Journal of Clinical Densitometry, vol. 5, no. 2, 143–149, Summer 2002

1094-6950/02/5:143–149/$11.75

Original Article

Efficacy and Tolerability of Cyclical Intravenous Pamidronate in Patients with Low Bone Mass

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Abstract

Oral bisphosphonates are an established mode of therapy for the prevention and treatment of osteoporosis. However, many patients are unable to take them either because of poor tolerability or some established contraindications. This retrospective study describes our clinical experience with the efficacy and tolerability of cyclical intravenous pamidronate in patients with osteopenia or osteoporosis at the American University of Beirut Medical Center. Twenty patients received intravenous pamidronate, as a 30-mg infusion administered intravenously over 2 h every 3 mo. All patients were maintained on calcium and vitamin D supplementation: 1000 mg of calcium and 400–800 IU of vitamin D, respectively. Bone mineral densities of the spine and/or hip were measured at baseline and within an average of 14 mo of study entry while on cyclical pamidronate. Two-thirds of patients had a significant increase in bone mineral density either at the lumbar spine or hip. Five patients (25%) developed the expected acute-phase reaction symptoms. Pamidronate constitutes an attractive alternative therapy in patients who cannot tolerate oral bisphosphonates.

Key Words: Pamidronate; bone density; efficacy; tolerability; responders.

Introduction

Bisphosphonates, since their introduction in the 1970s, have gained increasing attention as potent antiresorptive agents used in osteolytic bone disease, Paget's disease, and postmenopausal as well as steroid-induced osteoporosis *(1,2).* This class of drugs is an established modality of therapy in the prevention and treatment of osteoporosis *(3–11).* In particular, the nitrogen-containing bisphonates alendronate and risedronate have been shown not only to maintain or modestly increase bone mass but also to reduce fracture rates in the axial as well as appendicular skeleton in postmenopausal women with established osteoporosis *(3,5,8,9,11).* However, many patients cannot take oral bisphosphonates, either because of poor tolerance or the presence of well-established contraindications for their use *(12–14).* Alternatives to oral bisphosphonates are therefore needed in the management of postmenopausal bone loss.

The efficacy of intravenous bisphosphonates, such as pamidronate, ibandronate, alendronate, and zoledronate, is well established in the management of hypercalcemia of malignancy and the prevention of osteolytic bone disease *(15–17).* Intravenous ibandronate has also been shown to maintain bone mass, but is not available for clinical use yet *(18).* Intravenous pamidronate, is an established therapy

Received 06/06/01; Revised 08/03/01; Accepted 08/20/01.
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for Paget's disease, multiple myeloma, and metastatic bone lesions. To date, pamidronate is not yet approved by the Food and Drug Administration as a therapy for osteoporosis. However, it has been tried in small studies in patients with established osteoporosis. The results are promising, but the information is limited *(19–21).* The purpose of this study is to evaluate the safety and efficacy of pamidronate in patients who cannot take oral bisphosphonates.

Methods

Study Design

This is a retrospective study evaluating clinical experience regarding the efficacy and tolerability of periodic cyclical pamidronate administration in patients at the American University of Beirut Medical Center in the period starting March 1998 until December 2000.

Study Subjects

Twenty consecutive patients with either established osteoporosis or osteopenia receiving intravenous cyclical pamidronate for the prevention of bone loss were entered into the study. These patients received their care from endocrinologists at the American University of Beirut Medical Center (19 patients were cared for by a co-author GE-HF, and one by a referring endocrinologist). Patients were eligible for study entry if they had a baseline bone mineral density (BMD) within 6 wk, of starting pamidronate intravenously and did not take any other concomitant antiresorptive therapy. Patients with previous history of intake of other antiresorptive agents were included, provided these were stopped 6 mo prior to the baseline BMD and/or the start of pamidronate therapy, whichever came first. Of a total of 37 patients receiving intravenous pamidronate during the defined study period, only 20 fulfilled the above criteria: 7 male and 13 postmenopausal female patients. The other patients were excluded for the following reasons: Eight did not have a baseline BMD within 6 wk of starting pamidronate, five did not have their baseline and follow-up BMDs on the same densitometers, one had a reaction to the first infusion (severe bone pain), two did not take their infusions regularly every 3 mo, and one passed away. Included subjects had an age range of 31–77 yr with a mean age of 60± 13.5 yr (mean ± SD). Of these 20 patients, 7 have been on other bisphosphonates but stopped more than 6 mo prior to the baseline BMD and/or the start of pamidronate therapy. Patients were given intravenous pamidronate either because of intolerance or established contraindications to the use of oral bisphosphonates, as detailed in the Results, Subject's Characteristics section. All patients were asked to take calcium supplementation of 1000 mg/d and vitamin D between 400 and 800 IU/d during the treatment period.

