

ผลของยาที่มีต่อการเคลื่อนที่ของฟันในทางทันตกรรมจัดฟัน

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บทคัดย่อ

ในปัจจุบันพบว่า มีผู้ป่วยทันตกรรมจัดฟันจำนวนมากที่ใช้ยาในการบรรเทาอาการปวดภายหลังที่ผู้ป่วยได้รับการรักษาทางทันตกรรมจัดฟัน นอกจากนี้ผู้ป่วยบางรายมีโรคประจำตัวที่ต้องใช้ยารักษาอาการหรือมีการรับประทานอาหารเสริมเป็นประจำ การศึกษาต่างๆ ที่ผ่านมามีผลต่อการศึกษาว่า ยาเหล่านี้มีผลต่อการเคลื่อนที่ของฟัน โดยยาบรรเทาอาการปวดในกลุ่มที่มีไซโคลอ็อกซีจีเนสจะมีผลยับยั้งการเคลื่อนที่ของฟัน ส่วนยาบรรเทาอาการปวดในกลุ่มพาราเซตามอลจะไม่มีผลต่อการเคลื่อนที่ของฟัน นอกจากนี้ยังพบว่า ยา비스ฟอสฟอเนตที่ใช้ในผู้ป่วยมะเร็งจะมีผลยับยั้งการเคลื่อนที่ของฟัน โดยทำให้เกิดการหายของกระดูกที่ไม่สมบูรณ์และมีการเหนียวทำให้เกิดการตายของกระดูก ส่วนยาอื่นๆ เช่น อีทีพีอาร์-อะโกนิส, มิโซพรอสตอล และอีพีนิง ปริมาตรสูงจะช่วยเพิ่มอัตราการเคลื่อนที่ของฟัน ดังนั้นทันตแพทย์จัดฟันควรแจ้งให้ผู้ป่วยทราบถึงผลข้างเคียงของยาเหล่านี้ที่มีต่อการเคลื่อนที่ของฟัน เนื่องจากยาบางตัวอาจส่งผลให้เกิดการล่าช้าในการรักษา หรือทำให้เกิดความเสี่ยงในขณะทำการรักษาทางทันตกรรมจัดฟันได้

คำสำคัญ: ยา • การเคลื่อนที่ของฟัน • ทันตกรรมจัดฟัน

The effect of drugs on orthodontic tooth movement

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Abstract

Recently, many analgesic drugs are used for relief pain or discomfort in orthodontic patients. Some patients take dietary supplements or some drugs to relieve systemic diseases. Several studies that showed the side-effects of these drugs on orthodontic tooth movement were included in the review. Nonsteroidal anti-inflammatory drugs (NSAIDs) can inhibit orthodontic tooth movement as well as COX-2 inhibitors. Non-NSAID analgesics, paracetamol (acetaminophen), have no effect on orthodontic tooth movement. Bisphosphonates inhibit tooth movement by impaired bone healing and induced osteonecrosis. EP4 agonist, Misoprostal and Evening Primrose Oil can increase the rate of tooth movement. Orthodontists should inform their patients about side-effects of these drugs because some drugs may increase the treatment time or the risk to health when drugs are combined with orthodontic therapy.

Key words: Drugs • Tooth movement • Orthodontics

Introduction

Orthodontic tooth movement is based on bone metabolism such as bone modeling, bone remodeling and regulation of bone metabolism.^(1,2) Furthermore, the remodeling of periodontal structures, including the alveolar bone and periodontal ligament, is the biologic principle of orthodontic tooth movement⁽³⁾, so this

knowledge is important for all orthodontists to understand the nature of orthodontic tooth movement. Nowadays, orthodontic patients usually use analgesics for relieving discomfort or pain after orthodontic treatment. Many studies showed that some drugs can effect orthodontic tooth movement.

