

## Drug therapy in orthodontics – A review

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### Abstract

The aim of the review article is to analyze the current information regarding the role of pharmaceutical products which might have an impact on the rate of tooth movement that can be accomplished orthodontically. The biochemical pathway for orthodontic movement of a tooth or teeth is found to be accelerated by the tooth movement arising at the level of cells and molecules.

Many medications consumed by patients may have an adverse effect either by increasing or decreasing the movement of teeth orthodontically, so the clinician should be aware of such drugs along with the favourable and unfavourable effects on humans. This article extensively describes about the numerous possible medications that may cause changes in the maximum orthodontical movement of tooth.

**Keywords:** Bone and PDL, Tooth movement, Promotor agents, Suppressor agents.

### Introduction

An ideal orthodontic treatment is established through appropriate tooth movement. When a mechanical force is applied to the teeth the resultant biological response attained is known as the Orthodontic Tooth Movement (OTM). Such a movement occurs mainly due to the continuous application of disciplined mechanical force on a particular tooth or a group of tooth, which eventually leads to remodelling of the socket by bringing forth pressure and tension zones within the alveolar bone and PDL. A great impact on the tooth movement can be achieved through drugs that alter or interfere with the inflammatory method. Several studies have considered the influence of short and long term administration of medication on OTM. Davidovitch et al and Yamasaki et al have inferred in their study that the rate of OTM is altered by administering certain drugs locally or systemically.

DRUG can be defined as, the single active chemical entity present in a medicine that is used for diagnosis, prevention, treatment or cure of a disease.<sup>5</sup> According to WHO (1966) a drug is any substance or product that wishes to change or explore physiological systems or pathological states for the advantage of the recipient.<sup>1</sup>

The drugs usually employed in orthodontics could be broadly classified into two major groups:-

1. Promoter drugs
2. Suppressor agents

Promoter agents are those medications that usually act along with the inflammatory mediators and enhance the orthodontic tooth movement, which include Prostaglandin, Leukotrienes, Cytokines, Vitamin D, Osteocalcin, and Corticosteroids, Thyroid hormones, Parathyroid hormones.

Suppressor agents are those drugs which reduce bone resorption, the examples being; Nonsteroidal anti-inflammatory agents and bisphosphonates, Estrogens, Cholesterol-Lowering Drugs, and Fluorides.

### Promoter drugs

#### Prostaglandins

Prostaglandins (PGE) are eicosanoids. It acts by regulating the synthesis of cyclic AMP in many tissues. This Cyclic AMP is responsible for controlling the action of numerous hormones. A wide range of cellular and tissue functions can be affected by the prostaglandins. PG's act as neuromodulators in the brain by regulating neuronal excitability and sympathetic neurotransmission in periphery. PGE2 & PGI2 sensitize the afferent nerve endings to induce pain by chemical, mechanical & thermal stimuli.

#### Effect of Prostaglandins on bone & tooth movement

They act by stimulating the bone tissue resorption, root resorption, decreased collagen synthesis and increased cyclic AMP. The bone resorption is stimulated by increasing the number of osteoclasts and activating already existing osteoclasts. 0.1-1 microgram lower concentration of PGE2 appears to be effective in enhancing tooth movement. Higher concentration of these may lead to root resorption. Systemic administration is reported to possess higher impact than local administration. According to Klein and Raisz et al, Dowsett et al, prostaglandins play an important role in promoting bone resorption. In 1973, Goldhaber et al. reported that there is an increase in level of prostaglandins in periodontal diseases. It has been shown in a split mouth study that the local administration of PGE1 or PGE2 in the gingiva near the distal area of canines to be retracted, caused double the rate of tooth movement compared to the contralateral, control side. It was noted that there was no side effects seen in the gingiva. Studies on humans were conducted in 1984, Yamasaki et al studied the consequences of PGE1 administration on tooth movement during orthodontic treatment. According to the author, the rate of tooth movement was doubled as compared to control sides. Lee in a later study, compared lidocaine and PGE 1 and reported that PGE 1 was more effective in bone resorption but it had certain side effects such as local irritation and phlebitis.<sup>2</sup>

### Leukotrienes

Leukotrienes are a category of eicosanoid that could be a product of arachidonic acid conversion and are the only eicosanoids that are formed individually from the enzyme called cyclooxygenase (COX). They are produced when arachidonic acid is metabolised by lipoxygenase enzymes. Leukotrienes also play an important role in Inflammation, allergies, and diseases such as asthma. These conditions can be cured by using leukotriene inhibitors which block leukotriene receptors hence counteracts their effects. Examples of medication are montelukast and zafirlukast.

