Effect of Sodium Alendronate on Alveolar Bone Resorption in Experimental Periodontitis in Rats

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Background: Bisphosphonates are potent inhibitors of bone resorption and were shown to inhibit bone resorption in experimental periodontitis by unknown mechanisms. We studied the effect of the aminobisphosphonate sodium alendronate (SA) in experimental periodontitis. Wistar rats were subjected to ligation placement around the second upper left molars.

Methods: Animals were treated with SA 0.01 to 0.25 mg/kg subcutaneously (sc), either 1 hour before (prophylactic) or starting 5 days after (therapeutic) periodontitis induction and daily until the rats were sacrificed (11 days). Controls received saline. Animals were weighed daily. Alveolar bone loss was measured as the difference (in millimeters) between the cusp tip and the alveolar bone. The periodontium and the surrounding gingivae were examined at histopathology, and the neutrophil influx into the gingivae was assayed using myeloperoxidase activity. The local bacterial flora was assessed through culture of the gingival tissue in standard aerobic and anaerobic media.

Results: Alveolar bone loss was significantly and dose dependently inhibited by SA either as a prophylactic or therapeutic treatment compared to the control. SA reduced tissue lesion at histopathology, with partial preservation of the periodontium, coupled to decreased myeloperoxidase activity compared to the control. The reduced neutrophil influx was also shown in carrageenan-induced peritonitis, used as a control experiment for this parameter. SA also significantly inhibited the growth of pigmented bacilli and Fusobacterium nucleatum, which are important in the pathogenesis of periodontal disease. SA also inhibited the in vitro growth of isolated Peptostreptococcus sp.


KEY WORDS

Alendronate, sodium; bone resorption; inflammation; periodontitis.
display antimicrobial activity. Recently, it was demonstrated that sodium alendronate inhibited the in vitro growth of Streptococcus mutans,\textsuperscript{8} Staphylococcus aureus, and Pseudomonas aeruginosa,\textsuperscript{9} as well as of the protozoan Trypanosoma cruzi.\textsuperscript{10}

Periodontitis, a relevant cause of tooth loss in adults,\textsuperscript{11,12} is a chronic inflammatory disease that is characterized by localized bone resorption.\textsuperscript{13,14} The pathogenesis of periodontitis involves the presence of a bacterial plaque that may initiate a local inflammatory reaction in predisposed hosts. This leads to edema, leukocyte infiltration, and the release of inflammatory mediators, causing periodontal pocket formation, connective tissue detachment, and alveolar bone resorption, ultimately leading to tooth loss.\textsuperscript{15}

Previous studies have shown that BPs are effective in preventing alveolar bone loss in experimental periodontitis.\textsuperscript{1,3,12-14,16,17} The exact mechanism of action of these drugs in periodontitis is not yet clarified. In the present study, we present evidence that the prevention of alveolar bone resorption by sodium alendronate is, at least in part, due to its anti-inflammatory and antimicrobial properties.

**MATERIALS AND METHODS**

**Animals**

One hundred and fourteen female Wistar rats (160 to 200 g) from our own animal facilities were housed in temperature-controlled rooms and received water and food \textit{ad libitum}. All experiments were conducted in accordance with local guidelines on the welfare of experimental animals and with the approval of the Committee of Ethics in Animal Research of the Federal University of Ceará.

**Induction of Inflammatory Periodontal Disease**

A sterilized nylon (000) thread ligature was placed around the cervix of the second upper left molar of rats anesthetized with 10% chloral hydrate (400mg/kg intraperitoneally [ip]), as described elsewhere.\textsuperscript{18} The ligature was knotted on the buccal side of the tooth, resulting in a subgingival position palatinally and supragingival position buccally. The contralateral right side was used as the unligated control.\textsuperscript{19} Animals were weighed daily.

**Measurement of Alveolar Bone Loss**

The animals were sacrificed on day 11 of periodontitis induction by an overdose of ether and had their maxillae excised and fixed in 10% neutral formalin. Both maxillary halves were then defleshed and stained with aqueous methylene blue (1%) to differentiate bone from teeth. The horizontal alveolar bone loss, the distance between the cusp tip and the alveolar bone, was measured using a modification of the method of Crawford et al.\textsuperscript{20} as described by Samejima et al.\textsuperscript{19} Measurements were made along the axis of each root of the first (three roots), second, and third molar teeth (two roots). The total alveolar bone loss (in millimeters) was obtained by taking the sum of the recordings from the buccal tooth surface and subtracting the value of the right maxilla (unligated control) from the left maxilla.

