#7

ORIGINAL CONTRIBUTION

Effect of a Convenient Single 90-mg Pamidronate Dose on Biochemical Markers of Bone Metabolism in Patients With Acute Spinal Cord Injury

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Abstract

Background/Objective: To describe the biochemical and adverse effects of a convenient single 90 mg pamidronate dose in patients with acute spinal cord injury (SCI) and compare these effects with those observed in a previous similar study using a 30 mg/d × 3-day pamidronate dosing regimen.

Study Design: Retrospective cohort study.

Setting: University-based rehabilitation center in New York City.

Methods: A total of 32 patients with SCI were evaluated for biochemical response and adverse events associated with pamidronate therapy. All patients were screened at or near admission for acute rehabilitation, received calcium (1,000 mg daily) and calcitriol (0.25 μg daily) therapy daily, and on day 4, received a single dose of pamidronate, 90 mg by intravenous infusion, over 4 hours. Serum calcium and phosphate levels were closely monitored, and 2 weeks after pamidronate, biochemical bone markers were re-evaluated.

Results: Responses of biochemical markers of bone resorption (N-telopeptide and 24-hour urinary calcium excretion) to pamidronate 90 mg were consistent with an antiresorptive effect, although less than that observed with a 30 mg/d × 3-day pamidronate dosing regimen. The frequency of hypocalcemia was greater, and hypophosphatemia was less than the 30 mg/d × 3-day pamidronate dosing regimen. Fever was more frequent (78%) with the 90-mg single dose of pamidronate compared with the 30 mg/d × 3-day pamidronate dosing regimen (20%).

Conclusions: Single-dose pamidronate 90 mg is effective at reducing biochemical markers of bone hyperresorption in patients with acute SCI but is associated with a greater incidence of fever compared with a 30 mg/d × 3-day dosing regimen.

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INTRODUCTION

Bone hyperresorption with subsequent osteoporosis is a well-described complication of acute spinal cord injury (SCI) (1,2) and is associated more with the extent of neurological impairment than the level of injury (3). Garland et al (4) reported that in individuals with SCI, demineralization occurs disproportionately below the pelvis at a rapid linear pace, until a steady state ensues at 16 months, with retention of approximately two thirds of the original bone mass, near the fracture threshold. These changes are associated with increased risk for pathological fractures, nephrolithiasis, nephrocalcinosis, frank hypercalcemia, and heterotopic ossification at the knees (5–7). The effects of exercise and muscle contractions on bone mineral density in patients with SCI are contradictory and as yet unproven (8,9).

Bone hyperresorption has been shown after acute SCI, with increased and uncoupled osteoclastic activity and relatively low osteoblast activity. This is supported by

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a biochemical profile characterized by increased urinary excretion of N- and C-telopeptide (NTx and CTx; markers of bone resorption) and calcium, suppressed parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D_3 (1,25-D) levels, and decreased osteocalcin levels (a marker of bone formation) as early as 9 to 14 days after SCI (3,4,10–12). Subsequently, there is a mild increase in bone formation (13,14), but elevated markers of bone resorption peak at 10 to 16 weeks (14). These biochemical markers correlate with continued loss of unloaded cortical bone and persist for at least 10 years after injury, well beyond densitometric homeostasis at 16 months, beyond which there may still be a downward trend (15). Thus, it has been postulated that biochemical markers of bone resorption are sensitive indicators of fracture risk (12,16).

Efforts to attenuate ongoing bone loss focus on this metabolic disparity are therefore designed to inhibit osteoclast activity. Both etidronate (17) and alendronate (18), 2 oral bisphosphonates, can improve bone mineral density in patients with SCI. Pamidronate, one of the second-generation intravenous bisphosphonates, inhibits osteoclastic bone resorption and has been studied in treatment of bone hyperresorption in acute SCI (19,20), chronic critical illness (21), immobilization (22), post-transplantation (23–25), cancer (26), Paget disease (27), Crohn disease (28), and rheumatoid arthritis (29). Nance et al (20) found that a monthly 30-mg pamidronate dosing regimen for 6 months with calcium, 1,000 mg daily, but without vitamin D supplementation, was associated with significant reduction in loss of bone mineral density in patients with ASIA D, but not in patients with ASIA A ($N = 24$) within 6 weeks of injury.

