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# Orthodontic tooth movement after different coxib therapies

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SUMMARY Anti-inflammatory substances used for treatment of pain and discomfort related to orthodontic treatment (OT) could slow down tooth movement. Selective cyclooxygenase-2 inhibitors are an alternative to conventional non-steroidal anti-inflammatory drugs. The aim of this study was to compare different coxibs on dental movement in the rat.

Twenty-eight Wistar male rats (3 months old) divided into four experimental groups were studied: (1) Five rats underwent a 50 g coil spring implantation and received three injections of 0.5 mg/kg body weight (bw) of Rofecoxib in the maxillary gingiva, close to the first molar, on the day of implantation and after 3 and 5 days. Similar procedures were carried out (2) on six animals receiving 8 mg/kg bw of Celecoxib and (3) on five animals receiving 25 mg/kg bw of Parecoxib. (4) For the controls, 12 rats received the same OT but only equivolumetric 0.9 per cent saline solution injections. Tooth movement was measured on lateral cranial teleradiographs after 10 days of treatment. Non-parametric standard techniques (Wilcoxon, *H*, and Mann–Whitney, *U*) were used for statistical analysis.

Mesial tooth displacement in the control animals was 0.33 ± 0.07 mm. While no movement was found in rats treated with Rofecoxib, the Celecoxib- and Parecoxib-treated rats showed tooth movement of 0.42 ± 0.09 mm and 0.22 ± 0.04 mm, respectively. The differences were statistically significant ($H = 13.07$; $P < 0.004$).

Celecoxib and Parecoxib, but not Rofecoxib, seem appropriate for discomfort and pain relief while avoiding interference during tooth movement.

## Introduction

Patients undergoing orthodontic treatment (OT) may experience some degree of pain or discomfort (Ngan *et al.*, 1994). It is therefore important for this to be alleviated during OT (Bergius *et al.*, 2000; Polat and Karaman, 2005).

OT often implies the application of forces to the teeth that finally affect the fibrous joint (gomphosis) producing some mobility of the tooth in the alveolus. The alveolar periodontal bone plasticity constitutes the basis for orthodontic movement. The histological responses to these forces are mainly osteolysis on the pressure side but also on the side where tension stress develops (King *et al.*, 1991). The early stages of OT are generally accompanied by an acute inflammatory process including periodontal vasodilatation and some discomfort or pain, related to the stimulation of periodontal nerve endings (Sari *et al.*, 2004). These responses show great individual variability (Ren *et al.*, 2002).

From the physiological point of view, pain is an appropriate bodily response to tissue injury. It is associated with inflammation and, accordingly, treatments that control the inflammatory responses may also be effective in the control of pain. During inflammatory responses, several substances are produced both *in situ* or *ex situ*. Among them are prostaglandins (PGs) which mediate the osteoclastic response in a way not totally understood (Wong *et al.*, 1992). $PGE_1$ and $PGE_2$ locally injected in monkeys doubled the rate of tooth displacement during OT (Yamasaki *et al.*, 1982). Similar results were obtained with exogenous $PGE_2$ injected into rats (Leiker *et al.*, 1995). Moreover, endogenously generated PGs increase in periodontal tissues which have undergone orthodontic stress (Ong *et al.*, 2000). The *in vitro* effect of PGs on bone resorption (Davidovitch *et al.*, 1980) has been reported.

PGs are produced through two different pathways by the action of the enzyme cyclooxygenase on arachidonic acid: the constitutive isoform or cyclooxygenase-1 (COX-1) and the inducible isoform or cyclooxygenase-2 (COX-2). The PGs resulting after either pathway activation are different. COX-1 produces PGs that are protective at the gastrointestinal mucosa (Hla and Neilson, 1992). Therefore, the use of non-specific blockers, non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, that interfere with the COX-1 pathway associated with gastric and intestinal are side-effects (Silverstein *et al.*, 2000; Chan *et al.*, 2002). On the contrary, the selective inhibition of COX-2 maintains the anti-inflammatory effects causing less injury to the gastrointestinal mucosa than non-selective NSAIDs (Meade *et al.*, 1993; Masferrer *et al.*, 1994).

