Local application of zoledronate for maximum anchorage during space closure

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Introduction: Orthodontists have used various compliance-dependent physical means such as headgears and intraoral appliances to prevent anchorage loss. The aim of this study was to determine whether a local application of the bisphosphonate zoledronate could be used to prevent anchorage loss during extraction space closure in rats.

Methods: Thirty rats had their maxillary left first molars extracted and their maxillary left second molars protracted into the extraction space with a 10-g nickel-titanium closing coil for 21 days. Fifteen control rats received a local injection of phosphate-buffered saline solution, and 15 experimental rats received 16 μg of the bisphosphonate zoledronate. Bisphosphonate was also delivered directly into the extraction site and left undisturbed for 5 minutes. Cephalograms and incremental thickness gauges were used to measure tooth movements. Tissues were analyzed by microcomputed tomography and histology.

Results: The control group demonstrated significant (P <0.05) tooth movements throughout the 21-day period. They showed significantly greater tooth movements than the experimental group beginning in the second week. The experimental group showed no significant tooth movement after the first week. The microcomputed tomography and histologic observations showed significant bone loss in the extraction sites and around the second molars of the controls. In contrast, the experimental group had bone preservation and bone fill. There was no evidence of bisphosphonate-associated osteonecrosis in any sample. Conclusions: A single small, locally applied dose of zoledronate provided maximum anchorage and prevented significant bone loss. (Am J Orthod Dentofacial Orthop 2012;142:780-91)
The newest pharmacologic agents available for decreasing orthodontic tooth movement are the bisphosphonates, a class of synthetic drugs that limits bone resorption by inhibiting osteoclastic activity. Bisphosphonates are typically used to treat diseases of the bone such as osteoporosis, Paget’s disease, multiple myeloma, and metastatic bone cancer. Bisphosphonates are divided into 2 families: simple (nonnitrogen-containing) bisphosphonates and nitrogen-containing bisphosphonates. Various configurations of nitrogen-containing bisphosphonates create substantial increases in potency. The nitrogen-containing bisphosphonates first introduced (eg, pamidronate [Aredia] and alendronate [Fosamax]) were 10 to 100 times more potent than the simple nonnitrogen-containing bisphosphonates (eg, etidronate [Didronel]). The newest class of nitrogen-containing bisphosphonates has a heterocyclic ring (eg, zoledronate [Zometa]) and is up to 10,000 times more potent than etidronate.

Because of their effects on bone resorption, the clinical applications of bisphosphonates have been investigated in orthopedic surgery and dentistry. Bisphosphonate-coated orthopedic implants have significantly increased the mechanical fixation of orthopedic implants, accelerated the healing of fractures, improved fixation and bone volume surrounding orthopedic screws, and improved the stability of joint replacements. Bisphosphonates also have been used to treat periodontitis in rats and to prevent bone loss after mucoperiosteal flap surgery in rats. Bisphosphonates have been shown to reduce bone resorption, root resorption, ankylosis, and pulpal mineralization of reimplemented rat teeth after avulsion. They have recently been used to decrease skeletal relapse after maxillary expansion and mandibular distraction.

In orthodontics, bisphosphonates have been shown to reduce root resorption during tooth movements in rats. Bisphosphonates have also been used to decrease anchorage loss and postorthodontic relapse in rats. Two studies reported cessation of tooth movement in the experimental groups after the first week, and 3 others reported continued movement throughout the experiments. No previous study has demonstrated cessation of tooth movement with zoledronate. More importantly, the effects of bisphosphonates with the added strain on anchorage caused by tooth extraction has not been investigated.

The purpose of this study was to determine whether local application of the bisphosphonate zoledronate can provide maximum anchorage for extraction space closure in rats. Zoledronate was used because it is the most potent bisphosphonate available and has one of the highest bone affinities of all the bisphosphonates. These favorable pharmacokinetic characteristics should enable small doses of zoledronate to be used locally to minimize anchorage loss and unwanted side effects.