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Bone modeling

The process of bone modeling shows resorption and formation that occur at the separate sites. Modeling process produces a change in the size and/or shape of the bone by the addition of lamellar bone to surfaces without prior resorption, or the resorption of lamellar bone from surfaces without subsequent formation (activation-resorption cycle). Modeling is also controlled by means of hormones during growth and aging, so it leads to an overall net gain of bone. Facial growth, response to headgear and rapid palatal expansion are the good example of bone modeling.^(1,2)

Bone remodeling

Bone remodeling occurs as a coupling of the resorption and formation processes to replace bone. Bone turnover involves means of constant remodeling to preserve a normal function, while active remodeling will lead to bone loss.^(1,2)

Orthodontic tooth movement is accompanied by bone remodeling (alveolar bone turnover). The remodeling of bone is a cycle that starts with activation followed by resorption, reversal and formation phases. The activation period is about 10 days. There are cells recruitment, differentiation, proliferation and migration in this period followed by resorption. The resorption period takes 21 days that occurs by osteoclast activity. The next stage is reversal stage when inactive osteoblasts become activated and begin to form bone. Bone formation is determined by rate and duration of osteoblast activity. The new bone formation is completed over a period of 6 months with mineralization. The remodeling cycle from activation through to the start of the formation phase requires about 4 months in humans.⁽¹⁾ The amount of bone remodeling is related to the amount of tooth movement at that site.⁽⁴⁾

Mediators of bone remodeling^(2,5)

1. Hormones

Parathyroid hormone (PTH) affects both bone resorption and formation process. If PTH appears around bone cells, the effect of bone will be resorption. By contrast, low level of PTH results in bone formation. When the calcium level in blood decreases, PTH will stimulate osteoclastic activity to increase calcium and phosphate absorption in the gut, and decrease calcium excretion and tubular phosphate reabsorption in the kidney. This plays a role as

regulator of calcium homeostasis by PTH.⁽²⁾

Calcitonin inhibits bone resorption by acting directly on osteoclasts.^(2,5) In addition, calcitonin is the regulator of calcium homeostasis by increasing renal calcium excretion to decrease the extracellular calcium.^(5,6)

The effect of vitamin D may be the same as PTH. The rate of bone resorption will increase when vitamin D is in excess.⁽²⁾

Glucocorticoids will increase bone resorption by stimulating osteoclastogenesis that is the result of increasing the expression of receptor activator of NF- κ B ligand (RANKL) and decreasing the expression of its receptor. This hormone will decrease bone mineral density, so the main effect is an inhibition of bone formation.⁽⁷⁾

Thyroid hormone stimulates prostaglandin, so it increases osteoclastic bone resorption. Furthermore, it works through a separate prostaglandin-independent mechanism.⁽⁸⁾

Sex hormones play a role of bone metabolism. Estrogen has a direct effect on bone. It preserves calcium in bone by suppressing the activation frequency of bone remodeling. The remodeling activation will increase when menopause starts and the result is rapid bone loss leading to symptomatic osteoporosis.⁽⁹⁾

2. Cytokines

Cytokines are small proteins that are identified as mediators of bone resorption. One cytokine, Interferon (IFN)- γ , acts as a bone resorption inhibitor that is opposite to other cytokines.

Interleukin (IL)-1 has potential as a bone resorption stimulator by stimulation of prostaglandins. From experimental studies, applying tensile stress to periosteal fibroblasts will increase the level of IL-1 inhibitor. IL-1 has two molecular forms, alpha (IL-1 α) and beta (IL-1 β), and is secreted by many kinds of cells such as macrophages, B cells, neutrophils, fibroblasts, and epithelial cells. IL-1 and prostaglandins are synergistic.^(2,5,10)

Interleukin (IL)-2 shows in the attraction and proliferation of osteoclast progenitors as well as the stimulation of acid production by osteoclasts.⁽²⁾

Interleukin (IL)-6 is produced by lymphocytes, monocytes and fibroblasts.⁽¹¹⁾ It is one of an inflammatory cytokines that stimulates plasma cell proliferation and antibody production.⁽¹²⁾ Furthermore, this

cytokine stimulates osteoclast and bone resorption.^(5, 12)

Interleukin (IL)-11 stimulates osteoclast formation and bone resorption. The effect of osteoclast formation may be prostaglandins mediated.⁽²⁾

Tumor necrosis factor (TNF) and lymphotoxin are cytokines that are implicated in the stimulation of osteoclastic bone resorption. This effect is produced by prostaglandins mediation.

