

Study: The effects of over-the-counter analgesics on orthodontic tooth movement

By Kristina Sakas, fourth-year dental student, Ostrow School of Dentistry

The most frequently asked question in every orthodontic office may be: "When are my braces coming off?" In the fast-paced, busy lives of patients, there is little time to spend on lengthy orthodontic therapy. In the ever-advancing field of orthodontics, many barriers have been overcome, leading to healthier results and more beautiful smiles. Now, the focus is on reducing treatment time (Profit, 2013). Faster care without sacrificing quality would be advantageous in (a) reducing hygiene problems, (b) increasing patient acceptance of treatment plans and (c) creating a higher level of overall treatment satisfaction. This new focus can be seen through the development of techniques such as the accelerated osteogenic orthodontics known as Wilckodontics and the micropulse technology seen in AcceleDent (Kau, 2011).

With the emphasis on shortening treatment time, it is critical that practitioners be aware of all medications

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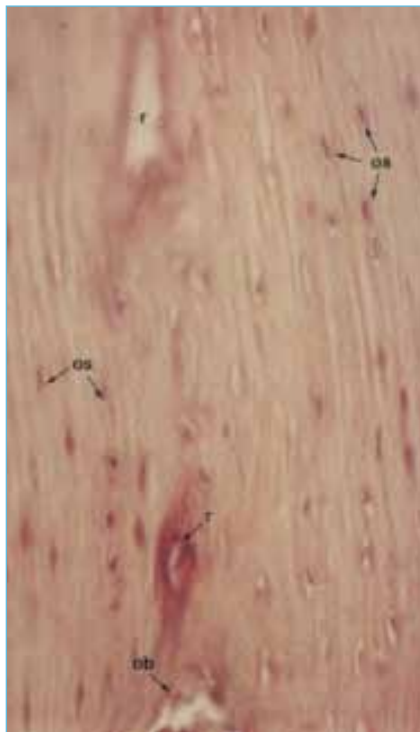


Fig. 1: Alveolar bone from pressure zone of rat treated with Ibuprofen/Aspirin. Note small resorption areas (r), with few osteoblasts (ob), osteoclasts (oc), and osteocytes (os) in osseous matrix (m). Photos/Drs. Arias and Marquez-Orozco

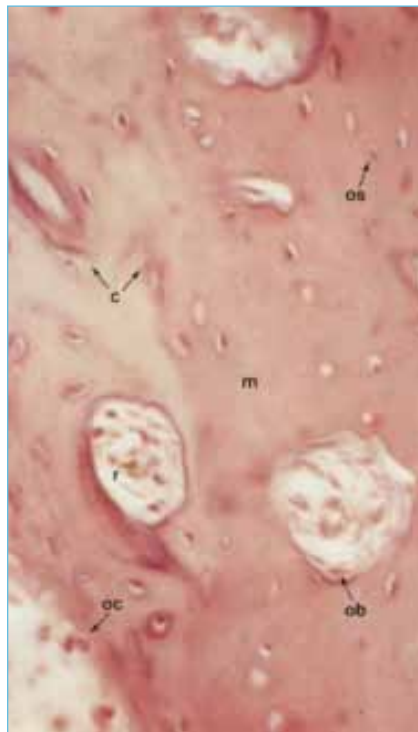


Fig. 2: Alveolar bone from pressure zone of rat treated with acetaminophen/control. Note large resorption areas (r), many osteoblasts (ob), differentiated osteoclasts (oc) and osteocytes (os) on growth lines (c) in osseous matrix (m).

2013 MSO session set for Kansas City

By Sierra Rendon, Managing Editor

The 2013 Midwestern Society of Orthodontists Annual Session will take place Sept. 20–22 at the Sheraton Kansas City Hotel at Crown Center in Kansas City, Mo. This year's session will be co-sponsored by the Missouri Society of Orthodontists and the South Dakota Society of Orthodontists.

The focus of this year's meeting is "Orthodontics: A Palette of Progress."

The group aims for attendees to learn the latest research and esthetics from scientific lecturers including Drs. Mark Berkman, Aaron Molen, Chung Kau, Sebastian Baumgaertel and Abraham Lifshitz.

