European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 9, Issue 9, 2022

REVIEW ARTICLE

Drugs influencing orthodontic tooth movement- A review

[1]Gurinderpal Singh, [2]Rajdeep Kaur, [3]Sukhpal Kaur

[1,3]Professor, [2]Senior Lecturer, Department of Orthodontics, Desh Bhagat Dental College and Hospital, Mandi Gobindgarh, Punjab, India

Correspondence:
Sukhpal Kaur
Professor, Department of Orthodontics, Desh Bhagat Dental College and Hospital, Mandi Gobindgarh, Punjab, India
Email: docs284@gmail.com

Received: 24 April, 2022 Accepted: 28 May, 2022

ABSTRACT

Orthodontic treatment is based on the premise that when force is delivered to a tooth and thereby transmitted to the adjacent investing tissues, certain mechanical, chemical, and cellular events take place within these tissues, which allow for structural alterations and contribute to the movement of that tooth. Various metabolites like prostaglandins, cytokines and interleukins are involved at the molecular level to affect tooth movement. Molecules present in drugs can reach the mechanically stressed paradental tissues through the circulation and interact with local target cells. The combined effect of mechanical forces and one or more of these agents may be inhibitory, additive, or synergistic. Current orthodontic research aims to develop methods of increasing the tissue concentration of molecules promoting tooth movement, while simultaneously decreasing the concentration of unwanted elements which can produce harmful side effects. This article reviews the various possible drugs that can bring about alterations in the desired orthodontic tooth movement.

Keywords: Orthodontic tooth movement, NSAIDs, hormones, immunomodulatory drugs, immunosuppressant drugs

INTRODUCTION

Remodeling of the paradental tissues facilitates orthodontic tooth movement in response to mechanical forces. Recent research has demonstrated, or rather outlined the sequence of events occurring as part of the tooth movement process. The synthesis, release, as well as the role of various inflammatory mediators, neurotransmitters, growth factors and other cytokines in response to applied mechanical forces were elucidated, and have become targets of thorough reviews in recent times.[1,2]

Although the exact mechanism for conversion of orthodontic force into cellular response is not understood, great advances recently have been achieved in discovering the role some factors such as cyclic adenosine monophosphate (cAMP), calcium, collagenase, and prostaglandins (PGs) play in mediating tooth movement in response to orthodontic force.Molecules produced in various diseased tissues, or drugs and nutrients consumed regularly by patients can reach the mechanically stressed paradental tissues through the circulation and interact with local target cells. The cumulative effects could be inhibitory, additive, or synergistic.

WHO (1966) has 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.[3] During orthodontic treatment, drugs are frequently prescribed to manage pain from force application to biological tissues, manage temporomandibular joint (TMJ) problems and tackle some infection throughout the course of treatment. Apart from these drugs, patients who consume vitamins, minerals, hormonal supplements, and other compounds for the prevention or treatment of various systemic diseases can also be found in every orthodontic practice. Hence, it is necessary to be acquainted with the mechanism of action and effects of commonly used drugs on tissue remodeling and orthodontic tooth movement. This article discusses various drugs and their desired and undesired effects on orthodontic tooth movement.

NSAIDs

The most common group of medications used in orthodontics consists of non-steroidal anti-inflammatory drugs (NSAIDs), for the control of pain following mechanical force application to teeth. These drugs are classified as being non-opioid, peripherally acting analgesics, functioning by inhibition of the enzyme cyclo-oxygenase (COX), which modulates the transformation of prostaglandins (PGs) from arachidonic acid in the cellular plasma membrane. The first reports on the use of analgesics in orthodontics were published by Simmons and Brandt[4] and by Pagenelli.[5]

NSAIDs inhibit PG synthesis and anti-inflammatory action may be exerted by reduced generation of superoxide by neutrophils, and TNF release, free radical scavenging, and inhibition of metalloprotease activity in cartilage. They suppress the production of all prostanoids (thromboxanes, prostacyclins, and prostaglandins) because of their inhibition of COX-1 and COX-2, which are essential enzymes in the synthetic pathways of the prostanoids. Inhibition of the inflammatory reaction produced by PGs slows the tooth movement. Also NSAIDs like aspirin(salicylates) decrease the tooth movement by effecting the differentiation of osteoclast thus decreasing the rate of bone resorption.[6,7]

