkanoic acid known to be a very potent cyclooxygenase inhibitor, these investigators reported a significant decrease in the resorption of alveolar bone of naturally occurring periodontitis. The decrease was even more striking in those animals that received flurbiprofen and surgical care, where a 91% decrease in bone loss rate was observed. Williams group also looked at the effect of topical application of the NSAID on the progression of periodontitis in beagles in 1988. The untreated control dogs showed slightly elevated rates of bone loss during the treatment period when compared with pretreatment rates. In contrast, bone loss rates decreased by 11% from baseline levels in the topical flurbiprofen-treated dogs. Because flurbiprofen is known to be rapidly absorbed through the mucosa within 10 min of its application, the topical application of the drug seems a logical extension of its use. It could be possible using this mode of application to increase better and more effectively the local tissue concentration of the drug rather than through systemic administration. Their data suggest that one major pathway of bone loss resorption in beagle periodontal disease may be via arachidonic acid metabolism and hence the bone loss was reduced by indomethacin.

Williams et al in 1988[16] demonstrated that high and low doses of ibuprofen in both sustained release and normal release formulations resulted in reduction in the rate of bone loss. The reduction of bone loss was significant in the higher dosage rates for both sustained release and normal dosing at 4 mg/kg, although reduction was not significantly less than control in the lower dose 0.4 mg/kg. In another study authors found that topical application of flurbiprofen in a gel vehicle significantly inhibits alveolar bone loss in beagles over a 7-month treatment period. They reasoned that the effects may be due to the rapid absorption of drug with local application.

In a study by Jeffcoat et al (1991)[520] in patients taking 500 mg naproxen bid for 3 months showed less bone loss, decreased uptake of technetium-99m, and increased bone gain when compared with patients receiving placebo therapy. They found that at 4 months of treatment the rate of bone loss in the naproxen-treated dogs was significantly less than pretreatment, but at 7 months of treatment the rate was no longer statistically significantly less than baseline. For this they reasoned that probably it reflects a dose response to naproxen treatment.[520] Similarly Howell and co-workers (1991),[27,28] investigating the use of naproxen in the treatment of naturally occurring periodontitis in beagle dogs, demonstrated that naproxen-treated dogs demonstrated significantly less bone loss during the treatment period than during the pretreatment period. This was likely due to the dose response to naproxen for the first 30 days of the treatment when dosage was at 2 mg/kg. This dosage was decreased tenfold due to intolerance of the beagle dogs for the higher dosage. The lower dosage appeared to be less effective in reducing the rate of bone loss. In addition, the number of "active" sites were decreased significantly in dogs taking naproxen over that seen in the control group. Similarly, dogs treated with naproxen continued to have more "nonactive" sites remaining "nonactive" during the treatment period than did the control animals.

In some cases, of Waite and co-workers[30] in patients with arthritis or ankylosing spondylitis the clinical parameters measured by plaque index, gingival index, probing depth, and attachment loss were also improved in those patients taking NSAID's. Patients taking NSAID's had lower gingival index and shallower periodontal pocket depths. Although, patients in this study took a variety of drugs, many of the patients had taken indomethacin. When patients taking indomethacin were examined as an individual cohort, the differences between the test and control groups appeared similar to the larger pooled sample. When statistics were applied, a significant difference was found in gingival index values, whereas other parameters measured (e.g. probing attachment loss) were not significantly different in the indomethacin group. This change in significance from pooled data could be due to the smaller sample size of the indomethacin-treated group. Authors concluded that anti-inflammatory agents might influence the response of the gingival tissues to dental plaque deposits. It was of interest to find that this effect could be detected clinically for a relatively small group of subjects and that this reduction in inflammation resulted in a trend towards a decrease in the loss of epithelial attachment.

