Intravenous Pamidronate Attenuates Bone Density Loss After Acute Spinal Cord Injury

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Objective: To compare the effects of a 6-month treatment with intravenous pamidronate (30-mg infusion once per month) to conventional rehabilitation without pamidronate on bone density of the spine and leg bones and on the excretion rate of N-telopeptide, a urinary marker of bone catabolism, in acutely spinal cord injured patients.

Design: A nonrandomized control trial in which 24 spinal cord injured subjects entered the study within 6 weeks of their injury. Fourteen subjects received pamidronate; 10 did not.

Outcome Measures: Bone density measurements by dual x-ray absorptiometry were performed before the initial treatment (within 6 weeks of the injury) and at 3, 6, and 12 months postinjury and was the primary efficacy parameter. Urine for N-telopeptide levels was the secondary efficacy parameter.

Results: After acute spinal cord injury, patients treated with intravenous pamidronate had significantly less bone density loss compared with those who did not receive pamidronate (parametric ANOVA, p < .02). Also, ambulatory subjects had significantly less bone density loss over the study period (p < .05) than nonambulatory subjects. In general, a high excretion level of the urinary bone-breakdown product N-telopeptide was found before intravenous pamidronate treatment, followed by a dramatic reduction in excretion after pamidronate treatment. Ambulatory subjects excreted significantly less N-telopeptide than motor-complete subjects at all time points.

Conclusion: Intravenous pamidronate treatment and ambulatory ability in the first 6 months after an acute spinal cord injury prevents bone density loss.

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phonates, including pamidronate, are known to be powerful inhibitors of bone resorption by osteoclasts. These medications are adsorbed onto the calcified bone matrix and are resistant to enzymatic hydrolysis. In tissue culture, they inhibit bone resorption and prevent osteolysis induced by parathyroid hormone. Some bisphosphonates, such as pamidronate, are used for the treatment of hypercalcemia. Etidronate, given as an intermittent therapy, was reported to be useful in the treatment of postmenopausal osteoporosis. Although a study in SCI patients has shown that clodronate attenuated bone loss, unusually high doses of the drug were required (1,600 mg per day for 3 months). A study comparing etidronate and pamidronate in the treatment of hypercalcemia showed that a single 60-mg infusion of pamidronate was safer and more effective in normalizing serum calcium levels than etidronate given as a daily dose of 7.5 mg/kg for 3 days. In comparative studies, pamidronate was found to be more potent than clodronate or etidronate in inhibiting osteoclastic resorption of calcified cartilage, alleviating bone pain, and lowering serum calcium.

Reid and associates have shown, using quantitative computed tomography, that pamidronate produces an early significant increase in both the vertebral mineral density and the hand bone cortical area to total bone area in patients with steroid-induced osteoporosis, compared to patients taking placebo. The increase in bone mass occurs between 6 and 6 months posttreatment, reaches a plateau by 6 months, and is maintained thereafter for up to 12 months of treatment. Galleas and coworkers have also shown that intravenous pamidronate prevents bone loss in glucocorticoid-treated patients over the course of 1 year with a 1.8% increase in femoral neck bone mineral density in treated patients. A single infusion of 30 mg pamidronate is effective in normalizing serum calcium levels within 48 hours in immobilization hypercalcemia and lasts for several weeks.

Before 1992, the most commonly cited indices of bone metabolism had been the urinary excretion of calcium, phosphorus, and hydroxyproline. These are nonspecific indicators of bone metabolism due to a number of factors unrelated to bone turnover, such as dietary intake of minerals and protein, intestinal transit time and absorption, degradation of nonbone collagen, and fecal excretion of calcium. The N-terminal telopeptide cross-linking domain of bone type I collagen (NTX) has been identified and characterized in urine by specific immunoassay. The unique amino acid sequence of this peptide provides a sensitive and specific marker for bone resorption. Urinary excretion of NTX is significantly increased after acute SCI, as shown by Roberts and colleagues. In the course of the treatment of postmenopausal osteoporotic women with alendronate, NTX was shown to be elevated before treatment. A response to treatment was detected that correlated significantly with bone mineral density measurements. Similarly, pamidronate treatment in healthy volunteers decreases NTX excretion and prevents elevation of the urinary excretion after an 8-day course of treatment with triiodothyronine.