PARACETAMOL (ACETAMINOPHEN)

Analgesia and hypothermia due to paracetamol are mediated by inhibition of a third COX isoenzyme (COX-3) which is isolated in brain and spinal cord and therefore does not have any effect on prostaglandin synthesis. It has no effect on orthodontic tooth movement. Acetaminophen is effective for controlling pain and discomfort associated with the orthodontic treatment.[8,9]

VITAMIN D

Colllins and Sinclair[10] reported that a weekly intraligamentous injection of a 1,25,2(OH)D3 (1,25-dihydroxy cholecalceferol), the active metabolite of Vitamin D produced a significantly increased amount of orthodontic tooth movement after a 21-day experimental period. There was an increased rate of recruitment and activation of mononuclear osteoclasts resulting in greater bone resorption of the alveolus on the pressure side of the periodontal ligament than in control teeth.

1,25,2(OH)D3 acts directly on the nucleus of the circulating monocytes and osteoprogenitor cells, which have specific receptors for it. Cells in the early stages of the resorption cycle before they fuse and become classic multinucleated osteoclasts. Vitamin D and its active metabolite, 1,25,2(OH)D3, together with parathyroid hormone (PTH) and calcitonin, regulate the amount of calcium and phosphorus levels. Vitamin D receptors have been demonstrated not only in osteoblasts but also in osteoclast precursors and in active osteoclasts.

FLUORIDE

Fluoride is one of the trace elements having an effect on tissue metabolism. Fluoride increases bone mass and mineral density, and because of these skeletal actions, it has been used in the treatment of metabolic bone disease, osteoporosis. Even a very active caries treatment with sodium fluoride during orthodontic treatment may delay orthodontic tooth movement and increase the time of orthodontic treatment.[11] Sodium fluoride has been shown to inhibit the osteoclastic activity and reduce the number of active osteoclasts. On the cellular level it has been shown to stimulate bone formation and, recently, it was discovered that the osteoclastic activity in rats is inhibited.[12]

BISPHOSPHONATES (BPNS)

Pharmacological site of action is in the osteoclast, which removes the outer ruffled border, inactivates function, and decreases the lifespan of the cell. Also it inhibits formation of actin ring in the cytoskeleton of osteoclasts. There is some evidence that they might also inhibit osteoclast precursors and osteoblast communication with osteoclasts.[13,14]

Bisphosphonates (BPNs) have strong chemical affinity to the solid-phase surface of calcium phosphate; this causes inhibition of hydroxyapatite aggregation, dissolution, and crystal formation. Bisphosphonates cause a rise in intracellular calcium levels in osteoclast-like cell line, reduction of osteoclastic activity, prevention of osteoclast development from hematopoietic precursors, and production of an osteoclast inhibitory factor.

Studies have shown that BPNs can inhibit orthodontic tooth movement and delay the orthodontic treatment. Histological examination showed that in the experimental animals fewer osteoclast appeared on the alveolar bone surface, and both bone resorption and root resorption were inhibited. Topical application of BPNs could be helpful in anchoring and retaining teeth under orthodontic treatment.

PARATHYROID HORMONE (PTH)

By local admistration of PTH analogues, both osteoblast and osteoclast activities are stimulated. The receptors of parathyroid hormone are only expressed on the cell membrane of osteoblasts. After the binding of parathyroid hormone molecules to their receptors, the osteoblasts are stimulated to produce more IGF-I via a cyclic adenosine monophosphate (cAMP) dependent mechanism, which functions as an autocrine/paracrine factor and activates its adaptor molecule insulin-receptor substrate-1 in osteoblast precursors in bone marrow, and causes osteoblast proliferation, differentiation, and function.[15,16]

On the other hand, osteoblasts stimulated by parathyroid hormone molecules also express more RANKL on the cell membrane, which binds to the receptor activator of nuclear factor kappa B (RANK) on the cell membrane of osteoclastic precursors through cell-to-cell contact and stimulates osteoclast proliferation, differentiation, and activation.

