REVIEW ARTICLE

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The effect of drugs on orthodontic tooth movement

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Structured Abstract

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Objective – 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 combined effect of mechanical forces and one or more of these agents may be inhibitory, additive or synergistic. The objective of this review is to outline the mechanisms of action and effects of some commonly used drugs on tissue remodeling and orthodontic tooth movement.

Design – All the existing published literature on the effects of various drugs that are prescribed by orthodontists, which are consumed by patients for systemic diseases and those that are known to promote and retard the tooth movement process was obtained and subjected to thorough review process.

Results – All the drugs reviewed have therapeutic effects, as well as side effects, that may influence the cells targeted by orthodontic forces. Therefore, it is imperative that the orthodontist pays close attention to the drug consumption history of each and every patient, before and during the course of orthodontic treatment. When the use of drugs is revealed, their effects and side effects on tissue systems should be explored, to determine their potential influence on the outcome of mechanotherapy.

Conclusion – Drug-consumption history must be an integral part of every orthodontic diagnosis and treatment plan.

Key words: adverse effects; disease; drugs; orthodontics; tooth movement

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). These endogenous molecules have been found to play important roles in the initiation, maintenance, and cessation of tooth movement. However, some of these ligands can also cause unwanted side effects, such as pain and root resorption. Current orthodontic research aims at developing methods to increase the tissue concentrations of molecules promoting tooth movement, while simultaneously decreasing the concentration of unwanted elements, which can produce harmful side effects.

Orthodontists often prescribe drugs to manage pain from force application to biological tissues, manage temporomandibular joint problems, and tackle fungal and viral infections throughout the course of treatment. A recent review of pharmaceuticals commonly used in orthodontic practice, provided an insight into the dosage, pharmacological actions and side effects of these agents (3). Apart from these drugs, patients who consume vitamins, minerals, and other compounds, for the prevention or treatment of various diseases, can also be found in every orthodontic practice. Some of these drugs may have profound effects on the short- and long-term outcomes of orthodontic treatment. However, in many cases little is known on the nature of this interaction between specific drugs and orthodontic tissue remodeling, thereby increasing the risk of negative effects. For example, a recent editorial has raised concern regarding increased use of methylphenidate (Ritalin), a drug used for the treatment of attention-deficit disorders in children of all ages. In these children, this drug has apparently caused an increase in the incidence of gingival enlargement, and a subsequent slow down of orthodontic tooth movement (4).

The objective of this review is to outline the mechanisms of action and effects of some commonly used drugs on tissue remodeling and orthodontic tooth movement.

Effects of drugs, commonly prescribed by orthodontists, on paradental tissue remodeling and clinical responses to mechanotherapy

Non-steroidal anti-inflammatory drugs

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 (5) and by Pagenelli (6). The former group used acetaminophen in their trial, while the latter researcher applied flurbiprofen. The first effort to compare various drugs for their effectiveness in managing orthodontic pain was performed by Ngan et al. (7). These investigators concluded that ibuprofen is more effective than aspirin and placebo in controlling pain. Subsequently, numerous studies evaluated the pain-reducing effects of various NSAIDs, including ibuprofen, acetylsalicylic acid, paracetamol, misoprostol (a PG analog which is often combined with a NSAID for reducing its adverse effect), indomethacin, naproxen sodium, and the recently introduced COX-2 inhibitor, rofecoxib (8–14). These studies not only demonstrated that NSAIDs effectively reduce pain and discomfort caused by the periodic activation of orthodontic appliances, but that these drugs may also affect the sequence of tooth movement by inhibiting, or at least by reducing the associated inflammatory and bone resorptive processes.