The purpose of this study was to test the effects of intravenous pamidronate treatment administered in patients with acute SCI, a clinical condition known to present with dramatically increased bone catabolism. The efficacy of treatment was assessed by the prospective measurement of both bone mineral density by dual energy x-ray absorptiometer (DEXA) and by the urinary excretion of NTX. The hypothesis was that pamidronate treatment would decrease the rate of bone density loss in these patients.

**METHODS**

**Subject Inclusion Criteria**

All patients admitted to our rehabilitation hospital with the diagnosis of SCI regardless of level or extent were advised of the nature of this study and given the opportunity to participate. Once able to tolerate oral feeding, all subjects were given a diet containing at least 1,000 mg of calcium. The American Spinal Injury Association (ASIA) Impairment Scale classification was used to grade the completeness of injury.

Serum levels of calcium, albumin, phosphate, and alkaline phosphatase and urinary excretion of creatinine were determined preinfusion, on 2 consecutive days after each infusion, and at 12 months postinfusion. Urine was collected, frozen, and stored for determination of creatinine-corrected N-telopeptide. For comparison, urine was collected at a minimum of 4-week intervals after infusion from 10 patients with SCI who were not treated with pamidronate. The control data from SCI subjects not treated with pamidronate were made available, and the control samples were not taken at all time points indicated for the treated patients. Where data points were missing from the control database, a mathematical interpolation was used to supply the missing points, which did not alter the mean values significantly.

Subjects were excluded if they met any of the following criteria: ventilator dependency, bed traction duration of more than 1 month, systemic anticoagulation therapy with heparin (excluding low-dosage thromboembolic prophylaxis), pregnancy, family history of idiopathic osteoporosis, or treatment with a bisphosphonate other than pamidronate.

Fourteen subjects were assigned to receive 30 mg pamidronate administered intravenously via 4-hour infusions (rate of 7.5 mg/h) every 4 weeks for six treatments, a total of 180 mg. Two subjects did not receive all planned treatments. Heart rate, body temperatures, and adverse events (if any occurred) were recorded after each infusion. Data from 10 control subjects, recruited before those who received pamidronate treatment, were collected, but three subjects were excluded due to treatment with etidronate, a first-generation bisphosphonate.

A 1-mm DEXA was used in this study for all bone mass measurements. The DEXA is precise and accurate for measuring bone mineral density, reported to be 0.5% to 2% precise and 3% to 5% accurate. A reproducibility study using the machine used in this study and able-bodied volunteers resulted in an average variance of 0.0003. The initial bone density assessments for each subject were performed upon entrance into the study, which was within 6 weeks of the SCI. Repeat bone density measurements were carried out at 3, 6, and 12 months postinfusion. The specific regions of interest quantified for each subject were as follows: spine (L1-L4), the right hip (femoral neck, Ward triangle, and trochanter), right femoral and tibial diaphyses, and right femoral and tibial epiphyses.

**Statistical Analysis**

An analysis of variance (ANOVA) for repeated measures using a CLRANOVA software and a Macintosh computer was used to analyze the bone density and NTX data generated from this study. The ANOVA for the bone density data used a 2 by-2 analysis with two between factors and two within factors. The two between-group factors were pamidronate treatment and ambulatory status. The bone density data for pamidronate-treated subjects were compared to data of control subjects not treated with pamidronate. The two within-group factors were bone density location (spine, hip, and femoral and tibial...
levels to the immediate posttreatment levels. In a separate analysis, the pretreatment excretion levels were compared to the control subjects at comparable time points after SCI. Similar to the bone density data comparison, the analysis was stratified for motor-incomplete versus motor-complete subjects. The second NTX data analysis is the result of an ANOVA for repeated measures with two between factors and one within factor.