Similarly Vogel et al (1986) studied the effect of topical application of indomethacin on periodontal disease in the squirrel monkey. The topical application of substituted oxazolopyridine derivative additionally inhibited gingival inflammation as assessed by bleeding index and loss of attachment. Indomethacin had no significant effects with respect to these parameters. They stated that both the drugs inhibit PG synthesis, it was assumed that the difference between the two drugs behavior may be due to the effects of the substituted oxazolo-pyridine derivative on periodontal inflammation, were related to the anti-inflammatory properties of the drug. The possibility that this compound may affect the bacterial flora as well cannot be ruled out by this study.

Offenbacher et al in 1987 confirmed the efficacy of flurbiprofen in the treatment of periodontal disease using the primate model. It was noted that in those animals treated with flurbiprofen, there was a statistically significant inhibition of attachment loss, gingival inflammation, and bleeding on probing in both the ligature-induced and naturally occurring periodontitis at 6 months. Thus, this investigation provides evidence that flurbiprofen is effective in the primate, as previously demonstrated in the beagle. The metabolism of flurbiprofen in dogs is considerably different than in primates. The drug half-life is 4-6 hours in humans and 1.5-3 hours in the rhesus monkey, but it is quite extended (35 hours) in the dogs. Furthermore, humans produce 3 metabolites of flurbiprofen and the dog only 2. Thus, the findings in the primate model more closely parallel the therapeutic outcome that may be expected in humans.

Jeffcoat et al, 1988[33] reported that in a 2-month trial, human periodontal disease progression was significantly slowed with flurbiprofen treatment, as measured by subtraction radiography and alveolar bone metabolism. They suggested that the metabolites of the cyclooxygenase pathway for arachidonic acid metabolism are decreased in the crevicular fluid when flurbiprofen is administered.

In further human experiments, Heasman et al (1990) reported that the systemic administration of flurbiprofen to a group of healthy volunteers decreased the gingival inflammation and crevicular fluid flow. Their reasoned that flurbiprofen may be detected in human CF after oral administration and that the levels are in excess of the plasma level, which in beagles has been shown to inhibit alveolar bone loss in periodontal disease. In a follow-up investigation by Heasman et al (1993)[34] their results indicated that flurbiprofen can be detected in human crevicular fluid following oral administration . This would help to further confirm the belief that systemic administration of the drug can result in concentrated amounts of flurbiprofen in the periodontal tissues.[32]

Several other NSAID's have also been evaluated for efficacy in the treatment of periodontal disease progression. Johnson et al (1990)[35] concluded that naproxen can enhance recovery of inflamed tissue following the removal of the inciting plaque agents. They reasoned that important mediators of many aspects of acute and chronic inflammation in human subjects. Drugs such as Naprosyn effectively block production of these mole-

cules.[32]

Flemmig TF (1996)[36] they found that conventional periodontal therapy and systemically administrated acetylsalicylic acid (ASA) is functionally synergistic. They reasoned that the combination of therapies and their different mechanisms of action, i.e., reduction of bacterial plaque and inhibition of destructive components of the immune responses, may result in functionally synergistic therapeutic efficacies in patients with untreated adult periodontitis.

Faquette DW (1997)[37] found that animals treated with dentifrice or systemic (S)-ketoprofen exhibited significantly reduced elevations in gingival index scores as compared to placebo treated animals they reasoned that this could be due to alteration in progression of periodontal disease by (S)-ketoprofen.

In a study by Howell and co-workers (1991)[27] the effect of topical application of piroxicam on developing gingivitis in beagles was investigated and they concluded that topically applied piroxicam can significantly inhibit the development of gingival inflammation in beagle dogs by significantly decreasing the gingival index and also number of bleeding sites.[27]

Longitudinal studies extending from two months to one year have shown that NSAID's not only reduce gingival inflammation but also reduce alveolar bone loss. Some of these studies showed similar results for topical and systemic forms of NSAID's. [32]

Yewey et al (1991) also reported reductions in mean pocket depth and bleeding when probing, using the local delivery of flurbiprofen in a biodegradable vehicle to the periodontal pockets of beagle dogs.

