OVERVIEW

The Influence of Drugs and Systemic Factors on Orthodontic Tooth Movement

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(Editor's Note: In this quarterly column, JCO provides a brief overview of a clinical topic of interest to orthodontists. Contributions and suggestions for future subjects are welcome.)

Orthodontic tooth movement is induced by the prolonged application of controlled mechanical forces, which create pressure and tension zones in the periodontal ligament and alveolar bone, causing a remodeling of the tooth sockets. The bone remodeling and tooth displacement occur by means of an inflammatory process involving osteoclasts, osteoblasts, neuropeptides,[1,2] and cytokines,[3,4] along with changes in innervation and local vascularization.[5,6]

Over the last few years, the discovery of new molecules and the development of new experimental techniques have allowed orthodontic movement to be studied at the molecular level. Research in molecular biology has identified the main mediators involved in the complex process of extravasation, inflammatory cell chemotaxis, and the recruitment of osteoclast and osteoblast progenitors[7] (Table 1). The aim of this overview is to update the clinician on the role of drugs and systemic factors capable of affecting bone metabolism and the rate of orthodontic tooth movement.

Effects of Drugs on Induced Tooth Movement

The drugs that can influence orthodontic movement are divided into four main categories:

1. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Investigation into the mechanisms involved in the transduction of mechanical forces into biological responses began in the 1970s. Harell and colleagues, in 1977, observed the synthesis of

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TABLE 1
FACTORS AFFECTING BONE-REMODELING PROCESS

Hormones and Systemic Factors
Parathyroid hormone
Calcitonin
Insulin
Growth hormone
Vitamin D
Glucocorticoids
Sex steroids
Thyroid hormones
Growth Factors
Insulin-like growth factors I & II
Transforming growth factor ß
Fibroblast growth factor
Platelet derived growth factor
Cytokines
Interleukin-1,4,6,11,13,18
Tumor necrosis factor
Osteoclast differentiating factor
Interferon-γ
Osteoprotegrin
*Colony-Stimulating Factors**
M-CSF
G-CSF
GM-CSF
Others
Prostaglandins
Leukotrienes
Nitric oxide

*Colony-stimulating factors (CSF) related to granulocytes (G-CSF), macrophages (M-CSF), or both cell types (GM-CSF).

prostaglandins from osteoblast-like cells cultured on orthodontic screws, which had been cemented to the bases of petri dishes.[8] In an interesting practical application of these findings, Yamasaki and colleagues, in 1980, found that indomethacin, a non-steroidal cyclooxygenase 1 and 2 (COX-1 and COX-2) inhibitor, reduced bone resorption and orthodontic tooth movement in rats.[9] These authors also demonstrated that the local injection of prostaglandin E-1 and E-2 into the submucosa overlying orthodontically treated teeth doubled the rate of tooth movement, both in monkeys[10] and in humans.[11]

Because prostaglandins appear to be important in the process of tooth movement, it has been suggested that the use of over-the-counter NSAIDs by orthodontic patients can significantly alter the efficacy of tooth movement. The influence of conventional NSAIDs (aspirin,[12] diclofenac, ibuprofen, indomethacin), specific COX-2 inhibitors (rofecoxib, celecoxib), and other drugs on orthodontic tooth movement is described in Table 2. Recently, Jerome and colleagues showed that Celebrex* administered in rats during the application of orthodontic forces did not interfere with tooth movement and appeared to offer some protection against root resorption.[13] Additional research is needed to analyze the effects of this drug in human orthodontic patients.

2. Corticosteroids

The increasing use of glucocorticoid therapy for many inflammatory and autoimmune diseases should alert clinicians to the variations from normal bone turnover that may be caused by this steroid.[14] In animal experiments, high doses of glucocorticosteroids have actually made the animals osteoporotic.[15-17] In 2004, however, Kalia and colleagues evaluated the rate of tooth movement in rats during short- and long-term corticosteroid therapy.[18] They demonstrated that bone remodeling seemed to slow down in acute administrations, whereas the rate of tooth movement increased in chronic treatment. Clinically, these results suggest that it is possible to treat patients undergoing corticosteroid therapy with a minimum of adverse effects. Patients who are within the short-term phase of drug use may be advised to postpone orthodontic treatment or, because their bone turnover will be delayed, should be scheduled for appliance adjustments at longer intervals. On the other hand, in long-term drug therapy, when the rate of tooth movement might be accelerated, orthodontic appliances should be adjusted as usual or even more frequently.

*Registered trademark of Pfizer, Inc., New York, NY.

