The effect of acetaminophen on tooth movement in rabbits

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Movement of teeth during orthodontic treatment is dependent upon resorption of alveolar bone. Although the histology of this remodeling process has been studied extensively, the biochemical mediators that initiate or facilitate it are still not fully understood.[1-3] In more recent years, the intracellular biochemical events associated with tooth movement have been examined.[4,5] Mediators such as the cyclic nucleotides and prostaglandins have been suggested as mediators of bone resorption and tooth movement.[5,6]

Prostaglandins, in particular, have been found to play a direct role in bone resorption in vitro. Furthermore, they have been found in the periodontal tissues of teeth that have been moved orthodontically.[7,8]

Blocking the synthesis of prostaglandins has resulted in slower tooth movement.[9,10] Although these studies showed that prostaglandin activity can almost be halted and tooth movement slowed, some tooth movement did occur. Thus, prostaglandins may not be the only mediators of bone resorption associated with tooth movement.[11]

Generally, nonsteroidal anti-inflammatory drugs, due to their potential for slowing tooth movement, are not recommended for use during orthodontic care. Therefore, acetaminophen has been suggested as the analgesic of choice for relieving the discomfort associated with orthodontic pain.[12]

Acetaminophen is considered to be a very weak prostaglandin inhibitor and possesses no signifi-

Abstract

Orthodontic patients have reported the use of analgesics during therapy. However, common anti-inflammatory analgesics, such as aspirin and ibuprofen, have been shown to slow the rate of tooth movement. Acetaminophen, another common analgesic, does not possess anti-inflammatory properties. The effect of acetaminophen on tooth movement was studied using New Zealand white rabbits. Experimental animals were matched to a control animal of the same sex and weight. Under anesthesia, springs were ligated between the lower first molar and incisor, resulting in approximation of these teeth. Under blinded conditions, seven of the rabbits received 1000 mgs of acetaminophen daily. Seven control animals received water. The animals were sacrificed after 21 days. The movement of incisors and molars was measured. Results showed considerable movement within both the experimental and control groups, but no significant difference in tooth movement between them. Acetaminophen has no effect on the rate of tooth movement in rabbits undergoing orthodontic treatment.

Key Words

Acetaminophen • Tooth movement • Prostaglandins

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Figure 1
A 100-gram coil spring ligated between teeth at the initiation of study

Figure 2
After 21 days of activation. Note bone formation distal to the retracted molar

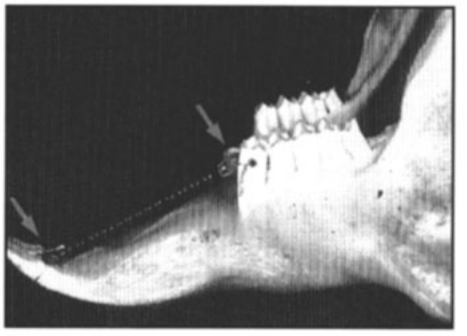

Figure 1

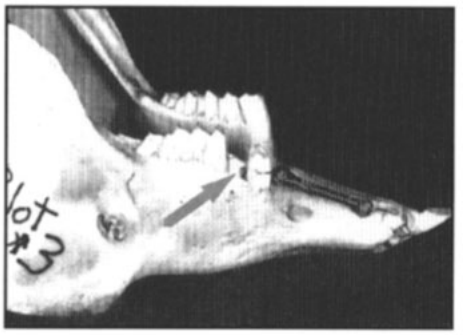

Figure 2

cant anti-inflammatory effects.[13] The exact mechanism by which acetaminophen relieves fever and pain is not fully understood, although it is believed to act primarily in the central nervous system.[14]

The purpose of this study was to evaluate the effect of acetaminophen administration on orthodontic tooth movement in an animal model.

Materials and methods

A pilot study was performed to estimate the variability expected in rates of closure between teeth in rabbits and to determine an adequate sample size to test the hypothesis. A sample of five rabbits underwent orthodontic tooth movement without the administration of analgesics. From the pilot study it was determined the main study would require 14 rabbits.