**MATERIAL AND METHODS**

A power analysis based on a conservative estimate of the standard deviations (0.6 mm) and effect sizes (0.7 mm) of orthodontic tooth movement previously reported in studies evaluating bisphosphonates showed that 15 rats per group were needed to obtain a power of 87% with an alpha at 5%. On that basis, 15 rats were randomly allocated to the experimental group, and 15 were allocated to the control group. Retired breeder adult male Sprague-Dawley rats (Harlan Laboratories, Indianapolis, Ind) were used and treated ethically in compliance with the regulations at Baylor College of Dentistry at Texas A&M Health Science Center in Dallas. The animals were acclimatized for at least 3 days before the experiment. They were fed a soft diet consisting of powdered rat chow (Harlan Laboratories), DietGel Recovery (ClearH2O, Portland, Me), HydroGel (ClearH2O), and water ad libitum, and were maintained in a room at 25°C with a 12-hour light and dark cycle. The animals were weighed at baseline (day 0) and every 7 days (days 7 and 14) until they were killed on day 21. A 21-day experimental period was chosen based on previous studies of tooth movements in rats.

After they were weighed, the rats were anesthetized with an intraperitoneal injection of xylazine (10 mg/mL), ketamine (100 mg/mL), and acepromazine (1 mg/mL). A 50-μL solution of phosphate-buffered saline, containing 16 μg of zoledronate (pH 7.0) or an equal volume of phosphate-buffered saline solution (pH 7.1) containing no zoledronate was injected into the experimental and control rats, respectively, by using a 3/10-mL syringe. The drug was injected by an operator (A.J.O.) who was blinded as to the contents of the syringes at 2 separate times to ensure that the bone adjacent to the tooth was adequately covered. Approximately one third of the solution was injected into the mesiopalatal and distopalatal aspects of the maxillary left second molar and the vestibule above the first molar. The maxillary left first molars of both the control and the experimental groups were then extracted by luxating the tooth with a 20.5-gauge needle. Accessible residual tooth roots were removed with a dental explorer. Great care was taken in removing the root tips; the root tips were left in place if it appeared that there was risk of damaging the bone in the extraction site. After extraction, another one third of the solution was injected into the same sites. The last one third of the solution was injected into the extraction site and left undisturbed for 5 minutes before appliance placement. A 1-minute lavage of zoledronate...
has been previously shown to be adequate; 5 minutes was chosen as the time to ensure adequate coverage and absorption into bone. Because of possible systemic effects of the zoledronate, no treatment was performed on the contralateral side.

An 0.008-in-diameter steel ligature was passed between the contact of the maxillary left second and third molars and twisted approximately 3 times to ensure that it was secure, but not tight, against the mesial aspect of the second molar. A 10-g closed-coil nickel-titanium spring (G&W Wire, Franklin, Ind; 0.006-in wire, 0.025-in lumen, 7 mm) was then attached to a free end of the steel ligature. The steel ligature was passed through the lumen of the spring at approximately the third coil to ensure adequate strength. Small retention grooves were cut into both maxillary central incisors (distofacially and distolingually) with a high-speed hand piece and a carbide bur. The mandibular incisors were trimmed weekly with a coarse diamond bur to ensure that they were out of occlusion and not at risk of breaking the appliance.

Another 0.008-in-diameter steel ligature was inserted into the free end of the spring at approximately the third coil, wrapped around the retention grooves on the maxillary central incisors, twisted, and cut to lie flat in the facial embrasure between the central incisors. Transbond (3M Unitek, Monrovia, Calif) self-etching primer was applied to the mesial and lingual surfaces of the second molar. Just enough Transbond XT (3M Unitek) was applied to the mesial and lingual surfaces to cover the wire and prevent it from slipping off the tooth. The cut end of the steel ligature was covered with a small amount of Transbond XT to prevent ulceration of the soft tissues. To ensure that the second and third molars were not inadvertently bonded together, free movement of the molars was confirmed with an explorer. One pediatric mandibular incisor stainless steel crown (3M Unitek) was cemented over the maxillary incisors with band cement (3M Unitek). Extra cement was added to the lingual surfaces to protect the spring from the mandibular incisors during mastication. All cements were cured according to manufacturer’s instructions by using a curing light. The same operator (A.J.O.) placed all appliances.

