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Effect of drugs on orthodontic tooth movement: A review

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ABSTRACT
Orthodontic treatment comprise of tooth movement caused by bone resorption and apposition. This is a complex process which takes place from tissue level to molecular level, transmitting force from tooth to adjacent tissues causing certain chemical, mechanical and cellular events leading to movement of tooth. Drugs and nutrients consumed by patientsreach these levels causing inhibitory, additive, or synergistic effect. This review article provides a brief outline on effects of drugs on orthodontic tooth movement.
KEY WORDS: Orthodontic tooth movement, Drugs, Hormones, NSAIDs, Bisphosphonates, Prostaglandins, Bone resorption, Bone deposition.

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Orthodontics is a profession that corrects dental malposition and malformations of the jaws to restore a functional and aesthetic dentition. Orthodontic treatments are limited to movement of teeth within the dentoalveolar complex where only alveolar bone needs to be remodelled. [1, 2] When force is delivered to a tooth, it gets transmitted to the adjacent investing tissues and leads to the movement of that tooth, [3] which is an interdependent process of physical phenomenon and biological tissue remodelling. [1, 2] The physical behaviour of tooth movement relies on Newton's Laws whereas the biological system is affected by change in force magnitude, time of force application and signalling cascades leading to bone remodelling and orthodontic tooth movement (OTM). [4]

Orthodontic tooth movement is defined by Proffit as "the result of a biological response to interfere in the physiologic equilibrium in the dentofacial complex by an externally applied force."[1] During tooth movement activation of various cell signalling pathways occur which leads to stimulation of periodontal ligament metabolism and results in localized bone resorption and deposition which creates space necessary for tooth movement on the pressure side and on the tension side heals the path of advancing socket. [5]

This remodelling process is documented as an inflammatory response and inflammatory mediators, neurotransmitters and growth factors play an important role in orthodontic tooth movement. The main mediators associated in this complex process are hormones and systemic factors, cyclic adenosine monophosphate (cAMP), cytokines such as IL-1, colony stimulating factors, calcium, collagenase and prostaglandins. [6]

Similarly constituents of food such as nutrients as well as drugs are both regularly and occasionally consumed by patients reaches the periodontal tissues and target the local cells producing cumulative effects that could cause inhibitory, additive or synergistic effect on orthodontic tooth movement. [7]

In 1996, WHO defined drug as "any substance or product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient". Drugs are sometimes prescribed during orthodontic treatment to manage pain resulting from force application to biological tissues, for temporomandibular joint (TMJ) problems and in case of some infection during the course of treatment. Apart from these drugs, orthodontic patients also consume various health supplements and other medication for the prevention and treatment of various systemic diseases. [3]

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Analgesic drugs do not alter consciousness and selectively relieve pain by acting on the Central Nervous System and peripheral pain mechanisms, without altering consciousness. Nonsteroidal anti-inflammatory drugs (NSAIDs) are most commonly

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used in orthodontics for pain control, with analgesic, antipyretic and anti-inflammatory action. [8,9]

NSAIDs act by inhibition of enzyme cyclooxygenase (COX-1 and COX-2) of arachidonic pathway leading to inhibition of production of all prostanoids (thromboxanes, prostacyclins, and prostaglandins). [10] Since prostaglandins (PGE1 and PGE2) are important mediators of bone resorption their inhibition leads to decreased tooth movement cause of altered vascular and extravascular matrix remodelling . [11]

Acetylsalicylic acid and its compounds acts by inhibition of inflammatory reaction produced by PGs effecting the differentiation of osteoclast thus decreasing the rate of bone resorption. [12] Ibuprofen showed reduced rate of orthodontic tooth movement. [13]

Coxibs (COX-2 inhibitors) are specific COX-2 inhibitor which has no effect on PGE2 synthesis thus possessing minimal toxicity with full anti-inflammatory efficacy. [14] Thus are considered as safe during orthodontic mechanotherapy causing no negative effects on tooth movement. These drugs are nowadays not prescribed due to risk of cardiovascular events.[3] A study by Carlos et al. found that both diclofenac and reofecoxib inhibited tooth movement after inhibition of COX2 in rats, whereas celecoxib and parecoxib did not inhibit. Celecoxib and parecoxib are acknowledged as better than rofecoxib in orthodontic tooth movement. [14] Celecoxib has been currently approved by FDA for treatment of pain syndromes.[15] Long-term effect of celecoxib has shown to reduce the rate of orthodontic tooth movement. [16]