The 2 kilogram, 8-week-old New Zealand White male rabbits were allowed 1 week to become accustomed to their new environment. All rabbits were stored in individual cages in a "Rabbit-specific pathogen-free" room. The humidity and temperature were monitored continuously and maintained for normal rabbit functions (16-21°C and 40-60% humidity). A standard diet regimen of pellets and water was available at all times and replenished daily.

After 1 week, the rabbits were prepared for the dental surgery. Prior to surgery, the rabbits were sedated, so cooperation and access were maximized. Ketamine was injected into the paravertebral muscles at a dose of 35mg/kg i.m., as recommended for rabbit anesthesia. Xylazine, a muscle relaxant, was administered in the same manner at a dose of 5 mgs/kg. Due to the standardization of their weights, the quantity of Xylazine and Ketamine was identical for all subjects.

Duolube, a surgical eye lubricant, was applied liberally to the rabbits' eyes, which were open during the operation. The sedated animals were weighed prior to the operative procedure. Adequate depth of anesthesia was determined by a cavity preparation test and visual inspection of tongue reflex when a dental mirror was placed in the oral cavity. The dental surgery commenced only after all oral muscular reflexes were suspended.

Using a straight nose cone, slow speed motor, and a #1 round bur, the lower first molar and incisor teeth on one side were prepared with a perforation hole buccolingually. Additionally, unwanted occlusal forces during tooth movement were eliminated by occlusal reduction. Since the maxilla has a second set of incisors directly lingual to and in the path of retraction of the first incisors, the maxilla was excluded from the study.

This method of securing the orthodontic appliances was selected in order to ensure ease of application and integrity of the appliances. Prior to selection of this technique a radiographic assessment was made of rabbit pulpal anatomy in order to ascertain the risk of potential direct or indirect pathological changes in the dental pulps as a result of the preparation procedure. Such radiographic evaluation, obtained on dry specimens, indicated a large degree of safety in the choice of this preparation technique.

An impression of the prepared teeth was taken and poured in stone to serve as a record of initial interdental distance. A vernier caliper was used to measure from the distal edge of the incisal fixation screw to the mesial aspect of the molar screw. Citricon, a polyvinyl siloxane putty, was chosen because of its high viscosity, rapid setting time, and dimensional stability following recovery of impression from the oral cavity. Because of the small oral aperture of the rabbit, the initial interdental distances were measured on the stone casts rather than intraorally.

A 100 gram (unloading) GAC Sentalloy™ coil was fixed with .009" ligature between the lower right first molar and the lower right central incisor (Figure 1).

The rabbits were returned to their pens to recover from the anesthesia. Postoperative evaluations, to determine tolerance of the surgical

Table 1A
Comparison of control and experimental animals in distance moved (mm)

Animal	Control			Experimental		
	Initial distance	Final distance	Difference	Initial distance	Final distance	Difference
1	23.7	17.8	5.9	23.0	17.2	5.8
2	22.5	16.8	5.7	21.9	15.2	6.7
3	21.6	16.0	5.6	20.9	16.0	4.9
4	22.0	15.0	7.0	21/3	16.5	4.8
5	24.5	18.4	6.1	21.7	15.6	6.1
6	24.9	17.5	7.4	23.0	17.0	6.0
7	23.0	17.5	5.5	22.0	15.3	6.7

procedure, were completed at 24 hours, 48 hours and then every 3 days until the end of the 21-day period.

Fourteen identical bottles containing either 21,000 mgs of Tylenol™ Infant Drops (McNeil) (100 mgs/ml in 210 mls of solution) or water for use in the control animals were obtained. Water in seven control bottles was dyed with Yellow #6 and Red #1 to mimic the orange color of the Tylenol™. Bottles and rabbits were independently and randomly assigned numbers from 1 to 14. Bottles and rabbits with corresponding numbers were matched. The principal investigator was blinded as to which solution was being supplied to the rabbits.