This appliance design provided 21 days of constant protraction of the maxillary left second molar into the extraction site of the first molar. One control appliance failed within the first week of placement and was immediately replaced.

Follow-up measurements were made every 7 days after appliance placement. The rats were anesthetized in a chamber with 3% isofluorane at a flow rate of 2 L/min of oxygen. Then the mandibular incisors were retrimmed with the diamond bur, and the appliances and soft tissues were checked. The rats always recovered from the anesthesia under an infrared thermal heater.

A cephalostat was used to ensure a constant distance of 6 in from source to sensor. Digital lateral cephalograms were taken with an x-ray unit (Intra; Planmeca U.S.A., Roselle, Ill) set at 60 kV and 6 mA for 0.080 seconds. A 10-mm metal bar was secured to the sensor to calibrate the images. Lateral radiographs were taken immediately after appliance placement and at 7, 14, and 21 days after appliance placement.

The animals were killed on day 21. They were anesthetized as on the day of appliance placement and killed by exsanguination. The tissues were fixed with 10% formalin. The mandibles were carefully dissected from the maxillae after decapitation. Photographs were taken, and the maxillae were stored in 10% formalin for the analyses.

The radiographs were randomized, and 1 operator (A.J.O.), blinded to group affiliations, made all measurements with imaging software (ImageJ, National Institutes of Health, Bethesda, Md) after calibrating each image with the 10-mm radiopaque bar.

Nasion (N, most anterior point on the nasal bone) and porion (Po, most posterior and superior point on the skull) were identified on each radiograph (Fig 1) by using landmark definitions previously described. The lines N-Po and occlusal plane were drawn, and a perpendicular line was constructed from N to intersect the occlusal plane (N'). A line perpendicular to N-Po was constructed through the most distal point of the wire (W) until it intersected the occlusal plane (W'). Measurement A was the distance N to a perpendicular from N-Po through W, measurement B was the distance N'-W', and measurement C was the distance from the most anterior-inferior point on the maxilla posterior to the incisors to W. Duplicate measurements were made by a blinded operator (A.J.O.), and the averages of the 2 measurements were used for the statistical analyses.

After the rats were killed, gross interdental tooth movements were measured by a blinded operator (A.J.O.) with incremental thickness gauges (Align Technologies, Santa Clara, Calif). The gauges were 0.10, 0.20, 0.25, 0.30, 0.40, or 0.50 mm thick. To measure total tooth movement from baseline to day 21, the gauges were placed between the contact points of the maxillary left second and third molars. The thickest gauge or combination of gauges that could be inserted without moving the teeth was used and recorded. If the 0.10-mm gauge did not fit between the teeth, 0.0 mm of movement was recorded. Two measurements were taken for each animal and averaged.
Three animals from both the control and experimental groups were randomly chosen for microcomputed tomography and histologic analyses. The steel ligature was removed from the second molar, and the section of the alveolus from the distal aspect of the third molar to the mesial aspect of the extraction site was excised with a thin diamond table saw. The samples measured approximately $15 \times 5 \times 5$ mm. The samples were scanned with microcomputed tomography (model 35; Scanco Medical, Basserdorf, Switzerland) with an isotropic resolution of $12\mu$m. X-ray energy levels were set to $55\text{kVp}$, the current was set to $145\text{mA}$, and the integration time was $400\text{ms}$.

The same 6 samples were then decalcified in 0.5 mol/L of EDTA in a microwave for 3 weeks. After decalcification, the samples were dehydrated, embedded in paraffin, and sectioned by using conventional methods at a thickness of $6\mu$m. The samples were stained with Harris hematoxylin and eosin Y alcohol (H&E stain) and mounted on glass slides for evaluation.