Marketing and management will be covered in a staff program featuring Amy Kirsch and Cathy Sundvall.

On Sunday, a doctor-staff lecture will focus on improving social media results with marketing and search engine optimization speaker Mary Kay Miller.

Attendees are also invited to tailgate with staff, family and colleagues in the MSO-private Budweiser Patio at the Saturday evening Royals vs. Rangers baseball game. Separate registration includes bus shuttle and complimentary buffet.

For more information on the annual meeting schedule and registration, visit www.msortho.org.

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ORTHO TRIBUNE

PUBLISHER & CHAIRMAN

Torsten Oemus t.oemus@dental-tribune.com

PRESIDENT/CHIEF EXECUTIVE OFFICER

Eric Seid e.seid@dental-tribune.com

EDITOR IN CHIEF ORTHO TRIBUNE

Prof. Dennis Tartakow
d.tartakow@dental-tribune.com

INTERNATIONAL EDITOR ORTHO TRIBUNE

Dr. Reiner Oemus roemus@dental-tribune.com

GROUP EDITOR

Kristine Colker k.colker@dental-tribune.com

MANAGING EDITOR ORTHO TRIBUNE

Sierra Rendon s.rendon@dental-tribune.com

MANAGING EDITOR

Fred Michmershuizen
f.michmershuizen@dental-tribune.com

MANAGING EDITOR

Robert Selleck, r.selleck@dental-tribune.com

PRODUCT/ACCOUNT MANAGER

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PRODUCT/ACCOUNT MANAGER

Will Kenyon w.kenyon@dental-tribune.com

PRODUCT/ACCOUNT MANAGER

Jan Agostaro j.agostaro@dental-tribune.com

MARKETING DIRECTOR

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a.wlodarczyk@dental-tribune.com

EDUCATION DIRECTOR

Christiane Ferret c.ferret@dtstudyclub.com

Tribune America, LLC

116 West 23rd Street, Suite 500
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Phone (212) 244-7181
Fax (212) 244-7185

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The new standard of care in orthodontics

Part 1

By Dennis J. Tartakow,
DMD, MEd, EdD, PhD, Editor in Chief

Still in the early stages of the new millennium, we are in an era of dentistry and orthodontics where more accurate diagnoses are possible thanks to technological advances in imaging and

scanning. We now have treatment capabilities that were not possible only a decade ago. Treatment outcomes have also improved with advances in periodontal treatment and operative dentistry. Diagnosis and treatment advances have improved the quality of dentistry and saved or prolonged permanent dentitions for millions of individuals.

Such changes in the standards of care,

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that patients are taking that could unknowingly slow down their orthodontic treatment. This must be accomplished by thorough evaluation of the patient's medical history with close attention to medications, including over-the-counter (OTC) analgesics. Various analgesics taken by patients during orthodontic treatment, including traditional non-steroidal anti-inflammatory drugs, aspirin and acetaminophen, have been scientifically shown to decrease the rate of tooth movement (Tyrovola, 2001).

Mechanism of tooth movement

Orthodontic tooth movement is mediated by specific reactions at a cellular level that take place in the tissues surrounding teeth. Cellular, chemical and mechanical reactions bring about the structural changes that prompt tooth movement. Bone is resorbed on the pressure side and deposited on the tension side of a tooth. An acute inflammatory response with periodontal vasodilation occurs. Cyclic adenosine monophosphate (cAMP), calcium, collagenase and prostaglandins mediate tooth movement as a response to orthodontic force. Chemicals in drugs taken by patients can pass through the bloodstream, reach the mechanically stressed tissues and interact with local cells. This can have an inhibitory effect on orthodontic tooth movement (Diravidamani, 2012).

Orthodontic patients often use over-the-counter analgesics to control the discomfort associated with tooth movement as well as to treat other ailments (Salmassian, Oesterle, Shellhart and Newman, 2009). Many of these pharmaceutical agents are known to systemically influence bone and the velocity of tooth movement by interfering with prostaglandin production and the inflammatory process. The pressure-tension theory describes tooth movement occurring in three stages: "alterations in blood flow associated with pressure in the periodontal ligament (PDL), formation or release of mechanical messengers and activation of cells" (Salmassian, et al., 2009). After force is applied, there is an increase of prostaglandin E and interleukin-1 B levels in the PDL and gingival crevicular fluid. This is a critical step in increasing the number of osteoclasts, the rate of bone resorption and orthodontic tooth movement, and is the step that is affected by NSAID medication (Salmassian, et al.).

