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Effect of Nonsteriodal Anti-Inflammatory Drugs on Orthodontic Tooth Movement – Review

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ABSTRACT : *Orthodontic tooth movement is a biological response towards mechanical force resulting in remodeling of the periodontal structure allowing for tooth movement. Periodontal remodelling is a complex process regulated in parts by prostaglandins and adversely affected by the use of nonsterioidal anti-inflammatory drugs. Orthodontists often prescribe drugs to manage pain from force application to biologic tissues. No steroidal anti-inflammatory drugs (NSAIDs) are the drugs commonly prescribed. NSAIDs block prostaglandin synthesis and result in slower tooth movement. Prostaglandins have been found to play a direct role in bone resorption. Aspirin, acetaminophen, ibuprofen, diclofenac, vadecoxib, and celecoxib are the commonly prescribed drugs. Acetaminophen is the drug of choice for orthodontic pain without affecting orthodontic tooth movement. This review concerns commonly used NSAIDs , mechanism of action and the effect on tooth movement.*

KEYWORDS – *Orthodontics, NSAIDs, tooth movement, pain control, prostaglandin*

I. INTRODUCTION

Tooth movement is the key principle behind any orthodontic treatment. Orthodontic tooth movement (OTM) is mainly a biological response towards mechanical force. It is induced by the prolonged application of controlled mechanical force on the tooth, which eventually causes remodeling of the tooth socket by creating pressure and tension zones in the alveolar bone and periodontal ligament.

The control of pain during orthodontic tooth movement is of interest of both the patient and orthodontist. Routinely the clinician prescribes the drugs for orthodontic pain. These drugs alter or interfere with the inflammatory process and therefore have an effect on the tooth movement. Several studies have proposed the effect of short and long term administration of medication on orthodontic tooth movement. Davidovitch et al.[1]and Yamasaki et al.[2] concluded in their study that the rate of orthodontic tooth movement can be altered by administrating certain drugs locally or systemically. The drugs used in orthodontics can be broadly classified into two major groups, promoter drugs and suppressor agents. Promoter drugs are agents that act with the secondary and primary inflammatory mediators and enhance the tooth movement, examples being; Prostaglandin, Leukotrienes, Cytokines, Vitamin D, Osteocalcin, and Corticosteroids. Suppressor agents are drugs which reduces bone resorption examples are; Nonsteroidal anti-inflammatory agents and bisphosphonates.

Thus the aim of this review article is to have proper knowledge of the mechanism of action and effects of some commonly used pharmaceutical products (NSAIDs) so that the clinician should select best therapeutic strategy in every individual.

II. EFFECT OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS ((NSAIDS) USED IN ORTHODONTICS FOR PAIN CONTROL:

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most common medications taken worldwide for the treatment of pain, inflammation, and fever.[3] NSAIDs act by inhibiting the prostaglandin (PG) synthase enzymes, colloquially known as cyclooxygenases. The inhibition of cyclooxygenase-2 (COX-2) is thought to mediate, in large part, the antipyretic, analgesic, and anti-inflammatory actions of NSAIDs, while the simultaneous inhibition of cyclooxygenase-1 (COX-1) largely but not exclusively accounts for unwanted adverse effects in the GI tract.

Orthodontic treatment is based on the biologic principle that prolonged pressure on teeth results in remodeling of periodontal structures, allowing for tooth movement. Periodontal remodeling is a complex process regulated in part by prostaglandins and adversely affected by the use of nonsteroidal anti-inflammatory drugs. Cyclooxygenase inhibition resulted in exacerbation of IL 1β–mediated collagenase B (MMP-9) production and activity, as well as attenuation of type IV pro-collagen synthesis levels by endothelial cells in vitro. Two isoforms of mammalian cyclooxygenase(COX) have been described: the constitutive COX-1 and the inducible COX-2. Of these, COX-1 is considered important in tissue homeostasis. However, COX-2 is transcriptionally induced by cytokines (TNFαandIL-1β) and appears to be important in the development of inflammation. Prostaglandin production during the inflammatory process depends on the enzymatic degradation of arachidonic acid through the constitutive isoform of COX-1 and the inducible isoform of COX-2 pathways. COX-1 produces prostaglandins that protect the gastrointestinal mucosa. The selective inhibition of COX-2 produces anti-inflammatory effects, causing less injury to the gastrointestinal mucosa than the nonselective NSAIDs. Consequently, the use of selective COX-2 inhibitors is increasing, replacing conventional NSAIDs, especially for chronic inflammatory conditions. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been developed that target these cyclooxygenases.