**Statistical analysis**

By using statistical software (SPSS, Chicago, Ill), intraexaminer reliability was evaluated based on comparisons of 120 replicate measurements. Systematic errors, evaluated by using Wilcoxon tests, ranged from $-0.0033$ to $-0.0298$ mm and were not statistically significant. Method error, quantified with the method error statistic ($\sqrt{\sum d^2}/n$), ranged from $0.0295$ to $0.0316$ mm. Single measures intraclass correlations ranged from 0.997 to 0.999. Intergroup comparisons were analyzed with the Mann-Whitney test, and changes over time were evaluated with Wilcoxon tests.

**RESULTS**

There was no statistically significant difference in weights between the groups at baseline. The experimental group did show significantly greater weight gains during the second week (days 7-14) than did the control group (Table I). There were no other statistically significant group differences in weight over time. At day 21, the controls returned to their initial weights; the experimental animals finished 21 g heavier than their initial weights, but the group differences at day 21 were not statistically significant ($P = 0.098$).

Line N-Po showed slight increases ($<0.2$ mm) over the experimental period, but no changes that occurred over time were statistically significant for either the

<table>
<thead>
<tr>
<th>Days</th>
<th>Control animals Mean</th>
<th>Control animals SD</th>
<th>Experimental animals Mean</th>
<th>Experimental animals SD</th>
<th>Group differences P</th>
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<td>$-29.53^*$</td>
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<td>0-21</td>
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<td>36.97</td>
<td>$21.07^*$</td>
<td>35.78</td>
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</table>

*Significant ($P < 0.05$) change over time.

Fig 1. Cephalometric measurements based on landmarks: N, The most anterior point on the nasal bone; W, the most distal end of the wire around the second molar; Po, the most posterior and superior point on the skull; Oc, the occlusal plane along the maxillary molars; N’, the intersection of the perpendicular from N to Oc; W’, the intersection of the perpendicular from N to Oc; lu, the most anterior-inferior point on the maxilla posterior to the maxillary incisors; and W”, a perpendicular from N-Po through W.
control or the experimental group (Table II; Fig 2). Both group exhibited statistically significant initial (baseline-day 7) tooth movements, with no significant group differences. The controls had statistically significant decreases in space for all 3 measurements (A, B, and C) over every time interval. For the experimental animals, measurement A demonstrated significant movements from baseline to day 14 and from baseline to day 21; these were due to the initial changes (baseline-day 7); the changes from days 7 to 14 and 14 to 21 were small and not statistically significant. With the exception of the initial change (baseline-day 7), no other changes of measurement B were statistically significant. The experimental animals had an initial decrease in measurement C, followed by a statistically significant increase in space between days 7 and 14. The significant decreases in space that occurred in measurement C from baseline to day 14 and from baseline to day 21 were again due to the initial (baseline-day 7) changes. There were consistent and statistically significant group differences in tooth movements for measurements A, B, and C over days 7 to 14, days 14 to 21, baseline to day 14, and baseline to day 21. There was also a statistically significant difference between the groups for the gross interdental tooth movements, with the control and experimental animals averaging 0.62 and 0.07 mm of separation, respectively.

Both groups showed signs of delayed healing or ulcers at the extraction sites, but there were no clinical signs of osteonecrosis (Fig 3). There were no signs of infection or exposed necrotic bone in any of the 30 animals. In the control animals, a diastema developed between the mesial aspect of the third molar and the distal aspect of the second molar. Diastemas did not develop in the experimental animals. Retained food debris and hair were found around the appliances and in the extraction sites in some control and experimental animals. Compared with the untreated side, there appeared to be some mesial movement of the third molar on the treated side of the control group, and the alveolar bone on the experimental side at the extraction site of the controls appeared to be wider and higher than the bone on the untreated side.

The microcomputed tomography images showed substantial differences between the control and experimental groups (Fig 4). Compared with the experimental animals, the controls had (1) diastemas between the second and third molars, (2) severely reduced alveolar heights, (3) moderately reduced alveolar widths, (4) thinner cortical bone and remodeling at the extraction sites.