Process of orthodontic tooth movement

In order to appreciate how NSAIDs can affect the rate of orthodontic tooth movement, one must first understand the complex process. Tooth movement due to orthodontic forces is induced by prolonged application of mechanical forces, creating pressure and tension zones in the periodontal ligament and alveolar bone (Gameiro, Pereira-Neto, Magnani and Nouer, 2007). Bone is deposited on the alveolar wall in the tension zone and resorbed by osteoclasts in Howship's lacunae in the pressure zone (Knop, Shintcovsk, Retamoso, Ribeiro and Tanaka, 2011).

Remodeling occurs in dental and parodontal tissues, including dental pulp, periodontal ligament, alveolar bone and gingiva. These tissues, when ex-

posed to mechanical loading, express significant macroscopic and microscopic changes. On a cellular level, orthodontic tooth movement is characterized by initial acute inflammation, followed by a chronic inflammatory process (Krishnan and Davidovich, 2006). The acute inflammatory process that characterizes preliminary orthodontic tooth movement consists of periodontal vasodilation and migration of leukocytes. This inflammation is mainly exudative, indicating that the plasma and leukocytes are exiting the capillaries in areas of parodontal strain. These migratory cells produce a variety of cytokines that act as local biochemical signals, interacting directly and indirectly with the population of resident parodontal cells.

Cytokines are responsible for evoking subsequent biological events and bone remodeling that accommodate tooth movement (Knop, et al., 2011). These target cells make up the functional units that are responsible for remodeling the parodontal tissues while facilitating tooth movement (Krishnan and Davidovich, 2006).

Approximately two days following application of orthodontic force, the acute phase of inflammation subsides. It is replaced by a chronic, proliferative process involving fibroblasts, endothelial cells, osteoblasts and alveolar bone marrow cells. During this time, leukocytes will continue to migrate into strained parodontal tissues, modulating the remodeling process. This chronic inflammation will persist until the next orthodontic adjustment appointment when another period of acute inflammation will begin (Krishnan and Davidovich, 2006).

It is during the acute inflammatory phase of orthodontic tooth movement that patients experience painful sensations and reduced chewing function. Ninety to 95 percent of orthodontic patients report experiencing this discomfort (Patel, et al., 2010). Indications of this phenomenon can be seen in the gingival crevicular fluid of moving teeth by significant elevations of inflammatory mediators such as cytokines and prostaglandins (Krishnan and Davidovich, 2006).

The discomfort associated with orthodontic tooth movement in patients can be decreased by inhibiting inflammation. NSAIDs are thus a viable option. However, because they inhibit prostaglandin synthesis, the rate of tooth movement may be affected because inhibition of prostaglandins prevents activation of osteoclastic cells that induce bone resorption (Sari, Olmez and Gurton, 2004). It would be appropriate for clinicians to understand this effect of NSAIDs so they can take heed to prescribe or suggest a pain medication that has minimal effect on prostaglandin

synthesis. This is also important in order to prevent prolonged orthodontic treatment time, which could lead to increased dental health risks.

Prostaglandins and NSAIDs

Many studies have confirmed that prostaglandins are critical mediators of the inflammatory process that allow for orthodontic tooth movement through their ability to increase vascular permeability and dilation (Sari, Olmez and Gurton, 2004). Studies show that injecting exogenous prostaglandins enhances the amount of tooth movement (Bartzele, Turp, Motschall and Maltha, 2009). Prostaglandin synthesis in humans is catalyzed by two forms of cyclooxygenase (COX): COX-1 and COX-2. COX-1 is present throughout the body and has physiologic functions such as vascular hemostasis and maintenance of the normal gastric mucosa. COX-2, on the other hand, is regulated by inflammatory mediators and creates prostaglandins that play a role in pathophysiological and inflammatory processes, including pain. Studies have also found that these prostaglandins not only mediate inflammation but also participate in bone formation and induction of bone resorption through activation of osteoclastic cells (Sari, et al., 2004).