Bone Mineral Density

Bone mineral density at the lumbar spine and/or hip was measured at baseline and within an average of 14 mo of study entry (range = 11–24 mo), using a Lunar DPX-L densitometer (Lunar, Madison, WI). The in vivo precision at our center, expressed as coefficient of variation percentage (CV%), is 0.92% (0.8) at the lumbar spine, 1.4% (1.2) at the femoral neck, and 1.1% (1.3) at the trochanter,as calculated from duplicate BMD measurements performed on the same day in 27–35 subjects. BMD response was expressed as percent change in BMD calculated as [(final BMD–original BMD)/original BMD] ×100. A percent change is assessed to be significant when the percent change in BMD exceeds $2\sqrt{2}$ CV% *(22).* Based on our precision data, these cutoffs for a significant change were 2.6% for the lumbar spine, 3.1% for the trochanter, and 4% for the femoral neck. For practical purposes and not to create different cutoffs for the two skeletal sites, any BMD decrease exceeding 4% over baseline value was considered statistically significant. This is consistent with another published cutoff of 4%, used to assess BMD response to treatment in two large osteoporosis randomized controlled trials *(23).* Osteoporosis and osteopenia were defined using the WHO operational definition for these terms: osteoporosis was a BMD T-score of ≤ –2.5; osteopenia was defined as a BMD T-score between –1 and –2.5 using the manufacturer's Caucasian database *(24).*

Pamidronate Administration

Each patient received cyclical (every 3 mo) pamidronate (Aredia) administered as 30 mg in a 500-ml solution of D5W run over 2 h. Seventeen patients received the infusion in the outpatient clinics and three were admitted to the hospital for 1 d. All patients were asked to take two tablets of aceta-

minophen right before the infusion and every 6 h for the first 24 h following the infusion, and to double their calcium intake the day before, the day of, and the day after the infusion.

Tolerability

Patients were retrospectively questioned about fever, myalgias, arthralgias, or bone pain following the pamidronate infusion either at their usual follow-up visits or, when that information was not available, by telephone calls several months after receiving their infusions.

Results

Subjects' Characteristics

The baseline characteristics are summarized in Table 1. There were 13 postmenopausal women and 7 men included. Fifteen patients (75%) had osteoporosis by BMD criteria at least at one skeletal site and five patients (25%) had osteopenia. The reasons for receiving intravenous (rather than oral) bisphosphonate therapy were as follows: poor gastrointestinal (GI) tolerance to alendronate in 11 patients, presence of a gastric or duodenal ulcer in 5 patients, presence of GI problems in 2 patients (dyspepsia and sensitive stomach), eosophageal varices in 1 patient, and poor compliance with oral medications in another.

Table 1
Baseline Demographic and Clinical Characteristics of the Study Subjects

	Male subjects	Female subjects	Total
Number *(N)*	7	13	20
Mean age (±SD) (yr)	54.7 ± 14.7	63.3 ± 12.3	60.4 ± 13.5
BMI	26.7 ± 2.7	25.0 ± 3.8	25.6 ± 3.5
Lumbar spine			
BMD (g/cm^2)	0.89 ± 0.14	0.85 ± 0.18	0.87 ± 0.16
T-Score	–2.9 ± 1.2	–2.9 ± 1.5	–2.9 ± 1.3
Femoral neck			
BMD (g/cm^2)	0.77 ± 0.10	0.68 ± 0.09	0.71 ± 0.10
T-Score	–2.4 ± 0.8	–2.5 ± 0.8	–2.5 ± 0.8
Trochanter			
BMD (g/cm^2)	0.70 ± 0.09	0.59 ± 0.10	0.63 ± 0.11
T-Score	–2.1 ± 0.9	–1.8 ± 0.9	–1.9 ± 0.9