Prostaglandins, a product of arachdonic acid metabolism, are local hormone-like chemical agents produced by mammalian cells, including osteoblasts, after cell injury. These 20-carbon essential fatty acid molecules are considered to have an important role as mediators of the inflammatory response, which facilitates tooth movement (15). Because of the slowing of tooth movement by inhibition of the inflammatory reaction, the utility of NSAIDs while performing tooth movement has been questioned (16). Recent research has demonstrated the molecular mechanisms behind

the inhibition of tooth movement by NSAIDs. The levels of matrix metalloproteinases (MMPs)-9 and -2 were found to be increased, along with elevated collagenase activity, followed by a reduction in pro-collagen synthesis, which are considered essential as far as bone and periodontal ligament remodeling is considered. The whole process is thought to be the result of inhibition of COX activity, leading to altered vascular and extracellular matrix remodeling, causing a reduction in the pace of tooth movement (17).

An interesting recent development in this area is an increase in the number of issued prescriptions of a specific COX-2 inhibitor, rofecoxib, a drug with no effect on PGE2 synthesis (11). These drugs selectively block the COX-2 enzyme, and impede the production of the chemical messengers (PGs) that cause the pain and swelling. Because they selectively block the COX-2 enzyme and not the COX-1 enzyme, these drugs are uniquely different from traditional NSAIDs. In light of these findings, it was suggested that rofecoxib can be safely employed during orthodontic mechanotherapy, without causing negative effects on tooth movement (18). This hypothesis does not go unchallenged and a recent report states that rofecoxib also disturbs the process of tooth movement (19). In addition the recently raised safety concerns regarding these drugs, the risk of cardiovascular events in patients on these drugs and voluntary withdrawal of these molecules by the companies have worked against these drugs and they are no more prescribed to the patients (20).

The administration of preemptive or preoperative analgesics, in order to decrease postoperative pain, has become the focus of recent research in orthodontics. It is assumed that preemptive analgesia will block the afferent nerve impulses before they reach the central nervous system, abolishing the process of central sensitization (12). Steen Law et al. demonstrated that the administration of preemptive ibuprofen at a dose of 400 mg, 1 h before separator placement, decreased pain during chewing, up to 2 h after the procedure (13). This finding was confirmed later by other studies. Polat et al. compared the effects of naproxen sodium (550 mg) and ibuprofen (400 mg) administered preoperatively, before arch wire placement. It was found that naproxen sodium is more effective than ibuprofen, 2 h, 6 h, and even during nighttime after arch wire placement. These authors recommended two postoperative doses, in addition to a preoperative dose, for a complete pain control during each orthodontic appointment (21). While various authors have stated that NSAIDs should be used with caution during orthodontic tooth movement, a recent publication reported that nabumetone, a drug belonging to the NSAID group, reduces the amount of root resorption along with the control of pain from intrusive orthodontic forces, without affecting the pace of tooth movement (22).

Management of root resorption

It has been demonstrated that the unwanted sequele of tooth movement, root resorption, could be reduced with the use of drugs and hormones. The main drug employed for this purpose is bisphosphonates (a group of anti-cancer drugs, which is also used for treatment of osteoporosis), which demonstrated a dose-dependent reduction of root resorption, when administered in rats (23,24). However, it has also been reported that these drugs produce cemental surface alterations, by inhibiting acellular cementum formation, thereby actually increasing the vulnerability of the dental root to the resorptive process (25,26). The main hormone prescribed to reduce root resorption is L-thyroxine, which increases the resistance of cementum and dentin to clastic activity (27,28). Shirazi et al. have confirmed this finding through the administration of increased doses of L-thyroxine to rats, which resulted in the reduction of the extent of root resorption (29). However, the results of the rat studies should be viewed with caution as no human trials on the use of L-thyroxine have been reported till now.

Management of temporomandibular disorders

Management of temporomandibular disorder patients in the orthodontic clinical setting includes either splint therapy for centric relation/occlusion coincidence (30), or prescription of muscle relaxants like cyclobenzaprin (Flexerol; 10 mg, three times daily), tricyclic antidepressants like amitryptilin (Elavil; 10 mg, one tablet at night time), and benzodiazepins like diazepam (Valium; 5 mg, at night time) (3). The main side effect associated with all these drugs is xerostomia, a significant condition in patients under orthodontic care (31,32). In these individuals, xerostomia can negatively affect proper maintenance of oral hygiene, increasing

the risk for caries and periodontitis. Xerostomia might particularly increase the incidence of root surface caries, as well as gingival hyperplasia and hypertrophy (33).