### Effects on bone and tooth movement

It stimulates bone resorption. According to Mohammed AH et al. 1989, leukotrienes causes increase in orthodontic tooth movement, through bone remodelling whereas, leukotriene inhibitors work the other way round. Therefore, the use of leukotriene inhibitors can delay orthodontic treatment, leukotrienes can be used in future clinical applications that could result in increasing tooth movement.<sup>3</sup>

### Vitamin D3

Vitamin D3 (1, 25 dihydroxycholecalciferol (1, 25 [OH] 2D3) is a vital key of calcium homeostasis. With the help of parathyroid hormones and calcitonin, Vitamin D3 will regulate the metabolic activity of calcium and phosphate levels. In latest studies reported that Vitamin D3 supplement is very useful for the treatment of osteoporosis because it will increase the amount of bone mass and it decreases the rupture of osteoporotic patients so it is called as active suppressor agent. But in some other studies authors consider vitamin D3 is a promoter agent due to stimulatory effects on osteoclasts. Collins et al in 1988 he conducted a study, by the local application of vitamin D3 in rats helps to increase the rate of tooth movement. So there should be more studies to be conducted regarding vitamin D3 to determine the exact effect in orthodontic tooth movement.<sup>4</sup>

### Corticosteroids

Adrenal cortex of adrenal gland secretes androgen (sex hormone) and corticoid hormones. Corticosteroids are classified as glucocorticoid and mineralocorticoid. Glucocorticoids are used in the treatment of various inflammatory and autoimmune conditions including rheumatoid arthritis, dermatitis, allergies, and asthma. They are also prescribed as immunosuppressive medications after organ transplantation. Corticosteroids check the formation of prostaglandins by influencing the arachidonic acid pathway. Lipocortin is an endogenous protein formed by steroids which blocks the activity of phospholipase A2, thus preventing the release of arachidonic acid .it influences the synthesis of prostaglandin, leukotrienes or thromboxanes. Corticosteroids reduce the production of lymphokines, serotonin and bradykinin at the injured sites. They play a vital role in inhibiting the intestinal calcium absorption, there by leads to direct inhibition of osteoblastic function and increase in bone resorption. In a study by, Kalia and colleagues in 2004 determined the rate of tooth movement

in rats during short and long term corticosteroid therapy. They arrived at a conclusion that bone remodelling was slowed down in acute administrations, however the rate of tooth movement increased in chronic treatment. This suggested that orthodontic treatment should be carried out later or postponed in patients undergoing short term corticosteroids. Those patients with long term corticosteroid therapy treatment can be continued with minimal adverse effect and more extensive retention that may prove to be helpful in retaining these teeth if the dentist decides to proceed with the orthodontic treatment. When prolonged use, the major side effect noticed is osteoporosis. It has been proved in several animal models with this sort of osteoporosis that the rate of active tooth movement is increased, whereas tooth movement is less stable since little bone is present and no bone formation is noticed. prolonged retention may be required.<sup>8</sup>

### Thyroid hormones

Thyroid gland produces Thyroxine and calcitonin are hormones. Thyroxine (T4) is a prohormone, it can be converted to its active form tri-iodothyronine (T3). This active form of thyroxine play a vital role in metabolism of cells, physical development and growth. Administration of thyroxine will lead to increase in bone remodelling, increase in bone resorption activity and reduces bone density. Thyroxine produces interleukin 1 (IL-1B). It is a type of cytokine which involved in bone formation by osteoclastic reaction. Studies have been conducted on rat to establish the relationship between exogenous thyroxine and tooth movement. The result was that there was a significant increase in orthodontic movement compared to the control. Calcitonin is a peptide hormone secreted by the thyroid.it has an antagonistic action, which decreases the intestinal calcium and renal calcium reabsorption. In bones, calcitonin inactivates osteoclasts thereby inhibiting bone resorption. It also enhances the bone forming activity of osteoblasts. Low-dosage and short-term thyroxine administrations reduces the frequency of "force induced" root resorption modification in bone remodelling process and a reinforcement of the protection of the cementum and dentin to "force induced" osteoclastic resorption may be the reason for decreased resorptive process.<sup>6</sup>