Acetaminophen (Paracetamol) is a weak COX-1 and COX-2 inhibitor and possesses no significant anti-inflammatory effects. It showed no effect on rate of orthodontic tooth movement in guinea pigs and rabbits. [17, 18] Acetaminophen and celecoxib are considered as drug of choice for relief of orthodontic pain and discomfort without affecting the rate of tooth movement. [19]

Table 1; Effect of NSAIDs on orthodontic tooth movement.

Nonsteroidal anti-inflammatory drugs (NSAIDs)	**Effects on orthodontic tooth movement**
Salicylates (Acetylsalicylic acid) - **Aspirin**	Reduce
Arylalkanoic acid - **Diclofenac** - **Indometacin** - **ketorolac**	 Reduce Reduce Reduce
Arylpropionic acids (profens) - **Ibuprofen** - **Flurbiprofen** - **Naproxen**	 Reduce Reduce Reduce
Oxicams - **Piroxicam** - **Meloxicam** - **Tenoxicam**	 Reduce Reduce Reduce
Coxibs - **Celecoxib** - **Rofecoxib** - **Valdecoxib**	 No effect Reduce No effect
Paraminophenols - **Acetaminophen**	 No effect

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Vitamin D

Calcium and phosphorus levels are regulated by Vitamin D, parathyroid hormone and calcitonin. Vitamin D and its active form 1, 25-dihydroxycholecalciferol are most potent stimulators of osteoclast precursors and have been demonstrated not only in osteoclast but also in osteoblasts. Collins and Sinclair demonstrated that a weekly administration of intra-ligamentous injections of vitamin D metabolite produced significant increase in number of osteoclasts and amount of tooth movement during canine retraction with light forces after a 21-day experimental period. [20]

Bran et al reported that rats treated with vitamin D showed increased bone formation on the pressure side of the periodontal ligament after application of orthodontic forces.[3] Kale et al observed that vitamin D induces well balanced bone turnover thus enhancing the rate of tooth movement in rats. [21] Kawakami observed an increased mineral appositional rate on alveolar bone after orthodontic force application; they suggested that local application of vitamin D could intensify the re-establishment of supporting alveolar bone, after orthodontic treatment. [22]

Dietary Calcium

Dietary recommendations for calcium intake are 800 mg/day for children aged 4–8 years and between 1000 and 1300 mg/day for adults. [23] Calcium supplementation is generally prescribed for the prevention of osteoporosis in postmenopausal women. The effect of dietary calcium on orthodontic tooth movement has been studied in dogs. The animals were fed low- or high-calcium diets for a period of 10 weeks. Canine retraction with light forces showed significantly higher rate of tooth movement in low-calcium diet than the high-calcium diet [24]. These results are in agreement with a comparable study in rats, in which lactating animals were fed a low-calcium diet for 1 week prior to force application showed higher tooth movement than in control group. [25]

Parathyroid hormone

The function of parathyroid hormone is to maintain a normal level of calcium and phosphorus in the blood plasma. Parathyroid hormone affects osteoblasts, gene transcriptional activity and cellular activity, and osteoclasts by stimulating the expression of RANK. Animal studies on rats showed that parathyroid hormone would accelerate orthodontic tooth movement by increasing bone turnover. [26]

Thyroid hormone

Thyroid hormones are recommended for hypothyroidism treatment and after thyroidectomy in substitutive therapy. Administration of thyroxin leads to an increase in bone remodeling and resorptive activity by reduced bone density, thus increasing the rate of orthodontic tooth movement. [27]

Calcitonin

Calcitonin has the opposite effects of parathyroid hormone; it inhibits bone resorption by acting on osteoclasts and also stimulates osteoblastic activity. Its physiological role is considered to inhibit the tooth movement. [3] A study by Guan et al on rats revealed that calcitonin can control undesirable root resorption, therefore act as an adjunctive orthodontic approach to enhance anchorage and prevent relapse after orthodontic tooth movement. [28]