Interferon (IFN)- γ is produced by activated T lymphocytes. It can inhibit bone resorption by inhibiting the differentiation of precursors into mature cells.⁽⁵⁾

Leukotriene B₄ (LTB₄) has a highly potential as a chemotactic agent. It induces the accumulation of inflammatory cells especially neutrophils and stimulates bone resorption.⁽²⁾

3. Prostaglandins (PGs)

Prostaglandins that comprise PGE, PGF and prostacyclin (PGI₂) have been associated with bone remodeling. They play a major role of local regulation of bone metabolism and bone remodeling process that is associated with mechanical stimulation such as orthodontic tooth movement. The bone resorption and bone formation effects of prostaglandins are the increasing of bone turnover rate that is the result of mechanical stimulation. The resorption effects may be induced by osteoclastic cAMP. For prostaglandin mediated bone resorption process, intracellular calcium is essential. Furthermore, IL-1 can stimulate prostaglandins as a potent stimulator of bone resorption.⁽²⁾ PGE₁ and PGE₂ are found to increase bone resorption.^(2, 13, 14) But PGI₂ inhibits osteoclastic activity and stimulates bone formation.⁽²⁾

4. Osteoclast activating factors

Macrophage colony-stimulating factor (M-CSF) is produced by osteoblasts and stromal cells. It is a soluble factor that is essential for osteoclastogenesis by inducing the hematopoietic cells to become osteoclasts.^(5, 15, 16)

5. Growth factors

Transforming growth factor (TGF)- β is stored in bone and secreted by osteoblasts, macrophages and PDL cells. It can stimulate formation of bone by involving the cartilaginous intermediate and induce granulation tissue formation.^(6, 17) TGF- β was found on the tension side of tooth movement and plays a negative role for osteoclastogenesis.⁽¹⁶⁾

Insulin-like growth factor (IGF) is secreted by PDL cells, macrophages, osteoblasts, plasma cells and stored in bone as well as TGF- β . It is an important mediator of postnatal longitudinal growth. Normally, IGF alone can not significantly stimulate bone healing, but it can work together with platelet-derived growth factor (PDGF) for enhancing bone healing process. So, IGF is synergistic with PDGF and stimulates extracellular matrix.^(5, 6, 17)

Fibroblast growth factor (FGF) is secreted by macrophages, osteoblasts and stored in bone. It has a direct effect to stimulate osteoblast proliferation.^(5, 6, 17)

Platelet-derived growth factor (PDGF) is secreted by PDL cells, macrophages, endothelial cells, and osteoblasts, and stored in bone. It has biologic effects of mitogenesis and chemotaxis on osteoblasts and fibroblasts. PDGF can promote skin healing, bone formation and periodontal regeneration.^(5, 6, 17)

Bone morphogenetic proteins (BMP_s) are stored in the osteoblasts and bone. They are the important factors that can initiate osteoblastogenesis.^(5, 6, 17)

6. Other mediators

Cyclosporin A can inhibit bone resorption because it is a potent immunosuppressive agent that stimulates osteoclast apoptosis.⁽⁵⁾ This effect on bone depends on the duration and dose of Cyclosporin. Sakakura's study showed that the osseointegration process of pure titanium implants was decreased if the administration period of Cyclosporin A was greater than four weeks.⁽¹⁸⁾

Osteocalcin is the main non-collagenous matrix protein in bone. Its function is a negative regulator for mineral apposition and bone formation. Furthermore, it is a chemotactic for osteoclast precursor cells.^(19, 20)

Receptor activator of NF- κ B ligand (RANKL) is a cell surface protein that is present in stromal cells such as osteoblasts and lymphocytes. The differentiation of osteoclasts and bone resorption are activated by this mediator. RANKL and its receptor, RANK, in hematopoietic cells have interaction together that is essential for osteoclast activation.^(5, 15)

Osteoprotegerin (OPG) is physiologically important inhibitor of osteoclastic bone resorption.^(5, 15) It is a soluble factor that binds with RANKL and inhibits the osteoclast differentiation.⁽⁵⁾

7. Secondary messengers

cAMP and cGMP are universal signaling molecules in the cellular environment. Extracellular signals

can generate intracellular signals by surface receptors. The surface receptors may open or close ion channels at the plasma membrane and change the ions into the cell. The important secondary messengers such as Ca^{2+} , cAMP, and cGMP, are the regulators of mechanically-induced tissue remodeling. Several studies showed resorption activity that responded to mechanical or chemical stimuli by the periodontal ligament cells and were characterized by synthesizing PGE with increasing of cAMP level.^(2, 21) This process is regulated by many mediators such as PTH, calcitonin, neurotransmitters and cytokines.^(2, 21)