RESULTS

Patient Characteristics

The average age of the pamidronate-treated group was 30.8 ± 8.3 years (range 20 to 45); the average age in the control group was 35.1 ± 10 years (range 25 to 57) (table 1). There were two women in the pamidronate-treated group, but none in the control group. There were equal proportions of cervical injuries compared to more caudal injury levels in the two groups. There was a higher proportion of ASIA grade D (motor function preserved below the neurologic level of injury, and most key muscles below the neurologic level have a muscle grade greater than or equal to 3/5) compared to ASIA grade A (complete injury with no motor or sensory function preserved in the sacral segments) injuries in the control group (6A/4D) than in the pamidronate-treated group (10A/4D). Two pamidronate-treated subjects were excluded because one had a family history of idiopathic osteoporosis and the other had a deep-vein thrombosis requiring heparin therapy. Of the pamidronate-treated subjects, two did not receive all six treatments. One was excluded because of idiopathic osteoporosis, and the other developed a pruritic rash after the second infusion and did not receive further pamidronate treatments but was included with the pamidronate-treated group for data analysis. This subject was included in the analysis because of the possibility of experiencing a treatment effect.

Bone Density

The effect of intravenous pamidronate on bone mineral density loss in patients with SCI was significant compared with those who did not receive pamidronate (treatment vs controls by ANOVA, \( F = 25.9, p < .0001 \)). Significant treatment group differences were detected at 6 and 12 months (\( p = .033 \) and \( p = .011 \), respectively) (fig 2). At 12 months postinjury, the control group lost an average of 2.7% in the treated group compared with 8.1% in the control group. The ASIA grades at 3, 6, and 12 months were unchanged. All ASIA grade D subjects were ambulatory by 3 months postinjury and those who walked had significantly less loss of bone density than those with an ASIA grade A injury, none of whom walked (\( F = 4.957, p = .04 \)). The average loss of bone density in the ASIA D group was 3.1% compared with 7.7% in the ASIA A group. There was no statistical evidence of an interaction between these two factors (\( p = .26 \)). The ambulatory subjects who received pamidronate treatment showed the best bone density preservation, (\( p < .005 \) by pairwise comparison using the Duncan test) (fig 1). The values taken from the ANOVA summary table are illustrated in figure 1. These values illustrate the factors being compared, leaving other factors, such as time and specific bone location, collapsed within the data. Only the specific bone locations listed in the Methods section were included in the analysis. Although the Lunar DEXA does provide a total-body bone mineral density, this was not a measurement used in this study, the analysis, or the illustrations.

The effect of time was highly significant (\( F = 25.9, p < .0001 \)). Significant treatment group differences were detected at 6 and 12 months (\( p = .033 \) and \( p = .011 \), respectively) (fig 2). At 12 months postinjury, the control group lost an...
Fig 2. Effect of time was a significant factor on the percent change in bone density from the baseline evaluation ($p < .001$). Specific group differences were apparent at the 6- and 12-month evaluation points where the control subjects showed a significantly greater loss of bone density than the pamidronate-treated subjects ($p = .03$ and $p = .01$, respectively).

The rate of density loss varied according to bone location ($F = 11.917, p < .0001$). In general, spine density is well maintained whereas the femoral neck, distal femur, and proximal tibia areas of the epiphyses decrease. The bone density loss from the femur was significantly less in the pamidronate-treated group than in the controls (fig 4). The average loss from the hips of the pamidronate-treated subjects was only 0.9% compared with 8.2% loss in the controls ($p = .012$). Respective losses from the distal femur were 4.7% and 10.8% ($p = .033$). A significant interaction between ambulatory status and bone location was observed ($F = 9.957, p < .0001$), where the spine and hip densities were comparable between the groups but obvious differences were detected about the knees. The loss of density in the proximal knee (distal femur) for ASIA A compared to ASIA D was 12.5% vs 3% ($p = .001$). Loss of density in the distal knee (proximal tibia) was 14.3% vs 3.25% ($p < .001$) (fig 5).

