

## *Sources of controversies over analgesics prescribed after activation of orthodontic appliances*

### *Acetylsalicylic acid or acetaminophen?*

Alberto Consolaro\*, Vanessa Bernardini Maldonado\*\*,  
Milton Santamaria Júnior\*\*\*, Maria Fernanda M-O. Consolaro\*\*\*\*

The wide range of available drugs raises questions about the desirable and undesirable effects on orthodontic movement. Could medications such as non-steroidal anti-inflammatory drugs (NSAIDs)—ASA, acetaminophen, diclofenac, ibuprofen, indomethacin and celecoxib—, corticosteroids and bisphosphonates have any impact on bone metabolism to the extent of interfering with orthodontic movement?<sup>23,18</sup>

When administered to control pain and discomfort after activation of the orthodontic appliance, what would be the influence of ASA and acetaminophen on tooth movement and the root resorption associated with it? To help in clarifying this question, Maldonado<sup>34</sup> and his team set out to quantitatively determine the influence of ASA and acetaminophen on induced tooth movement and on root resorption by means of optical microscopy. In another study they described the history and action mechanisms of these two medications.<sup>14</sup>

However, when analyzing the literature on the subject, it appears that no work repeated the same experimental model of any other work. The appliance used to move a tooth, the

force applied, the dosage and duration of drug use, route of administration, the experimental animal, the teeth that were moved, the types of tissue section and tooth movement assessment as well as many other details differ from study to study, thus precluding comparisons. Without comparisons and without relevant discussions grounded and based on relevant literature it becomes difficult to draw inferences for clinical applications.

#### **Fundamentals and assumptions**

Orthodontic movements occur by the application of continued and controlled mechanical forces on the tooth pushing it against the bone, resulting in areas of pressure and tension in the periodontal ligament. The sort of bone remodeling that promotes tooth movement is the result of cellular stress and occasionally inflammation involving clast cells, osteoblasts, osteocytes, cementoblasts and fibroblasts. Mediators—such as various cytokines, growth factors and arachidonic acid products such as prostaglandins and leukotrienes—participate in the process as interaction molecules between cells.<sup>11,13,16</sup>

\* Full Professor of Pathology at FOB-USP and at FORP-USP Postgraduate courses.

\*\* Master's degree from FORP-USP and private clinic in Ribeirão Preto.

\*\*\* Doctor of Orthodontics and Professor of postgraduate studies in Orthodontics at the University of Araras.

\*\*\*\* Doctor and Professor of Orthodontics at the postgraduate course of Oral Biology at USC.

Kinins primarily induce pain in free nerve endings and prostaglandins potentiate the effect of kinins, which after 5 to 6 hours no longer produce desirable effects. This potentiation of kinin effects by prostaglandins also occurs in microcirculation vessels increasing vascular permeability. The action mechanism of NSAIDs and acetaminophen has been proven by specific studies conducted on the subject.<sup>1,4,6,7,8,10,15,19,20,21,26,30,31,35,39,42,45,46,53</sup>

Apparently, drug prescription after activation of the orthodontic appliance poses a paradox: *If, on the one hand, they suppress the patient's pain and discomfort with analgesics that reduce the level of prostaglandins, could it be that, on the other hand, they reduce the effectiveness of cellular stress and inflammation as a mechanism of bone resorption and induced tooth movement?*

Based on reports found in the literature and the behavior of orthodontic clinical cases within the framework advanced by Maldonado<sup>34</sup> the authors developed the following hypothesis:

*Could the prescription of ASA or acetaminophen have no effect on the biological reactions related to effective orthodontic movement and the frequency and severity of root resorption associated with it? Could the occasional and random administration of such drugs or longer periods of administration produce different effects?*

Studies that focused on shorter periods of use of these drugs have been criticized<sup>3,56</sup> for ignoring the option of longer administration periods. As proposed by Maldonado,<sup>34</sup> could the results of the experimental group undergoing the long and short-term administration of acetaminophen and acetylsalicylic acid help in answering how the short and long-term administration of these drugs influence orthodontic movement? In the view of Jerome et al,<sup>25</sup> anti-inflammatory medication might even offer protection against root resorption during

orthodontic movement.