Specifically, it is believed that they are responsible for increasing the number of osteoclasts through enhancement of their ability to form a ruffled border, thus effecting bone resorption (Krishnan and Davidovich, 2006). Prostaglandins also stimulate osteoblastic differentiation and new bone formation (Knop, Shintcovsk, Retamoso, Ribeiro and Tanaka, 2011). Therefore, prostaglandins play a significant role in mediating orthodontic tooth movement.

The discomfort associated with archwire placement and subsequent tooth movement can be controlled by inhibiting the inflammatory response. This makes nonsteroidal anti-inflammatory drugs a logical choice for treating this type of pain. However, NSAIDs are also powerful inhibitors of prostaglandin synthesis, which recent studies have shown to be responsible for delaying or inhibiting orthodontic tooth movement. This area of research is critical to the field of orthodontics because it is important for orthodontists to be aware of it in order to find the analgesic of choice for treating patients experiencing discomfort that will not prolong the patient's orthodontic treatment. The orthodontist can then educate his or her patients on proper pain management during treatment.

Clinical studies on effects of various analgesics on orthodontic tooth movement

Nonsteroidal anti-inflammatory anal-

'Tooth movement due to orthodontic forces is induced by prolonged application of mechanical forces, creating pressure and tension zones in the periodontal ligament and alveolar bone.'

gesics such as aspirin, ibuprofen and naproxen have been found to reduce the rate of orthodontic tooth movement. Research shows these effects result from diminishing the number of osteoclasts through inhibition of biosynthesis of prostaglandins when they act over the cyclooxygenase-mediated catabolism of arachidonic acid (Arias and Marquez-Orozco, 2006). When the number of osteoclasts are diminished, there is a decrease in bone resorption and, therefore, a reduction in the rate of tooth movement.

Histological studies were performed comparing bone in the pressure zone from rats that had been administered these drugs, with bone from rats that received acetaminophen or a control, while undergoing orthodontic tooth movement. The NSAID administered bone (Fig. 1) showed less remodeled areas, few and smaller osteoblasts, indistinguishable osteoclasts in the pressure region, abundant parallel layered osteocytes, reduced Howship lacunae (Knop, et al., 2011), and no observed growth lines (Arias and Marquez-Orozco, 2006).

The control and acetaminophen group (Fig. 2) showed abundant remodeled areas, distinguishable multinuclear osteoclasts, mesenchymal appearing osteogenic cells, epithelial osteoblasts and normal appearing trabeculation. Numerous growth lines were also apparent, typically concentric around osteons. The results of the histological analysis of the acetaminophen and control groups are indicative of normal, uninhibited orthodontic tooth movement (Arias and Marquez-Orozco, 2006).

Acetaminophen as the drug of choice

Acetaminophen is a nonopioid analgesic in the family of paraminophenols. The exact mechanism of action of acetaminophen has not been determined. Acetaminophen differs from other nonsteroidal anti-inflammatory drugs and prostaglandin inhibitors because although it has similar antipyretic and analgesic properties, it exhibits little effect on inflammation.

According to Anderson (2008), the analgesic effect is produced at the central nervous system level without inhibiting peripheral prostaglandin secretion via cell membranes as typical NSAIDs do. Acetaminophen, being inactive as an anti-inflammatory agent in peripheral tissues, does not inhibit tooth movement (Arias and Marquez-Orozco, 2006). Beyond the fact that it is not detrimental to orthodontic tooth movement, acetaminophen is a readily available, over-the-counter, inexpensive analgesic that has been found to be equally effective

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as ibuprofen and a placebo in controlling discomfort after archwire placement (Salmassian, Oesterle, Shellhart and Newman, 2009). Therefore, acetaminophen might be the drug of choice in treating mild to moderate discomfort associated with orthodontic treatment.

NSAID use and the orthodontic practitioner

Clinicians are responsible for comprehensive evaluation of a patient's medical history and for its use as an integral part of the patient's diagnosis. This includes an understanding of how a patient's medication — prescription or over-the-counter — will affect his or her treatment.