Fig 3. Although ambulatory status and time had significant effects on the percent change in bone density from the baseline time point, a significant interaction was also detected ($p = .002$), with a clearly illustrated difference at 1 year after the injury.

N-terminal Telopeptide (NTX)

As expected, a high excretion level of the urinary bone-breakdown product NTX was found. The average ± SD baseline pretreatment level of this product relative to creatinine excretion in all subjects entered into the trial (within 6 weeks of the spinal cord injury) was 219 ± 184 units, which decreased by an average of 61% immediately after the first treatment. High excretion levels recurred before treatments 2 to 6 as follows: 176 ± 137, 177 ± 117, 162 ± 130, 113 ± 86, and 138 ± 148. The final 12-month postinjury average level, which was approximately 5 months after the last infusion, was 106 ± 83 units. The NTX data were stratified into four groups based on completeness of spinal cord injury (ASIA grade) and...
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Table 2: Percent Change in Femoral Neck Density Compared With Baseline Over Time

<table>
<thead>
<tr>
<th>Area</th>
<th>3 Months (%)</th>
<th>6 Months (%)</th>
<th>12 Months (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control, ASIA-A</td>
<td>-0.3</td>
<td>-0.7</td>
<td>+0.4</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>-3.1</td>
<td>-6.2</td>
<td>-14.6</td>
</tr>
<tr>
<td>Femoral metaphysis</td>
<td>-2.0</td>
<td>-8.7</td>
<td>-27.4</td>
</tr>
<tr>
<td>Tibial metaphysis</td>
<td>-6.8</td>
<td>-13.6</td>
<td>-27.0</td>
</tr>
<tr>
<td>Pamidronate-treated, ASIA-A</td>
<td>+1.1</td>
<td>+2.0</td>
<td>+3.8</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>+0.3</td>
<td>+0.8</td>
<td>+6.6</td>
</tr>
<tr>
<td>Femoral metaphysis</td>
<td>-1.5</td>
<td>-9.6</td>
<td>-26.0</td>
</tr>
<tr>
<td>Tibial metaphysis</td>
<td>-1.0</td>
<td>-9.0</td>
<td>-28.5</td>
</tr>
<tr>
<td>Control, ASIA-D</td>
<td>-2.1</td>
<td>-4.2</td>
<td>-5.7</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>-5.1</td>
<td>-10.3</td>
<td>-9.8</td>
</tr>
<tr>
<td>Femoral metaphysis</td>
<td>-4.6</td>
<td>-8.9</td>
<td>-13.4</td>
</tr>
<tr>
<td>Tibial metaphysis</td>
<td>-3.4</td>
<td>-6.3</td>
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<tr>
<td>Pamidronate-treated, ASIA-D</td>
<td>+2.7</td>
<td>-0.7</td>
<td>-2.3</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>+0.3</td>
<td>-0.3</td>
<td>+0.4</td>
</tr>
<tr>
<td>Femoral metaphysis</td>
<td>+1.2</td>
<td>+2.7</td>
<td>+4.3</td>
</tr>
<tr>
<td>Tibial metaphysis</td>
<td>+1.0</td>
<td>-0.4</td>
<td>-0.03</td>
</tr>
</tbody>
</table>

There was a significant effect of completeness of SCI on NTX excretion (mean complete 232.67 vs incomplete 112.33, p = .02). There was no overall effect of time (p = .13), unless one examines the simple effects on the treatment by time interaction. Here, time was significant on the controls (p = .04) with the maximum mean differences at 12 weeks post-SCI. There was a significant interaction between completeness and time as shown by the simple effects, where complete subjects were significantly different from incomplete subjects at 8 weeks (p = .03), 12 weeks (p = .003), and a trend at 16 weeks (p = .08).