In our previous study, combined calcitriol 0.5 μg daily and calcium 1,000 mg daily with 30 mg pamidronate for 3 days significantly reduced NTx levels in patients with SCI, suggesting a beneficial role on bone hyperresorption (10). This pamidronate dose is recommended by the manufacturers of Aredia (pamidronate; Novartis, East Hanover, NJ) in the package insert for the treatment of Paget's disease (30,31) and has also been used previously for bone hyperresorption in the chronically critically ill patient (21). The rationale of pretreatment with calcitriol is twofold. First, suppressed 1,25-dihydroxyvitamin D (1,25-D) levels are a consistent finding in SCI and can aggravate bone demineralization. Second, correction of an occult vitamin D deficiency may blunt the unwanted hypocalcemic and hypophosphatemic effect of bisphosphonate therapy.

In the acute rehabilitation unit, however, multiple intravenous infusions of pamidronate over 3 days are inconvenient, with respect to a patient's physical therapy schedule and the maintenance of a peripheral intravenous site, and are associated with certain adverse effects, such as hypocalcemia, hypophosphatemia, and fever. The purpose of this study was to assess the effects of the more convenient single 90-mg pamidronate infusion in patients with acute traumatic SCI, based on the hypothesis that the therapeutic and adverse effects would be comparable with the previously reported 30 mg/d × 3-day pamidronate dosing regimen.

MATERIALS AND METHODS

Participants

This retrospective study involving chart review was approved by the Mount Sinai School of Medicine Institutional Review Board, and informed consent was waived. Medical records were reviewed by the authors for patients with acute traumatic SCI who were admitted to our rehabilitation unit from January 2002 through July 2004. All patients with acute SCI were evaluated with metabolic bone markers for possible calcitriol-pamidronate therapy. Chart abstraction by the authors was not blinded to the study purpose. Data were verified by comparison with the electronic hospital laboratory record. There were a total of 32 patients with traumatic SCI who had complete bone hyperresorption laboratory data. There were 7 women and 25 men, with a mean age of 42 years (range, 17–79 years). There were 11 patients with paraplegia (2 women and 9 men) and 21 patients with tetraplegia (5 women and 16 men). There were 11 patients with incomplete injuries (4 women and 7 men) and 21 patients with complete injuries (3 women and 18 men). There were 22 patients with ASIA A injuries, 5 with ASIA B injuries, and 5 with ASIA C injuries.

In the previous study performed by our group investigating a 30 mg/d × 3-day pamidronate-dosing regimen in SCI, there were a total of 21 patients with traumatic SCI who had bone hyperresorption laboratory data. There were 4 women and 17 men, with a mean age of 34 years (range, 16–78 years). There were 8 patients with paraplegia and 13 patients with tetraplegia; 4 patients had incomplete injuries and 17 patients had complete injuries. There were 17 patients with ASIA A injuries, 2 with ASIA B injuries, and 2 with ASIA C or D injuries. The clinical setting, treatment protocols, and biochemical methodologies were identical to this study except for the pamidronate dosing regimen.

Treatment Protocols

All patients with SCI admitted to the rehabilitation unit were screened for significant bone hyperresorption with 24-hour urinary calcium excretion rates, a spot urine sample for NTx, and serum levels for calcium, phosphorus, albumin, intact PTH, 25-D, and 1,25-D. In those patients with elevated urinary calcium excretion or NTx, a diagnosis of bone hyperresorption was made, and calcitriol-pamidronate therapy was planned. Patients with baseline urinary calcium less than 250 mg/24 h were treated with 1,000 mg elemental calcium (1,250 mg calcium carbonate orally twice daily) and 0.25 μg calcitriol daily. Then, on the fourth day, patients received a single 4-hour intravenous infusion of pamidronate, 90 mg, with continuation of daily calcitriol and calcium. In those patients with a baseline urinary calcium of at least

250 mg/24 h, a single 4-hour intravenous infusion of pamidronate, 90 mg, was administered, and daily calcium and calcitriol therapy was deferred until the urinary calcium was less than 250 mg/24 h (measured 1 week after the pamidronate dose). Serum calcium, phosphorus, and albumin levels were determined daily for the first 3 days after pamidronate therapy and then weekly thereafter. Two weeks after pamidronate therapy, urinary calcium and NTx and serum intact PTH, 25-D, and 1,25-D determinations were performed to assess the response. Vital signs, including ear temperature measurements (First Temp Genius; Sherwood Medical, St Louis, MO) set on the "core" mode, were recorded each 8-hour shift per hospital protocol. Patients were monitored for fever (ear temperature $>$ 38°C) after pamidronate administration and any clinical signs or symptoms of hypocalcemia. Patients with frank hypercalcemia were excluded from this study analysis and were treated with pamidronate without calcitriol and calcium pretreatment.