Cell and molecular responses during orthodontic tooth movement

During orthodontic tooth movement, bone remodeling process is related to the expression of mediators. Acute inflammatory response is presented in the early phase of orthodontic tooth movement. Inflammatory mediators may stimulate the biological processes that associated with alveolar bone resorption and deposition. Furthermore, orthodontic forces can induce the bone remodeling process by the local mediators, such as prostaglandins, cytokines and growth factors, that play an important role in bone remodeling. PGE_2 has been involved in bone remodeling and especially recognized as a potent stimulator of bone resorption.⁽²²⁾

Pharmacologic control of orthodontic tooth movement

There are several studies showing the usage of pharmacologic agents to induce bone resorption and deposition for control of tooth movement. For example, the study of Yamasaki shows the usage of local injection of prostaglandin to stimulate tooth movement.^(13, 14) Other pharmacologic agents such as calcitonin⁽¹⁶⁾, and $1,25(\text{OH})_2\text{D}_3$ ⁽²³⁻²⁵⁾ can also induce tooth movement. The daily injection of osteocalcin into the palatal subperiosteum in rat showed it can stimulate tooth movement significantly in the early period but not significantly after day 5th.⁽¹⁶⁾ One injection of $1,25(\text{OH})_2\text{D}_3$ per 7 days into the PDL of cats increased tooth movement 60% as well as in the human that received PGE_1 submucosal injection.⁽²⁵⁾ Although the pharmacologic agents can induce the tooth movement in both human and animal study but they have side effects during the injection procedure such as local pain and discomfort, so these techniques are not practical to use for the patient.⁽²⁶⁾

Prostaglandins and orthodontic tooth movement

Prostaglandins are synthesized at phospholipids cell membranes. Enzyme phospholipase A_2 will change fatty acid in phospholipids membranes into arachidonic acid. There are two major enzyme systems to change arachidonic acid; the first is cyclooxygenase, and the second is lipoxygenase. The cyclooxygenase enzyme system plays a role in prostaglandins synthesis. This enzyme can change arachidonic acid into the stable prostaglandins (PGE_2 , PGF_{2a} , PGD_2), the unstable but potent anti-platelet substance (prostacyclin, PGI_2), and more unstable platelet activator, thromboxane A_2 .^(2, 21)

For bone remodeling process, prostaglandins effect both bone resorption and bone formation by increase of bone turnover rate that is the result of mechanical stimulation. Intracellular Ca^{2+} is essential for prostaglandins to stimulate bone resorption. Furthermore, osteoclastic cAMP may mediate the resorption process and IL-1 is a potent stimulator of bone resorption, involving stimulation of prostaglandins. In applying mechanical stress, it has been found that the fibroblasts of periodontal ligament respond to this stress by synthesis PGE. Bradykinin from the inflammatory reaction may mediate PGE_2 , PGI_2 and IL- 1β .⁽²⁾

In addition, prostaglandins release can be stimulated by tissue trauma. The local concentration of prostaglandins is increased when the tissue is manipulated by very gentle procedure, so the resulting ischemia can stimulate prostaglandin syntheses. For the orthodontic tooth movement, it has been found that the area of PDL compression has a local concentration of prostaglandins that is relate to the inflammatory process at that site. So, this process may induce orthodontic bone resorption and remodeling.^(14, 21) In the bone resorption process, prostaglandins may be mediated by the macrophages that invade and remove the hyalinized tissue and by osteoclast stimulations.⁽²¹⁾ Several studies have shown that increase in the rate of orthodontic tooth movement is associated with PGE_1 and PGE_2 that increase the bone resorption process.^(2, 13, 14)

Pain and orthodontic tooth movement

When orthodontic force is applied to the patient, discomfort or pain will be present for about 2 to 4 days, and will disappear until the next visit and the orthodontic appliance is reactivated.^(26, 27) Mild or no pain indicates

that the optimum force is applied to the tooth, while severe pain indicates excessive force. The degree of patient's pain, especially orthodontic pain, may vary and depend on pain experience in each person.⁽²⁶⁾ Ischemic areas in the PDL that produce sterile necrosis or hyalinization are the cause of orthodontic pain.⁽²⁶⁾ During tissue inflammation, pain response is associated with the release of prostaglandins, bradykinin, and substance P.^(13, 28) After separation of incisors by orthodontic force, the substance P level increases and peaks at 36 hours.⁽²⁸⁾

