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DRUG THERAPY IN ORTHODONTICS:

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Appropriate tooth mobility establishes the optimum orthodontic treatment plan. The biological response that occurs when teeth are subjected to a mechanical stimulus is called the Orthodontic Tooth Movement (OTM). This kind of movement is mostly brought about by the consistent application of controlled mechanical stress to a single tooth or to a group of teeth. This process eventually causes the socket to remodel by creating pressure and tension zones in the PDL and alveolar bone.
Medication that modifies or interferes with the inflammatory process can have a significant effect on the mobility of the tooth. Numerous research have looked at the impact of both short- and long-term drug administration on OTM. In their research, Davidovitch et al. and Yamasaki et al. deduced that the local or systemic administration of specific medications affects the rate of OTM. A drug is any single active ingredient in a medication intended for use in the diagnosis, treatment, prevention, or curing of a disease. A drug is any chemical or product that seeks to alter or investigate physiological systems or pathological conditions for the benefit of the user, according to WHO (1966)[1].
The drugs usually employed in orthodontics could be broadly classified into two major groups: -
1. Promoter drugs
2. Suppressor agents

Promoter agents, such as prostaglandin, leukotrienes, cytokines, vitamin D, osteocalcin, corticosteroids, thyroid hormones, and parathyroid hormones, are drugs that typically work in tandem with inflammatory mediators to improve orthodontic tooth movement.
Drugs known as suppressor agents, such as bisphosphonates and nonsteroidal anti-inflammatory drugs, oestrogens, cholesterol-lowering medications, and fluorides, decrease the resorption of bone.

Promoter drugs

Prostaglandins

Eicosanoids are prostaglandins (PGE) . In various tissues, it works by controlling the synthesis of cyclic AMP. The action of many hormones is regulated by this Cyclic AMP. The prostaglandins have the ability to influence a broad spectrum of tissue and cellular activities.

By controlling peripheral sympathetic neurotransmission and neuronal excitability, PGs function as neuromodulators in the brain. Afferent nerve terminals are made more sensitive to chemical, mechanical, and thermal stimuli by PGE2 and PGI2.

Effect of Prostaglandins on bone & tooth movement:
They work by inducing the resorption of bone tissue, resorption of roots, reduction in collagen synthesis, and elevation of cyclic AMP. Osteoclast activation and cell proliferation are the two ways in which bone resorption is induced. PGE2 at concentrations between 0.1 and 1 micrograms seems to be useful in improving tooth mobility. Increased levels of these could cause root resorption[2]. Systemic administration is reported to possess higher impact than local administration. As per the findings of Dowsett et al. and Klein and Raisz et al., prostaglandins are crucial in facilitating bone resorption. According to a study by Goldhaber et al(1973), periodontal disorders are associated with higher prostaglandin levels. In a split mouth investigation, it was demonstrated that local PGE1 or PGE2 treatment in the gingiva close to the canine distal area generated twice as much tooth movement as on the contralateral control side. It was observed that the gingiva showed no signs of adverse consequences. Studies on humans were conducted in 1984, The effects of PGE1 injection on tooth mobility during orthodontic treatment were investigated by Yamasaki et al. The author claims that as compared to control sides, the rate of tooth movement was twice. In a subsequent study, Lee examined the effects of lidocaine and PGE 1, reporting that PGE 1 was more effective in resorption of bone but with specific adverse effects, including phlebitis and local discomfort[2].

Vitamin D3
A crucial component of calcium homeostasis is Vitamin D3 (1, 25 dihydroxycholecalciferol, or 1, 25 [OH] 2D3). Vitamin D3 will control the metabolic activity of calcium and phosphate levels with the aid of parathyroid hormones and calcitonin. According to recent research, vitamin D3 supplements are particularly helpful in treating osteoporosis since they improve bone mass and reduce fractures in osteoporotic patients. This makes vitamin D3 an active suppressor agent. However, because vitamin D3 stimulates osteoclasts, some researchers believe it may be a promotional agent. Collins et al.'s 1988 study found that giving rats localised vitamin D3 administration sped up their teeth's movement[4].

Leukotrienes
Leukotrienes are the only eicosanoids that are produced separately from the enzyme cyclooxygenase (COX). They belong to the category of eicosanoids that may be the result of arachidonic acid conversion. They are created during the lipoxygenase enzymes' metabolism of arachidonic acid. Leukotrienes play important role in inflammation, allergies, and conditions like asthma. Using leukotriene inhibitors, which block leukotriene receptors and so neutralise their effects, certain conditions can be treated. Medication examples are zafirlukast and montelukast.