**Drug Treatments**

In an initial experiment, 18 animals subjected to experimental periodontitis (see above) were divided into three equal groups of six animals to receive 0.01, 0.05, or 0.25 mg/kg body weight of sodium alendronate\textsuperscript{1} subcutaneously (sc), starting 1 hour before periodontitis induction and daily until sacrifice on day 11 (prophylactic treatment). Saline (0.2 ml) or SA (0.25 mg/kg) was administered after the periodontitis induction from day 5 and daily for 11 days (therapeutic treatment). Data represent the mean ± SE of six rats for each group. *P < 0.05 was considered significantly different compared to the saline group; †P < 0.01 was significantly different compared to SA 0.01 mg/kg (ANOVA; Bonferroni’s test).

**Histopathologic Analysis**

Three other groups of animals were subjected to periodontitis and received either saline sc (saline group) and a group of six rats that received no manipulation (naive group).

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treatment and were used for the histolopathological study. The excised maxillae were fixed in 10% buffered formalin and demineralized in a 7% nitric acid solution, followed by dehydration and paraffin embedding. The specimens were stained either with hematoxylin and eosin (H&E) or Mallory trichrome. Sections of 6 μm thickness, corresponding to the area between the first and second molars where the ligature had been placed, were evaluated under light microscopy. The analysis considered scores of 0 to 3 as follows: score 0, absence of or only mild cellular infiltration (the inflammatory cellular infiltration is sparse and restricted to the region of the marginal gingiva), preserved alveolar process, and cementum; score 1, moderate cellular infiltration (the inflammatory cellular infiltration is present all over the inserted gingiva), minor alveolar process resorption, and intact cementum; score 2, severe cellular infiltration (the inflammatory cellular infiltration is present in the gingivae and the periodontal ligament [PL]), extensive degradation of the alveolar process, and partial destruction of cementum; and score 3, severe cellular infiltrate, total destruction of the alveolar process, and severe destruction of the cementum.

Buccal Gingival Analysis

Animals were treated 1 hour before the periodontitis induction with sodium alendronate (0.25 mg/kg) or saline (0.2 ml) sc. Six hours after the surgical procedure, rats were sacrificed under terminal anesthesia. In another group of animals, sodium alendronate (0.25 mg/kg) was administered starting at day 5 and daily until sacrifice on day 11. The buccal gingivae from the area surrounding the upper left molars were removed, fixed in 10% neutral formalin, and paraffin embedded. Sections of 4 μm thickness were stained with hematoxylin and eosin and evaluated under light microscopy.
Measurement of Neutrophil Influx
The myeloperoxidase (MPO) activity in the gingival tissue, collected 6 hours after periodontitis induction of rats that received either prophylactic sodium alendronate (0.25 mg/kg/day ip) or saline ip, was determined as a measurement of neutrophil accumulation. A spectrophotometric assay was used to measure MPO activity, as described previously.21 The buccal gingivae surrounding the upper left molars were removed and stored at −70°C. The material was suspended in 0.5% hexadecyltrimethylammonium bromide (HTAB) in 50 mm potassium phosphate buffer, pH 6.0, to solubilize MPO. After being homogenized in an ice bath (15 seconds), the samples were freeze-thawed twice. Additional buffer was added to the test tube to reach 400 μl buffer per 15 mg tissue for 12 minutes. After centrifuging (1000 g/12 minutes), 0.1 ml supernatant was added to 2 ml 50 mm phosphate buffer, pH 6.0, containing 0.167 mg/ml o-dianisidine dihydrochloride, destilled water, and 0.0005% hydrogen peroxide to give a final volume of 2.1 ml per tube. The absorbance was measured spectrophotometrically (460 nm). One unit of activity was defined as that degrading 1 μmol peroxide/minute at 25°C. Results are expressed in myeloperoxidase units per milliliters. Staining of smears for MPO activity was performed by the method of Kaplow.22

