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The Physiological and Pharmaceutical Aspects of the Orthodontic Tooth Movement

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Abstract

The purpose of this paper was to review the various medications that can influence the required orthodontic tooth movement. The circulation can carry molecules from medications and foods that patients regularly consume to mechanically stressed parenchymal tissues, where they can interact with nearby target cells. Mechanical forces, induced by orthodontic treatment, may have an inhibitory, additive, or synergistic effect when combined with one or more of these substances. The literature search led to several scientific works that were selected on the basis of their relevance in order to extract the data. The results found were presented according to each type of molecule that is mostly found in medical prescriptions. In conclusion, the dental displacement caused by orthodontic appliances may be as well compromised as favoured by the medication taken by the patient during his orthodontic treatment.

Subject Areas

Dentistry

Keywords

Tooth Movement

1. Introduction

Orthodontic treatment is based on the principle that when a force is applied to a tooth and transmitted to adjacent tissues, certain mechanical, chemical and cellular events occur in those tissues, allowing structural changes and contributing to tooth movement [1].

This induced movement requires the complex molecular signalling pathways responsible for periodontal tissue homeostasis for the transduction of mechanical stress into bone remodelling. Theoretically, these events could be modulated

by any medication. During the last few years, the possible influence of different pharmaceutical substances on tissue homeostasis and the events leading to orthodontic tooth movement have been reviewed and various changes, based on a limited number of studies, have been noted [2] [3].

Molecules present in drugs and nutrients consumed regularly by patients can reach the mechanically stressed paradental tissues through 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 [2].

The earliest report on orthodontic tooth movement in English literature was published in 1911. Oppenheim [3] carried out studies on baboons to determine what histologic changes occurred during tooth movement. Reitan and others have conducted research into the nature of tooth movement. These studies gave rise to the pressure-tension model of tooth movement, in which the two sides of the tooth respond to forces as if they were apart [4].

The purpose of this article was to review the various medications that can influence the required orthodontic tooth movement.

2. The Physiology of Tooth Movement

During induced tooth movement, two bone activities are carried out in the desmodontal space of the tooth that is subject to orthodontic migration: apposition and resorption. Resorption of the alveolar bone occurs on the side towards which the tooth moves during physiological tooth movement. Simultaneously, reconstruction of the ligamentous support between the tooth and the bone takes place [5].

2.1. Osteoclastogenesis in Orthodontic Tooth Movement

Application of force during orthodontic tooth movement leads to the initiation of osteoclastogenesis. Two associated changes occur during this stage. First, tissue damage occurs with further production of inflammatory processes in the periodontal ligament (PDL). Second, alveolar region deformation takes place. A few days after the application of the force, the first osteoclast progenitor cells appear at the compression sites in the alveolar crest vasculature and marrow spaces, and the PDL space widens [6] [7]. Osteoclasts appear in higher quantity at the compression sites compared to tension sites [8]. In addition, proinflammatory cytokines such as IL-6, IL-8 and TNF-α are produced, which suggests the importance of inflammation in initiating osteoclastogenesis during tooth movement [9] [10].

During the period of 5 - 7 days following force activation [11], osteoclasts are cleared from compression sites. This may be due to osteoclast apoptosis followed by secondary necrosis [12]. A second pathway for osteoclast death occurs through integrins (specific receptor-like molecules), focal adhesion proteins and cy-

toskeleton.

Osteocytes, the predominant bone cells in the alveolar bone during orthodontic movement, have not been well studied in the scientific literature. These cells are well-equipped to facilitate bone adaptation to loading [13]. The physiological changes in periodontal tissue during orthodontic tooth movement affect the activity, metabolism, and communication of osteocytes [14]. Nitric oxide (NO) is an important regulator of bone response to mechanical loading. It is produced by endothelial nitric oxide synthase (eNOS) or inducible nitric oxide synthase (iNOS) [15], and has been shown to: mediate adaptive bone formation [16] and osteoclast activity [17], and prevents osteocyte apoptosis [18] [19]. Several authors have shown that inhibition of NO production increases osteoclastogenesis [20] [21]. Orthodontic force results in strain within the bone giving rise to fluid flow leading to production of NO by osteocytes [22]. Additionally, it has been suggested that iNOS mediates inflammation-induced bone resorption in the compression area [22]. It has been shown that osteocytes and osteoclasts undergo apoptosis at orthodontic compression sites [14]. However, this concept is not fully understood.