Lasfargues and Saffar in1983[38] evaluated the effect of indomethacin on bone destruction in the golden hamster, it was found that, although the indomethacin treated animals had decreased bone loss and decreased numbers of osteoclasts, neither was significantly different from the control. Throughout these experiments, no correlation was found between the amount of bone loss and the number of osteoclasts present. Indomethacin seems more effective when administered in the established stage of the disease (curative treatment) than in the incipient stage (preventive treatment). The reason for this is unclear since the time of exposure to indomethacine was the same. The incomplete effect of Indomethacin in decreasing osteoclastic resorption could be due to a partial inhibition of PG synthesis and/or to the action of other factors promoting bone resorption. In the acute phase of the inflammatory response, PGs could have a proinflammatory action and could promote tissue damage and bone resorption. As the inflammatory reaction becomes chronic, PGs could have an anti-inflammatory effect. In this way, Indomethacin had little effect on bone destruction. Authors reasoned that in addition to indomethacin's inhibitory effect on PG synthesis, it induces humoral and cellular immunity in low doses.[32]

Brägger U et al (1997)[39] the results of their study could not justify general administration of flurbiprofen for the purpose of reduction of bone resorption after periodontal surgical procedures in patients with adult periodontitis. The possible explanation for the lack of effect given by authors was the limitation in sensitivity of both the radiographic and the clinical methods applied to reveal differences that may have been present due to the drug intake.

No association between the intake of NSAID's or rheumatoid arthritis was shown with respect to changes in attachment loss by Del Puente et al in1988. These findings were supported by Heasman and Seymour in1990. Patients studied were taking various dosages of a variety of NSAID's, which included ibuprofen, piroxicam, naproxen, and indomethacin. No significant differences were found in plaque index, gingival index, probing depth, attachment loss, or bone loss. However, the rate of gingival fluid flow was significantly higher in the control group than in the study population taking NSAID's, suggesting that chronic ingestion of NSAID's may affect the vascularity and permeability of small blood vessels. The findings in this recent study are in contrast to previous reports on the effect of NSAID's on human periodontal disease that indicated NSAID's reduced periodontal disease. Several explanations for this difference in result were offered by the authors, including the fact that the group studied was very healthy with general probing depths of less than 3 mm and that the wide variety of drugs and dosages may have masked any effect that one of the individual medications may have had when examined alone. The authors suggested that blocking the cyclooxygenase or lipoxygenase pathway alone may not be sufficient to decrease the inflammatory response, a finding not seen by other investigators.[32]

Heasman et al reported that with topical flurbiprofen treatment there was no significant difference on the degree of gingival inflammation when compared with the quadrants treated with a topical placebo. They reasoned that despite the high speed aspiration used during irrigation process, some flurbiprofen may have been absorbed through the floor of the mouth or buccal tissues, thus having a systemic effect on the gingival tissues of both test and control sides of each jaw.

Lasfargues and Saffar (1983)[38] compared calcitonin and indomethacin and found calcitonin to be more effective than Indomethacin in preventing bone destruction. The combination of the two drugs did not appear to optimize the effect of calcitonin alone on bone loss. They concluded that calcitonin is not only an inhibitor of bone resorption but also an anti-inflammatory agent. They questioned the effectiveness of dose (2 mg/kg/day) of indomethacin used in their study.

Similarly Vogel et al (1986)[40] studied the effect of topical application of indomethacin on periodontal disease in the squirrel monkey. Both systemically administered and topically applied NSAIDs inhibited the resorption of interproximal alveolar bone. They hypothesized that some of the bone that was initially resorbed by the acute inflammation associated with the trauma of ligature placement was reapposed in the form of osteoid after the acute inflammatory response subsided. Both the indomethacin and the substituted oxazolo-pyridine group had significantly greater area of bone than did the ligated placebo group.