The use of NSAIDs which inhibits the release of PGs and stops inflammation is effective in the treatment of discomfort related to OT (Ngan *et al.*, 1994). However, the extended use of NSAID is inappropriate because they could slow

down tooth movement (Chumbley and Tuncay, 1986). As a result, the use of selective COX-2 inhibitors is increasing, replacing conventional NSAIDs, especially for chronic inflammatory conditions. It has previously been shown that some COX-2 inhibitors do not interfere with orthodontic tooth movement in such a radical way as non-specific COX inhibitors (Kehoe *et al.*, 1996).

Several pharmacological studies have determined the existence of differences in the specificity of COX inhibitors and their results used to be expressed as COX-1/COX-2 ratio (Brooks *et al.*, 1999; Miehle, 1999). According to this, it is reasonable to assess and to compare the effects of these different drugs on orthodontic tooth movement and hence to consider their suitability as pain relief for patients undergoing OT.

The main purpose of this study was to compare the effect of Rofecoxib, Celecoxib, and Parecoxib on the inhibition of dental movement induced with a coil spring in the rat.

## Materials and methods

Twenty-eight 3-month-old Wistar male rats obtained from the vivarium of the University of Oviedo, Spain, with an approximate average weight of 350 g at the beginning of the experiment, were used. The protocol was reviewed and approved by the appropriate institutional review board (University of Oviedo). The animals were exposed to the standard 12-hour light/dark cycle. In order to minimize the risk of appliance displacement during mastication, they were fed *ad libitum* with soft food (finely grounded standard pellets) and tap water.

A force of 50 g was generated by a unilateral closed-coil spring that was stretched between the maxillary left first molar and the incisor. For this, the teeth were prepared with perforation holes (buccolingually for the molar and distomesially for the incisor).

The animals were killed by $CO_2$ inhalation and decapitated 10 days after the orthodontic appliances were placed. The magnitude of tooth movement was blindly determined, always by the same technician, on lateral cranial teleradiographic images obtained for each animal. An intraoral radiographic apparatus (Siemens, Heliodent 70, Benshein, Germany) was used along with Kodak DF-50 radiographs and a specially constructed craniostat.

Measurements were based on the cephalometric system of Ruf and Pancherz (1996) using, as the horizontal reference, the longitudinal cranial plane defined by the most anterior point of the nasal bone (Na) and the most posterior point of the squama occipitalis (Oc), and, as the vertical reference, a plane defined by the most superior point of the parietal bone (Pa) and the most inferior point of the tympanic bone (T). Outline definition was used to minimize location errors. The distance between the first and second molar, determined by two parallel lines to the Pa–T plane, one on the most posterior point of the posterior border of the crown of the upper first molar and the second on the most anterior point of the anterior border of the crown of the upper second molar, was deemed as the actual mesial tooth movement after OT (de Carlos *et al.*, 2006).

Rofecoxib (Vioxx®, MSD, Madrid, Spain) was freshly prepared for each injection by dissolving 25 mg tablets in 12.5 ml of 0.9 per cent saline solution, Celecoxib (Celebrex®, Searle, Madrid, Spain) by dissolving 200 mg tablets in 5.8 ml of 0.9 per cent saline solution and Parecoxib (Dynastat®, Pharmacia, Barcelona, Spain) by dissolving the content of vials of 40 mg in 0.8 ml of 0.9 per cent saline solution.

### *Experimental design*

The animals were divided into four experimental groups: (1) Five rats underwent a 50 g coil spring implantation and received three injections of 0.5 mg/kg body weight (bw) of Rofecoxib in the maxillary gingiva, close to the first molar, on the day of implantation and after 3 and 5 days. Similar procedures were carried out (2) on six animals receiving 8 mg/kg bw of Celecoxib and (3) on five animals receiving 25 mg/kg bw of Perecoxib. (4) For controls, 12 rats received the same OT and only equivolumetric 0.9 per cent saline solution injections.

### *Statistical analysis*

Due to the limited sample size and variability, the statistical analysis used in this study followed a non-parametric approach (Wilcoxon, $H$, and Mann–Whitney, $U$). It implies an intrinsic loss of power versus parametric analysis, whereas it does not invalidate the validity of the comparisons and significances found. The results are expressed as mean ± standard error of mean. Values of $P < 0.05$ were deemed as statistically significant.