Effects on bone and tooth movement
It promotes the resorption of bone. Mohammed A H et al. (1989) claim that leukotrienes improve orthodontic tooth movement by remodelling bone, but leukotriene inhibitors have the opposite effect. Leukotrienes may therefore be utilised in future therapeutic applications that may increase tooth movement, whereas leukotriene inhibitors may postpone orthodontic treatment[3].

Corticosteroids
The adrenal gland's cortex secretes both corticoid and androgen hormones. Corticosteroids are divided into two categories: glucocorticoid and mineralocorticoid. Glucocorticoids are prescribed as immunosuppressive medications following organ transplantation, and they are used to treat a variety of autoimmune and inflammatory conditions, such as rheumatoid arthritis, dermatitis, allergies, and asthma. 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 affects how prostaglandin, leukotrienes, or thromboxanes are synthesised. At the sites of injury, corticosteroids decrease the release of lymphokines, serotonin, and bradykinin. They are essential in preventing the intestinal absorption of calcium, which in turn causes an increase in bone resorption and a direct reduction of osteoblastic activity.

The rate of tooth movement in rats receiving short- and long-term corticosteroid medication was measured in a study conducted in 2004 by Kalia and colleagues. They came to the conclusion that while tooth mobility accelerated during chronic treatment, bone remodelling was slowed down during acute doses. This implies that individuals receiving short-term corticosteroids should have their orthodontic treatment delayed or completed later. Patients receiving long-term corticosteroid medication can continue receiving it with no side effects and more retention, which could be useful if the dentist decides to move forward with orthodontic treatment and help keep these teeth in place. When prolonged use, the major side effect noticed is osteoporosis[8].

Thyroid hormones

The thyroid gland secretes hormones calcitonin and thyroxin. Prohormone thyroxine (T4) can be changed into tri-iodothyronine (T3), which is its active form. This active form of thyroxine is essential for cell metabolism, growth, and physical development. Thyroxine administration will result in decreased bone density, increased bone resorption activity, and increased bone remodelling. Interleukin 1 is produced by thyroxin (IL-IB). This particular type of cytokine is involved in the osteoclastic response, which forms bones.

Rats have been used in studies to determine the connection between tooth mobility and exogenous thyroxine. When compared to the control, the orthodontic movement significantly increased as a result. The thyroid secretes a peptide hormone called calcitonin. Due to its antagonistic activity, less calcium is absorbed by the kidneys and intestines. Osteoclasts in bones are rendered inactive by calcitonin, which prevents bone resorption. Additionally, it increases osteoblasts' capacity to create bones. The frequency of "force induced" root resorption modification in the bone remodelling process is decreased by lowdosage and short-term thyroxin administrations; the reason for this decreased resorption process could be attributed to reinforcement of the cementum and dentin's protection against "force induced" osteoclastic resorption[6].

Parathyroid hormones

Ensuring the proper metabolism of calcium and phosphorus is the primary role of parathyroid hormone. It preserves a steady ratio of the minerals to one another as well as the typical level of diffuse calcium and phosphorous in the plasma. Gene transcription activity, various protease secretion, and osteoblasts' cellular metabolic activity are all influenced by PTH. It affects osteoclasts through activating nuclear factor kappa-B ligand through the RANK-L receptor.It is a protein that is essential to the creation and activity of osteoclasts. Research conducted on animals in the 1970s demonstrated that PTH could stimulate increased bone turnover, which would hasten the movement of teeth in orthodontic treatment. Recent research has shown that rats receiving PTH, either locally or systemically, exhibit a higher rate of tooth movement. These findings suggest that orthodontists should be aware of patients receiving PTH treatment, such as in situations of severe osteoporosis[9].

Alcohol Use

An decrepit skeleton and an elevated risk of osteoporosis are the outcomes of long-term alcohol intake. When comparing these individuals to non-alcoholics, they are more likely to experience delayed fracture healing. Because more force may result in root resorption and tooth mobility, orthodontists treating patients with chronic alcoholism should be mindful of the bone-remodelling response and exercise caution while making tooth adjustments. In order to prevent the consequences, the force used during orthodontic treatment should be kept to a minimum. Furthermore, it might result in a variety of health, dental, social, and dietary issues for which the orthodontist should provide the appropriate recommendations[1,2].

