

EFFECTS OF DRUGS ON PERIODONTAL TISSUE REMODELING AND CLINICAL RESPONSES TO ORTHODONTIC MECHANOTHERAPY

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SUMMARY

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

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.

Effects and side effects of the drugs which may be used by the patients undergoing orthodontic treatment have been reviewed. Drug-consumption history must be an integral part of every orthodontic diagnosis and treatment plan.

Key words: Adverse effects, remodeling drugs, orthodontics, tooth movement

INTRODUCTION

Remodeling of the periodontal tissues facilitates orthodontic tooth movement in response to mechanical forces. 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. 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.¹ 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. 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 drug 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. This information should enable the orthodontist to increase the precision of forecast of the treatment duration and outcome. The objective of this review was to outline the mechanisms of action and effects of some commonly used drugs on tissue remodeling and orthodontic tooth movement.

Non-steroidal anti-inflammatory drugs

The most common group of medications used in orthodontics consists of non-steroidal anti-inflamma-

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tory drugs (NSAIDs) for the control of pain following mechanical force application to teeth. Studies done by Simmons, Pagenetti, Nagan 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.¹⁻⁸

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.⁹

Drugs effecting root resorption

It has been demonstrated that the unwanted sequel 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.¹⁰

However, it has also been reported that these drugs produce cemental surface alterations, by inhibiting a cellular cementum formation, thereby actually increasing the vulnerability of the dental root to the resorptive process.¹¹ The main hormone prescribed to reduce root resorption is L-thyroxine, which increases the resistance of cementum and dentin to elastic activity.¹² 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.¹³ 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.

Medicines used in temporomandibular disorders

Management of temporomandibular disorder patients in the orthodontic clinical setting includes either splint therapy¹⁴ or muscle relaxants like cyclobenzaprine

(Flexerol 10 mg, three times daily), tricyclic antidepressants like amitriptylin (Elavil 10 mg, one tablet at night time) and benzodiazepins like diazepam (Valium 5 mg at night time).¹⁵ The main side effect associated with all these drugs is xerostomia, a significant condition in patients under orthodontic care.¹⁶ 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.¹⁷

Drugs used in Osteoporosis

Among the most prevalent diseases that afflict women of adult age group is osteoporosis. 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 due to increase in the mineralization of old bone.¹⁸ Sato et al reported on irregular ruffled borders in osteoclasts of rats administered with bisphosphonates. 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, 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.¹⁹

Medicines used in 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.²⁰ Most of the drugs used for RA 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.²⁵

Drugs used in 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. The drugs, which are important to orthodontists 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.²⁴ Currently there are over 20 agents with differing mechanisms of action for managing these patients.²⁵ It is to be noted that orthodontic treatment is not at all contraindicated in patients with seizure disorders. 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.

Medications in 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.²⁶ 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. 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 taken before and during the orthodontic treatment period. The importance of aggressive oral hygiene measures and topical fluoride application should be emphasized to these patients.²⁷ 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.²⁸ This emphasizes the applications of low forces for these patients, just enough to produce tooth movement without any adverse effects like root resorption.

Drugs used in childhood cancer

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. 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.²⁸ Patients on immunosuppressant therapy with cyclosporine 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.²⁹ 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.

Effect of medicines used in Psychiatric problems

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 methylphenidate, dextroamphetamine, atomoxetine,

bupropion, 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. 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 (ex autism) are treated with second-generation neuroleptics (ex aripiprazole), which often lead to challenging unreasonable worries, inflexibility, odd behavior and misbehavior with office staff.³⁰

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 (cyclosporine 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.¹¹

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.³²

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 leukotrienes) released from parodontal cells in sites of compression and tension have significant stimulatory effects on bone remodeling. Yamasaki et al found an increased number of osteoclasts in rats' alveolar bone after local injection of PGEI.³³ A similar regimen in human subjects increased significantly the rate of canine and premolar movement.³⁴ 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- α), PGE2 stimulated osteoblastic cell differentiation and new bone formation, coupling bone resorption in vitro.³⁵ 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.³⁶

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