## Results

The orthodontic appliances were well tolerated in all four groups of rats. The animals ate and drank without any noticeable problems. Although their weight diminished immediately after surgery, by the end of the experiment, no statistical differences were found between their initial and final weights.

No naked-eye effects or differences in tooth movement were observed at the end of the experimental period, although tooth movement was found in many rats when assessed on lateral teleradiographs.

The results are summarized in Figure 1. Mesial tooth displacement measured in the control animals after 10 days was 0.33 ± 0.07 mm. While no movement was found in the rats treated with Rofecoxib, Celecoxib- and Parecoxib-treated rats showed some tooth movement (0.42 ± 0.09 mm and 0.22 ± 0.04 mm, respectively).

When all four groups were compared, the differences in tooth movement reached statistical significance ($H = 13.07$; $P < 0.004$). In addition, tooth movement with Celecoxib versus Rofecoxib and Parecoxib versus Rofecoxib was also

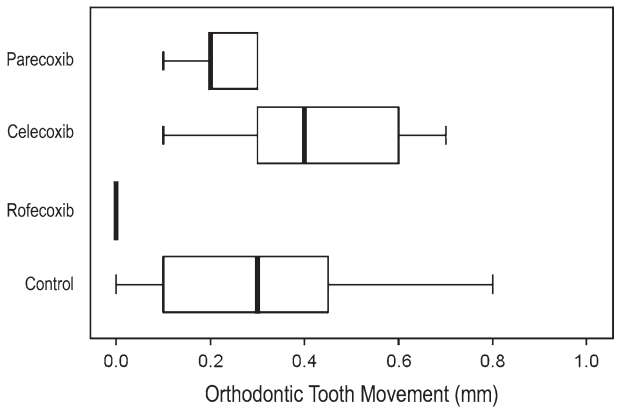


**Figure 1** Tooth movement in Rofecoxib-treated, Celecoxib-treated, Parecoxib-treated, and vehicle rats. Upper and lower limits of boxes represent 75th/25th percentiles, respectively. Whisker caps represent 95th/5th percentiles. Median values are represented as horizontal lines and outliers as black dots.

statistically significant ($U = 0.0$, $P < 0.004$ and $U = 0.0$, $P < 0.005$, respectively). However, no statistically significant differences were found between the control and Celecoxib-treated rats ($U = 26.5$; not significant) or between the control and Parecoxib-treated rats ($U = 22.5$; not significant).

## Discussion

Forces applied on teeth trigger an inflammatory response involving pain and/or discomfort and bone resorption, which constitutes the basis of tooth movement (Ransjö *et al.*, 1998; Alhashimi *et al.*, 2001; Kanzaki *et al.*, 2002). Analgesics, including several NSAIDs, have been largely prescribed for alleviation of the symptoms felt by patients undergoing OT. Among others, PGs are typical inflammatory and pain mediators which result from the degradation of arachidonic acid. Its synthesis is mediated by two different COX isoenzymes. The constitutive COX-1 does not exhibit dynamic regulation while COX-2 expression is subject to regulation by several environmental conditions (Breyer and Harris, 2001). In recent years, COX-2-selective non-steroidal anti-inflammatory substances, also named coxib, have become widely available and their use more common. Coxib shows anti-inflammatory properties, preserving the COX-1 pathway and therefore allowing the natural production of some PGs important for their gastrointestinal protective role (Hla and Neilson, 1992; Laudanno *et al.*, 2001).

In analgesic treatment during orthodontic procedures, acetaminophen, a very weak COX inhibitor, has been proposed as the drug of choice (Kehoe *et al.*, 1996; Roche *et al.*, 1997). NSAIDs have proved to be inappropriate for treatment of discomfort and pain during OT since they tend to limit or even block tooth movement due to interference with the accompanying inflammatory process (Chumbley and Tuncay, 1986). The importance of achieving good anti-inflammatory effects with minimum interference of the COX-1 pathway has resulted in a wide variety of coxibs being developed and made commercially available in recent years. Some of these have been the object of debate and even withdrawn from the market due to reports of unwanted cardiovascular and renal side effects. Coxibs, promising minimal NSAID-typical toxicity with full anti-inflammatory efficacy, have been used for treatment of orthodontic discomfort and pain (Sari *et al.*, 2004).