### Table II. Radiographic tooth movements (in millimeters) over the 21-day experimental period

<table>
<thead>
<tr>
<th>Days</th>
<th>Control animals</th>
<th>Experimental animals</th>
<th>Group differences</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
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<tr>
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<tr>
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<td>0.10</td>
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<td>0.18</td>
</tr>
<tr>
<td><strong>Measurement A</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0-7</td>
<td>−0.18*</td>
<td>0.24</td>
<td>−0.23*</td>
</tr>
<tr>
<td>7-14</td>
<td>−0.21*</td>
<td>0.17</td>
<td>0.07</td>
</tr>
<tr>
<td>14-21</td>
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<td>0.30</td>
<td>0.05</td>
</tr>
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<td>−0.168*</td>
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<td>0.45</td>
<td>−0.118*</td>
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<td><strong>Measurement B</strong></td>
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<td>0.08</td>
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<td>14-21</td>
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<td>0.25</td>
<td>0.07</td>
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<td>0-14</td>
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<td>0-21</td>
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<tr>
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<tr>
<td>7-14</td>
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*Significant (P <0.05) change over time.
(5) furcation involvement of the second and third molars, and (6) mesial tipping and extrusion of the second molars.

Histologically (Fig 5), the controls showed a thick band of fibrous connective tissue running along the apices of the second and third molars, from the distal aspect of the third molar to the mesial limit of the extraction site. In the control animals, the extraction site resembled a large crater filled with fibrous connective tissue; there was connective tissue in the tooth sockets of the controls. Bone loss involving the furcation of the second molar was evident. In contrast, the experimental sections showed some periodontal ligament widening but no bands of fibrous connective tissue, as seen in the controls. There was interproximal bone in the second and third molars, and in the extraction sites of the experimental animals.

There was also significant modeling of the bone around the apices of the teeth in the controls (Fig 6, A), as well as significant root resorption on the mesial surface of the distal root of the second molar (Fig 6, B). In the experimental animals, interproximal and furcation bone heights were maintained, and there were no signs of root resorption or bone remodeling, despite the stretched periodontal ligament on the tension side (Fig 6, C).

**DISCUSSION**

In this study, we demonstrated that a single low-dose application of the bisphosphonate zoledronate provides maximum anchorage by preventing bone resorption. The zoledronate maintained the bone in the furcation of the second molar and in the interproximal bone between the first and second molars. Previous studies have shown dose-dependent reductions in orthodontic tooth movement with various bisphosphonates, including risendronate (Actonel), AHBuBP,27 clodronate (Bonefos), pamidronate (Aredia), alendronate (Fosamax),24,29 and zoledronate (Zometa, Aclasta, and Reclast).26 After the initial movements during the first 7 days, 2 studies showed cessation of movement.8,27 Liu et al, whose study most closely compares with ours, reported a small but significant difference in orthodontic tooth movement between the control (0.34 mm) and experimental (0.21 mm) rats, but they failed to show cessation of tooth movement after 21 days. However, they used 50 µL of 500 µmol/L zoledronate, administered 11 times during the experiment, resulting in a total dose that was 6.9 times greater than the dose of our study. It is possible that our study had a more significant effect because the dose was sufficiently high to prevent bone resorption, yet sufficiently low that osteoblast...
viability and angiogenesis were not impeded. The low dose might also explain why the alveolar bone did not undergo necrosis. Importantly, the group differences could not be explained by loosening of the applied forces; the trimmed mandibular incisors prevented the anterior teeth from occluding, and the stainless steel crown cemented over the maxillary incisors maintained the appliances similarly in both groups.

Because of its viscoelastic properties, the periodontal ligament surrounding rat maxillary molars is resistant to displacement during the first hour after force application. In an in-vivo microcomputed tomography study of the effects of force on tooth movements in rats, Gonzales et al reported approximately 0.01 mm of periodontal ligament compression within 1 hour of application of 10 g of force. Nakamura et al also reported only slight changes in periodontal ligament thickness 1 hour after loading a rat molar with 10 g, with significant changes appearing 6 hours after appliance placement. On that basis, it can be assumed that the initial (baseline) radiograph (taken immediately after appliance placement) captured a nondisplaced periodontal ligament.