2.2. Osteogenesis in Orthodontic Tooth Movement

It has been shown that tensile strains stimulate the proliferation of the osteoblast progenitor cells in the PDL. This leads to bone formation and inhibition of bone resorption. Molecules linked to osteogenesis in orthodontic tooth movement are: TGF-β [23], BSP [24], BMPs [25] and epidermal growth factor [26].

The mechanism of osteogenesis during orthodontic tooth movement on the tension side is not well understood. Once orthodontic force is applied, the mechanical forces are first received by the fibroblasts in the PDL. An *in vitro* study has shown that cyclic strain results in an increased osteogenic gene expression in PDL fibroblasts [27]. In addition, eNOS which produces NO has been identified to mediate bone formation in the tension area during orthodontic tooth movement [22].

Osteoclastogenesis and osteogenesis associated with tooth movement are two separate concepts orchestrated simultaneously facilitating orthodontic tooth movement. More studies need to be done for understanding the concept of alveolar bone remodeling during orthodontic tooth movement.

3. Medication and Orthodontic Tooth Movement

3.1. Pain Relief Drugs

Although clinical examination and records constitute the basis of diagnosis and treatment plan elaboration in orthodontics, detailed information pertaining to medical history is important [28]. Pain relief drugs are used and misused widely; however, only a few studies per investigated substance were retrieved. On the basis of the compiled information, various effects on the rate of orthodontic tooth movement were noted following long-term consumption. Although these

results should be seen with caution as the assessed level of evidence implies, the clinician should not ignore the fact that some patients may take pain relievers independently of orthodontic treatment for long periods of time, as well as the possible implications [28]. It is meaningful for the practitioner to be able to identify prospective patients' pharmaceutical history and possible changes during the course of treatment, especially since prescription medication consumption has expanded significantly.

Pain-relieving medications, both in the form of prescription and over-the-counter formulations, are used widely. During orthodontic treatment, substances such as paracetamol and ibuprofen are often consumed for a few days to counter the discomfort associated with specific procedures, such as separator placement, archwire changes, and appliance activation. Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen are available over the counter and inhibit the cyclooxygenase enzymes, which are essential for the production of prostaglandins. Prostaglandins raise the levels of metalloproteinases, including collagenase, followed by a decrease in procollagen production, which is important for bone and periodontal ligament remodelling [29].

Thus, it has been suggested that prostaglandin inhibition generates a cascade of events that may affect the rate of orthodontic tooth movement [30].

The pharmacokinetic effect of NSAIDs:

Several mediators are released by osteocytes during orthodontic tooth movement. One of the most significant is prostaglandins, which undertake the role of stimulating osteoclasts and osteoblasts [31]. NSAIDs that are commonly used to reduce pain and inflammation, act on cyclooxygenases, which regulate the formation of prostaglandins from arachidonic acid and might potentially affect the process of orthodontic tooth movement [32]. Ibuprofen and loxoprofen, which are both parts of the propionic acid derivatives group, did not show any significant effects on the rate of movement. However, long-term administration of indomethacin, ketorolac, and high doses of etoricoxib was shown to decrease it. The administration of indomethacin and ketorolac has been shown to result in a reduced number of osteoclasts during orthodontic tooth movement [33] [34]. Etoricoxib inhibits cyclooxygenase-2, resulting in reduced production of prostaglandins [35].

Inconsistent or conflicting effects were noted after treating animals with other NSAIDs such as acetylsalicylic acid, celecoxib, and meloxicam. Reports on the overall effects of NSAIDs on bone metabolism have also been discrepant, which has been attributed among others to differences in study design, dosages, routes of administration, treatment periods, and even study animal species or gender [36] [37]. Marked differences between animal species regarding the chemical composition, the density and the cellular content of the osseous tissue, as well as bone biomechanical properties have been described in small rodents [38]. The pharmacokinetic behaviour of NSAIDs could also be different between animals of different species [39]. Moreover, it has been suggested that the cyclic changes in the oestradiol levels observed during the oestrous cycle in female animals may

be associated with the variations in the rate tooth of orthodontic movement through its effects on bone resorption [40]. However, further studies are warranted to strengthen these assumptions [37].