In the search for an idoneous NSAID treatment it was hypothesized that coxibs with differences in COX-1/COX-2 selectivity ratio could affect, in a different manner, the movement of teeth during OT. The present study intended to compare the effects of orthodontic tooth movement of the first coxib substances approved for relief of acute pain by the US Food and Drug Administration [Celecoxib (US Food and Drug Administration, 1998); Rofecoxib (US Food and Drug Administration, 1999) and Parecoxib (European Medicines Evaluation Agency, 2002)]. The results seem to confirm the hypothesis. While Rofecoxib completely inhibited tooth movement in rats after 50 g force application, Celecoxib and Parecoxib did not. This is compatible with the idea that factors depending on synthesis via COX-1 are involved in the bone remodelling process during orthodontic tooth movement. The fact that such a specific coxib substance such as Rofecoxib had this striking effect could probably be related to the fact that prostacyclins increase the number of multinuclear osteoclasts, osteoclastic bone resorption, and rate of orthodontic tooth movement in rats (Gurton *et al.*, 2005).

However, it is also possible that other differences between the drugs themselves (bioavailability, half life, etc.) could account for the different effects of these two drugs.

## Conclusion

From the findings of this animal study, Celecoxib and Parecoxib, but not Rofecoxib, are appropriate for discomfort and pain relief while avoiding interference during tooth movement. These results, based on animal protocols, short-term duration, and high-intensity forces, need to be confirmed and re-evaluated under other experimental conditions, on other species including humans. The debate regarding coxib substances and safety issues will probably evolve; eventually it will lead to the introduction of new anti-inflammatory substances (Casturi *et al.*, 2005).

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## References

Alhashimi N, Frithiof L, Brudvik P, Bakhiet M 2001 Orthodontic tooth movement and *de novo* synthesis of proinflammatory cytokines. American Journal of Orthodontics and Dentofacial Orthopedics 119: 307–312

Bergius M, Kiliaridis S, Berggren U 2000 Pain in orthodontics. A review and discussion of the literature. Journal of Orofacial Orthopedics 61: 125–137

Breyer M D, Harris R C 2001 Cyclooxygenase 2 and the kidney. Current Opinion in Nephrology and Hypertension 10: 89–98

Brooks P *et al*. 1999 Interpreting the clinical significance of the differential inhibition of cyclooxygenase-1 and cyclooxygenase-2. Rheumatology (Oxford) 38: 779–788

Casturi S R, Hegde P, Ramanujam R 2005 Development of COX-2 selective inhibitors—therapeutic perspectives. Current Medicinal Chemistry—Immunology, Endocrine and Metabolic Agents 5: 241–248

Chan F K *et al*. 2002 Celecoxib versus Diclofenac and Omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. New England Journal of Medicine 347: 2104–2110

Chumbley B A, Tuncay O C 1986 The effect of indomethacin (an aspirin-like drug) on the rate of orthodontic tooth movement. American Journal of Orthodontics 89: 312–314

Davidovitch Z, Finkelson M D, Steigman S, Shanfeld J L, Montgomery P C, Korostoff E 1980 Electric currents, bone remodeling and orthodontic tooth movement. American Journal of Orthodontics 77: 33–47

de Carlos F, Cobo J, Díaz-Esnal B, Argüelles J, Vijande M, Costales M 2006 Orthodontic tooth movement following inhibition of COX-2. American Journal of Orthodontics and Dentofacial Orthopedics 129: 402–406

European Medicines Evaluation Agency 2002 Parecoxib: approval number: ATC M01AH04 (http://www.emea.europa.eu)

Gurton A U, Akin E, Sagdic D, Olmez H 2005 Effects of $PGI_2$ and $TxA_2$ analogs and inhibitors in orthodontic tooth movement. Angle Orthodontist 74: 526–532

Hla T, Neilson K 1992 Human cyclooxygenase 2 cDNA. Proceedings of the National Academy of Sciences of the United States of America 266: 7384–7388

Kanzaki H, Chiba M, Shimizu Y, Mitani H 2002 Periodontal ligament cells under mechanical stress induce osteoclastogenesis by receptor activator of nuclear factor kappaβ ligand up-regulation via prostaglandin $E_2$ synthesis. Journal of Bone and Mineral Research 17: 210–220