Laboratory Evaluations

The intact PTH levels were collected, placed on ice, and expeditiously transported to the stat laboratory. The intact PTH assay was performed by the hospital's clinical laboratory using a solid-phase, 2-site chemiluminescent enzyme immunometric assay on an automated analyzer (Immunlite Immunoassay Analyzer; Diagnostic Products, Los Angeles, CA; reference range = 12–72 pg/mL; sensitivity = 1 pg/mL). The 1,25-vitamin D assay was performed by using column chromatography and radioimmunoassay (Lab Corp, Raritan, NJ; reference range = 18–62 pg/mL). The 25-hydroxyvitamin D assay was performed using a competitive protein-binding assay (Lab Corp; reference range = 16–74 ng/mL). All 24-hour urine collections were assayed for creatinine to assure an adequate collection for determination of creatinine-corrected NTx (Osteomark assay; Ostex International, Seattle, WA). Assay values are corrected for dilution by urinary creatinine analysis and expressed as nanomoles BCE per millimole creatinine (reference range: 12–80 nmol BCE/mmol Cr). Rate determinations for 24-hour urinary calcium and creatinine excretion were performed by the hospital's clinical laboratory.

Statistical Analysis

Laboratory values are shown as mean ± SD. All laboratory data were evaluated for normality, using the Kolmogorov-Smirnov test, plots of means vs variance, and the Levene test for homogeneity of variance. Distributions of all measured parameters were normally distributed, except for NTx before treatment, which was normally distributed after logarithmic transformation.

To determine the difference in biochemical markers between groups before and after the treatment, a paired *t*-test was used. To determine the frequency differences in demographic data between this study and our previous study using the 30 mg/d × 3-day pamidronate-dosing regimen, a χ^2 test was used. To determine differences in mean ages and biochemical data between this study and our previous study, a pooled *t*-test was used. All statistics were performed using computer software (Statistica for Windows, Release 6.1; StatSoft, Tulsa, OK). A *P* value less than 0.05 was considered to be statistically significant.

RESULTS

Demographics from the current SCI study population, which received a single 90-mg pamidronate dose, were compared with the previously reported SCI study population, which received the 30 mg/d × 3-day pamidronate dosing regimen. There were no significant differences between the 2 groups with respect to age, sex, level of injury (paraplegia vs tetraplegia), completeness of injury, or ASIA classification (Table 1). There were also no significant differences in baseline NTx, urinary calcium excretion rates, PTH, 25-D, 1,25-D, and calcium levels between this study and the previous study (Table 1).

There was a high pretreatment urinary NTx excretion rate in all 32 patients, with a mean of 192.8 ± 117.6 nM BCE/mM Cr (reference range, 12–80 nM BCE/mM Cr), which decreased to 70.2 ± 42.0 nM BCE/mM Cr 2 weeks after pamidronate therapy ($P < 0.001$; Figure 1). This corresponds to a decrease of 64%, which is significantly lower than the 71% decrease observed with the 30 mg/d × 3-day pamidronate dosing regimen ($P < 0.05$), in which the baseline NTx was 269.6 ± 147.2 nM BCE/mM Cr (10). The absolute decreases in NTx were also different between the 2 pamidronate dosing regimens, with a mean decrease of 200.2 BCE/mM Cr in patients treated with a single 90-mg dose compared with a mean decrease of 122.6 BCE/mM Cr in patients treated with 30 mg/d × 3 days.

There was a similar pattern for the urinary calcium excretion rates in this study. In the pretreatment group, the mean was 270.7 ± 204.8 mg/24 h (with 15 patients [47%] with values $>$ 250 mg/24 h), which decreased significantly to 152.5 ± 135.2 mg/24 h 2 weeks after pamidronate treatment ($P < 0.002$; Figure 2). This corresponds to a decrease of 50%, which is significantly less than the 73% decrease observed with the 30 mg/d × 3-day pamidronate dosing regimen ($P < 0.01$), in which the baseline urinary calcium excretion rate was 391.8 ± 252.0 mg/24 h (10). The absolute decreases in urinary calcium were also different between the 2 pamidronate dosing regimens, with a mean decrease of 297.2 ± 219.1 mg/24 h in patients treated with a single 90-mg dose compared with a mean decrease of 150.1 ± 169.6 mg/24 h in patients treated with 30 mg/d × 3 days.