Microbiological Analysis
Groups of rats subjected to periodontitis received either sodium alendronate (0.25 mg/kg/day ip) therapeutically or saline ip daily, until sacrifice, at 11 days. The buccal gingivae surrounding the upper left molars were removed and placed in 0.3 ml of brain heart infusion (BHI) broth. The total transfer time to the microbiology laboratory was less than 1 hour. Immediately after transfer, the collected fragment was homogenized and plated in 1:100 and 1:1000 dilutions. A spectrophotometric assay was used to determine MPO activity, as described previously.21 The microbiology laboratory was less than 1 hour. Im-
mediately after transfer, the collected fragment was homogenized and plated in 1:100 and 1:1000 dilutions into Bacteroides bile-esculin agar, phenethyl alcohol agar, and brain heart infusion agar (supplemented with 5% defibrinated sheep blood and hemin/menadione 10 μg/ml). The anaerobic environment was obtained using commercially available kits for anaerobiosis. Suspected organisms were transferred to brain heart infusion broth and the strains were identified by established methodology.23 To verify the antimicrobial activity of sodium alendronate in vitro, Peptostreptococcus sp. was isolated from the gingival tissue of rats subjected to periodontitis. A subculture was made by passing a small inoculum (0.6 ml) into tubes with BHI containing medium alone or medium with sodium alendronate (28 mg/ml). Twenty four hours later the turbidity of the medium of each tube was compared to the McFarland standard. Peptostreptococcus sp. (ATCC 27337) and Fusobacterium nucleatum (ATCC 25586) were used as controls in the experiments.

Peritonitis
As shown below, our data revealed that sodium alendronate prevented the neutrophil infiltration observed in the gingival tissue of rats subjected to periodontitis. To demonstrate that this effect was not specifically linked to the periodontal tissue, we investigated the effect of sodium alendronate on the neutrophil influx in the carrageenan-induced peritonitis. Briefly, 1 ml carrageenan (300 μg/cavity) or saline was injected ip in naïve rats or in rats that received sodium alendronate (0.25 mg/kg) 1 hour prior to the carrageenan. The animals were sacrificed 4 hours after the ip injection of carrageenan, and the peritoneal cells were harvested by washing the cavities with 10 ml phosphate buffered saline (PBS) containing 5 U heparin/ml. The total and differential cell counts were performed as described elsewhere.24,25 The results are reported as the number of leukocytes and neutrophils per milliliters of exsudate.

Statistical Analysis
The data are presented as the mean ± SE or as the medians, where appropriate. A univariate analysis of variance (ANOVA) followed by Bonferroni’s test was used to compare means, and the Kruskal-Wallis test was used to compare medians. A probability value of P<0.05 was considered to indicate significant differences.

RESULTS
Effect of Sodium Alendronate on Experimental Periodontal Disease in Rats
Sodium alendronate, injected 1 hour before periodontitis induction and daily until day 11 (prophylactic treatment), caused a significant (P<0.05) and dose-dependent inhibition of the alveolar bone loss compared to the saline-treated rats. The most effective prophylactic dose of sodium alendronate, when administered therapeutically, i.e., starting 5 days after induction of the periodontitis until 11 days, also significantly inhibited (P<0.05) the alveolar bone loss compared to saline-treated rats (Fig. 1). Compared to the normal periodontium of a rat (Fig. 2A), the

Table 1.

Histologic Analysis of Rat Maxillae With Experimental Periodontitis

<table>
<thead>
<tr>
<th>Group</th>
<th>Saline</th>
<th>Prophylactic</th>
<th>Therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scores</td>
<td>3 (2-3)</td>
<td>0 (0-1)*</td>
<td>1 (1-1)*</td>
</tr>
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* P<0.05 compared to saline-treated animals (Kruskal-Wallis).
histopathologic analysis of the region between the first and second molars of the periodontium of animals subjected to experimental periodontitis (saline group) exhibited accentuated inflammatory cell infiltration, destruction of alveolar bone and collagen fibers of PLo, and intense resorption of cementum (Fig. 2B), receiving a median score of 3 (2-3) (Table 1). The periodontium of rats treated with sodium alendronate (0.25 mg/kg), as prophylactic and therapeutic treatments showed preservation of the alveolar process and cementum, partial preservation of collagen fibers of periodontal ligament, and a reduction of the inflammatory cell infiltration (Figs. 2C and 2D), receiving median scores of 0 (0-1) and 1 (1-1), respectively (Table 1). These values were statistically different ($P < 0.05$), when compared to the saline group.