Effects of drug to orthodontic tooth movement

Nowadays, orthodontists suggest the patients to take analgesics to relieve pain from orthodontic treatment.^(27, 29, 30) There are many drugs in common use that have effects on orthodontic tooth movement. Many drugs can inhibit tooth movement, while some drugs that stimulate tooth movement are rarely found. Normally, many analgesics are used in orthodontic patient to relieve pain during treatment such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAID). These drugs may affect tooth movement in different ways.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

These drugs can relieve pain by the results of their analgesic and antipyretic actions. The anti-inflammatory effects happen by inhibition of the biosynthesis of PGs when these drugs act on the cyclooxygenase involved in catabolism of arachidonic acid in the phospholipid membrane.⁽³¹⁾ Some studies reported that the specific inhibitors of PGs such as indomethacin and flurbiprofen can reduce the tooth movement (50% of the dental movement index) in cats and rabbits that received orthodontic force. It is a result of reducing the amount of osteoclasts in the alveolar bone.^(32, 33) For that reason, Chumbley and Tuncay⁽³³⁾ recommended that orthodontic patient should avoid to using aspirin and other nonsteroidal anti-inflammatory analgesics to relieve pain because these drugs can prolong orthodontic treatment time. Mohammed *et al*⁽³⁴⁾ found that orthodontic tooth movement are inhibited by indomethacin in rats. Furthermore, Arias's study⁽³⁵⁾ showed the effect of aspirin and ibuprofen on orthodontic tooth movement in the rats. Fewer osteoclasts were observed in the pressure side of the teeth because these drugs inhibited the production of PGs. Because the bone resorption was reduced, the teeth moved less than average. Williams *et al*⁽³⁶⁾ studied the effect of ibuprofen on alveolar bone

in dogs. Their result showed that ibuprofen can inhibit alveolar bone loss when the dogs were treated with 4 mg/kg of ibuprofen daily for 13 months. Kehoe *et al* confirmed that ibuprofen inhibits PGE₂ synthesis in the PDL of guinea pig significantly by decreasing the degree and rate of orthodontic tooth movement.⁽³⁷⁾ Kyrkanides *et al*⁽³⁾ investigated the effect of indomethacin on orthodontic tooth movement. Their results indicated loss of prostaglandin mediated cellular effects subsequent to cyclooxygenase inhibition by this drug. The cyclooxygenase inhibition resulted in exacerbation of IL-1 β -mediated collagenase B (MMP-9) synthesis and activity, as well as attenuation of type IV procollagen synthesis levels by endothelial cells. Furthermore, Ito *et al*⁽³⁸⁾ reported that the induction of MMP-9 synthesis caused cyclooxygenase inhibition in rabbit articular chondrocytes. So, Kyrkanides *et al*⁽³⁾ stated that the use of anti-inflammatory drugs may influence orthodontic tooth movement by altering biochemical pathways that mediate extracellular matrix remodeling. At the present, the use of cyclooxygenase-2 (COX-2) inhibitor for relief orthodontic pain is increasing, and replacing conventional NSAIDs⁽³⁹⁻⁴¹⁾ because its anti-inflammatory effect is less injurious to gastrointestinal mucosa than the nonselective NSAID.⁽⁴²⁾ Furthermore, Chan *et al*⁽⁴³⁾ reported that new COX-2 specific inhibitors decreased serious gastrointestinal perforations, obstructions and bleeding when compared with conventional NSAID. de Carlos *et al*⁽⁴⁴⁾ studied orthodontic tooth movement that resulted from the effect of rofecoxib (COX-2 inhibitor) and compared with diclofenac (a traditional NSAID). The results showed both rofecoxib and diclofenac can inhibit COX-2 action that means that the orthodontic tooth movement was inhibited by these drugs. Gameiro *et al*⁽⁴⁵⁾ reported the short- and long-term effects of celecoxib (COX-2 inhibitor) on orthodontic tooth movement in rats. The short-term treatment was simulated the preoperative administration of analgesics to decrease post-operative pain whereas the long-term effect treatment was simulated the situation that patients receive celecoxib in treatment of chronic disease all time of tooth movement. The results showed that tooth movement was inhibited by celecoxib action in both situations. Moreover, they stated that celecoxib not only affected COX-2 level but also affected IL-1 and IL-6 that had the result of bone resorption and tooth movement.^(45,46) However, Sari *et al*⁽⁴⁷⁾ suggested that the one drug, rofecoxib, can be used to relieve pain or patient discomfort during orthodontic treatment because

the inhibitory effect on PGs synthesis with rofecoxib was less than the inhibition effect of aspirin during the first 24 hours. In addition, Wong *et al*⁽⁴⁸⁾, stated that aspirin does not change the orthodontic tooth movement in guinea pigs. However, they found that the dose of the analgesic used was lower than the dose that can reduce the secretion of PGs because the metabolic rate of these animals is faster than humans. For this reason, they require higher doses than the does to produce the same orthodontic effect in humans.^(49, 50)