It is a fact that prostaglandins induce cellular, tissue and vascular alterations but there is no evidence of inhibition of orthodontic tooth movement by painkillers and NSAIDs.<sup>56</sup> Bone resorption induced by tooth movement is not mediated solely by prostaglandins<sup>9,58</sup> but by a pool of mediators such as leukotrienes, cyclic adenosine monophosphate (cAMP),<sup>16,58</sup> collagenase and many others,<sup>29</sup> which are generated by forces applied to periodontal tissues.

The molecular life of prostaglandins consists of only a few seconds. Occasional, randomly administered doses over short periods of time lead to a transient reduction of prostaglandins but are enough to reduce the pain and discomfort after the activation of orthodontic appliances. It is only the long-term reduction of prostaglandins after the administration of regular and repeated doses that would be able to reduce the edema effect and the efficiency of the inflammatory cells, known as anti-inflammatory effect, widely used in postoperative surgical periods.<sup>12,13</sup>

### Inconsistencies in the literature and possible explanations

The literature on the effects of drugs during induced tooth movement is still lacking standardized methodology in all its aspects. Results are often very diverse and inconsistent and cause confusing interpretation. The literature on the subject often demonstrates inexperience with the experimental model and the animal used. Thus, veritable "literature trends" arise whereby one study cites the other without checking basic methodological details. The main variables involved in the lack of consistency between the results reported in the literature are described below.

#### 1. Medication inconsistencies

The doses of ASA or acetaminophen and the

administration periods used in the various studies about induced tooth movement differ widely:

- Wong et al<sup>57</sup> (1992): 65mg of acetylsalicylic acid for 28 days.
- Kehoe et al<sup>27</sup> (1996): 200mg of acetaminophen for 11 days.
- Roche et al<sup>47</sup> (1997): 1,000mg de acetaminophen for 21 days.
- Sari et al<sup>50</sup> (2004): 500mg of acetylsalicylic acid for 2 days.
- Arias et al<sup>2</sup> (2006): 100mg of acetylsalicylic acid and 200mg of acetaminophen for 10 days.
- Salmassian et al<sup>48</sup> (2009): 600mg of acetaminophen for 7 days.
- Stabile et al<sup>52</sup> (2009): 200mg de acetaminophen for 2 days.

These differences led two groups of researchers to review the matter: Walker and Buring<sup>56</sup> and Bartzela et al.<sup>3</sup> In a systematic review of Bartzela et al<sup>3</sup> on induced tooth movement and the use of NSAIDs, including acetaminophen, the authors found 49 articles. The selection criteria were experimental design, magnitude of force and medication. The authors criticized the results of studies using NSAIDs in induced tooth movement concluding that most of these studies evaluated short-term experiments underestimating the effects of prolonged drug administration.

A similar review was conducted in 2001 by Walker and Buring<sup>56</sup> with conclusions similar to those reached by Bartzela et al<sup>3</sup> in 2009. The authors emphasized that there is no evidence nor any reasonable grounds to account for a complete inhibition of induced tooth movement either with short or long-term drug administration. They justified their conclusions based on the concept that prostaglandins are not the only modulators of bone resorption. Furthermore, based on previous studies, they claim that the exact amount of force necessary to create tooth movement has not been

standardized, and conclude that animal studies have been limited and short-term.

## 2. Inconsistencies regarding animals used and teeth moved

Methods using induced tooth movement accompanied by drug administration are numerous in the literature, but the choice of experimental model insofar as the orthodontic appliance and the animals are concerned is fraught with inconsistencies. Rabbits,<sup>47</sup> cats,<sup>9</sup> pigs<sup>27,57</sup> and rats<sup>2,17,32,33,36,37,38,40,41,49,52,54,55,59</sup> have been used.