Hence, the use of over-the-counter nonsteroidal anti-inflammatory drugs during tooth movement may result in aberrant remodeling of periodontal vasculature and other structures, ultimately affecting orthodontic treatment efficacy. The use of analgesics such as nonsteroidal anti-inflammatorydrugs (NSAIDs) that inhibit the release of prostaglandin (PGs) and stop inflammation are effective in the treatment of pain related to orthodontic treatment. Nevertheless, the extended use of NSAIDs is inappropriate for orthodontic discomfort, because, as research and clinical experience suggests, their use could slow down tooth movement.[3] NSAIDs are a chemically heterogeneous group of compounds, which nevertheless share certain therapeutic actions and adverse effects. The class includes derivatives of salicylic acid (e.g., aspirin, diflusinal), propionic acid (e.g., naproxen, ibuprofen, flurbiprofen, ketoprofen), acetic acid (e.g., indomethacin, etodolac, diclofenac, ketorolac), enolic acid (e.g., piroxicam, phenylbutazone), fenamic acid (e.g., mefenamic acid, meclofenamic acid), alkanones(nabumetone), and diaryl heterocyclic compounds (e.g., celecoxib, valdecoxib, rofecoxib, etoricoxib) (Figure 1).

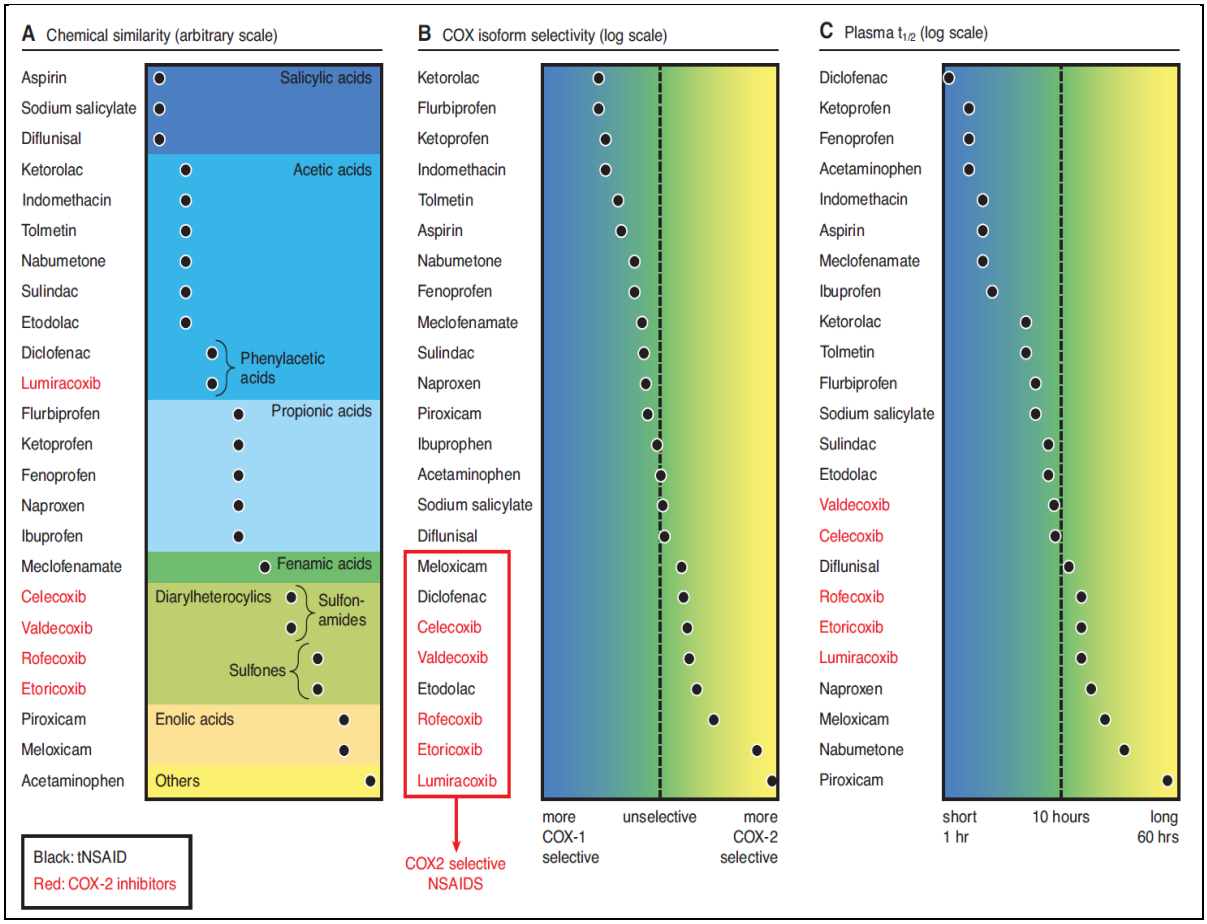

Fig 1. Classification of NSAIDs by chemical similarity (panel A), cyclooxygenase (COX) isoform selectivity (panel B), and plasma t1/2 (panel C). The COX selectivity chart is plotted from data published in Warner et al., 1999, and FitzGerald and Patrono, 2001.tNSAIDs, traditional nonsteroidal anti-inflammatory drugs.

Most NSAIDs are rapidly absorbed following oral ingestion, and peak plasma concentrations usually are reached within 2-3 hours. All COX-2–selective NSAIDs are well absorbed. The poor aqueous solubility of most NSAIDs often is reflected by a less than proportional increase in area under the curve (AUC) of plasma concentration–time curves, due to incomplete dissolution, when the dose is increased. Food intake may delay absorption and sometimes decreases systemic availability (i.e., fenoprofen, sulindac). Antacids, commonly prescribed to patients on NSAID therapy, variably delay, but rarely reduce, absorption.

Common adverse events that complicate therapy with NSAIDs are outlined in Table 1.

Side Effects of NSAIDs	
SYSTEM	**MANIFESTATION**
GI	• Abdominal pain • Nausea • Diarrhea • Anorexia • Gastric erosions/ulcers • Anemia • GI hemorrhage • Perforation/obstruction
