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). PGE1 and PGE2 locally injected in monkeys doubled the rate of tooth displacement during OT (Yamasaki et al., 1982). Similar results were obtained with exogenous PGE2 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 CO2 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, Bensheim, 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 Parecoxib. (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
and Parecoxib-treated rats (treated rats). However, no statistically significant differences were found between the control and Celecoxib-treated rats ($U = 0.0, P < 0.004$ 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).

**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.

**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. 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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