Kehoe M J, Cohen S M, Zarrinnia K, Cowan A 1996 The effect of acetaminophen, ibuprofen, and misoprostol on prostaglandin $E_2$ synthesis and the degree and rate of orthodontic tooth movement. Angle Orthodontist 66: 339–349

King G J, Keeling S D, Wronski T J 1991 Histomorphometric study of alveolar bone turnover in orthodontic tooth movement. Bone 12: 401–409

Laudanno O M *et al*. 2001 Gastrointestinal damage induced by Celecoxib and Rofecoxib in rats. Digestive Diseases and Sciences 46: 779–784

Leiker B J, Nanda R S, Currier G F, Howes R I, Sinha P K 1995 The effects of exogenous prostaglandins on orthodontic tooth movement in rats. American Journal of Orthodontics and Dentofacial Orthopedics 108: 380–388

Masferrer J L *et al*. 1994 Selective inhibition of inducible cyclooxygenase 2 *in vitro* is anti-inflammatory and nonulcerogenic. Proceedings of the National Academy of Sciences of the United States of America 91: 3228–3232

Meade E A, Smith W L, DeWitt D L 1993 Differential inhibition of prostaglandin endoperoxide synthase (cyclooxygenase) isozymes by aspirin and other non-steroidal anti-inflammatory drugs. Journal of Biological Chemistry 268: 6610–6614

Miehle W 1999 [Non-steroidal anti-inflammatory drugs and cyclooxygenase-2-specific inhibitors]. Wiener Medizinische Wochenschrift 149: 541–545

Ngan P, Wilson S, Shanfeld J, Amini H 1994 The effect of ibuprofen on the level of discomfort in patients undergoing orthodontic treatment. American Journal of Orthodontics and Dentofacial Orthopedics 106: 88–95

Ong C K L, Walsh L J, Harbrow D, Taverne A A R, Symons A L 2000 Orthodontic tooth movement in the prednisolone-treated rat. Angle Orthodontist 70: 118–125

Polat O, Karaman A I 2005 Pain control during fixed orthodontic appliance therapy. Angle Orthodontist 75: 214–219

Ransjö M, Marklund M, Persson M, Lerner U H 1998 Synergistic interactions of bradykinin, thrombin, interleukin 1 and tumor necrosis factor on prostanoid biosynthesis in human periodontal-ligament cells. Archives of Oral Biology 43: 253–260

Ren Y, Maltha J C, Van't Hof M A, Von Den Hoff J W, Kuijpers-Jagtman A M, Zhang D 2002 Cytokine levels in crevicular fluid are less responsive to orthodontic force in adults than in juveniles. Journal of Clinical Periodontology 29: 757–762

Roche J J, Cisneros G J, Acs G 1997 The effect of acetaminophen on tooth movement in rabbits. Angle Orthodontist 67: 231–236

Ruf S, Pancherz H 1996 The effect of Herbst appliance on the mandibular plane angle: a cephalometric roentgenographic study. American Journal of Orthodontics and Dentofacial Orthopedics 110: 225–229

Sari E, Olmez H, Gurton U 2004 Comparison of some effects of aceylsalicylic acid and Rofecoxib during orthodontic tooth movement. American Journal of Orthodontics and Dentofacial Orthopedics 125: 310–315

Silverstein F E *et al*. 2000 Gastrointestinal toxicity with Celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib long-term arthritis safety study. Journal of the American Medical Association 284: 1247–1255

US Food and Drug Administration 1998 Celecoxib: approval number: NDA 020998 (http://www.fda.gov)

US Food and Drug Administration 1999 Rofecoxib: approval number: NDA 021052 (http://www.fda.gov)

Wong A, Reynolds E C, West V C 1992 The effect of acetylsalicylic acid on orthodontic tooth movement in the guinea pig. American Journal of Orthodontics and Dentofacial Orthopedics 102: 360–365

Yamasaki K, Shibata Y, Fukuhara T 1982 The effect of prostaglandins on experimental tooth movement in monkeys (*Macaca fuscata*). Journal of Dental Research 61: 1444–1446