Given the frequency of NSAID use in this country, clinicians in the dental field are likely to encounter patients who are using these drugs regularly. Furthermore, the future of analgesics in the United States is likely to hold tremendous growth because of the aging population that is facing conditions such as arthritis, which requires treatment using NSAID medications to allow for increasingly active lifestyles. Given that more orthodontic practices are focusing on treating patients of all ages, this issue of increased NSAIDs use is more prevalent than ever (Turpin, 2009).

Common analgesics prescribed

Prescription and over-the-counter use of analgesics among adults in the United States is extremely high. Most of these drugs are non-steroidal anti-inflammatory drugs that have analgesic, antipyretic and anti-inflammatory action. They are used in treating headaches, arthritis, sports injuries, menstrual cramps and other illnesses. Aspirin, a drug considered to be in the NSAID category but distinguished from it by its irreversible inhibition of COX enzymes (Grosser, 2011), is also often taken regularly by patients to inhibit blood clotting and to prevent heart attack and stroke. Acetaminophen is also segregated from the NSAIDs by its weak anti-inflammatory effect, although it has similar analgesic and antipyretic effects. Important to note is that cold and allergy medications often contain these analgesics as well.

In a survey of American adults, OTC analgesics were shown to be the most frequently used of all medications and are taken by 20 percent of the adult population in a given week (OTC Medications, n.d.). The non-prescription analgesics acetaminophen, aspirin and ibuprofen are the most frequently used drugs in the United States (Slone Survey, 2006). In any given week, 23 percent of adults in the United States report use of acetaminophen products, 17 percent used ibuprofen, 17 percent used aspirin and 3.5 percent use naproxen (NSAIDs, n.d.).

Over-the-counter analgesics are also regularly used by children. Of all prescription and OTC drugs taken by children in the United States, ibuprofen and acetaminophen are the two most frequently used (OTC Medications, n.d.). NSAIDs are mainly used in children in treating inflammatory pain, including chronic conditions such as juvenile idiopathic arthritis, where it is used for both its anti-inflammatory and analgesic properties.

NSAIDs are also used in children to treat mild to moderate acute pain where

inflammation is the source (Gazarian and Graudins, 2006). Acetaminophen is the first drug of choice for analgesia and treatment of febrile illness in single-dose therapy for children because its analgesic and antipyretic efficacy is equivalent to NSAIDs but with less adverse effects. The combination of ibuprofen and acetaminophen or any alternating regimen of these two in treating fever in children is not recommended as it may potentiate the risk of toxicity of either drug (Gazarian and Graudins, 2006).

Adverse side effects of commonly used analgesics

In spite of the therapeutic efficacy and widespread usage of aspirin and NSAIDs, there are unwanted and serious side effects that have been recognized. It is doubtful that if these drugs were developed in this century that they would have been regulatory approved because of the many and serious adverse effects (Jones, 2008).

The most common side effects that occur with aspirin and NSAID use are gastrointestinal (GI) (Grosser and Smyth, 2011), but other organ systems are also affected (Jones, 2008). GI symptoms occur in approximately 60 percent of users of these drugs (Jones, 2008). They are potentially serious and include nausea, dyspepsia, reduced appetite, abdominal pain and diarrhea. These effects may be due to the creation of gastric or intestinal ulcers that occur in 15-30 percent of regular users of aspirin and NSAIDs (Grosser and Smyth, 2011). Blood loss from ulcerations may be slow, leading to anemia, or become acute and life threatening.

Risk is increased by consumption of alcohol, use of glucocorticoids, *heliobacter pylori* infection and other factors that injure the mucosa (Grosser and Smyth, 2011). The vast majority of deaths related to NSAID and aspirin use are because of gastrointestinal bleeding (NSAIDs, n.d.). GI effects of aspirin and NSAIDs occur at their recommended doses and the risk is dose related. In a study of users of aspirin and NSAIDs at OTC doses by Blot and McLaughlen, it was found that there was a two-fold risk of GI complications at lower than the maximum recommended OTC dosage, a four-fold increase at doses near the maximum and a six-fold or greater increase at doses higher than the recommended daily OTC dose (NSAIDs, n.d.). Studies have shown that combining NSAIDs with low-dose aspirin synergistically increases the risk of GI bleeding (Grosser and Smyth, 2011).