RANKL/osteoprotegerin and IGF-1 are essential molecules for the effect of parathyroid hormone on bone metabolism. RANKL/osteoprotegerin mediates osteoclastogenesis, whereas IGF-1 mediates osteoblastogenesis. The expression levels of both RANKL and IGF-1 increased, indicating that intermittent parathyroid hormones stimulated both osteoclastogenesis and osteoblastogenesis. The biphasic effect of intermittent parathyroid hormone administration results in an increased bone turnover rate that accelerates tooth movement.Unlike other osteoporosis-treating medicines (eg, bisphosphonates), parathyroid hormone has a more balanced effect on bone metabolism, stimulating both osteoblastic and osteoclastic activities.

ESTROGEN

Estrogen is known to inhibit osteoclasts both directly and indirectly. It inhibits the production of various cytokines which are involved in bone resorption by stimulating osteoclast formation and osteoclast bone resorption. Studies have shown that estrogens decrease the velocity of tooth movement.[17,18] Oral contraceptives, taken for long periods of time, can influence the rate of tooth movement. Androgens also inhibit bone resorption, modulate the growth of the muscular system, and may affect the length and results of the orthodontic treatment.

Orthodontic therapy should be planned according to the menstrual cycle since tooth movement, under the application of force, is faster during low estrogen levels. Xuet al[19] reported that orthodontic force after each ovulation may promote tooth movement, thereby shortening the course of orthodontic treatment.

THYROID HORMONES

Thyroid hormones are used in the management of hypothyroidism and after thyroidectomy in substitutive therapy. Thyroxin administration leads to increased bone remodeling, increased bone resorptive activity and reduced bone density. Effects on bone tissue may be related to the augmentation of interleukin-1 (IL-1B) production induced by thyroid hormones at low concentrations, cytokine stimulated osteoclast formation and osteoclastic bone resorption.

Thyroid hormone increases the speed of orthodontic tooth movement in patients undergoing such medication.[20] Low dose and short-term thyroxin administration has been reported to lower the frequency of “force-induced” root resorption. Decrease in resorptionmay be correlated to a change in bone remodeling process and a reinforcement of the protection of the cementum and dentin to “force-induced” osteoclasticresorption.

RELAXIN

Relaxinis a pregnancy hormone that is released just before child birth to loosen the public symphysis, so that the relaxed suture will allow widening of the birth canal for parturition.Madan et al (2005)[21] showed that the administration of relaxin might accelerate the early stages of orthodontic tooth movements in rats.McGorray et al[22] used gingival injections of relaxin to relieve rotational memory in the connective tissues of maxillary lateral incisors that had been orthodontically rotated. Nicozisis et al (2000)[23]suggested that relaxin might be used as an adjuvant to orthodontic therapy, during or after tooth movement, for promotion of stability, for rapid remodeling of gingival tissue during extraction space closure, for orthopedic expansion in non – growing patients, by reducing the tension of the stretched soft tissue envelope, particularly the expanded palatal mucosa, after orthognathic surgery.

CALCITONIN

Calcitonin inhibits bone resorption by direct action on osteoclasts, decreasing their ruffled surface which forms contact with resorptive pit. It also stimulates the activity of osteoblasts. Because of its physiological role, it is considered to inhibit the tooth movement; consequently, delay in orthodontic treatment can be expected.

CORTICOSTEROIDS

Glucocorticoids enhance the responsiveness of osteoblasts to PTH by increasing the expression of PTH receptors in thesecells.Evidence indicates that the main effect of corticosteroid on bone tissue is direct inhibition of osteoblastic function and thus decreases total bone formation. Decrease in bone formation is due to elevated PTH levels caused by inhibition of intestinal calcium absorption which is induced by corticosteroids.

Corticosteroids increase the rate of tooth movement, and since new bone formation can be difficult in a treated patient, they decrease the stability of tooth movement and stability of orthodontic treatment in general.[24]When they are used for longer periods of time, the main side effect is osteoporosis. It has been demonstrated in animal models with this type of osteoporosis that the rate of active tooth movement is greater, but tooth movement is less stable since little bone is present and there is no indication of bone formation. A more extensive retention may be required.