Record, Monitor and Proceed with caution

Your patients are on drugs

In most orthodontic practices, 20–30% of all patients are adults. In this age group, many individuals consume regularly prescribed and over-the-counter drugs, meant to address various systemic and local conditions. Occasionally, younger patients are also compelled to use medications regularly. All these medications can potentially affect target cells throughout the body, including those located in paradental tissues (34). Tissue systems of particular importance in orthodontics are the nervous, vascular, immune, endocrine, and skeletal systems. Drugs aimed at any of these systems may reach the mechanically stressed PDL, interact with local target cells, and modify their reactions to the applied force. To avoid undesirable influences on tooth movement, the orthodontist should be aware of any drugs taken by each individual patient. Moreover, when taken drugs are listed by the patient before the onset or during the course of orthodontic treatment, the orthodontist should explore and document their published effects and side effects (35). This information should enable the orthodontist to increase the precision of forecast of the treatment duration and outcome.

Osteoporosis

Among the most prevalent diseases that afflict women of adult age group is osteoporosis. It is a condition resulting in a loss of bone mass and strength, a decrease in bone turnover with increased resorptive activity, found predominantly in post-menopausal women, but also in adult males. Most of the approved osteoporotic drugs are anti-resorptive, slowing down the destructive phase (resorption) of bone turnover. The anti-resorptive medications commonly used by osteoporotic patients include bisphosphonates (alendronate and risedronate), estrogen, selective estrogen receptor modulators, and calcitonin. These drugs and hormones produce modest increases in bone density, with the help of increases in the mineralization of old bone (36). Sato et al. reported on irregular ruffled borders in osteoclasts of rats administered with bisphosphonates. They also observed a decrease in the subcellular localization and expression of both vacuolar types H (+) – ATPase and Cathepsin K, which are enzymes essential for bone resorption (37). Another drug used to treat osteoporosis, doxycycline, when taken in low doses, was reported to reduce root resorption, without significant influences on the alveolar bone. The apparent mechanism involved consists of significant reductions in the numbers of odontoclasts, osteoclasts, and mononuclear cells on the dental roots, as well as in the alveolar bone, ultimately slowing down the bone remodeling process thereby the pace of tooth movement (38).

Rheumatoid arthritis

Rheumatoid arthritis (RA) is characterized by the presence of immune-mediated inflammatory synovitis that exhibits the capacity to invade and destroy the extracellular matrices of joint cartilage and bone (39). It is demonstrated that specific CD4+ T cells are involved in the induction of the immune response, most likely as a response to an unknown exogenous or endogenous antigen. Consequently recruited monocytes, macrophages, and fibroblasts produce cytokines such as tumor necrosis factor (TNF) alpha and interleukin 1 within the synovial cavity. These cytokines are central to the damaging cascade, ultimately triggering production of MMPs and osteoclasts resulting in irreversible damage to soft tissues and bones. Most of the drugs used for treatment of RA include immunomodulatory agents (Leflunomide), TNF antagonists (Etanercept, Infliximab, Adalimumab) or interleukin antagonists (Anakinra) (40). The immunomodulatory drug leflunomide modulates nuclear factor kappa B, tyrosine kinases in the signaling pathway, interleukin 6, MMPs and PGE2, all of which are essential for the bone remodeling process (41–44). TNF alpha antagonists will block TNF alpha in inflammatory cytokines released by activated monocytes, macrophages and T-lymphocytes, which are essential for inflammatory responses following force application (45). Anakinra inhibited interleukin 1 produced by monocytes, macrophages and some specialized cells, which are important for the inflammatory response and induction of interleukin 6

and COX-2 (40). In short, all these drugs will influence the inflammatory response following force application, reducing the pace of bone remodeling, thereby tooth movement. Orthodontists treating patients with RA should be aware of these effects of the drugs and should expect slow response to tooth moving forces.