Their study demonstrated that both systemically administered indomethacin and a topically applied substituted oxazolo-pyridine derivative inhibited the resorption of interproximal alveolar bone associated with ligature induced periodontitis. The substituted oxazolo-pyridine derivative additionally inhibited gingival inflammation, as assessed clinically by a bleeding index, and loss of attachment as compared to a ligated placebo group, with indomethacin having no significant effects with respect to these parameters. They reasoned that the substituted oxazolo-pyridine derivative is topically active and would probably have minimal systemic effects, since it is rapidly metabolized and excreted once it enters the circulation. With respect to indomethacin, these results of this study are similar to those reported by Nyman et al (1979)[12] and Weeks-Dybvig et al (1982). [14] In 1988, Williams et al[16] administered indomethacin (1 mg/kg/day) to beagle dogs to investigate its effect on the rate of bone loss. The rate of decrease in the flurbiprofen group was the same as reported in their previous study. In addition, the decreased rate of bone loss in indomethacin dogs, although significant when compared with the untreated control dogs during the treatment period, was not significantly different than the rate seen in the pretreatment period. It was determined that the rate of bone loss was decreased further at 6 months than had been seen at 3 months, indicating that the effect of indomethacin may take somewhat longer to be observed clinically than that for flurbiprofen. The investigators noted that although the two drugs were similar in that they inhibit cyclooxygenase, the metabolism by the body may be significantly different and mean blood levels for both agents may vary significantly. It was also possible that the two NSAIDs affected the cyclooxygenase enzyme in different ways, thereby explaining the differences in results seen between the two compounds.

In their other reports (Williams et al, 1987, 1988), these investigators noted that by 24 months of flurbiprofen and indomethacin treatment the rate of bone loss between the two groups was statistically not significantly different. At the time, no explanation was given for the loss of effect of flurbiprofen, although the authors were able to conclude that flurbiprofen was a potent inhibitor of bone

loss in the human for an 18-month period. These investigators also suspected that compliance was a problem with some patients not taking flurbiprofen toward the end of the 2-year treatment period.[32]

Kornman et al (1990)[41] reported that the topical application of either of two NSAIDs, ibuprofen or meclofenamic acid, to the gingiva of monkeys significantly inhibited bone loss and that meclofenamic acid also increased bone density in the primate model. These effects on bone were observed in the presence of continuing clinical gingivitis and plaque accumulation, indicating that these NSAID's can work in the presence of significant local factors that would influence the progression of the disease. These observations on the disease effects of two NSAID's may suggest specific and perhaps different modes of action, a specificity which was also reflected in the differences observed in PMN chemotaxis. The concentrations of the two drugs differed and were established for this study based on toxicity studies in dogs. The actual administered topical dosage of meclofenamic acid was approximately twice the usual systemic dosage as determined by the weight of the animals, whereas the topical ibuprofen was administered at a dosage equivalent to the usual systemic dosage for this agent. The differences observed between agents in this study may be attributable to the different doses.

In 1983, Vogel and co-workers[32] demonstrated the effect of NSAID's on the progression of periodontal disease in man and found that NSAID's have little effect in the presence of plaque. No statistically significant differences were found between the Sulindac and Fluocinonide or placebo groups throughout the study period. Authors explained that it is possible due to the short experimental period of this study, adequate time was not given for a significant effect to be demonstrated.

Ng VW (1998) found that the adjunctive use of systemic doxycycline alone or in combination with Ibuprofen results in a statistically significant, yet modest clinical, improvement beyond that obtained by scaling/root planing. The additional clinical improvement achieved by the adjunctive use of doxycycline alone or in combination with Ibuprofen is slight, but statistically significant was attributed not only to the antibacterial effect, but also to the anticollagenolytic effect of doxycycline.

Bezerra MM (2000) found that both IND and MLX reduced alveolar bone loss and histopathologic changes. Neutrophilia and lymphomonocytosis were also significantly reversed. MLX displayed similar efficacy and less gastric damage than IND. MLX may provide a better risk/benefit ratio in the treatment of human periodontitis than non-selective COX inhibitors. They reasoned that MLX selectively inhibit COX-2 and hence the reduction in inflammation was observed. Similar results were obtained by Holzhausen M et al [42] and Pinho MN et al[43] with celecoxib and etricoxib and loxoprofen studied separately or as an adjunct to scaling and root planing.