Platelets	• Inhibited platelet activation • Propensity for bruising • Increased risk of hemorrhage
Renal	• Salt and water retention • Edema, worsening of renal function in renal/cardiac and cirrhotic patients • Decreased effectiveness of antihypertensive medications • Decreased effectiveness of diuretic medications • Decreased urate excretion (especially with aspirin) • Hyperkalemia
Cardiovascular	• Closure of ductusarteriosus • Myocardial infarction • Stroke • Thrombosis
CNS	• Headache • Vertigo • Dizziness • Confusion • Hyperventilation (salicylates)
Uterus	• Prolongation of gestation • Inhibition of labor
Hypersensitivity	• Vasomotor rhinitis • Angioneurotic edema • Asthma • Urticaria • Flushing • Hypotension • Shock

Table 1. Adverse effects of NSAIDs.

2.1 Salicylates: Aspirin (prototype)

Salicylic acid (orthohydroxybenzoic acid) only be used externally; therefore various derivatives of this acid have been synthesized for systemic use. These comprise two large classes, namely esters of salicylic acid obtained from substitutions within the carboxyl group and salicylate esters of organic acids, in which the carboxyl group is retained and substitution is made in the hydroxyl group.

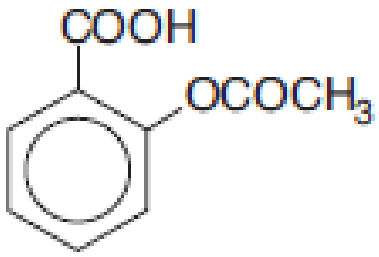

Fig 2.Chemical structures of aspirin

Mechanism of Action: Salicylates generally act by virtue of their content of salicylic acid. Aspirin (fig 2) covalently modifies COX-1 and COX-2, irreversibly inhibiting COX activity. This is an important distinction from all the NSAIDs because the duration of aspirin's effects is related to the turnover rate of COXs in different target tissues. The duration of effect of non-aspirin NSAIDs, which inhibit the active sites of the COX enzymes competitively, relates to the time course of drug disposition. The importance of enzyme turnover in recovery from aspirin action is most notable in platelets, which, being enucleate, have a markedly limited capacity for protein synthesis.

Salicylates also can influence the metabolism of connective tissue, and these effects may be involved in their anti-inflammatory action. For example, salicylates can affect the composition, biosynthesis, or metabolism of connective tissue mucopolysaccharides in the ground substance that provides barriers to the spread of infection and inflammation.