### Parathyroid hormones

The main function of parathyroid hormone is to maintain calcium and phosphorus metabolism.it maintain the normal level of diffuse calcium and phosphorous in the blood plasma and to keep a constant ratio of the minerals with each other. PTH influences the osteoblasts' cellular metabolic activity, gene transcriptional activity, and multiple protease secretion. Its influence on osteoclasts occur by the production of RANK-L Receptor activator of nuclear factor kappa -B ligand).it is a protein playing a crucial role in osteoclasts' formation and activity., studies on animals in 1970s proved that PTH could induce an increase in bone turnover that would accelerate orthodontic tooth movement. in recent studies, an increased rate of tooth

movements has been noticed in rats treated with PTH, whether administered systemically or locally. These results give the inference that orthodontists should take note of patients being treated with PTH, as for example, in cases of severe osteoporosis.<sup>9</sup>

### Alcohol Use

Chronic alcohol consumption results in an osteopenic skeleton and an increased risk for osteoporosis. These patients are prone for delayed fracture healing when compared with non-alcoholics. Orthodontists treating patients with chronic alcoholism should therefore be aware of the bone-remodelling response and should be cautious while applying force to the teeth, because greater force may lead to root resorption & tooth mobility. So the force applied during orthodontic treatment should be minimized to avoid the sequelae. In addition, it may lead to many medical, dental, social and dietary problems for which the orthodontist should make the proper referrals.<sup>1</sup>

### Nicotine use

Smoking has injurious intraoral effects, such as increases in the progression of periodontal disease, as well as carious lesions. Nicotine is a very addicting material found within cigarette smoke. The increase in bone resorption observed with nicotine is mediated through the COX enzyme, which converts arachidonic acid to PGs (Baljoon *et al.*, 2005). Nicotine causes an increase in the expression of the COX-2 gene and PGE2 release from human gingival fibroblasts, which increases the pace of orthodontic tooth movement in a time- and dose-dependent manner. Orthodontists should encourage their patients to stop using tobacco due to its adverse effects on longevity, quality of life, and oral tissues. Nicotine-replacement therapy, such as nicotine patches or nicotine gum, should not interfere with light force orthodontic therapy, since nicotine has the potential to possibly increase OTM.<sup>13</sup>

### Suppressor Agents

#### Estrogens

Estrogen (female sex hormone), they have 3 major endogenous estrogens, those are estradiol, estrone, estriol, Estradiol is formed from menarche to menopause and it has a major role in estrous cycle. Estrone is formed after menopause when the whole volume of estrogens has reduced. Estriol is commonly seen in pregnancy. Estrogen does not have any effect on bone tissue but there are some studies indicated that estrogen has the ability to stimulate bone formation. Estrogen can inhibit cytokines such as interleukin-1,6 and tumor necrosis factor- $\alpha$ , which helps for bone resorption. In some studies have revealed that throughout the orthodontic treatment estrogen hormone will decrease the amount of tooth movement. Contraceptive pills taken for a longer duration, be able to control the velocity of OTM. Androgen (hormone) can also inhibit bone resorption and control the development of muscular system which can affect the span and outcomes of orthodontic treatment.<sup>8</sup>

### Bisphosphonates

Bisphosphonates are almost similar to the pyrophosphate analogues, and they are class of drugs that can vigorously inhibit bone resorption. Bisphosphonates are commonly used in medical conditions such as osteoporosis, Paget's disease, and bone-related types of cancer. When bisphosphonates are administered either topically or systemically this drug can decrease in the rate of OTM during the treatment. Studies have shown that topical application of bisphosphonates is very useful for anchorage and stabilizing the teeth during orthodontic treatment. When the use of bisphosphonate drugs is used for a long period of time can lead to osteonecrosis, particularly in the maxillary and the mandibular alveolar bones.