The serum levels of both intact PTH and 1,25-D were suppressed in the pretreatment groups at 21.8 ± 23.7 and 24.5 ± 20.6 pg/mL, respectively. These values increased to 40.0 ± 43.2 pg/mL ($P < 0.01$; Figure 3)

Table 1. Comparison of Demographics and Biochemical Markers of Bone Metabolism Between the Current Study and a Previous Study Using Different Intravenous Pamidronate Dosing Regimens

Parameter	Previous Study 30 mg dose × 3 days*	Current Study a single 90 mg dose*	*P* Value
Percent men/women	81.0/19.1 [21]	78.1/21.9 [32]	0.803
Percent para/tetraplegic	38.1/61.9 [21]	34.4/65.6 [32]	0.782
Percent complete/ incomplete	19.0/81.0 [21]	34.4/65.6 [32]	0.226
Percent ASIA A/B/C	81.0/9.5/9.5 [21]	68.8/15.6/15.6 [32]	0.615
Age	34.2 ± 18.2 years	41.8 ± 15.1 years	0.587
Baseline serum calcium	9.27 ± 1.03 mg/dL [20]	9.12 ± 0.61 mg/dL [39]	0.507
Baseline 25-D	17.9 ± 7.8 ng/mL [13]	18.8 ± 8.8 ng/mL [39]	0.955
Baseline 1,25-D	17.0 ± 12.6 pg/mL [13]	22.9 ± 18.8 pg/mL [40]	0.223
Baseline PTH	16.4 ± 12.0 pg/mL [11]	19.1 ± 19.1 pg/mL [36]	0.472
Post-Tx PTH	42.2 ± 30.0 pg/mL [11]	40.9 ± 44.5 pg/mL [16]	0.876
Δ PTH	25.8 ± 32.8 pg/mL [11]	21.9 ± 28.6 pg/mL [15]	0.746
Baseline urinary calcium	391.8 ± 252.0 mg/24 h [12]	302.3 ± 144.5 mg/24 h [31]	0.111
Δ Urinary calcium	**−297.2 ± 219.2 mg/24 h [12]**	**−150.1 ± 169.6 mg/24 h [19]**	**0.044**
Baseline NTx	269.6 ± 147.2 nM BCE/ mg Cr [16]	191.5 ± 119.6 nM BCE/ mg Cr [32]	0.056
Posttreatment NTx	69.4 ± 65.6 nM BCE/ mg Cr [16]	69.7 ± 37.0 nM BCE/ mg Cr [32]	0.962
Δ NTx	**−200.2 ± 143.5 nM BCE/ mg Cr [16]**	**−122.6 ± 102.5 nM BCE/ mg Cr [32]**	**0.036**

* Mean ± SD [N].
Bold represents statistically significant differences with $P < 0.05$.

and 37.5 ± 21.2 pg/mL ($P < 0.02$; Figure 4), respectively, 2 weeks after pamidronate treatment.

The principle adverse effects of calcitriol-pamidronate therapy are fever, hypocalcemia, and hypophosphatemia. In this study, the baseline serum calcium and phosphorus levels were 9.1 ± 0.6 mg/dL (reference range, 8.5–10.5 mg/dL) and 4.4 ± 0.5 mg/dL (reference range, 2.5–4.5 mg/dL), which decreased to 7.9 ± 0.9 mg/dL ($P < 0.0001$) and 2.9 ± 0.4 mg/dL ($P < 0.0001$), respectively, within the first 5 days after treatment with pamidronate. Seventy-five percent of patients became hypocalcemic (<8.5 mg/dL; compared with 44% receiving the 3-day 30 mg pamidro-

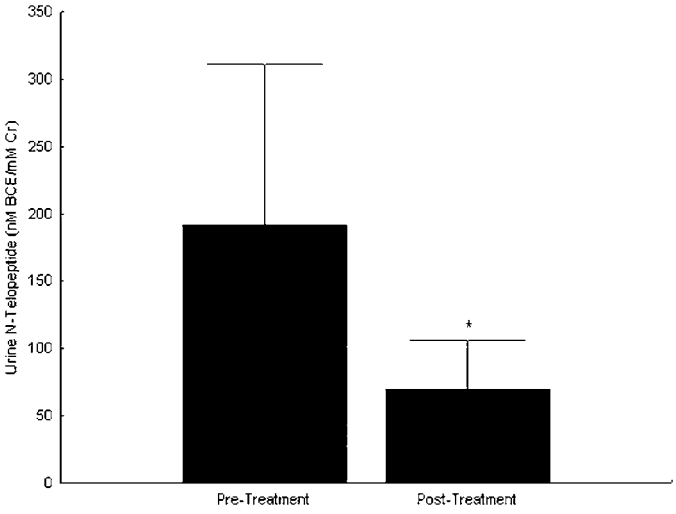

Figure 1. Baseline and posttreatment NTx values in patients with acute SCI receiving a single 90-mg dose of pamidronate.