Bisphosphonate

Bone metabolism disorders are treated by bisphosphonates. It increases intracellular calcium levels in osteoclastic cell line, reduce osteoclastic activity and prevent osteoclastic development from its precursors and produces osteoclast inhibitory factor. [11] Studies have shown that bisphosphonate administration can inhibit orthodontic tooth movement, augments anchorage and delay the orthodontic treatment. [29]

Estrogen

Bone metabolism in women is affected by estrogen hormone. It inhibits the assembly of cytokines involved in bone resorption thus stimulate osteoclast formation and bone resorption. The rate of tooth movement can be influenced by oral contraceptives if taken for long as estrogens decrease the rate of tooth movement, they have no anabolic effects on bone; directly stimulate the bone forming activity of osteoblasts. Similarly androgens also inhibit bone resorption and affect the orthodontic treatment. [30]

Corticosteroid

Corticosteroid causes inhibition of osteoblastic function. They induce inhibition of intestinal calcium absorption causing elevated parathyroid hormone levels thus decrease bone formation. Corticosteroids in low dose suppresses osteoclastic activity and decreases orthodontic tooth movement whereas in high dose causes increased rate of tooth movement by increasing osteoclastic activity. [32]Verna et al did a study to compare the effect of acute and chronic corticosteroid therapy on orthodontically induced root resorption and found more resorption in acute group. [33]

Prostaglandin

Prostaglandin stimulates resorption of bone and root, decrease collagen synthesis, and

increase cAMP. They activate already existing osteoclasts and increase the number of osteoclasts stimulating bone resorption. Prostaglandin in lower concentration enhance tooth movement whereas in higher concentration leads to root resorption. They produce better effect when administered systemic than local. [34]

Fluoride

Fluoride is ionic from of fluorine and has been used for prevention of enamel and caries. Sodium fluoride prevents calcium ion release thus inhibiting the osteoclastic activity and reduces the number of active osteoclasts. [35] Gonzales et al found that if fluoride is administered in drinking water since childhood it reduces the severity of root resorption in orthodontic patient but decreases the amount of tooth movement. [36]

Antihistamine

Antihistaminesare a used in treatment of respiratory disorders like bronchial asthma. Meh et al administered cetrizinein rats to found an increase in alveolar bone density and observed reduction in tooth movement. [37, 38]

Table 2; Effect of drugs on orthodontic tooth movement.

Drug	Effect on orthodontic tooth movement
NSAIDs	Decrease
Vitamin D	Increase
Calcium	Increase
Parathyroid hormone	Increase
Thyroid hormones	Increase
Calcitonin	Decrease
Bisphosphonates	Decrease
Estrogens	Decrease
Corticosteroids	Increase
Prostaglandins	Increase
Fluoride	Decrease
Antihistamine	Decrease
Anti Convulsant	Increase

Anti Convulsant

Anti Convulsant are generally seen to cause oral hygiene problems but as it has direct effects on bone mass it can affect orthodontic tooth movement. Phenytoin induces gingival hyperplasia,Valproicacid induces gingival bleeding even with minor trauma, and Gabapentin produces xerostomia. Akhoundi MSA et al evaluated the effect of anti convulsant in rats showed increased width of periodontal ligament, decreased bone density in phenytoin group, indicating accelerated amount of tooth movement in anticonvulsant therapy. [39]

CONCLUSION

With patients being demanding and seeking orthodontic treatment in shortest possible duration, orthodontistsbecome more and more focused on methods for acceleration of treatment. Clinicians are very often confronted with patients that use medications on a regular basis, as prescription and/or over the counter drug or prescribed by professional. These medications although aimed at specific illnesses always have systemic effects on other systems, organs, tissues, and cells of body and cause alterations in their function. These alterations can affect the course and outcomeof any therapeutic procedures like orthodontic treatment. Thus, it is imperative for an orthodontist to take proper list of medication consumed during treatment and also predict the outcome of these drugs to assess outcome of treatment.

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