From the non-opioid analgesics, acetaminophen is similar in efficacy to aspirin but has no demonstrable anti-inflammatory activity [41]. Thus, it has been suggested that acetaminophen is an appropriate alternative to NSAIDs for patients under orthodontic treatment [42].

The pharmacokinetic effect of the opioids:

However, on the basis of the material retrieved in this review, inconsistent effects were noted on the rate of orthodontic tooth movement. As suggested previously, the observed discrepancies could be explained by disparities in study designs, drug administration routes, and duration, as well as the species and the gender of the experimental animals [36] [37] [38] [40].

Morphine, the archetypal opioid, is a very effective analgesic [41]. Although endogenous opioids have been shown to increase the rate of orthodontic tooth movement in cholestatic rats by interacting with nitric oxide, the rate of movement was shown to decrease after administering morphine [43]. Following treatment with tramadol, conflicting effects on orthodontic tooth movement were observed. It is possible that its dual action, being a serotonin norepinephrine reuptake inhibitor and a weak μ-opioid receptor agonist may account for these results [44]. Tramadol has been shown not to affect osteoclast numbers [45]. At the same time, it has been reported that it inhibits the function of substance P receptors. Substance P is a neurotransmitter involved in the remodelling of the periodontal ligament and alveolar bone during orthodontic tooth movement [46] [47].

Even from this limited set of animal data, clinicians could gain insight into considerations relevant to patients using analgesic substances. The assessment of the duration of treatment could be changed when a patient is taking medications that may decrease the rate of orthodontic tooth movement. In terms of mechanotherapy, these patients may present additional difficulty in closing the pre-existing or post-extraction spaces.

In addition, it must be recognized that the data collected in this review were extracted from systematic reviews including animal studies and so cannot be directly extrapolated to humans. This is further complicated by the fact that the drugs have been administered at doses sometimes different from those used in routine human clinical settings [41] and by routes of administration with possibly different effects on pharmacokinetics and bioavailability [48].

Based on the information compiled, pain relievers can have various effects on the rate of orthodontic tooth movement after long-term consumption, the clinician should not ignore patients taking pain relievers, as well as the possible implications.

3.2. Corticosteroids

The main effect of corticosteroids on bone tissue has been shown to be the direct

inhibition of osteoblast function and thus a decrease in total bone formation. The decline 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 [49].

When the corticosteroids 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. More extensive retention may be required [49].

3.3. Antidiabetic Agents

Metformin has been shown to result in a decrease and subsequent normalization not only in the high rate of orthodontic tooth movement observed in controlled diabetic subjects, but in the number of osteoclasts as well [50]. On the other hand, the administration of insulin showed conflicting results [51] [52].

3.4. Thyroid Hormones

Thyroid hormones are recommended for the treatment of hypothyroidism and used after thyroidectomy in substitutive therapy. 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 [53].

The thyroid hormone increases the speed of orthodontic tooth movement in patients undergoing such medication. Low dosage and short-term thyroxine administration are reported to lower the frequency of "force-induced" root resorption. A decrease in resorption may be correlated to a change in bone remodeling process and a reinforcement of the protection of the cementum and dentin to "force-induced" osteoclastic resorption [53].

3.5. Parathyroid Hormone PTH

PTH affects osteoblasts' cellular metabolic activity, gene transcriptional activity, and multiple protease secretion. In the 1970s, animal studies demonstrated that PTH could induce an increase in bone turnover that would accelerate orthodontic tooth movement. More recently, an increased rate of tooth movements has been observed in rats treated with PTH, whether administered systemically or locally [54]. These results indicate that orthodontists should take note of patients being treated with PTH, for example, in cases of severe osteoporosis.

3.6. Oral Contraceptives: Hormones

Estrogen is considered to be the most important hormone affecting the bone metabolism in women. It inhibits the production of various cytokines which are

involved in bone resorption by stimulating osteoclast formation and osteoclast bone resorption. It also inhibits osteoblasts' responsiveness to PTH. Estrogens do not have any anabolic effects on bone tissue; they directly stimulate the bone forming activity of osteoblasts [55].

Studies have shown that estrogens decrease the velocity of tooth movement. 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 [55].