DISCUSSION

The results of this experiment are consistent with previous reports that showed a significant decrease of bone mineral...
The distribution of bone density loss is unique are shown. The effect of pamidronate can be seen in the decreased with pamidronate (indicated by the upper line graph for controls) and 18 SCI patients not treated NTX excretion after treatment.

Subjects who were all wheelchair users over a 53-month period number of femoral neck fractures occur as well. The data loss after SCI and somewhat less than observed in other reports, possibly due to the predominance of ambulatory subjects and density in the lower paralyzed limbs of SCI patients. The average amount of bone loss during the first year after injury is about 40% to 70%, depending on the site and the age of the patient. The distribution of bone density loss is unique compared to endocrine causes of osteoporosis or spastic cerebral palsy. In children with SCI, the bone density of the three sites of the hip range from 56% to 65% of able-bodied nonadults, but the bone mineral density increases with growth, and males tend to attain higher bone density, generally. Szoliar and colleagues observed that significant bone density loss occurs at the three sites of the hip by 1 year postinjury for all persons younger than 60 years and that the decline continues until 19 years after SCI. The loss in bone density increases the risk of SCI patients to incur a leg bone fracture associated with minor trauma. Reviews of lower extremity fractures after SCI reveal that the most commonly fractured bone is the femur, most often in the supracondylar region (the “paraplegic fracture”); a significant number of femoral neck fractures occur as well. The data from the current longitudinal study show that without specific intervention, bone density will be lost in the lower extremities after SCI. The average loss at the end of 1 year, regardless of injury completeness or ambulatory status, was 12.2% at the femoral neck and 18.7% at the proximal tibia. Biering-Sørenson and associates reported the change of bone density in eight SCI and associated subjects who were all wheelchair users over a 53-month period as 60% to 70% loss at the femoral neck and 40% to 50% loss at the proximal tibia. Garland and coworkers observed that significant bone density loss at the proximal tibia. Garland and coworkers reported an average loss of distal femur bone mineral density of 12 ASIA A subjects was 22% in the first 3 months, 27% by 4 months, and 32% at 14 months. Wilnet and colleagues reported an average loss of trabecular bone density in the legs of 4% per month in the first year after SCI, with ambulatory subjects showing a slightly slower rate of loss. Thus, the control data reported here are a conservative projection of the magnitude of bone density loss after SCI and somewhat less than observed in other reports, possibly due to the predominance of ambulatory subjects and one subject aged 57 years, a point that has been reviewed previously.

The types of interventions to improve bone density in patients with SCI that have been reported have involved either electrical stimulation of muscle or pharmacologic targeting of bone metabolism. Rodgers and associates reported that muscle performance improved, but bone density of the tibia did not, using electrical stimulation of the quadriceps muscles in a knee extension exercise system. Sloan’s group reported observations in 12 patients with SCI given electrical stimulation of the quadriceps during cycling on a Kincom isokinetic dynamometer; two with serial bone density assessments showed progressive loss in bone density at the 6- and 12-month observation periods. Using quantified computerized tomography to measure bone density of the tibia, Hangartner and coworkers showed that electrically stimulated knee extension or leg cycle ergometry did not increase bone density but did attenuate the expected rate of trabecular bone loss. Neither BeDell and colleagues nor Needham-Shropshire and associates observed improvement in bone density at the femoral neck, Ward triangle, or the greater trochanter in 12 and 15 ASIA A SCI subjects, respectively, after 8 weeks of electrically stimulated REGYS I ergometer exercise or 12 weeks of electrically evoked walking using the Parastep 1 ambulation system. Bloomfield and coworkers showed that four subjects trained on a REGYS I system at high intensity (more than 18W) had an average increase of 17.8% in bone density over 9 months only at the distal femur. Similarly, Moli’s group observed that electrically stimulated cycling exercise training for 12 months (3 days per week) in 10 motor-complete SCI subjects increased the bone mineral density of the proximal tibia by 10%, but those improvements were lost after 6 more months of reduced-frequency exercise (once per week). These observations, although somewhat contradictory, could be viewed as consistent with the data presented here. The lack of effect of electrically induced exercise upon the regions about the hip are consistent and the positive effects about the knee are also consistent. The marginal effects reported by Hangartner may be related to insufficient intensity or frequency of the exercise. The present data show that ambulatory status has the most profound effects upon the high-percentage trabecular bone regions about the knee, the distal femur, and proximal tibia, and relatively less effects on the hip, which is consistent with the lack of effect of ambulatory status in the femur, but a positive correlation with an index of mobility in the tibia.