The teeth used for induced tooth movement are yet another variable that influences the wide variety of results achieved by such studies. Compared with human incisors rodent incisors are quite different in their morphology. Moreover, their odontogenesis is continuous. For example:

- Wong et al<sup>57</sup> (1992) used guinea pig incisors.
- Kehoe et al<sup>27</sup> (1996) studied guinea pig incisors.
- Roche et al<sup>47</sup> (1997) investigated rabbit molars.
- Sari et al<sup>50</sup> (2004) experimented using human gingival fluid.
- Arias et al<sup>2</sup> (2006) used the upper incisors of rats.
- Salmassian et al<sup>48</sup> (2009) measured the painful effects of fixed orthodontic appliances in humans.
- Stabile et al<sup>52</sup> (2009) investigated rat incisors.

Research in animals is justified because it is numerically more representative than evaluation in humans. The microscopic analysis of induced tooth movement in humans is limited since it requires extraction, which ruptures periodontal ligament fibers. As a result, part of the tissue that should be examined remains attached to the alveolar bone thereby precluding the analysis of the ensuing changes.<sup>5</sup>

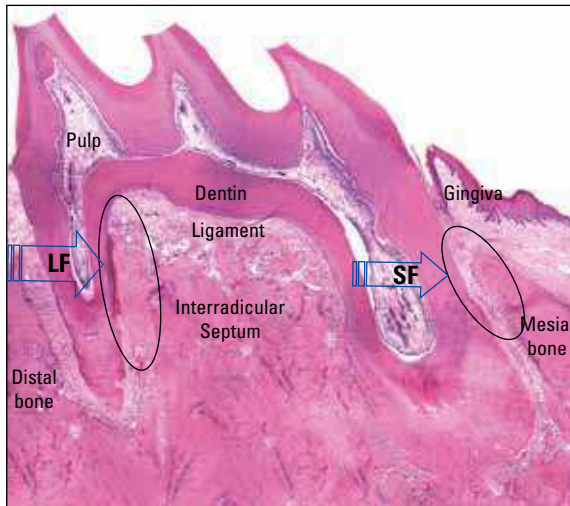


FIGURE 1 - By observing the longitudinal section of a murine first molar one can compare the similarities between a murine tooth and a human molar. In the experimental model proposed by Heller and Nanda<sup>22</sup> the forces applied to the mesial root are considered light (LF) due to its volume and size. The small dimensions of the distobuccal root imply strong forces (SF) with greater action exerted on the periodontal ligament, which is consequently extensively hyalinized (red area in the larger circle).

The model of induced tooth movement in rats is universally accepted due to the fact that it is more ethical and can be extrapolated to humans, considering the favorable root morphology of rodents, the size of their molars (Figs 1, 2 and 3) and their anatomical peculiarities, although their metabolism is twice as high as that of humans.<sup>12,43,51</sup>

### 3. Inconsistencies regarding the design of the experimental orthodontic appliance

Many different appliance designs are employed to obtain experimental tooth movement and these designs influence the results, regardless of whether or not associated with drug use.

- V-shaped appliances are intended to separate the incisors,<sup>2,52</sup> which in rodents undergo continuous root formation.
- When placed between the first and second molars elastomers exert a not so efficient or continuous force, which tends to dissipate swiftly, as it acts on two teeth,



FIGURE 2 - By observing the cross-section of a murine first molar one can compare the similarities between this murine tooth and a human molar and its reactions with greater histomorphometric accuracy—in the face of light forces (small arrow) and intense forces (large arrow)—such as the hyaline areas in the periodontal ligament (circles) and the attendant dental resorption. In these cross-sections one can observe all five roots of the murine first molar and adjacent bone.

instead of just one. Moreover, the force is further absorbed by a considerable deflection of the bony ridges and septa of two teeth, and not just one.<sup>40,55</sup>

- When expansion screws are placed between the first molars they cause upper first molar proclination.<sup>23,24</sup> Transverse coil springs for molar proclination<sup>28</sup> work both on the teeth and on the palatal sutures, and it is not possible to determine with any degree of reliability the extent