NSAID use also can have serious cardiovascular effects. According to studies made by regulatory agencies in the United States, Europe and Australia, "all NSAIDs have the potential to increase the risk of heart attack and stroke"

(Grosser and Smyth, 2011). Patients who are at high risk of cardiovascular disease are most likely to be subject to adverse events when they are taking NSAIDs (Grosser and Smyth, 2011). Low dose use of aspirin has been prescribed for its cardioprotective effect but at high doses can lead to congestive heart failure and pulmonary edema (Grosser and Smyth, 2011).

Studies have shown that NSAID use produces an increase in mean blood pressure of approximately 5 mmHg. This is significant, considering that a 5-6 mmHg increase in diastolic blood pressure lasting for a few years is associated with a 67 percent increased stroke risk and increase in coronary heart disease by 15 percent (Johnson, 1997). The hypertensive effect is related to the inhibition of COX-2 in the kidneys and vasculature, which decreases sodium excretion and increases peripheral vasculature volume (Grosser and Smyth, 2011). Large studies of women in 2002 and men in 2007 at Harvard Medical School both show association between ibuprofen, acetaminophen and aspirin with hypertension. Compared with those who took no analgesics, men who took NSAIDs six to seven times per week showed a 38 percent greater chance of developing high blood pressure, as compared to those who took acetaminophen with a 34 percent greater risk and to aspirin users who showed a 26 percent greater risk (Forman, Rimm and Curhan, 2007).

NSAIDs and aspirin have also been associated with adverse effects in other organ systems. Renal and renovascular side effects can occur, especially in patients who have heart, liver or kidney disease (Grosser and Smyth, 2011). Hypersensitivity to aspirin and NSAIDs is also seen in some individuals. NSAID and aspirin use are contraindicated late in pregnancy because of an increased risk of postpartum hemorrhage and potential fetal risk (Grosser and Smyth, 2011). Aspirin has other adverse effects that contribute to its potential misuse and toxicity.

At anti-inflammatory doses, aspirin and other salicylates stimulate respiration by increasing oxygen consumption and production of carbon dioxide, and also by direct stimulation of the respiratory center in the medulla. Salicylates, at high doses, can cause injury to the liver. Use is contraindicated in patients younger than age 20 with viral illness associated with fever because of its correlation with a severe hepatic injury and encephalopathy seen in Reye's syndrome.

Aspirin ingestion prolongs bleeding time through irreversible inhibition of platelet function. A 325 mg dose of aspirin can double a person's bleeding time for four to seven days. This calls for usage to be stopped at least one week prior

to surgery and for caution or avoidance in patients with hepatic damage, hypoprothrombinemia, vitamin K deficiency, hemophilia or who are undergoing long-term treatment with oral anti-coagulants. Long-term use also increases thyroidal uptake and iodine clearance, and at high doses, hearing impairment and tinnitus commonly occur (Grosser and Smyth, 2011).

Acetaminophen, which is used for its analgesic and antipyretic effects, is a drug that is generally well-tolerated at therapeutic doses, showing low incidence of GI side effects and no cardiovascular or respiratory side effects. Acute overdose of acetaminophen, however, can cause liver damage (Grosser and Smyth, 2011). With acetaminophen being the most commonly used OTC medication in the United States, it is important that patients are informed about guidelines for its usage. Overdose of acetaminophen is the most common cause of acute liver failure (Wolf, et.al., 2012).

Poor product labeling has been identified as a factor that has contributed to overdose of acetaminophen. A study published in the Journal of General Internal Medicine by Wolf, et. al. (2012) that surveyed 500 adult patients taking acetaminophen showed that 23.8 percent of participants would take more than the recommended maximum daily 4 gram dose of acetaminophen per day and 5.2 percent would have taken a dangerously high dose of more than 6 grams per day. In another part of this study, 45.6 percent of patients would have exceeded maximum recommended doses by taking two products that contain acetaminophen.