Seizure disorders

Seizure disorders, the most common serious chronic neurological conditions, are characterized by sudden involuntary time-limited alterations in neurologic function resulting from abnormal electrical discharge of cerebral neurons. The treatment of these conditions is directed toward eliminating or reducing the frequency of seizures. The main methodology for this purpose involves polypharmacy with multiple anticonvulsant medications (46). Currently there are over 20 agents with differing mechanisms of action for managing these patients (47). The drugs, which are important to orthodontic clinicians, are Valproic acid, Phenytoin and Gabapentin. Valproic acid has the potential to induce gingival bleeding even with minor trauma, making orthodontic maneuvers difficult. Phenytoin induces gingival hyperplasia with involvement of the interdental papilla, making application of orthodontic mechanics, as well as maintenance of proper oral hygiene difficult. Gabapentin produces xerostomia, making oral hygiene maintenance difficult. It is to be noted that orthodontic treatment is not at all contraindicated in patients with seizure disorders (46). But orthodontists should be aware of possible difficulties that they might encounter during the treatment period, and discuss it with the patients and/or with the parents, and educate them so that adequate measures to maintain oral hygiene are followed.

Asthma

Episodic narrowing of the airways that results in breathing difficulties and wheezing, characterizes asthma. The pulmonary distress developed by this disease can be debilitating and without doubt, affects the quality of life of the patients (48). Simon et al. found higher incidence for this disease in blacks (15.8%) followed by whites (7.3%), Asians (6%), and Latinos (3.9%) (49). Given the frequency of incidence, it is highly possible that orthodontists will meet these patients in their routine clinical practice. Orthodontic treatment should not be performed in patients who experience very frequent flare-ups despite being adequately medicated. For patients at low to moderate risk, morning appointments with short waiting times are advised. Orthodontists should make sure that the patient has taken adequate medications and if needed has his/her inhaler present at the time of treatment appointments (50). It is to be understood that these patients are sensitive to certain medications, such as erythromycins, aspirin, antihistamines and local anesthetics with epinephrine. Chronic use of inhalers with steroids by these patients often results in oral candidiasis and xerostomia. Appropriate measures to these conditions with topical antifungal agents and salivary substitutes have to be performed before and during the orthodontic treatment period. The importance of aggressive oral hygiene measures and topical fluoride application should be emphasized to these patients (50). Asthma involves periodic production of large amounts of proinflammatory cytokines in the airway mucosa and the skin. Primed leukocytes derived from these tissues may travel through the circulation into the extravascular space of the tissues surrounding orthodontically treated teeth. Consequently, patients with a history of asthma seem to be at a high risk for developing excessive root resorption during the course of orthodontic treatment (51). This emphasizes the prescription of low forces for these patients, just enough to produce tooth movement without any adverse effects like root resorption.

Childhood cancer

It is now estimated that one in every 900 young adults between the ages of 16 and 44 is a survivor of childhood cancer (52). An increased number of these patients are now attending orthodontic clinics for possible treatment. However, before providing care, orthodontists should be aware of the adverse reactions that might arise in these patients. There is every chance of observing disturbances in dental, as well as general body growth and development, due to the adverse effects of chemotherapeutic agents and radiotherapy. The conditions observed and risks for mechanotherapy are beyond the scope of this article, and are described in detail elsewhere. It is clearly stated that patients who had been on chemotherapy with busulfan/

cyclophosphamide, and who have had less than 2 years of disease-free life, belong to the high-risk group, as far as orthodontic treatment is concerned. These drugs are known to produce damage to precursor cells involved in bone remodeling process thereby complicating tooth movement (51). Patients on immunosuppressant therapy with cyclosporin A as part of cancer treatment also belong to the high-risk group, due to the development of gingival hyperplasia as a side effect of this drug (52). The importance of proper medical history for each and every patient is re-emphasized here, as is the need for proper medications and auxiliaries to manage these patients in every orthodontic office.