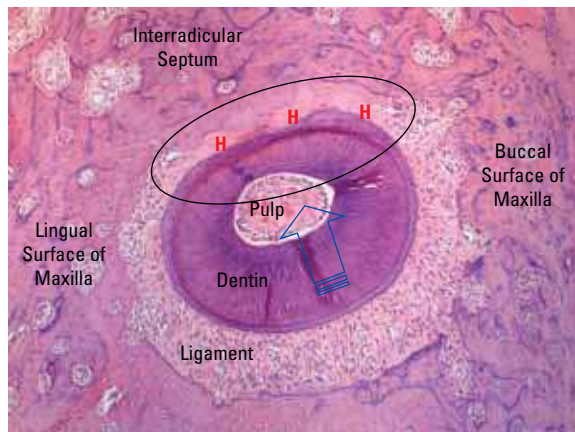


FIGURE 3 - By magnifying a cross-section of a murine first molar root one can measure its reactions with histomorphometric accuracy in the face of the forces (arrow) applied, such as the hyaline areas (H) in the periodontal ligament (circle) and related bone and tooth resorption when these are present.

of such occurrences. The bone plate of the rat is very thin and does not allow a standardized use of these springs.

- The use of coil springs interposed between incisors and molars in order to move molars mesially is currently widespread enabling the quantification and standardization of forces deployed in the experimental model, thereby imparting greater credibility to the extrapolation of results.<sup>17,36,37,38,41,49,54,59</sup> This model was designed by Heller and Nanda<sup>22</sup> and perfected by Martins-Ortiz<sup>36</sup> (Figs 1, 2 and 3).

#### 4. Inconsistencies regarding the intensity and distribution of forces

Perhaps the most decisive factors influencing the differences and diversities of the results regarding this matter do not concern only the experimental appliance but especially the intensity and distribution of forces applied to achieve tooth movement:

- Wong et al<sup>57</sup> (1992) moved guinea pig

incisors with a V-shaped appliance using a force of 8cN.

- Kehoe et al<sup>27</sup> (1996) moved guinea pig incisors using a V-shaped appliance and applied forces up to 25cN.
- Roche et al<sup>47</sup> (1997) moved rabbit molars mesially using springs interposed to the incisors by applying forces up to 100cN.
- Sari et al<sup>50</sup> (2004) moved human canines distally applying forces up to 120cN.
- Arias et al<sup>2</sup> (2006) separated the upper incisors of rodents using a V-shaped appliance and a force of 35cN.
- Salmassian et al<sup>48</sup> (2009) did not standardize force intensity.
- Stabile et al<sup>52</sup> (2009) moved the upper incisors of rats with a V-shaped appliance using a force of 30cN.

These significant discrepancies could also be found in the data reported in 2004 after a systematic review of Ren.<sup>44</sup> In 20% of the studies on induced tooth movement the forces applied were lower than 20cN; 27% of the studies used elastomers of unknown forces; 37% applied forces ranging from 20 to 50cN and 12% used forces ranging from 50 to 100cN.

#### 5. Inconsistencies regarding result interpretation and measurement

The criteria for interpreting and measuring the effects of applied forces on cells and tissues, of associated root resorption and the influence of drugs on periodontal tissues represent another variable limiting the extrapolation of the clinical results previously reported in the literature.

For example, in research on induced tooth movement areas of hyalinization in the periodontal ligament mean that the forces applied were effective in light of a microscopic analysis of experimental results. The results found by Bohl et al<sup>5</sup> about the extent of hyalinization areas after experimental tooth movement are

rather inadequate in the literature due to:

- Wide variation among the methods.
- Variability in size and time as regards the emergence of hyaline areas.
- Considerable type and intensity differences in terms of force application.

In 2007, Fracalossi<sup>17</sup> revealed that, under microscopic analysis, the differences may also occur in the cross-section plane of the moved teeth. Cross-sections allowed a better assessment of tissue effects making it easy to visualize the roots in a single, parallel plane<sup>17</sup> (Figs 1, 2 and 3).