Acetaminophen

It is nonsteroidal anti-inflammatory drug in the paraminophenols family. It does not effect orthodontic tooth movement because it does not inhibit the secretion of peripheral PGs or only inhibit them slightly. So, acetaminophen is considered to be a very weak PGs inhibitor and has no anti-inflammatory effect.⁽⁵¹⁾ Antipyretic and analgesic actions are the same as aspirin but analgesic effect is produced at the central nervous system^(52, 53) and does not act at the cell membrane as do aspirin or ibuprofen.⁽⁵³⁾ Kehoe *et al* found that at the level of PDL, acetaminophen inhibited the peripheral PGs synthesis but the degree and rate of orthodontic tooth movement were not significantly different when compared with control group.⁽³⁷⁾

The study of Arias *et al*⁽³⁵⁾ showed the presence of osteoclasts in the pressure side of the orthodontically moved incisors in rats treated with acetaminophen. The bone resorption lacunae and dental movement are the same as the control group. Furthermore, the bone is actively regenerated because of orthodontic treatment that activates the secretion of PGs and the osteoclasts that act in bone resorption. These results did not happen in the groups treated with aspirin and ibuprofen. Roche claimed that acetaminophen has no effect on orthodontic tooth movement in rabbits because acetaminophen is a weak inhibitor of cyclooxygenase-1 and cyclooxygenase-2, and analgesic action lacks the anti-inflammatory properties.⁽⁵⁴⁾

Bisphosphonate

For bone metabolic disorders such as osteoporosis, bone disease, and bone pain from bone cancer, the drugs of choice are bisphosphonates. However, they have side-effects in dental treatment that inhibit tooth movement, impaired bone healing, and induced osteonecrosis in the maxilla and mandible. Bisphosphonates directly inhibit osteoclastic activity that results in decreasing bone resorption.⁽⁵⁵⁾ For long term

treatment with bisphosphonates, it is claimed that if osteoclastic activity decreases sufficiently, the osteoblastic activity will decrease too.⁽⁵⁶⁾ The study of Igarashi *et al*⁽⁵⁷⁾ showed that after giving of subcutaneous bisphosphonates for 3 weeks in rats, tooth movement was decreased by 40%. In addition, the alveolar bone adjacent to the periodontal ligament showed the reducing of osteoclasts after giving a single dose of intravenous bisphosphonate (pamidronate) during tooth movement.⁽⁵⁸⁾ Marx *et al*⁽⁵⁹⁾ stated that bisphosphonate osteonecrosis showed the decrease of microcirculation of bone until the stage of necrosis happened. Because the osteoclast cannot absorb the mineral matrix of bone, and the capillary formation in new bone cannot be stimulated completely, acellular and avascular bone will occur.⁽⁵⁹⁾ The typical osteonecrosis in patients who received intravenous bisphosphonate appeared as painful abscess teeth. When they are extracted, the underlying necrosis bone will be exposed, and abnormal healing causes bone loss in the future.^(59, 60) Bisphosphonate osteonecrosis symptoms such as severe bone loss or dental abscess look like dental or periodontal disease. For this reason, if routine dental and periodontal treatment can not treat these diseases, it should be considered as a possible diagnosis of osteonecrosis.⁽⁶¹⁾ At the present, there should be concerned about orthodontic treatment in the patients who received bisphosphonates.^(62, 63) High intravenous doses of bisphosphonates can inhibit tooth movement more than lower oral doses.⁽⁵⁶⁾ Orthodontic tooth movement may increase the uptake of bisphosphonates locally, so it decreases osteoclastic activity. The result of this process shows as slower tooth movement.⁽⁵⁶⁾