Psychiatric problems

Adolescents are challenged with a multitude of tasks in their lives. They may be extremely sensitive to social successes and/or failures. The latter can often lead to psychiatric problems like attention-deficit/hyperactivity disorders, depression, eating disorders, anxiety disorders, and oppositional defiant/conduct disorders (53). Most of these disorders require medication as part of their management, which has definite influences on dental, as well as orthodontic care. The attention-deficit/hyperactivity disorder is mainly treated with central nervous system stimulants, such as methyl phenidate, dextroamphetamine, atomoxetine, buproprion, clonidine, guanfacine. These drugs may have immediate impact on orthodontic treatment, related to problems with patient compliance and home care, as well as maintenance of oral hygiene (53).

Depressed patients are managed with antidepressants and mood stabilizers. Orthodontists can expect these patients to be overly concerned about their appearance, while at the same time be non-compliant. Anxiety disorders or psychological stress are usually managed with benzodiazepines, which can raise undue concerns in patients' minds. They will be more concerned about side effects and outcomes, but will utilize every chance to disrupt office visits. Psychiatric disorders of developmental origin (exautism) are treated with second-generation neuroleptics (exaloanzipine), which often lead to challenging unreasonable worries, inflexibility, odd behavior and misbehavior with office staff (53). Staff members should be informed and educated about the possible behavioral alterations and their management strategies. Psychological stress affects the hypothalamic–pituitary–adrenal (HPA) axis, and the immune system. As osteoclasts and odontoclasts are derived from the immune system, modification of their function by psychological stress may impact the process of root resorption. A recent survey revealed a high risk for developing excessive root resorption during the course of orthodontic treatment in patients with psychological distress (51). Among the reasons for partial and total loss of scalp hair (alopecia areata and alopecia totalis) is psychological stress, probably through effects on the HPA axis. Davidovitch et al. reported a case of an adolescent orthodontic patient who developed alopecia totalis during orthodontic treatment. A review of the case revealed a normal medical background, with a presence of a persistent psychological stress due to the exposure to orthodontic mechanotherapy. Consequently, the patient's pediatrician and the endocrinologist concluded that his alopecia had been most likely caused by psychological stress evoked by the orthodontic treatment (54).

Immunosuppressant drugs

Patients with chronic renal failure or kidney transplants and on immunosuppressant drugs on a daily basis form another group, which might encounter some difficulty during orthodontic treatment. The drug consumed for prevention of graft rejection (cyclosporin A) produces pronounced or severe gingival hyperplasia, making orthodontic treatment, as well as maintenance of oral hygiene difficult. It is suggested that for the first six months (when gingival hyperplasia is at its peak), orthodontic treatment should be deferred in these patients. Treatment should be started or resumed once oral hygiene is very good and after surgical removal of excessive gingival tissue. Whenever possible, fixed appliances should be kept to a minimum period with only brackets, and avoiding the use of cemented bands. Use of removable appliances in these patients is not recommended, due to failure of proper fit (55).

Alcohol abuse

Consumption of low or moderate amounts of alcohol may have beneficial effects on the cardiovascular system, but chronic ingestion of large amounts of alcohol on a daily basis may have devastating effects on a number of

tissue systems, including the skeletal system. Alcoholism may lead to severe complications, such as liver cirrhosis, neuropathies, osteoporosis, and spontaneous bone fractures. Circulating ethanol inhibits the hydroxylation of vitamin D_3 in the liver, thus impeding calcium homeostasis. In such situations the synthesis of parathyroid hormone is increased, tipping the balance of cellular functions toward enhanced resorption of mineralized tissues, including dental roots, in order to maintain normal levels of calcium in the blood (10 mg %). Davidovitch et al. have found that chronic alcoholics receiving orthodontic treatment are at a high risk of developing severe root resorption during the course of orthodontic treatment (56).