### Acetylsalicylic acid or acetaminophen?

In the work of Maldonado,<sup>34</sup> the comparative results between the short and long-term administration of acetylsalicylic acid and acetaminophen were obtained using the model created by Heller and Nanda<sup>22</sup> and later modified by Martin-Ortiz<sup>36</sup> since it allows for force and movement type standardization. The first molars of young rats are very similar in morphology to that of humans and their formation is not continuous as is the case with rat incisors.

Result reproducibility was based on the measurement of two important parameters, namely, the occurrence of hyaline areas (Figs 1, 2 and 3) and the presence of root resorption. Hyaline areas indicate that there was vascular compression and areas of hypoxia that determine cell migration and necrosis. In other words, this means that the force was active in the first hours and days of the experiment. The areas of root resorption in turn indicate cell mobilization, especially of clast cells, indicating that the forces continued to operate even several days after the force had been applied and the teeth moved.

The dosage administered in the Maldonado<sup>34</sup> investigation was based on the dosage recommended for humans taking into account that the rat's metabolism is twice that of humans.

For the relief of human pain, these drugs—acetylsalicylic acid and acetaminophen—are prescribed and patients recommended to swallow them whenever the need arises, i.e., administration follows a random pattern in time. Thus, the administration of these drugs for short periods attempted to simulate this situation of randomness and contingency. However, certain patients endowed with higher sensitivity to pain can take them several times over a period of just a few days. Long-term administration was meant to simulate this situation.

In this study, a histomorphometric analysis was performed of the effects of induced tooth movement in rats (200g) with springs interposed between the upper molars and the incisors and a force of 75cN associated with 25mg of ASA and 25mg of acetaminophen (short-term administration/2 days, and long-term/9 days). When compared with the control, the authors found no statistically significant differences in percentage means of hyaline areas in the periodontal ligament. Tissue reactions in the experimental groups were similar to those in the control group.

Root resorption was also assessed by the quantitative histomorphometric method and no statistically significant differences were found in the percentage means of the areas of root resorption between the acetylsalicylic acid group and the acetaminophen group compared with the control group, in the time periods used for evaluation.

The same findings were observed when comparing the experimental acetylsalicylic acid group with the acetaminophen group in terms of the percentage of hyaline areas found. In the authors' opinion, no statistically significant difference was found in the means of the hyaline areas between the experimental groups at 5, 7 and 9 days. The microscopic effects were similar in the experimental groups.

A comparison between the acetylsalicylic

acid group and the acetaminophen group (short and long term), in light of the percentage means of root resorption areas found no statistical difference in the time periods under evaluation.

The findings were difficult to be compared directly with those of other authors as the experimental model in almost all respects differed significantly.

In this experimental model results can be more safely and directly extrapolated to humans using the measurements and analysis conducted by the authors. In particular, this is due to the fact that this experimental model allows the observation and measurement—on the same tooth—of the tissue and cellular effects brought about by light and heavy forces, both without drugs and under their influence. Such precautions were suggested by Bartzela et al,<sup>3</sup> Walker and Buring.<sup>56</sup>

### Final considerations

The results of the study carried out by Maldonado<sup>34</sup> indicated that acetylsalicylic acid and acetaminophen did not interfere in the cell and tissue phenomena caused by induced tooth movement or in the degree and frequency of

the attendant root resorption. This corroborates the finding of Walker and Buring<sup>56</sup> that prostaglandins—the main targets of acetylsalicylic acid and acetaminophen—are not the only local mediators of bone resorption. These drugs act as modulators of prostaglandin production to control pain and discomfort rather than inhibiting total prostaglandin synthesis in the cellular stress and inflammation region, while other mediators of bone resorption continued to operate normally in the periodontal tissues.

When prescribing an analgesic to relieve the patient's pain and discomfort after activation of orthodontic appliances—always in writing and using the prescription pad—the choice should take into account the patient's history with side effects and the possibility of drug hypersensitivity. If any of these situations is characterized, the choice between ASA and acetaminophen depends on the accessibility or cost of the drug, at the discretion of the professional and/or the patient. The results show no influence on the effectiveness of orthodontic movement and frequency of root resorption associated with both ASA and acetaminophen.

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#### Contact address

Alberto Consolaro  
E-mail: consolaro@uol.com.br