The initial movements from baseline to day 7 were small and similar for both control and experimental groups. Similar changes have been previously reported during the first week of tooth movement. They can be explained by compression of the second molar’s periodontal ligament, which has been reported to range between 0.10 and 0.15 mm. The periodontal ligament would not be expected to be affected by zoledronate because bisphosphonates target calcified tissues. These observations suggest that, despite the added strain on anchorage because of the regional acceleratory phenomenon associated with extractions, zoledronate prevented orthodontic tooth movement in the experimental group.

Although we only quantified the mesial migration of the second molar, the microcomputed tomography images showed a pattern of mesial tipping, extrusion of the distal roots, and intrusion of the mesial root of the controls, presumably from the combined effects of tooth movement and severe bone loss around the second molar (Fig 4). There appeared to be no such effect in the experimental animals. The fact that the results were based on small subsamples randomly chosen from the larger sample limits the ability to generalize the results. Our results are consistent with the tooth movements reported by Gonzales et al. The results also support literature showing that control animals exhibit moderate root resorption (Fig 6, B), whereas experimental
animals receiving bisphosphonates show little or no root resorption (Fig 6, C).\(^8,24,27\)

Doses smaller than the 16 \(\mu\)g of zoledronate used in this study might produce similar results. Using zoledronate-coated orthopedic implants, Peter et al\(^{11}\) demonstrated increasing implant osseointegration in healthy rats of 0.2 to 2.1 \(\mu\)g per implant. We might have achieved similar results with local applications of zoledronate as low as 0.2 \(\mu\)g.

Importantly, a pronounced reduction in alveolar bone loss resulted from the application of a small dose of zoledronate directly into the extraction site. Although...
it was left undisturbed for 5 minutes, an even shorter amount of time might have proven to be effective. Skoeglund et al\textsuperscript{42} demonstrated that fixation of a stainless steel screw in the tibiae of rats was significantly enhanced by a single dose of ibandronate directly applied to the pilot hole before insertion of the screw. Miettinen et al\textsuperscript{30} showed that a 20-\textmu mol/L zoledronate solution applied for only 1 minute was effective for enhancing the osseointegration of titanium implants in rats.

Recent studies have suggested that bisphosphonate-associated osteonecrosis of the jaws develops from toxicity of bisphosphonates released from the bone after injuries such as dental extractions.\textsuperscript{35,43} Soft-tissue toxicity results in delayed epithelialization of the injury site and subsequent secondary infection of the exposed bone by oral bacteria, ultimately leading to bisphosphonate-associated osteonecrosis of the jaws. In our study, delayed healing was observed in both groups, but none of the 30 rats showed signs of osteonecrosis. The rat with the most complete healing of the extraction site was in the experimental group (Fig 3).

The control rats had severe bone loss, whereas the zoledronate group preserved their original bone heights and showed evidence of bone fill (Fig 5), probably due to enhanced osteoblast proliferation and function.\textsuperscript{33,44,45} Despite initial suppression of new bone formation 5 days after extraction,\textsuperscript{26} bisphosphonates have been shown not only to significantly prevent the postextraction resorption of buccal and lingual bone in rats,\textsuperscript{46} but also to increase new bone formation 10 days after extraction in rats\textsuperscript{47} and 8 weeks postextraction in dogs.\textsuperscript{48} Moreover, the extraction methods used could have resulted in bone loss, suggesting that the rats in the experimental group added new bone to maintain their original bone heights; the extractions by themselves could not have played a role in the group differences observed because of random group assignments.

The severe bone loss in the control animals was probably due to at least 3 factors. First, an acute inflammatory reaction around the second molar might have induced periodontal bone loss.\textsuperscript{16,17,49} Although induction of acute periodontitis was not an aim of this study, it is possible that the steel ligature and resin placed around the second molar served as a plaque trap and caused an acute inflammation. Orthodontic tooth movement in an environment of uncontrolled inflammation is known to exacerbate periodontal bone loss, which might help to explain the severe bone loss in the control group.\textsuperscript{50} In contrast, this study demonstrated that zoledronate prevented bone loss, thus adding to the various bisphosphonates, including alendronate (Fosamax),\textsuperscript{51} risedronate (Actonel),\textsuperscript{49}