Over the 21 day period, each rabbit was forcefed 1000 mgs of Tylenol (10 ml of solution) per day. Using a flexible, but moderately stiff latex tube with an orifice at both ends, the fluid was delivered directly into the stomach to insure it entered the digestive tract. The rabbit was restrained and the mouth was clenched closed manually so the orogastric tube would not perforate. The tube was passed through the interdental space toward the oropharynx where the swallowing reflex introduced the tube into the esophagus. Gentle pressure and peristalsis helped pass the tube into the stomach. Gastric secretion sounds confirmed entry into the stomach. Care was taken to prevent introduction of the tube into the trachea and lungs, since inadvertent deposition of drugs or viscous fluids could result in pneumonia and death. Additional testing of the tube placement was performed by watching nostril flare and covering the free end of the tube with a fingertip to momentarily restrict oxygen flow, resulting in excessive attempts by the animal to restore a patent airway.

Table 1B
Mean changein distance moved (mm) and value

Control	Experimental	
6.171	5.857	.4503
SD=0.74	SE=0.77	
SE=0.27	SE=0.29	

Corrective measures, if necessary were immediately performed.

Rabbits can readily tolerate water-based solutions at volumes up to 6 ml/kg. The experimental rabbits could therefore accept up to 15 ml of liquid. A 10 ml syringe was used to draw the solution and deposit it into the free end of the orogastric tube. The fluid passed uneventfully into the stomach after which the tube was removed and the rabbit returned to its respective pen. This procedure occurred once per day, at similar times, for each of the rabbits.

On day 21, the rabbits were sacrificed by a Nembutol overdose of 250 mgs i.v., through the lateral ear vein. Five minutes prior to the barbiturate overdose, the rabbits were administered 5000 units of heparin intravenously in order to prevent coagulation, thus allowing better preservation for future histological studies. The mandibles were immediately dissected and examined to insure that springs were still active. The springs were then removed and the mandibles were fixed in buffered 10% formalin. Impressions of the final interdental distance were obtained and poured in stone for future examination. All springs were still active at the end of the 21-day period when final interdental measurements

Table 2A
Comparison of control and experimental animals in weight change (kg)

Animal	Control Initial weight	Control Final weight	Control Difference	Experimental Initial weight	Experimental Final weight	Experimental Difference
1	2.30	2.50	.20	2.40	2.55	.15
2	2.44	2.55	.11	2.25	2.40	.15
3	2.33	2.45	.12	2.33	1.85	-.48
4	2.30	2.65	.35	2.33	1.70	-.63
5	2.25	2.50	.25	2.25	2.35	.10
6	2.30	2.60	.30	2.30	2.65	.35
7	2.25	2.50	.25	2.20	2.40	.20

Table 2B
Mean weight change (kg)

Control	Experimental	T-Value
0.2257	-0.0228	.1335
SD=0.09	SE=0.37	
SE=0.03	SE=0.14	

were recorded by a vernier caliper between the distal edge of the incisal fixation screw and the mesial aspect of the molar screw.

Descriptive statistics were generated through histograms and normal probability plots to determine if the values obtained were distributed normally. Scatter plots were also generated to describe the association between the two variables, and to assess the linearity of the association. The results were analyzed by a two-tailed *t*-test with an alpha level of .05.

Results

The rabbits tolerated all procedures extremely well.

Pilot study results measured from mandibular incisor to mandibular first molar demonstrated that the rate of closure ranged from .250 mm/day to .295 mm/day, with a standard deviation of .019 mm/day. A power analysis based upon pilot study results indicated that 14 rabbits would be needed to test the hypothesis that there was no difference in the rate of tooth movement between a group of rabbits receiving acetaminophen and a group of control rabbits using a statistical framework of alpha = .05 and beta = .20 for a two-tailed *t*-test.

The mandibular teeth moved predictably, in both the pilot and the main study, with the given forces and duration of force. The application of orthodontic forces resulted in significant tooth movement in all rabbits (Figure 2, Table 1A). All coil springs were still active at the end of the 21 days, indicating a force was delivered to the teeth throughout the experiment. Both the incisor and the molar, in all rabbits, moved toward each other as a result of the coil spring and the reciprocal anchorage system. Both the experimental and the control group demonstrated normal bell-shaped distribution values fulfilling the assumptions for a two-tailed *t*-test.