ANTICONVULSANTS

Phenytoin, one of the most commonly used drugs prescribed in seizure disorders induces gingival hyperplasia due to overgrowth of gingival collagen fibers, which involves the interdental papilla, making application of orthodontic mechanics and maintaining oral hygiene difficult. Valproic acid has a potential to induce gingival bleeding even with minor trauma, making orthodontic manoeuvres difficult. Gabapentin produces xerostomia, making oral hygiene maintenance difficult during orthodontic treatment.

Significant histological changes in the periodontal tissues such as increased density of fibroblasts, decreased number of osteoclasts in contact with alveolar bone wall of the pressure side and deeper layer of non-mineralized osteoid on the tension side were observed in an animal study using phenytoin.[25]

IMMUNOSUPPRESSANT DRUGS

Patients with chronic renal failure or kidney transplants and on immunosuppressant drugs can encounter some difficulty during orthodontic treatment. Drug consumed for prevention of graft rejection (cyclosporine A) produce severe gingival hyperplasia, making orthodontic treatment and maintenance of oral hygiene difficult. Treatment should be started or resumed after surgical removal of excessive gingival tissues once there is good oral hygiene. Whenever possible, fixed appliances should be kept to a minimum period with brackets and avoiding the use of cemented bands. Removable appliances in these cases are not recommended due to improper fit.[30,31,32]

IMMUNOMODULATORY DRUGS

Most of these drugs used for treatment of rheumatoid arthritis include immunomodulatory agents like Leflunomide, TNFantagonists (Etanercept), interleukin antagonists (Anakinra). Immunomodulatory drugs modulate nuclear

factor kappa – Beta , tyrosine kinases in signaling pathway, IL – 6, MMPs and PGE2, all of which are essential for the bone remodeling process.[33,34,35]

ANTICANCER DRUGS

These are used for the treatment of childhood cancers. There is every chance of observing disturbances in dental as well as general body growth and development due to the adverse effects of the chemotherapeutic agents.[1] It is clearly stated that patients who had been on chemotherapy with busulfan/cyclophosphamide belong to the risk group for orthodontic treatment These drugs are known to produce damage to precursor cells involved in bone remodeling process, thereby complicating tooth movement.

PROSTAGLANDINS

Experiments have shown that PGs may be mediators of mechanical stress during orthodontic tooth movement. They stimulate bone resorption, root resorption, decrease collagen synthesis, and increase cAMP. They stimulate bone resorption by increasing the number of osteoclasts and activating already existing osteoclasts. A lower concentration of PGE2 (0.1

μg) appears to be effective in enhancing tooth movement. Higher concentration leads to root resorption. Systemic administration is reported to have better effect than local administration. Researchers have injected PGs locally at the site of orthodontic tooth movement to enhance the bone remodeling process and the pace of tooth movement.

ECHISTATIN AND RGD PEPTIDES

Another approach made recently is local injection of integrin inhibitors like echistatin and RGD (Arginine–Glycine–Aspartic acid) peptides on rats to prevent tooth movement, thereby enhancing anchorage. Recent research has demonstrated decrease in root resorption following orthodontic force application after administration of Echistatin.[26,35,36,37]

CONCLUSION

Orthodontists have long observed that teeth move at different rates and individuals differ in their response to treatment. Some of the differences are caused by change in bone remodelling induced by drugs and systemic factors. All the drugs reviewed have therapeutic effects as well as side effects that influence the cells targeted by orthodontic forces. The value of a thorough medical history is increasingly significant as young and old alike are exposed to a greater range of therapeutic agents. Therefore, it is imperative that the orthodontists need to pay attention to drug consumption and history of each and every patient, before and during the course of orthodontic treatment, so that the best treatment strategy (including force control and appointment intervals) can be selected for each case. Acetaminophen, which does not have significant influence on the rate of tooth movement, can be recommended for controlling pain during orthodontic treatment.

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