TABLE 2
EFFECTS OF DRUGS ON INDUCED TOOTH MOVEMENT

	Effects on Bone Metabolism	Effects on Tooth Movement
Non-Steroidal Anti-Inflammatory Drugs		
Aspirin	↓ bone resorption	↓ tooth movement
Diclofenac	↓ bone resorption	↓ tooth movement
Ibuprofen	↓ bone resorption	↓ tooth movement
Indometacin	↓ bone resorption	↓ tooth movement
Celecoxib	↓ bone resorption (in vitro)	no influence
Corticosteroids	↑ bone resorption (chronic use)	↑ tooth movement
Bisphosphonates	↓ bone resorption	↓ tooth movement
Acetaminophen	unproven	no influence

3. Bisphosphonates

Because this class of pharmacological agents selectively inhibits osteoclasts, it has been used to treat various metabolic bone diseases associated with excessive bone resorption.[19] Laboratory studies have demonstrated that orthodontic tooth movement can be inhibited by the topical application of bisphosphonates.[20,21] In 1994, Adachi and colleagues suggested that topically applied bisphosphonates could be useful in orthodontic anchorage and retention of teeth.[20] In 2004, Liu and colleagues applied a bisphosphonate without a nitrogen atom (clodronate) in the subperiosteal molar regions of rats submitted to orthodontic forces for three weeks. The local application of clodronate not only reduced the amount of orthodontic movement and the number of osteoclasts, but also reduced root resorption.[21]

Further studies are required before these drugs can be used in clinical orthodontic therapy. Orthodontists should also be aware of their interactions. In 2005, Schwartz reported an important case of a female orthodontic patient who was being medicated with Zometa** to control bone metastases related to breast cancer.[22] At the time the patient began treatment with this drug, when the premolar spaces were about one-third closed, all orthodontic movement stopped.

**Registered trademark of Novartis Pharmaceuticals Corporation, East Hanover, NJ.

4. Acetaminophen

Acetaminophen (paracetamol), a weak COX-1 and COX-2 inhibitor that also reduces urinary prostaglandin levels after systemic administration, has shown no effect on orthodontic tooth movement in guinea pigs[23] and rabbits.[24] Comparative studies[25,26] and our clinical experience have demonstrated that acetaminophen is effective for controlling pain and discomfort associated with orthodontic treatment.

Effects of Systemic Factors on Induced Tooth Movement

There are five major categories of systemic factors capable of influencing the rate of orthodontic tooth movement (Table 3):

1. Sex Hormones

Estrogen is considered the most important hormone affecting bone metabolism in women. It inhibits the production of cytokines involved in osteoclastic activation and bone resorption, such as interleukin-1, tumor necrosis factor-a, and interleukin-6.[27] in 2001, Yamashiro and Takano-Yamamoto demonstrated an acceleration of tooth movement in spayed female rats.[28] On the other hand, Miyajima and colleagues, in 1996, attributed a female patient's slow turnover of alveolar bone

TABLE 3
EFFECTS OF SYSTEMIC FACTORS ON INDUCED TOOTH MOVEMENT

	Effects on Bone Metabolism	Effects on Tooth Movement
Estrogen	↓ bone resorption	↓ tooth movement
Androgen	↓ bone resorption	unproven
Relaxin	↑ bone resorption	↑ tooth movement
Thyroid hormones	↑ rate of bone remodeling	↑ tooth movement
	↑ bone resorption	↓ root resorption
Parathyroid hormone	↑ bone resorption	↑ tooth movement
Vitamin D	↑ rate of bone remodeling	↑ tooth movement
	↑ bone resorption	

to her menopausal status and to the estrogen supplement she had been taking for three years.[29] They also suggested that young women taking oral contraceptives might experience a reduced rate of tooth movement, although further studies are required in this area. The inhibitory effect of androgens on bone resorption has been demonstrated,[30] but their influence on orthodontic tooth movement has not been clarified.

2. Relaxin

Relaxin has been known for decades as a pregnancy hormone. It is released just before childbirth to loosen the pubic symphysis, so that the relaxed suture will allow widening of the birth canal for parturition. It has also been shown to have effects on a multitude of other physiological processes, including the regulation of vasotonus, plasma osmolality, angiogenesis, collagen turnover, and renal function.[31]

Relaxin's influence on soft-tissue remodeling and on several mediators that stimulate osteoclast formation have attracted attention from orthodontic researchers. In 2005, Liu and colleagues showed that the administration of human relaxin might accelerate the early stages of orthodontic tooth movement in rats.[32] Stewart and colleagues used gingival injections of relaxin in dogs to relieve rotational memory in the connective tissues of maxillary second incisors that had been orthodontically rotated.[33] The results were not significant, but the authors suggested that a refinement of the dosages and treatment techniques might improve the response in future studies. In 2000, Nicozisis and colleagues demonstrated that the presence of relaxin abolished the integrity of sutures in vitro.[34] These authors suggested that relaxin might be used as an adjunct to orthodontic therapy, during or after tooth movement, for promotion of stability; for rapid remodeling of gingival tissue during extraction space closure; or 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. Whether these findings will hold true in clinical practice remains to be investigated.