Corticosteroid therapy

A recently expressed concern has been about orthodontic treatment in patients undergoing corticosteroid therapy for its anti-inflammatory and immunosuppressive effects. The cited side effects of long-term steroid therapy include disturbances in mineralized tissue metabolism and wound healing, discrepancies in chondrogenesis and osteogenesis, bone loss and osteoporosis.

Rat studies on acute and chronic corticosteroid treatment revealed that the tooth movement rate increased in the chronic group. Force application resulted in a significant increase in the relative extension of resorption and formation in both groups, indicating that the orthodontic force level should be reduced and controlled more frequently in patients on chronic steroid treatment (57,58).

Drugs that promote or retard orthodontic tooth movement

Prostaglandins and analogs

Remodeling activities associated with inflammatory reactions induced by mechanical stimuli form the biological basis for orthodontic tooth movement. Certain eicosanoids (PGs and leucotrienes) released from paradental cells in sites of compression and tension have significant stimulatory effects on bone remodeling. This finding led researchers to inject PGs locally at the site of orthodontic tooth movement, to enhance the bone remodeling process, and thereby enhance the pace of tooth movement. Yamasaki et al. found an increased number of osteoclasts in rats' alveolar bone after local injection of PGE1 (59). A similar regimen in human subjects increased significantly the rate of canine and premolar movement (60). Apparently, PGs act by increasing the number of osteoclasts, and by promoting the formation of ruffled borders, thereby stimulating bone resorption. Among the PGs that had been found to affect bone metabolism (E1, E2, A1, and F2-alpha), PGE2 stimulated osteoblastic cell differentiation and new bone formation, coupling bone resorption *in vitro* (61). A recent evaluation of the effect of prostacyclin and thromboxane A2 on orthodontic tooth movement, revealed an increase in the number of osteoclasts, and in the amount of alveolar bone resorption by these analogs (62). The main side effect associated with local injection of PGs is hyperalgesia, due to the release of noxious agents such as histamine, bradykinin, serotonin, acetylcholine, and substance P, from nerve endings both peripherally and centrally (15). This indicates that although they enhance the tooth movement process, their side effects are very serious to consider its clinical use. Recent trends are directed toward combining local anesthetics with PGs, in order to reduce pain while injected locally. Research in this regard is still in its preliminary phase.

Echistatin and RGD peptides

Another approach made recently was local injection of echistatin and arginine-glycine-aspartic acid (RGD) peptides on rats to prevent tooth movement, thereby enhancing anchorage. Dolce et al. made the first attempt in this aspect and reported that ELVAX-40 (a non-biodegradable, non-inflammatory, sustained release polymer) could be used to deliver integrin inhibitors like echistatin and RGD peptide agents (known to perturb bone remodeling), to reduce tooth movement at a local level (63). Recent research has even demonstrated decrease in root resorption following orthodontic force application after administration of echistatin (64). Further research is progressing in this area at different laboratories worldwide.

It is clear from the ongoing discussion that up till now no well-established means are available to promote or retard orthodontic tooth movement in clinical setting.

Conclusions

Inflammatory reactions occurring within the paradental tissues, triggering the processes associated with bone remodeling in response to applied mechanical forces, form the biological basis of orthodontic tooth movement. However, in individual patients some or all of these responses may be overshadowed by events occurring elsewhere in the body. 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 combined effect of mechanical forces and one or more of these agents may be inhibitory, additive, or synergistic. Orthodontists should be aware of the fact that orthodontic treatment is provided to biologically active and reactive organisms, rather than to typodonts in laboratories. Many patients use drugs on a daily basis, and all these drugs have therapeutic effects, as well as side effects, that may influence the cells targeted by orthodontic forces. Therefore, it is imperative that the orthodontist pays close attention to the drug consumption history of each and every patient, before and during the course of orthodontic treatment. Furthermore, when the use of drugs is revealed, their effects and side effects on tissue systems should be explored, to determine their potential influence on the outcome of mechanotherapy.

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