Experimental animals exhibited 5.85 mm (SD 0.77) of tooth movement, while control animals showed a mean tooth movement of 6.17mm (SD = 0.74). These findings were not statistically significant (Table 1B).

Experimental animals exhibited a mean weight change of -0.02kg (SD=0.37), while the control group had a mean weight change of 0.22kg (SD=0.09). There was no statistically significant difference in mean weight change (Table 2B).

Five of the experimental rabbits showed similar weight gains; however, two of the seven rabbits showed a weight decrease by the end of the 21-day period (Table 2A). All the control animals were found to increase body weight over the 21-day period (Table 2A).

Discussion

In the model represented in this study acetaminophen does not seem to retard orthodontic tooth movement, possibly related to its lack of anti-inflammatory properties. Nonsteroidal anti-inflammatory drugs which inhibit prostaglandin production have been shown to markedly reduce the rate of tooth movement in other animal mod-

els.[6,9-11] The existence of some tooth movement in these studies suggests that other pathways may be involved in tooth movement under mechanical stresses.

Acetaminophen's mode of action is believed to be concentrated in the central nervous system as opposed to the peripheral sites of action of NSAIDS.

Acetaminophen did not appear to impede tooth movement in normally growing test subjects. Two experimental rabbits failed to thrive, and these two rabbits also recorded the shortest tooth distance moved among the fourteen subjects. It is not clear whether the two "outliers" suffered toxic effects from the acetaminophen, were intrinsically ill, or had pain of such magnitude that feeding and growth were affected. Somatic growth may be a critical prerequisite for tooth movement in a rabbit model, as it is in humans. Anorexic or bulimic patients may display significantly less tooth movement than healthy patients. Clearly, malnutrition or the lack of bioavailability of essential nutrients can be retarding to growth and reparative systems. However, of all pilot test and control animals, both outliers were in the test groups, suggesting that intrinsic illness was not a factor.

The 1000 mgs/day dose of acetaminophen delivered to the rabbits was estimated from veterinarian protocol and previous acetaminophen studies to approach the maximum nontoxic dosage. There is no published maximum, nonulcerating or nontoxic dose of acetaminophen for rabbits. Maximizing the daily dose to a level just below toxicity would also maximize any possible effects on the rate of tooth movement. Based on our experience, it seemed our doses were near or about at the maximum nontoxic level for rabbits. In future studies, slightly lower doses of acetaminophen or larger numbers of test animals may minimize the impact of outliers.

Sandy and Harris, using the same 100 gram force on rabbit molars, found a considerable prostaglandin response.[10] Such a response can be blocked by an NSAID, such as indomethacin, and perhaps diminish tooth movement.[15] In the current study, acetominophen, which is not known to possess prostaglandin inhibition properties, showed no effect on clinical outcomes.

The conclusion from this study is model specific. Over a 21-day period of retracting a rabbit's incisor and protracting its molar reciprocally using 100 grams of force we found that acetaminophen had no effect on tooth movement. Although there may have been extrusive components to the observed tooth movements, no attempts were made to distinguish among the various planes of tooth movement.

Tooth movement by its nature initiates an inflammatory response that may include some degree of discomfort secondary to this response. A drug that relieves pain but does not alter the inflammatory response nor delay tooth movement would be ideal. The results of this preliminary study suggest that acetominophen may be such a drug. Although acetaminophen is thought to have some peripheral actions, these actions did not appear to influence the tooth movement in this model.

Further studies should compare aspirin, ibuprofen, acetaminophen, and a control, in the same or similar model, to determine which has the most favorable effect on the rate of tooth movement. Such information may be useful in application to clinical practice.

Conclusions

1. Acetaminophen has no effect on the rate of tooth movement in rabbits undergoing orthodontic tooth movement.
2. Acetaminophen, a proven analgesic that lacks the anti-inflammatory properties of NSAIDS, appears to be the drug of choice for the relief of orthodontic pain.
3. Some test subjects may have exhibited deleterious effects on somatic growth due either to acetominophen toxicity or to orthodontically induced pain.

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