3.7. Anticonvulsants

Phenytoin and phenobarbital did not exhibit any statistically significant effects on the rate of orthodontic tooth movement [56] [57]. Anticonvulsant medication may contribute to the development of osteoporosis, which may result in an increment in the rate of orthodontic tooth movement [58]. Nevertheless, the gingival enlargement that may occur after prolonged phenytoin use may also contribute to the obstruction of space closure [56].

3.8. Antidepressants

Inconsistent or conflicting effects regarding the rate of orthodontic tooth movement have been noted after the administration of fluoxetine [59] [60] [61]. Several components of the serotonergic system, such as 5-HT receptors and 5-HT transporters, are expressed in osteoclasts and osteoblasts, and fluoxetine has been demonstrated to have an anti-inflammatory effect [61].

3.9. Vitamins

Vitamin C (ascorbic acid) has been shown to increase the rate of orthodontic tooth movement in short-term [62]. In the pathways related to bone resorption, vitamin C initially triggers osteoclast formation, but later limits the average lifespan of osteoclasts [63].

Vitamin D receptors have been demonstrated not only in osteoblasts but also in osteoclast precursors and in active osteoclasts. In 1988, Collins and Sinclair [64] demonstrated that intraligamentary injections of vitamin D metabolite, 1,25-dihydroxy cholecalciferol, caused an increase in the number of osteoclasts and amount of tooth movement during canine retraction with light forces [64]. Similarly and in an animal study, Kale *et al.*, 2004 [65], observed that local applications of vitamins enhanced the rate of tooth movement in rats due to the well-balanced bone turnover induced by vitamin D [65].

Vitamin E supplements positively affected bone formation on the tension side of the teeth during experimental orthodontic tooth movement in rats [66].

3.10. Minerals and Electrolytes

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 and 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 [67]. Sodium fluoride has been shown to inhibit osteoclastic activity and reduce the number of active osteoclasts.

Calcium carbonate [68], calcium gluconate [69] and strontium ranelate [70] caused a reduction in the rate of orthodontic tooth movement. Variations in calcium levels could be associated with the recruitment, differentiation and activation of osteoclasts, and therefore, bone remodelling. In addition, strontium is believed to modify bone metabolism by connecting itself to the calcium-sensitive receptors in osteoblasts and osteoclasts, and subsequently reducing bone resorption [70].

No interference with the rate of tooth movement was demonstrated after the administration of zinc compounds [71]. Nevertheless, bone metabolism may be modified by zinc through stimulating the activity of osteoblasts and reducing bone resorption. It should be kept in mind that the duration of administration might influence the effects of zinc on bone [71].

3.11. Bisphosphonates

Bisphosphonates are drugs used to treat metabolic bone disorders such as osteoporosis, bone diseases and bone pain due to certain types of cancer. Their half-life can be more than 10 years [72]. Bisphosphonates have unique pharmacological characteristics that are different from any other group of drugs. Millions of adults take oral bisphosphonates for the long-term treatment of osteoporosis and osteopenia, and some of these individuals may be receiving orthodontic treatment [73].

Since bisphosphonates have a mode of action that interferes with bone resorption by osteoclasts, several side effects may occur, including inhibition of tooth movement, which has been confirmed in all studies [72], impaired bone healing and induced osteonecrosis in the maxilla and mandible.

Only one retrospective cohort study concluded that in the bisphosphonate group, the duration of treatment was longer and there was a higher risk of incomplete closure of the extraction space at the end of treatment compared to the control group [74].

4. Conclusions

In conclusion, it remains, to a degree, unclear which types of medication may have a clinically significant effect in everyday clinical scenarios. However, since both prescription and over-the-counter medication use have recently increased significantly among all age groups, good practice would suggest that it is important to identify patients consuming medications and consider the possible implications.

In terms of mechanotherapy, patients taking drugs that increase tooth movement may present augmented needs for anchorage preparation, while patients, where movement is pharmacologically hindered, might exhibit difficulty in closing pre-existing or post-extraction spaces. Furthermore, appointments might need to be more frequent for patients in the first category in order to check and control the progress of the treatment. On the other hand, it is possible that there would hardly be any benefit in having shorter appointment intervals when patients are receiving medication that may decelerate the tooth movement.

Conflicts of Interest

The authors declare no conflicts of interest.

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