\textbf{Fig 5.} Histologic comparisons of the control (left) and experimental (right) animals. The controls show remarkably more fibrous connective tissue and bone resorption in the furcation of the second molar (\textit{closed arrowheads}), no interproximal bone between the first and second molars, and no bone in the extraction socket. The experimental group shows maintenance of bone height and bone fill in the extraction socket (\textit{*}) and residual root tips (\textit{open arrowheads}).
clodronate (Bonefos), and TRK-530, that have been used to prevent experimentally induced periodontal bone loss. The second factor that might have contributed to the severe bone loss in the control group was the extrusion of the second molar, which could have caused secondary occlusal trauma and accelerated the bone loss. Third, the force applied to the single molar was disproportionately large and could have contributed to the severe bone loss. It has been estimated that a human molar is 20 times larger than a rat molar, so a 10-g force applied to a rat molar corresponds to a force of approximately 200 g in a human. Despite the large and consistent group differences that were observed, the ability to generalize these results is limited by the small sample sizes.

There are 3 primary concerns regarding the use of zoledronate that must be allayed before bisphosphonates can be used in dentistry. First, there are concerns regarding their possible adverse effects on growth. Applications of bisphosphonates in animal models have thus far shown no negative effects on growth or on bone away from the site of application. Bisphosphonates used to treat children with osteogenesis imperfecta do not appear to impair bone growth.

The second concern pertains to the risk of bisphosphonate-associated osteonecrosis of the jaws. In adults, it has been shown that bisphosphonate-associated osteonecrosis of the jaws is caused by a confluence of factors and not simply by the administration of the drug, even at high doses. With respect to the use of bisphosphonates in children, there are currently no cases of bisphosphonate-associated osteonecrosis of the jaws related to orthodontic tooth movement. Also, children with osteogenesis imperfecta treated with intravenous bisphosphonates (a high risk factor for developing bisphosphonate-associated osteonecrosis of the jaws) have not developed bisphosphonate-associated osteonecrosis of the jaws, even after extractions to facilitate orthodontic treatment. It appears that the development of bisphosphonate-associated osteonecrosis of the jaws is associated with comorbidities, which can affect bone metabolism, healing, and the body’s immune response. Recent attempts to establish an animal model have shown that administration of zoledronate or other bisphosphonates alone is not sufficient to induce bisphosphonate-associated osteonecrosis of the jaws, even at doses much higher and more frequent than those used in this study. There is presently no evidence of bisphosphonate-associated osteonecrosis of the jaws in healthy rats treated with zoledronate alone. Longer periods of time might also be necessary to induce bisphosphonate-associated osteonecrosis of the jaws.

The final concern pertains to the exceptionally long half-life of bisphosphonates, suggesting that zoledronate could have residual effects years after administration. The high bone affinity of zoledronate enables it...
to strongly attach to bone, where it is stored in an inactive form. Because bisphosphonates only affect osteoclasts when the drugs are incorporated into the cell, they are active only when osteoclasts resorb zoledronate-laden bone. Otherwise, the bisphosphonate remains attached to the bone and is released only during times of active remodeling. Because remodeling of bone usually occurs slowly after the administration of the drug, small amounts of the drug can be detected in plasma and urine many weeks or months after its discontinuation.62 In areas of greater bone turnover, such as the alveolar region, zoledronate should be released more quickly, with the amounts remaining in bone decreasing more rapidly over time. Regardless, future studies evaluating the safety, efficacy, minimum effective dose, biodistribution, and distant effects of local delivery are needed to determine the clinical potential of zoledronate.

CONCLUSIONS

1. A single, small, locally applied dose of zoledronate was sufficient to provide maximum anchorage in extraction space closure.
2. Zoledronate prevented severe periodontal bone loss at the extraction site and around the second and third molars.
3. There were no signs of bisphosphonate-associated osteonecrosis of the jaws in any rat.

REFERENCES

26. Liu C, Sun X, Chen Y, Hu M, Liang T. The effects of local administration of zoledronate solution on the tooth movement and