### Effects Bisphosphonates on tooth movement

Several studies have explained, these drugs can prevent the orthodontic tooth movement and increase the duration of orthodontic treatment. A major possible adverse-effect of bisphosphonates is osteonecrosis which is seen in the mandibular or maxillary region. This is due to the osteoclast death along with inhibition of bone vascular, decreasing the circulation of the smallest blood vessels of the maxillary and mandibular region.<sup>10</sup>

### Nonsteroidal Anti-Inflammatory Drugs (NSAIDS)

Nonsteroidal Anti-Inflammatory Drugs are typically referred to as NSAIDS, and they are generally used for pain management. NSAIDs have anti-inflammatory, analgesic, antipyretic properties, and they are prescribed for many medical conditions. During orthodontic treatment, Orthodontists should strictly advise the patient's no to take this medication without the knowledge of the dentist. During the transformation of arachidonic acid, NSAID will inhibit the production of prostanoids through blocking Cyclooxygenase (COX) enzyme. Prostanoids are the subdivision of eicosanoid hormones which can help for bone resorption.

### Effect of Nonsteroidal Anti-Inflammatory Drugs on tooth movement

Some research studies explained the mechanism of molecules behind the restriction of tooth movement by NSAID's have shown that there is an increase in the levels of enzymes called that Matrix Metallo-proteinases, besides with increased activity of collagenase, followed by a decreased synthesis of procollagen which is very important for remodeling of both the alveolar bone and periodontal tissues. And this whole procedure is organized by inhibiting the activity of the COX enzyme which can lead to change in the remodeling of the vascular and extravascular matrix, causing a reduction in the speed of orthodontic tooth movement.<sup>7</sup>

### Paracetamol

Paracetamol (acetaminophen) is an analgesic agent. It does not act on COX-1 and COX-2 inhibitors. The main difference between Nonsteroidal and anti-inflammatory drugs and Acetaminophen is, NSAIDs will block the

enzymes of COX-1 and COX-2 inhibitors, whereas acetaminophen will act on a COX-3 inhibitor, which manifests in the brain and spinal cord.

### Effect of acetaminophen on tooth movement

In some studies shown that the systemic administration of Acetaminophen will decrease the prostaglandin levels and have shown no effect on the movement of teeth in guinea pigs and rabbits during orthodontic treatment. It has an effect on pain control and decreases the discomfort during Orthodontic treatment.<sup>4</sup>

### Cholesterol-Lowering Drugs

Mundy (2001) stated that statins are the most common and widely prescribed drugs for their high cholesterol-lowering activity, and more than 3 million Americans take statins daily. All the studies mentioned previously were performed on animal models and human trials are underway in different institutions worldwide. It may be hypothesized that orthodontic patients on statins might show reduced bone resorption, and the orthodontist may expect a slow pace of tooth movement in these patients. In addition, when attempting orthodontic treatment in patients who are on a statin, the orthodontist should always be conscious about the antiangiogenic property of these agents, which in turn can lead to osteonecrosis of the jaws.<sup>12</sup>

### Fluorides

Fluoride is one of the most important elements that can be used to strengthen the enamel. It is used as a remineralizing agent which can prevent caries and initial signs of tooth decay. It increases bone mineral density and used for the treatment such as osteoporosis, During orthodontic treatment, when sodium fluoride is used to prevent active caries several studies have shown that it may decrease the tooth movement and increases the orthodontic treatment time. It has been shown that sodium fluoride decreases osteoclastic activity.<sup>1</sup>

### Insulin

Type-1 Diabetes Mellitus (DM) is caused by the immune destruction of the beta cells of Langerhans of pancreas and Insulin secretion is gradually diminished. Several studies have demonstrated a positive role between bone mineral density and insulin directly or indirectly by increasing IGF1 (hepatic insulin). Osteoblast like cells have the insulin receptors and it stimulates the proliferation of these cells. Hamid et al conducted a study in rats, and they concluded that insulin therapy reversed type-1 diabetes mellitus to nearly the same level as normal and there was no difference in orthodontic tooth movement as well as osteoclast count between normoglycemic and insulin-treated diabetic mice under optimal force level.<sup>11</sup>

### Conclusion

Since too many structural analogs are being used to prevent resistance in the name of new drugs, physicians today will

certainly review their information on the medical efficacy of the new medications and also the useful and deleterious effects on human beings. It is the best option for an orthodontist to check the health status of patients with the physician undergoing orthodontic treatment. The orthodontist should expect that so many patients are taking drugs that can be prescribed by the physicians, so the clinician should take thorough drug history and their use of food supplements from the patients. Thus, the orthodontist can classify these patients and consider part of any orthodontic diagnosis.

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