The potential side or adverse effects of pamidronate that were monitored are as follows: postinfection fever, nausea, hypocalcemia, hyperperistalsis, hyper/hypokalemia, leukopenia, allergic reaction, and local reactions at the site of infusion. One subject experienced a generalized, red, itchy rash after the second infusion. None of the other potential side or adverse effects were observed.

Other medications have been evaluated as potential preventive treatments in post-SCI-related bone mineral density loss. A clinical trial with SCI patients stratified for ambulation capacity failed to show a drug effect with a first-generation bisphosphonate, etidronate, but did reveal a significant interaction between ambulatory ability and drug treatment; however, inhibitory effects on bone formation may limit its usefulness during recovery from a fracture. A report that tiludronate, a newer-generation bisphosphonate, at the higher dose tested (400mg/d), produced a slight increase in the bone volume/total volume of a transiliac bone biopsy, is supporting evidence that a high-potency bisphosphonate would be generally effective in reducing bone density loss after SCI. A long-term follow-up of
women treated for 2 years with pamidronate showed that 1 year after stopping treatment, bone mineral density loss resumes throughout the skeleton except for the lumbar spine, femoral neck, and Ward triangle. Furthermore, pamidronate has been used successfully to reduce bone mineral density loss in patients with reflex sympathetic dystrophy. Finally, a new bisphosphonate that can be administered orally, risedronate, has been shown to significantly improve spinal bone mineral density by 5.3% in 11 multiple myeloma patients treated for 6 months. As other bisphosphonates, such as zoledronate, are evaluated, perhaps greater efficacy may be discovered.

Active rehabilitation programs often include wheelchair sports and gait retraining, which increase the demand upon the leg bones. It is logical that prevention of osteoporosis will diminish the risk of fractures and reasonably permit the inclusion of walking retraining in general rehabilitation programs. If mobilization strategies such as functional electrical stimulation for walking are to be carried out with maximal safety in SCI patients, bone density must be maintained at normal or near-normal levels. With the prediction of predictable adverse events, such as low-impact fractures, and the overall improvement in general by improved exercise performance and mobility, the quality of life for SCI patients would be expected to be enhanced. The positive results from this study confirm the original hypothesis that intravenous pamidronate can reduce significantly bone resorption after acute SCI. However, the data are not uniform in that not all bony locations for all patients were protected, suggesting that the original treatment protocol is not optimal. The data indicate that nonambulatory SCI patients are likely to require a longer duration of treatment.

CONCLUSIONS

The data reported in this prospective trial of SCI subjects support the hypothesis that pamidronate treatment during the acute phase of SCI will retard the development of osteoporosis after SCI with a low incidence of side or adverse effects. The fact that pamidronate must be given as an intravenous injection, however, is a significant limitation. The stratification of subjects based on ambulation capacity shows that nonambulatory subjects are not adequately protected by the treatment protocol described in this report and that more work is needed to find such a protocol. From the NTX excretion data presented, it appears that the dosage frequency is insufficient. However, from the ambulatory stratification, one could speculate that early weight-bearing in combination with longer-term bisphosphonate treatment, or a different bisphosphonate with greater potency and longer duration of action, may improve the protection of bone density in the tibia.

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b. Lunar DPX; Lunar Corporation, 313 West Beltline Highway, Madison, WI 53713.
c. CLRANOVA Software, Anova version 1.1; Clear Lake Research, Inc., 7300 East 14th Street, Tulsa OK 74104.