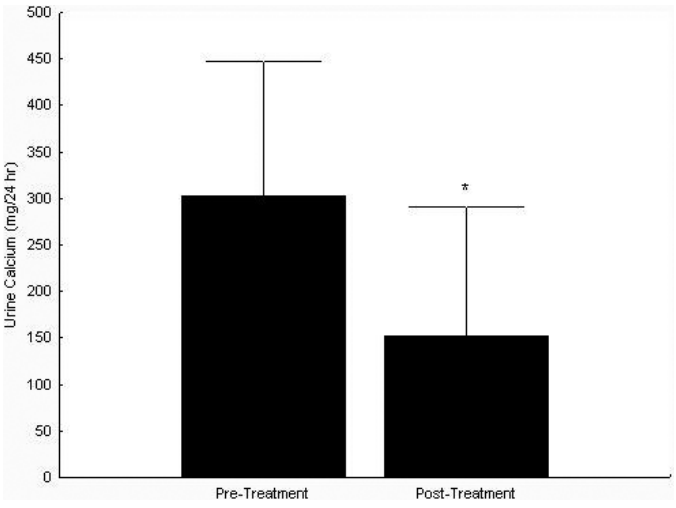

Figure 2. Baseline and posttreatment 24-hour urinary calcium excretion rates in patients with acute SCI receiving a single 90-mg dose of pamidronate.

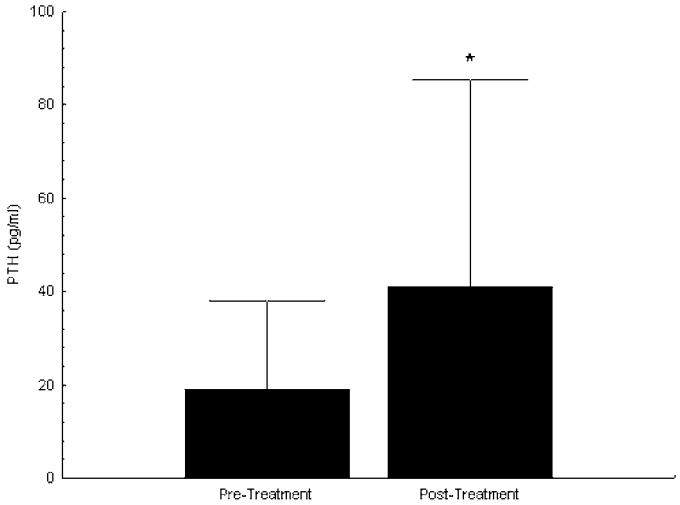

Figure 3. Baseline and posttreatment intact PTH values in patients with acute SCI receiving a single 90-mg dose of pamidronate.

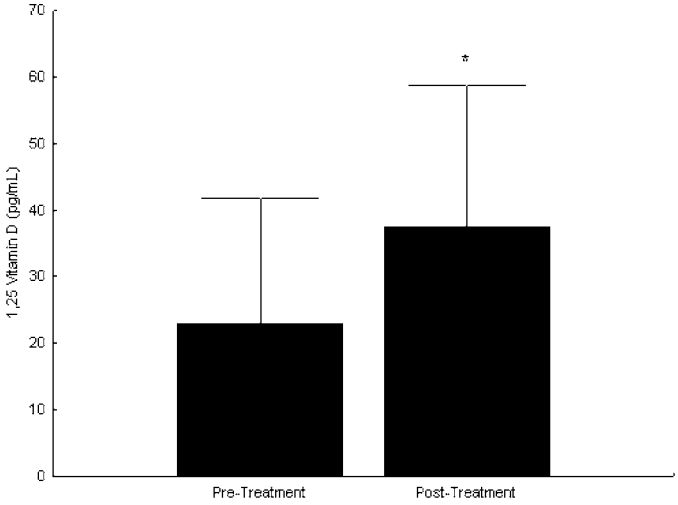

Figure 4. Baseline and posttreatment 1,25-D values in patients with acute SCI receiving a single 90-mg dose of pamidronate.

nate dosing [10]; $P < 0.02$), and 22% of patients became hypophosphatemic (<2.5 mg/dL; compared with 53% receiving the 3-day 30-mg pamidronate dosing [10]; $P < 0.02$). Patients were clinically asymptomatic despite these decreases in serum calcium and phosphate. When noted, hypocalcemia was treated with additional oral calcium carbonate and hypophosphatemia was treated with oral sodium phosphate supplementation.