Consumers do not adhere closely to labeled instructions and also do not recognize active ingredients in OTC pain medications (Wolf, et.al., 2012). Because of these studies, in July 2011, Johnson & Johnson McNeil division lowered the maximum dose for Tylenol from 4,000 mg (eight extra strength Tylenol pills) to 3,000 mg (six extra strength Tylenol pills) to reduce the risk of accidental acetaminophen overdose and possible liver failure and death (Mitchell, 2011). With acetaminophen included in more than 600 OTC medications, as well as certain prescription analgesics, people can unknowingly ingest too much acetaminophen. Patients with liver disease or who drink alcohol heavily should avoid acetaminophen to decrease the risk of liver disease (Wolf, et.al., 2012).

In children, it is uncommon to have serious toxicity associated with NSAID use; however, similar effects that occur in adults can occur in children but with some variation. Although serious GI effects are uncommon in children,

'With acetaminophen being the most commonly used OTC medication in the United States, it is important that patients are informed about guidelines for its usage. Overdose of acetaminophen is the most common cause of acute liver failure.'

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NSAIDs should be given with food to reduce mild gastrointestinal symptoms that can occur. Hepatitis is another side effect that can occur in children during NSAID treatment, but is most common with aspirin.

Therefore, liver function in children should be monitored in those receiving long-term NSAID treatment. Incidence of renal toxicity in pediatric patients is low, with 0.2-0.4 percent prevalence in children with juvenile idiopathic arthritis (Gazarian and Graudins, 2006). CNS effects, including headache, skin reactions and bronchospasm, can also occur in children using NSAIDs. Long-term NSAID use in children can also prolong bleeding time through inhibition of platelet aggregation (Gazarian and Graudins, 2006).

Discussion

Knowledge of the effects of NSAIDs on orthodontic tooth movement must encourage dental professionals to take a step back and focus on the foundation of patient care, starting with the medical history. Consideration of medications taken by patients that can interfere with tooth movement is important in order to reduce negative effects of prolonging orthodontic treatment.

Many studies on NSAIDs, such as those by Knop, Shintcovsk, Retamoso, Ribeiro and Tanaka, as well as Arias and Marquez-Orozco, have been conclusive in showing that NSAIDs slow down tooth movement by blocking the inflammatory response through inhibition of prostaglandins.

In spite of the fact that these studies are scientific and well-designed, there is some uncertainty when extrapolating data and applying it to humans in a clinical scenario. Weaknesses include animal subjects, variability in experimental design, drug administration techniques and force characteristics (Bartzela, Turp, Motschall and Maltha, 2009).

The future of this research should include a design for further studies analyzing the effects of NSAIDs in humans during orthodontic treatment. With the information provided today, acetaminophen appears to be the analgesic of choice for orthodontic patients because it has been shown to have no effect on tooth movement, while being equally as effective as other NSAIDs in controlling orthodontic discomfort.

Summary

The practice of orthodontics is based on tooth movement through bone in response to application of mechanical forces. The bone remodeling that takes place occurs through an inflammatory process that is mediated by prostaglandins.

Many orthodontic patients use OTC analgesics such as NSAIDs to control the discomfort associated with the inflammatory process, unaware that studies have shown these NSAIDs inhibit orthodontic tooth movement. Chemicals in the drug can pass through the bloodstream, reach the mechanically stressed tissues and interact with local cells. In doing so, NSAIDs inhibit prostaglandin synthesis, therefore inhibiting the rate of orthodontic tooth movement as well.

It is suggested that practitioners be

'Acetaminophen should, therefore, be considered the analgesic drug of choice for patients undergoing orthodontics, unless contraindicated by the patient's medical history or physician.'

aware of all medications taken by patients that could interfere with tooth movement in order to reduce the negative effects of prolonging orthodontic treatment. Research has shown that traditional NSAIDs, such as ibuprofen and aspirin, decreased the rate of orthodontic tooth movement.

Acetaminophen, an inactive inflammatory agent, had no effect. Acetaminophen should, therefore, be considered the analgesic drug of choice for patients undergoing orthodontics, unless contraindicated by the patient's medical history or physician.

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About the author



KRISTINA SAKAS graduated in 2010 from Indiana University with a bachelor of arts degree in biology and a minor in chemistry. With a love for dentistry, she has continued her education at the Ostrow School of Dentistry of USC as a candidate for doctor of dental surgery. Kristina is currently a fourth-year dental student. In the future, she hopes to pursue a career as an educator in the field of orthodontics. For any additional information regarding this article, please contact sakas@usc.edu.

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