Aspirin is rapidly deacetylated in the gutwall, liver, plasma and other tissues to releases salicylic acid which is the major circulating and active form. It is ~80% bound to plasma proteins and volume of distribution - 0.17 L / kg. It slowly enters brain but freely crosses placenta. Both aspirin and salicylic acid are conjugated in liver with glvcine converted to salicyluric acid (major pathway); and glucuronic acid

Sari et al. [4]in his study has found that prostaglandin E2 levels of GCF decreased by 12.4pg/µL and in between 24 and 168 hours was 24.8pg/µL in the aspirin group. This indicated that aspirin inhibits prostaglandin (PG) synthesis during the first 24 hours. The PGE2 levels peaked at 24 hours and decreased nearly to baseline levels by 168 hours. Aspirin significantly (*P* _.01) reduced the numbers of resorption lacunae and osteoclasts in the pressure areas of orthodontic tooth movement.

Orthodontic tooth movement slows down during the 10 days of the study of Arias and Marquez-Orozco et al [5] in the rats treated with aspirin group.

2.2 Para-Aminophenol Derivatives

Phenacetin introduced in 1887 was extensively used as analgesic-antipyretic, but is now banned because it was implicated in analgesic abuse nephropathy. Acetaminophen (Paracetamol; *N*-acetyl-*p*-aminophenol;TYLENOL, others) is the active metabolite of Phenacetin (fig 3). Paracetamol (acetaminophen) the de-ethylated active metabolite of phenacetin, was also introduced in the last century but has come into common use only since 1950.[6]

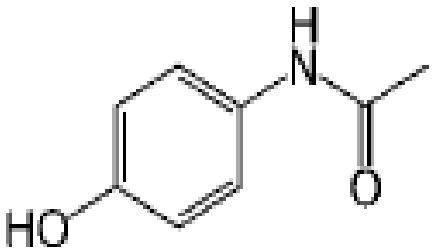

Fig3. Chemical structure of Acetaminophen

Acetaminophen raises the threshold to painful stimuli, thus exerting an analgesic effect against pain due to a variety of etiologies. It is available without a prescription and is used as a common household analgesic. The drug also is available in fixed-dose combinations containing narcotic and non-narcotic analgesics (including aspirin and other salicylates), barbiturates, caffeine, vascular headache remedies, sleep aids, toothache remedies, antihistamines, decongestants, expectorants, cold and flu preparations, and sore throat treatments. Acetaminophen is an effective alternative to aspirin as an analgesic–antipyretic agent; however, its anti-inflammatory effects are much weaker. Acetaminophen is well tolerated and has a low incidence of gastero-intenstinal side effects. However, acute over dosage can cause severe hepatic damage, and the number of accidental or deliberate poisonings with acetaminophen continues to grow.

Mechanism of Action: Acetaminophen has analgesic and antipyretic effects similar to those of aspirin. It has only weak anti-inflammatory effects, and it has been thought to have a generally poor ability to inhibit COX in the presence of high concentrations of peroxides, as are found at sites of inflammation. A dose of 1000 mg results in ~50% inhibition of both COX-1 and COX-2 in whole blood assays *ex vivo* in healthy volunteers. The central analgesic action of paracetamol is like aspirin, i.e. it raises pain threshold, but has weak peripheral anti-inflammatory component. Analgesic action of aspirin and Paracetamol is additive. Paracetamol is a good and promptly acting antipyretic. Paracetamol has negligible anti-inflammatory action. It is a poor inhibitor of PG synthesis in peripheral tissues, but more active on COX in the brain.

Acetaminophen is suitable for analgesic or antipyretic uses and particularly valuable for patients in whom aspirin is contraindicated (e.g., those with peptic ulcer, aspirin hypersensitivity, children with a febrile illness). The conventional oral dose of acetaminophen is 325-650 mg every 4-6 hours; total daily doses should not exceed 4000 mg (2000 mg/day for chronic alcoholics). A dose of 10 mg/kg also may be used. Acetaminophen usually is well tolerated at recommended therapeutic doses. Single or repeated therapeutic doses of acetaminophen have no effect on the cardiovascular and respiratory systems, platelets, or coagulation.