The histologic analysis of the gingivae of rats subjected to periodontitis that received saline showed an intense inflammatory cell infiltrate with predominance of neutrophils 6 hours after the induction of periodontitis (Fig. 3B) and predominance of mononuclear cells on day 11, together with areas of hemorrhage and edema (Fig. 3D) compared to the naive group (Fig. 3A). Similar to what was observed in the periodontium, animals treated with sodium alendronate also displayed a significant reduction in the cell infiltration, regardless of the therapeutic strategy (Figs. 3C, 3E, and 3F). The reduction of the cell infiltration was further substantiated by a significant decrease in the myeloperoxidase activity in the gingival tissue compared to saline-treated rats. Analysis of the buccal gingivae of animals that received sodium alendronate...
prophylactically revealed a significant \( (P < 0.001) \) reduction of myeloperoxidase activity compared to saline-treated rats (Fig. 4). There was also a statistical difference \( (P < 0.05) \) between the naive group and the other groups with periodontitis that received treatment with SA or saline.

**Effect of Sodium Alendronate on Polymorphonuclear Migration in Carrageenan Peritonitis**

The ability of sodium alendronate to reduce the neutrophil influx seen in the periodontitis model was confirmed in the carrageenan-induced peritonitis. Animals that received prophylactic sodium alendronate displayed a significant inhibition of neutrophil recruitment into the peritoneal cavity compared to saline-treated rats (Fig. 5).

**Antibacterial Effect of Sodium Alendronate in Bacteria Involved in Experimental Periodontal Disease in Rats**

In the gingival tissue of rats subjected to the experimental periodontal disease and treated with saline, *F. nucleatum* and Gram-negative pigmented bacilli were identified in 100% of the animals (Table 2). Sodium alendronate, given therapeutically, inhibited the growth of bacteria characteristic of periodontal disease, such as *F. nucleatum* and Gram-negative pigmented bacilli. The local bacterial flora of the animals treated with sodium alendronate was significantly changed so that it resembled that of naive rats. Actually, Gram-negative pigmented bacilli were no longer detected, and *F. nucleatum* was identified in only 23% of sodium alendronate-treated animals.

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**Figure 4.**

*Effect of SA on the absorbance variation in assay of myeloperoxidase.* SA (0.25 mg/kg) or saline (0.2 ml) was injected sc 1 hour before the periodontitis induction. After 6 hours, the animals were sacrificed, and the buccal gingivae from the left upper molar region were removed. MPO was assayed spectrophotometrically after 30 seconds and 1 and 3 minutes from the beginning of colorimeter reaction by the method of Kaplow. **A** Curves represent the absorbance variation according to time. **B** Bars represent the mean \( \pm \) SE of the area under the curve value. *P < 0.001* was considered significantly different compared to the naive group; †P < 0.001 was considered significantly different in relation to saline group (ANOVA; Bonferroni’s test).

**Figure 5.**

*Effect of SA on the leukocyte and neutrophil migration in the peritonitis model.* SA (0.25 mg/kg) or saline (0.2 ml) was administered sc 30 minutes before peritonitis induction by injection of 1 ml carrageenan (Cg, 300 \( \mu \)g/ml ip). After 4 hours, animals were sacrificed, and 6 ml peritoneal washing fluid was harvested. There were significant reductions in the number of leukocytes (A) and neutrophils (B) in the peritoneal cavities of the group treated with SA. Bars represent mean \( \pm \) SE. *P < 0.001* (ANOVA; Bonferroni’s test).
Sodium alendronate inhibited the growth of *Peptostreptococcus* sp. in BHI resulting in turbidity equivalent to a two McFarland standard compared to the control tube (BHI without sodium alendronate), which presented turbidity equivalent to that of a 10 McFarland standard.

The weight loss that is characteristically seen in the animals subjected to the experimental periodontitis was reversed by the administration of sodium alendronate when the compound was given prophylactically and therapeutically (Fig. 6).