Nicotine usage:

Smoking causes harmful intraoral effects, including carious lesions and accelerated periodontal disease progression. The highly addictive substance contained in cigarette smoke is nicotine. The

COX enzyme, which changes arachidonic acid into PGs, mediates the increase in bone resorption linked to nicotine which converts arachidonic acid to PGs (Baljoon et al., 2005).

Nicotine accelerates orthodontic tooth movement in a dose- and time-dependent way by increasing the expression of the COX-2 gene and releasing PGE2 from human gingival fibroblasts. Considering the detrimental consequences of tobacco use on life expectancy, quality of life, and oral tissues, orthodontists ought to counsel their patients to give up the habit.

Since nicotine has the ability to promote OTM, light force orthodontic therapy shouldn't be interfered with by nicotinereplacement therapy, such as nicotine gum or patches[13].

Suppressor Drugs

Estrogens

Estradiol, estrone, and estriol are the three main endogenous components that make up estrogen, the female sex hormone. The production of estradiol occurs from menarche to menopause and is crucial to the estrous cycle.During pregnancy, estrogen is frequently found. While some research suggests that oestrogen can promote the production of new bones, estrogen itself has no effect on bone tissue. Tumour necrosis factor and interleukin-1,6, two cytokines that aid in bone resorption, can be inhibited by estrogen. According to certain research, the estrogen hormone will reduce the amount of tooth movement during orthodontic treatment. Long-term contraceptive pill use has the potential to slow down the rate of OTM. Additionally, androgen (hormone) can regulate muscle growth and prevent bone resorption, which may impact the duration and results of orthodontic therapy[8].

Bisphosphonates

Bisphosphonates are a class of medications that can effectively suppress bone resorption; they resemble pyrophosphate counterparts in practically every way. In the treatment of diseases like osteoporosis, Paget's disease, and cancers related to the bones, bisphosphonates are frequently utilised. During treatment, the rate of OTM can be reduced by the topical or systemic administration of bisphosphonates. According to studies, using bisphosphonates topically helps stabilise and anchor teeth during orthodontic therapy. Osteonecrosis can result with long-term usage of bisphosphonate medications, especially in the maxillary and mandibular alveolar bones.

Effects Bisphosphonates on tooth movement

According to numerous studies, these medications have the ability to stop orthodontic teeth from moving and lengthen the orthodontic treatment period. Osteonecrosis, which affects the mandibular or maxillary region, is one of the main side effects of bisphosphonates that might occur. This is because the death of osteoclasts and suppression of bone vascular growth have reduced blood flow to the smallest blood vessels in the mandibular and maxillary regions[10].

Nonsteroidal Anti-Inflammatory Drugs (NSAIDS)

Typically referred to as NSAIDS, are generally used for pain management. NSAIDs have anti-inflammatory, analgesic, antipyretic properties, and they are prescribed for many medical conditions. Orthodontists should strongly warn patients not to take this medication without first consulting them during orthodontic treatment. By preventing the Cyclooxygenase (COX) enzyme from functioning, NSAIDs will prevent the synthesis of prostanoids during the transformation of arachidonic acid. The subclass of ecasanoid hormones that can aid in bone resorption is called prostanoids.

Effect of Nonsteroidal Anti-Inflammatory Drugs on tooth movement Studies that have elucidated the molecular mechanism underlying the restriction of tooth movement caused by nonsteroidal anti-inflammatory drugs (NSAIDs) have revealed that, in addition to increased collagenase activity, there is an increase in the levels of Matix Mettallo-proteinases.

This is followed by a decrease in the synthesis of procollagen, which is crucial for remodelling the alveolar bone and periodontal tissues. Furthermore, the entire process is structured around blocking the activity of the COX enzyme, which may alter the vascular and extravascular matrix's remodelling and slow down the movement of teeth in orthodontics[7].

Paracetamol

Acetaminophen, also known as paracetamol, is an analgesic. Inhibitors of COX1 and COX-2 are not affected by it.

Acetaminophen and nonsteroidal antiinflammatory medicines (NSAIDs) differ primarily in that the former act on COX-3 inhibitors, which are found in the brain and spinal cord, while the latter acts on the enzymes of COX-1 and COX-2 inhibitors.

Effect of acetaminophen on tooth movement.

According to certain research, paracetamol given systemically lowers prostaglandin levels and has no effect on how teeth move in guinea pigs and rabbits undergoing orthodontic therapy. It has an effect on pain control and decreases the discomfort during treatment[4].