Generally, nonsteroidal anti-inflammatory drugs, due to their potential for slowing tooth movement, are not recommended for use during orthodontic treatment. Therefore, acetaminophen has been suggested as the analgesic of choice for relieving the discomfort associated with orthodontic pain.

Simmons and Brandt were the first to recommend the use of acetaminophen for managing orthodontic pain. Acetaminophen has minimal effects on prostaglandin synthesis. Paracetamol is thought to reduce pain centrally rather than peripherally by inhibition of COX-3 in the brain and the spinal cord. Hypothetically, because acetaminophen is inactive as an anti-inflammatory agent in peripheral tissues, it should have no adverse effect on PG biosynthesis and subsequent bone resorption associated with orthodontic tooth movement, unlike the NSAIDs

Roche, Cisneros et al [7] in their study concluded that acetaminophen has no effect on the rate of tooth movement in rabbits undergoing orthodontic tooth movement. Bartzela et al[8] stated that the effect of paracetamol on OTM in rabbits studied with the administration of 500 mg/kg per day with a force of 100 cN has no effect on the rate of mesial molar movement. As acetaminophen, a proven analgesic that lacks the anti-inflammatory properties of NSAIDs and also does not affect the rate of orthodontic tooth movement it should be the drug of choice for the relief of orthodontic pain.

2.3Acetic Acid Derivatives (Diclofenac)

Diclofenac, a phenylacetic acid derivative, is among the most commonly used NSAIDs (fig 4). It is an analgesic-antipyretic anti-inflammatory drug, similar in efficacy tonaproxen. It inhibits Prostagladin synthesis and is somewhat COX-2 selective. It is marketed as a potassium salt (ZIPSOR, others) for oral administration, as an epolamineform (FLECTOR) for transdermal administration, and as a sodium salt for topical (SOLARAZE gel; VOLTAREN ophthalmic drops, others) or oral (VOLTAREN, VOLTAREN-XR, others) administration.

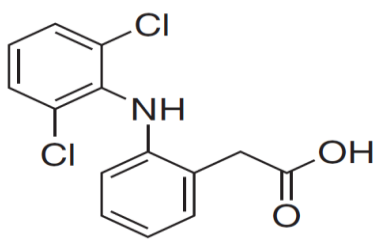

Fig 4. Chemical structure of Diclofenac

Mechanism of Action: Diclofenac has analgesic, antipyretic, and anti-inflammatory activities. Its potency is substantially greater than that of indomethacin, naproxen, or several other tNSAIDs. The selectivity of diclofenac for COX-2 resembles that of celecoxib. In addition, diclofenac appears to reduce intracellular concentrations of free arachidonic acid in leukocytes, perhaps by altering its release or uptake.

Diclofenac has rapid absorption, extensive protein binding, and a t1/2 of 1-2 hours. The short t1/2 makes it necessary to dose diclofenac considerably higher than would be required to inhibit COX-2 fully at peak plasma concentrations to afford inhibition throughout the dosing interval. It is well absorbed orally, 99% protein bound, metabolized and excreted both in urine and bile. The usual daily oral dosage is 100-200 mg, given in several divided doses. Diclofenac is among the most extensively used NSAID; employed in rheumatoid and osteoarthritis, spondylitis, toothache, dysmenorrhoea, post-traumatic and postoperative inflammatory conditions-affords quick relief of pain and wound edema. The early phase of orthodontic tooth movement involves sterile acute inflammation of the periodontal ligament in response to biomechanical forces. Orthodontic tooth movement is achieved by the remodeling of periodontal ligament and alveolar bone in response to mechanical loading. Potassium diclofenac is a potent non - steroidal anti-inflammatory drug. It inhibits COX-1 and COX-2, the enzymes responsible for the formation of prostaglandins from arachidonic acid. The influence of NSAIDs on orthodontic movement is supported by de Carlos *et al.*[9] who evaluated that two local injections of potassium diclofenac (10mg/kg) completely eliminated first molar movement in rats. The result showed that after the application of a 50-g force demonstrated that diclofenac was totally effective in blocking tooth movement in rats. These results are in accordance with the concept of PG mediated tooth movement. Nevertheless, there is general agreement that many factors influence osteoclast and osteoclast-like activity during the mechanical stress of orthodontic tooth movement. Moreover, with a 100-g appliance, diclofenac significantly reduced tooth movement. Since diclofenac a traditional NSAID that inhibits COX-1 and COX-2, tooth movement was greatly inhibited or totally abolished. Absolute inhibition seems to be difficult to achieve because the tooth would be expected to move at least the width of the periodontal ligament. Therefore, the appropriate anti-inflammatory treatment could depend on the intensity of the forces generated by the orthodontic appliances