EP4 agonist

Bone anabolic responses to external loading are induced by stimulation of prostaglandin receptor EP4. Chung *et al*⁽⁶⁴⁾ claimed that the activation of the EP4 receptor of the paradental region might induce osteoblasts and stimulate new bone formation in vivo. Their study reported that the local administration of EP4 agonist can induce tooth movement and increase bone volume at least in the tension side. Furthermore, PGE stimulates bone resorption through the EP4 receptor via a mechanism involving an increase of cAMP and RANKL in osteoblasts. So, there is a high possibility of increased bone resorption.⁽⁶⁵⁾ Chung *et al* stated that the role of EP4 agonists not only enhances bone formation during tooth movement but

also stimulate osteoblasts to produce increased amounts of RANKL that increase osteoclastogenesis and bone resorption.⁽⁶⁴⁾

Misoprostal

Misoprostal is a synthetic PGE₁ analog which is used in the patients that receive NSAIDs for a long time.⁽³⁷⁾ Because its effect can increase the secretion of bicarbonate in duodenum and gastric mucosa,⁽⁶⁶⁾ this drug can help to protect gastric mucosal damage from the effect of NSAIDs. In a mouse study, misoprostol has analgesic effect in a same dose as morphine. This drug can act together with recognized NSAIDs, so the usual dose level can be decreased.⁽³⁷⁾ Furthermore, Kehoe *et al* studied the effect of misoprostal, acetaminophen and ibuprofen on orthodontic tooth movement. They claimed that misoprostal could be induced tooth movement because the inhibitory effect on local PGE₂ production was insignificant, and their results showed the degree and rate of tooth movement was increased when compared with the other groups. The acceleration of tooth movement may be the result from increasing bone resorption activity of PGE₁.⁽³⁷⁾

Evening Primrose Oil

At the present, evening primrose oil (EPO) is a popular encapsulated dietary supplement which contains gamma linolenic acid (GLA). Some studies found that GLA can help to relieve the inflammatory disorders such as rheumatoid arthritis.^(67, 68) The metabolite of GLA is dihomo-gamma-linolenic acid (DGLA) that is precursor of PGE₁ synthesis.⁽⁶⁹⁾ For this reason, the dietary EPO supplement has been reported to enhance orthodontic tooth movement. Taweichaisupapong *et al*⁽⁷⁰⁾ studied the effect of EPO on osteoclasts during tooth movement in rats. They found that the increase of osteoclasts was significant in an experimental (EPO) group because EPO induced more PGE₁ synthesis. The increase of PGE₁ level was the cause of increasing osteoclasts appearance. So, they concluded that the oral administration of EPO may accelerate orthodontic tooth movement .

Conclusion

NSAIDs such as Ibuprofen and aspirin can inhibit orthodontic tooth movement. They reduce the synthesis of PGs that results in decreasing osteoclasts in the pressure sides. Because they have potential for slowing tooth movement, it is not recommended to use them for relief of orthodontic pain. Nowadays, the numbers of adult orthodontic patients are increased, so orthodontists

should be aware that adult patients who received NSAIDs for long-term treatment for chronic diseases such as arthritis, tricyclic antidepressants, and antiarrhythmics that can experience reduced rate of tooth movement. COX-2 inhibitor reduce the osteoclast activity and inhibit tooth movement as well as NSAIDs. Orthodontists should be aware of the patients who under short- and long- term therapy with COX-2 inhibitors because these drugs can decrease the rate of orthodontic tooth movement. Acetaminophen acts at the central nervous system and does not stimulate PGs synthesis, so it does not interfere with the orthodontic tooth movement. The numbers of osteoclasts in the pressure areas are not decreased, and the bone regeneration does not change by acetaminophen. So, it is a drug of choice that orthodontists should recommend to their patients for relieving the discomfort during orthodontic treatment. Bisphosphonate is used in patients who have bone metabolism disorders. It can inhibit tooth movement. Furthermore, it impairs bone healing and induces osteonecrosis in alveolar bones of maxilla and mandible. Medication screening and patient counseling are essential in these patients. EP4 agonist, Misoprostal and Evening Primrose Oil can increase the rate of tooth movement. For this action, these drugs can reduce orthodontic treatment time in the future. Furthermore, EP4 agonist can increase bone volume in the tension side, so it may be useful for inducing bone formation in patients who have bone loss.

For post-orthodontic treatment care, orthodontists should inform the patients about the side-effects of analgesics, especially NSAID and COX-2 inhibitors that may increase the treatment time and the risk of orthodontic therapy.

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