**DISCUSSION**

In the present study, we have demonstrated that treatment with the bisphosphonate sodium alendronate, given either as a prophylactic or therapeutic intervention, significantly prevented the inflammatory changes and alveolar bone loss typically seen in rats subjected to an experimental periodontal disease. Furthermore, weight loss was also prevented in the animals that received sodium alendronate compared to vehicle-treated animals, regardless of the administration strategy. Our data are in accordance with previous studies showing the beneficial effect of bisphosphonates on experimental periodontal disease.

The macroscopic analysis of the alveolar bone was confirmed at the tissue level by the histopathological analysis, demonstrating partial preservation of the alveolar bone, cementum, and periodontal ligament in the animals that received sodium alendronate.

The ability of bisphosphonates to inhibit bone resorption is well described in the literature. This effect prompted the use of these compounds in various disease states such as postmenopausal osteoporosis, corticosteroid-induced osteoporosis, hypercalcemia of malignancy, and pain associated with bone metastasis. The mechanisms of this bone-sparing effect of the bisphosphonates are yet to be clarified. Data from the literature showing that these compounds are able to inhibit osteoclast differentiation and osteoclast bone resorption mediated by the osteoblasts and to induce apoptosis of osteoclasts suggest a direct effect of bisphosphonates on bone cells.

In the present study, the neutrophil influx into the inflamed gingivae was significantly reduced by sodium alendronate. Moreover, sodium alendronate also inhibited the neutrophil influx seen in carrageenan-induced peritonitis. Neutrophils are important cells in host defense against infecting bacteria. However, these cells have also been linked to tissue destruction in a number of inflammatory diseases such as rheumatoid arthritis and periodontitis. Actually, the lysosomal enzymes and reactive nitrogen/oxygen radicals that are important in the host defense response were found to be decreased in neutrophils from rats treated with sodium alendronate.

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defense against invading microorganisms may also be responsible for tissue lesion in some disease states. The reduction of neutrophil infiltration was confirmed by the measurement of the myeloperoxidase activity in the gingival tissue, a neutrophilic enzyme whose activity was shown here to be greatly increased in the gingivae of animals submitted to periodontal disease. These data are consistent with a previous study that demonstrated a reduction of the myeloperoxidase activity by the non-chlorinated bisphosphonate etidronate, just like sodium alendronate. Further, a previous report showed that the aminobisphosphonate icandronate significantly reduced the neutrophilic influx into the gingivae of rats subjected to Porphyromonas gingivalis-induced periodontitis. Moreover, in addition to the inhibitory effect of SA on neutrophil infiltration, we found that sodium alendronate, as a prophylactic or therapeutic intervention, reduced the mononuclear cell infiltration in gingival tissue at day 11 of periodontal disease. Considering that circulating monocytes may differentiate locally into osteoclasts, thereby exerting bone-resorbing activity, the reduction of mononuclear cells in the tissue surrounding the periodontium may contribute to the bone sparing effect of sodium alendronate in this model. These data are in accordance with a previous study that demonstrated that icadronate, which is also an aminobisphosphonate, suppressed the migration of macrophages in vitro.

According to the literature, the local periodontal microbial flora changes during periodontitis so that anaerobic Gram-negative bacilli predominate, including F. nucleatum and pigmented Gram-negative bacilli. Interestingly, we observed that sodium alendronate inhibited the growth of the bacteria characteristic of periodontal disease and completely inhibited the growth of pigmented Gram-negative bacilli. In addition, the growth of F. nucleatum was also significantly reduced by sodium alendronate. It is possible that the antibacterial activity of sodium alendronate observed here might result, at least partially, from the prevention of bone destruction and reduction of the periodontal pocket. However, we also demonstrated that sodium alendronate was able to inhibit the in vitro growth of Peptostreptococcus sp. Consistent with our data, it was recently demonstrated that sodium alendronate displays antibacterial activity against S. mutans, S. aureus, and P. aeruginosa and to the protozoan Trypanosoma cruzi.

In summary, this study demonstrates that the aminobisphosphonate sodium alendronate prevents alveolar bone resorption and has anti-inflammatory and antimicrobial effects in experimental periodontitis. The fact that these compounds are currently used as chronic treatments in postmenopausal osteoporosis with a relatively safe profile highlights the need for further research to demonstrate the beneficial effect of such compounds in human periodontitis.

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