2.4 Propionic Acid Derivatives (Ibuprofen)

Ibuprofen (fig 5) was the first member of this class to be introduced in1969 as a better tolerated alternative to aspirin. Ibuprofen, the most commonly used NSAID in the U.S., was the first member of the propionic acid class of NSAIDs to come into general use and is available without a prescription in the U.S.[3]

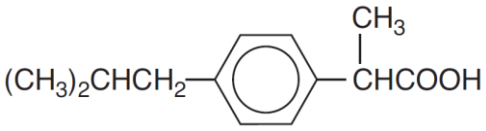

Fig 5. Chemical structure of Ibuprofen.

Mechanism of Action: Propionic acid derivatives are nonselective COX inhibitors with the effects and side effects common to other traditional NSAIDs. Although there is considerable variation in their potency as COX inhibitors, this is not of obvious clinical consequence. Some of the propionic acid derivatives, particularly naproxen, have prominent inhibitory effects on leukocyte function, and some data suggest that naproxen may have slightly better efficacy with regard to analgesia and relief of morning stiffness.

Ibuprofen is well absorbed orally, highly bound to plasma proteins(90-99%), but displacement interactions are not clinically significant also dose of oral anticoagulants and oral hypoglycaemics need not be altered. Ibuprofen has been rated as the safest conventional NSAID by the spontaneous adverse drug reactions reporting system in U.K. Ibuprofen(400mg) has been found equally or more efficacious than a combination of aspirin (650 mg) + codeine (60mg) in relieving dental surgery pain. Concurrent treatment with ibuprofen has been found to prevent irreversible COX inhibition by low dose aspirin. Thus it may antagonize the anti-platelet and cardioproactive effect of low dose aspirin. Doses of ≤800 mg four times daily can be used in the treatment of rheumatoid arthritis and osteoarthritis, but lower doses often are adequate.. For pain or fever, intravenous ibuprofen is administered at a dose of100-800 mg over 30 minutes every 4-6 hours.

Discomfort and pain after initial separator or arch wire placement are common experiences among orthodontic patients. The probable mechanism for preoperative anti-inflammatory effect is the blockage of prostaglandin synthesis in peripheral tissue. If NSAIDs were given before the procedure, the body absorbs them before prostaglandin production, and this decreases the inflammatory response.

Bradley RL et al[10] have evaluated the efficacy of preoperative analgesic consumption and both have found that ibuprofen taken one hour before archwire or band application decreases the pain levels from two hours after bonding until nighttime. They found that pre-emptive ibuprofen significantly decreased pain to chewing at two hours compared with postoperative ibuprofen. The pain scores in patients taking pre- or postoperative ibuprofen compared with patients taking only postoperative ibuprofen. Kehoe etal[11] found that ibuprofen significantly inhibited the production of prostaglandin E (PGE) in the periodontal ligament and, subsequently, decreased the rate of tooth movement. Walker and Buring[12] reported that NSAIDs inhibit the cyclooxygenase pathway and therefore the production of PGE, and it was thought that NSAIDs may inhibit the osteoclastic activity necessary for tooth movement and slow the rate of orthodontic tooth movement. Bartzela et al [8] in their systematic literature review reported that after ibuprofen administration of 30 mg/kg twice a day in rats, the rate of orthodontic tooth movement decreased significantly.

III. CONCLUSION

As orthodontists are routinely used these NASIDs during treatment they must have understanding of fundamentals of drug therapy. Before prescribing these drugs, orthodontist should aware of patient medical history and also converse with patient about the dosage, potential adverse effects. The NSAIDs effectively reduce the pain and discomfort caused by orthodontic tooth movement but they also affect the tooth movement by inhibiting or reducing the inflammatory or bone resorption process. Acetaminophen has been suggested as safe and effective the analgesic of choice for relieving the discomfort associated with orthodontic pain. Ibuprofen is also effective in reducing preoperative as well as postoperative orthodontic pain. Thus today's clinicians should mandatorily update the knowledge on the clinical efficacy of the new drugs as well as the beneficial and harmful effects on human tissues.

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