Temperature elevations in the range of 38°C to 40°C range were observed in 25 of the 32 patients (78%), with the majority occurring 24 hours after pamidronate treatment, without any other identifiable cause for fever. The temperature elevation persisted for 4 to 5 days in most cases, with a few cases lasting more than a week, and was significantly more frequent than that observed in our previous study (20%; $P < 0.01$) (10).

DISCUSSION

In this observational, retrospective study, a single intravenous infusion of 90-mg pamidronate decreased biochemical markers of bone hyperresorption in patients with acute traumatic SCI. The degree of suppression of urinary NTx and calcium excretion was effective, but to a lesser extent than with the 30 mg/d × 3-day intravenous pamidronate infusion as described in our previous study (10). The incidence of transient, asymptomatic hypocalcemia was greater and hypophosphatemia was lower than that observed in our previous study (10). Of particular importance, the percentage of patients with temperature elevation after a 90-mg pamidronate infusion was significantly higher than those of our previous study and others using a 30 mg/d × 3-day pamidronate infusion regimen (20–50%) (10,32).

Fever was observed at a greater frequency after a single 90-mg pamidronate dose compared with 3 daily 30-mg doses. Nitrogen-containing bisphosphonates, such as pamidronate, share several structural homologies with nonpeptide γδ T-cell ligands, such as bacterial pyrophosphomonoesters (isopentenyl pyrophosphate [IPP]) (33). Pamidronate-stimulated γδ T cells results in variable dose-dependent tumor necrosis factor (TNF)-α and interferon-γ (IFN) release patterns and inhibition of bone resorption (34–38). TNF-α, as well as other cytokines, also interacts with hypothalamic thermoregulatory centers causing temperature elevation (39). In addition, patients with SCI have impaired autonomic nervous system function below the level of injury that results in reduced sweat capacity (40) and blood flow (41). The impaired thermoregulatory response in patients with SCI is further compromised with higher levels of injury (>T6) (42–44). This can result in a loss of supraspinal control of the sympathetic nervous system (SNS) (42–44). Increased core and skin temperatures in patients with tetraplegic > paraplegic SCI , relative to able-bodied controls, have been observed frequently (45,46). A higher pamidronate dose may be associated with a greater endogenous pyrogen milieu. Thus, even though single-dose pamidronate 90 mg was associated with comparable biochemical benefit, the increased frequency of significant fever was bothersome to the patients and confusing to physicians who may be concerned about infectious or inflammatory complications.

This study was undertaken to review the risks and benefits of a more convenient method of administering calcitriol-pamidronate to patients with acute SCI. Comparison with a previously published 30 mg/d × 3-day pamidronate dosing regimen was valid because of the similarities in patient demographics, baseline levels of biochemical markers for bone metabolism, clinical setting, laboratory methodologies, and protocol design. Shortcomings are related to the observational and retrospective methodology, lack of a control group, and

failure to analyze various groups within the SCI population. Measurement of ear temperature using tympanic membrane infrared probes has been associated with overestimation of deep core temperature (47). However, this methodology was uniformly applied to all study patients; therefore, the detection of temperature elevations is valid. Long-term biochemical benefits and effects on clinical outcome, including bone density, fracture risk, nephrolithiasis, and heterotopic ossification, were beyond the scope of this study.

It is noteworthy that in a recent, yet small, prospective, randomized placebo-controlled trial, patients within 2.5 months of SCI failed to show long-term clinical benefit of antiresorptive therapy (48). In this study, pamidronate, 60 mg, administered intravenously at baseline and 1, 2, 3, 6, 9, and 12 months, with unmonitored daily calcium 700 mg and vitamin D intake, was associated with an early decrease in NTx (<1 month after injury) and decrease in loss of total leg bone mineral density (<12 months after injury), but these salutary effects were not sustained for the duration of the 24-month study period (48). There was no mention regarding fever in this study. Notwithstanding the lower pamidronate dose of 60 mg and the possibility of inadequate calcium and vitamin D provided, this study suggests that optimal management of SCI-associated metabolic bone disease may ultimately involve interventions beyond simple antiresorptive therapy and reliance on more sensitive clinical markers.

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