3. Thyroid Hormones

Thyroid hormones play an essential role in the normal growth and development of vertebrates. They enhance the response to growth hormone, stimulate cartilage growth and differentiation, and promote bone maturation and resorption. In bone remodeling, they act directly by stimulating the action of osteoclasts, but they also have an indirect effect through growth factors that are closely related to bone metabolism, such as insulin-like growth factor I (IGF-I), which is produced locally in bone cells by the action of thyroid hormones.[35]

According to a 1999 study by Shirazi and

colleagues, thyroid hormone administration not only increased the rate of tooth movement in rats, but also reduced the extent of root resorption, as seen from scanning electron micrographs.[36] In 1994, Poumpros and colleagues reported a protective effect from thyroxin on root-resorptive lesions that had been induced by the application of orthodontic forces.[37] More recently, Vazquez-Landaverde and colleagues showed that animals treated with thyroid hormones (intraperitoneal or oral) had significantly less force-induced root-resorptive lesions than were found in a control group.[38] They suggested that low doses of thyroid hormones may have a protective effect on root surfaces, either during orthodontic treatment or in patients who present spontaneous root-resorptive lesions. The clinical applications of these drugs still need to be clarified.

4. Parathyroid Hormone

Parathyroid hormone (PTH) is produced by the parathyroid glands to regulate serum calcium concentration. In the kidneys, PTH increases renal calcium reabsorption and stimulates the excretion of urinary phosphate. In bone, PTH can induce a rapid release of calcium, but also mediates longer-term changes by acting directly on osteoblasts and indirectly on osteoclasts. PTH affects osteoblasts' cellular metabolic activity, gene transcriptional activity, and multiple protease secretion. Its effects on osteoclasts occur through the production of RANKL, a protein that plays a crucial role in osteoclast formation and activity.[39] Animal studies in the 1970s demonstrated that PTH could induce an increase in bone turnover that would accelerate orthodontic movement.[40,41] More recently, Soma and colleagues observed an increased rate of tooth movement in rats treated with PTH, whether administered systemically[42] or locally.[43] These results indicate that orthodontists should take note of patients being treated with PTH—for example, in cases of severe osteoporosis.[44]

5. Vitamin D

In 1988, Collins and Sinclair demonstrated that intraligamentous injections of a vitamin D metabolite, 1,25-dihydroxycholecalciferol (1,25D), caused an increase in the number of osteoclasts and the amount of tooth movement during canine retraction with light forces in cats.[45] Similar results were observed by Takano-Yamamoto and colleagues in 1992.[46] Corroborating these findings, Kale and colleagues, in 2004, observed that local application of vitamin D enhanced the rate of tooth movement in rats; according to the authors, this effect was due to the well-balanced bone turnover induced by vitamin D.[47]

In addition, the stimulatory action of vitamin D on osteoblasts can help stabilize orthodontic movement. In a 1996 study by Baran and colleagues, rats treated with vitamin D showed increased bone formation on the pressure side of the periodontal ligament after the application of orthodontic forces.[48] In 2004, Kawakami and Takano-Yamamoto also observed an increase in the mineral appositional rate on alveolar bone after the application of orthodontic forces in rats.[49] They suggested that local application of vitamin D could intensify the reestablishment of supporting tissue, especially alveolar bone, after orthodontic treatment.

Conclusion

Orthodontists have long observed that teeth move at different rates, and that individuals have differing responses to treatment. Some of these differences are caused by changes in bone remodeling induced by drugs and systemic factors.

NSAIDs (except celecoxib), bisphosphonates, and sex hormones can reduce the rate of orthodontic movement, while corticosteroids, relaxin, thyroid hormones, parathyroid hormone, and vitamin D can increase the rate of tooth movement. Therefore, clinicians should pay careful attention to the medications being used by their patients, so that the best treatment strategy—including force control and appointment intervals—can be selected for each case. Acetaminophen, which does not have a significant influence on the rate of tooth movement, can be recommended for controlling pain during orthodontic treatment.

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