Aspirin

COX activity, which is responsible for converting unsaturated fatty acids in the cell membrane to polyglyclic acids (PGs), is inhibited by acetylsalicylic acid and its related chemicals. Based on clinical experience, individuals receiving long-term acetylsalicylic therapy exhibit relatively sluggish tooth movement during orthodontic treatment. Through reduction of PG production, salicylate treatment reduces bone resorption and may influence osteoclast development from precursors. Consequently, it is suggested against prescribing aspirin and similar medications to patients undergoing orthodontic treatment for extended periods of time[1].

Calcitonin

Through its direct action on osteoclasts, calcitonin slows bone resorption by reducing the ruffled surface of these cells that makes contact with the resorptive pit. Additionally, it increases osteoblast activity. Due to its physiological function, it is thought to impede tooth mobility; as a result, orthodontic therapy may take longer than planned[1].

Immunosuppressant drugs

Orthodontic patients who are immunosuppressed, have had kidney transplants, or chronic renal failure may experience certain challenges. Cyclosporine A, a medication used to prevent graft rejection, causes severe gingival hyperplasia, which makes maintaining dental hygiene and orthodontic treatment challenging.

Once there is good oral hygiene, treatment should begin or continue following surgical excision of excessive gingival tissues. When using brackets, fixed appliances should be used as little as possible. Cement bands should be avoided. In these situations, it is not advised to use removable equipment because of incorrect fit[1].

Phenytoin

Because of the overgrowth of gingival collagen fibres, it causes gingival hyperplasia, affecting the interdental papilla and making it more difficult to maintain oral hygiene and apply orthodontic mechanics. It can cause foetal hydantoin syndrome, which is characterised by hypoplastic phalanges, cleft palate, hare lip, and microcephaly, if taken while pregnant. Even little trauma might cause gingival bleeding when exposed to valproic acid, which makes orthodontic manoeuvres challenging. Because Gabapentin causes xerostomia, maintaining good dental hygiene becomes challenging while receiving orthodontic treatment[1].

Cholesterol-Reduction Medicines

Because of their strong ability to decrease cholesterol, statins are the most often prescribed medication **(Mundy, 2001),** with over 3 million Americans using them on a daily basis. All of the previously discussed investigations were conducted using animal models, and human trials are currently being conducted at various universities across the globe. It's possible that statin-using orthodontic patients will exhibit less bone resorption, and the orthodontist may anticipate that these patients' teeth will move more slowly. Furthermore, the orthodontist should constantly be aware of the antiangiogenic nature of statins, which might result in osteonecrosis of the jaws, while doing orthodontic therapy on such patients[12].

Fluorides

One of the most crucial substances that can be utilised to fortify enamel is fluoride. It works as a remineralizing agent to stop early indications of tooth decay and caries. It is used to treat conditions like osteoporosis and enhances bone mineral density. Several studies have indicated that applying sodium fluoride to prevent active caries during orthodontic therapy may cause the tooth to move less freely and lengthen the orthodontic treatment period. Sodium fluoride has been demonstrated to reduce osteoclastic activity[1]. Karadeniz et al.
(1999) conducted a study on 48 patiens with application of 2 ppm high fluoride heavy force, 0.05 ppm low fluoride heavy force, high fluoride light force, low fluoride light force respectively, ortho springs were applied and conclusion drawn was Fluoride and heavy forces both increase OTM.

Insulin

Insulin secretion eventually decreases as a result of the immune system destroying the beta cells of the pancreatic Langerhans, resulting in Type-1 Diabetes Mellitus (DM). Numerous research studies have indicated a positive correlation, either directly or indirectly, between insulin and bone mineral density through the elevation of IGF1 (hepatic insulin). Because osteoblast-like cells have insulin receptors, the hormone promotes the growth of these cells. In a rat study, Hamid et al. found that insulin therapy reversed type-1 diabetes mellitus to almost normal levels and that, at the optimal force level, there was no difference in the movement of orthodontic teeth or the number of osteoclasts between normoglycemic and insulin-treated diabetic mice[11].

Conclusion

A surprisingly complex series of processes, including biochemical and mechanical ones, bone cell activity, and the modelling and remodelling of the alveolar process in response to mechanical stress, all contribute to the movement of orthodontic teeth.Orthodontists will need to pay more attention to each patient's medical and drug consumption history both before and during orthodontic treatment because they will understand how common medications affect the molecules that increase or decrease homeostasis in tissues next to the moving tooth subjected to orthodontic forces. Ultimately, it is now evident that additional well planned human research is required in order to effectively draw conclusions about how different drugs affect OTM.

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