Along with all the beneficial effects NSAIDs comes for a price. The various problems associated with NSAIDs include the GI toxicity and renal toxicity, this toxicity could be minimized by using COX-2 selective inhibitors like celecoxib, rofecoxib but these drugs have also known to cause cardiac disturbances. Williams et al[15] have demonstrated that the NSAID's given for a period of [12] months reduce the bone loss but have a rebound effect once the therapy is stopped. They also showed that if the therapy is continued for more than 18 months the reduction in bone loss does not remain significant. Hence long term therapy is need for NSAID's to show its effect but with very long term therapy the significant difference is lost. Also the long term therapy is an economic liability as well as have greater side effect. It is also evident that low doses of NSAID's are comparatively less effective hence a higher dose is needed which again have higher chances of toxicity.

NSAID's have been used for dental pain. The best strategy for minimizing pain onset is administration of an NSAID's prior to the induction of COX-2 post-operatively. For patients who do not receive satisfactory relief from an NSAID alone, combining it with an opioid may provide additive analgesia but will also be accompanied by more frequent side-effects.

Collectively, the above data suggest that indomethacin is able to reduce bone destruction in various animal model systems. None of the aforementioned studies were successful in directly relating the inhibition of prostaglandin synthesis and its effects to indomethacin, although sufficient evidence certainly exists to indicate that this is the most significant factor in the effectiveness of the drug in blocking bone resorption.

Indomethacin, flurbiprofen, ibuprofen naproxen and meclofenamic acid have shown to reduce the bone loss and inflammation, all of these drugs are shown to be more potent than aspirin. Comparative studies between indomethacin and flurbiprofen shows flurbiprofen to be more effective as compared to indomethacin. Among ibuprofen and meclophenamic acid, meclophenamic acid has shown better results. It appears that indomethacin is most effective in those animals that are relatively plaque free. As plaque continues to accumulate on the gingival margin, the drug appears to be less able to reverse or mediate the effects of the ongoing inflammatory process. Hence the above studies have confirmed the effectiveness of NSAID's on the inhibition of bone loss in periodontal disease and, whether administered systemically or topically, the drug flurbiprofen appears to be a potent agent in the treatment of the disease. Hence it will also be important to see if other routes of administration of NSAID's, such as local delivery, will be effective in preventing or slowing periodontal disease progression. Piroxicam and flurbiprofen seems to be more effective topically as compared to other NSAIDs, also the lower doses of NSAID's could be efficacious in slowing bone loss, and this needs to be examined. But as NSAID's do come with a price tag, the drawbacks include long term therapy needed for desired effects, long term therapy is also an economic liability, as well as patient compliance is difficult, also GI and renal toxicity and cardiac disturbances pose a problem. Hence there also must be a continual examination of the side effects of taking NSAID's for prolonged periods of time. An important question to be answered in future is, do the beneficial effects of NSAIDs on slowing periodontal disease progression outweigh potentially harmful side effects?

Conclusion

Ever since NSAID's have been discovered they are being used for relief of pain, fever and inflammation, but their mechanism of action remained undiscovered until late 1970s when Vane discovered that their analgesic, antipyretic and anti-inflammatory properties are based on the inhibition of PG synthesis. Since then NSAID's have come a long way.

Both systemic and local administration of NSAID's have been extensively used in periodontics.

Comparative studies of piroxicam and indomethacin shows piroxicam to be more effective, in the comparative studies of indomethacine and flurbiprofen seems to be more effective because it penetrates in inflamed tissues easily and has an extended plasma half-life, and minimal toxic side effects.

As the adverse effects of NSAID's are comparatively more, which includes GI and renal toxicities, requirement of long term therapy for desired effects may lead to reduced patient compliance and increased economic liability.

Reference:

References are available on request at editor@healtalkht.com