BMD Response

The BMD response to cyclical intravenous pamidronate was studied at the lumbar spine and/or femoral neck and trochanter. Total hip measurements were not performed on all patients because of the unavailability of the appropriate software at the time of the study. The spine site was more likely to show a significant increase in BMD, followed by the trochanter, and, finally, by the femoral neck. Indeed, out of 13 patients, 8 (62%) showed a significant increase at the lumbar spine, 3 (23%) maintenance, and 2 (15%) experienced significant loss. These numbers were 7, 8, and 4 out of 19 patients (i.e., 37%, 42%, and 21%) for the trochanter, and 5, 9, and 5 out of 19 patients (i.e., 26%, 48%, and 26%) for the femoral neck, for increase, no change, and decrease respectively. A significant increase was achieved by 13 out of 20 patients (65%) at either the spine or hip. An overall positive response, defined as maintenance or increments in BMD (see the Methods section for details) was achieved at the lumbar spine, trochanter, and femoral neck in 85%, 74%, and 79% of patients, respectively. A total of eight patients, four females and four males, lost significantly at the lumbar spine and/or hip. Two patients, one female and one male, lost at both skeletal sites. In six of these patients, a workup to rule out secondary causes of bone loss, including calcium level, 25-hydroxyvitamin D, and TSH level, was negative. Subgroup analyses were performed by gender and showed no significant difference in BMD response by gender, although there was a trend for less response in male patients who did not achieve significance (Table 2).

The mean percent change at 1 yr was 3.2% for the lumbar spine, 3.8% for the trochanter, and 2.9% for the femoral neck in female subjects, with wide interindividual variations, as shown in Fig. 1. The mean percent changes were less dramatic in the male subjects, again with interindividual variations (Fig. 1).

Tolerability to Pamidronate

Intravenous pamidronate was generally well tolerated by the patients. The acute-phase reaction side effects were experienced by five patients. Three of these had fever, subjectively reported with the first infusion in all three patients and lasting a maximum

Table 2
BMD Response (Percent Change) in Male and Female Subjects

	Gender				
	Male		Female		
	N	%	*N*	%	*p*-Value[a]
BMD spine % change[b]					
Increase	3	60	5	62	
No change	1	20	2	25	
Decrease	1	20	1	13	
BMD trochanter % change					0.8
Increase	2	29	5	42	
No change	3	43	5	42	
Decrease	2	29	2	17	
BMD femoral neck % change					0.1
Increase	0	0	5	42	
No change	4	57	5	42	
Decrease	3	43	2	17	

[a] *p*-Value calculated by chi-square comparison between the genders.
[b] % Change: increase: >4% compared with baseline; decrease: <4% compared with baseline; no change: within 4% of baseline.

of 48 h. In one patient, the feeling of warmth recurred only with the second infusion, whereas it was repetitive in the other two patients. Myalgia was another common side effect developed by three patients to different extents and frequencies. One of these patients developed polyarthralgia in addition to the myalgia and fever upon the first infusion, and repetitively but less severely upon later infusions. An isolated case of elevated blood pressure with some dizziness following each infusion was noted. The other patients tolerated the infusions with no recalled side effects (Table 3).

Discussion

Our results demonstrate that cyclical pamidronate, administered at a dose of 30 mg every 3 mo, was overall well tolerated and prevented bone loss in the majority of patients with osteopenia or osteoporosis.

Although pamidronate is not approved by the Food and Drug Administration for use in osteoporosis, it has been tried in small studies with positive results; albeit limited details regarding response were available *(19–21).* The dose of 30 mg was chosen in our practice in view of the currently available data, suggesting maintenance of bone density with that dose *(19–21).* We are unaware of any formal dose-response studies systematically evaluating the impact of various doses of pamidronate given intravenously on the magnitude of BMD changes over time. One study evaluated different doses of pamidronate; however, direct comparison between the doses was not possible because of confounding by the frequency of intravenous infusions ranging from weekly to every 3 mo *(21).*

In view of the lack of a control group (calcium/vitamin D only) and because of the nature of the data acquisition from a clinical practice setting group, we are unable to unequivocally conclude that the observed results in BMD change were the result of the pamidronate infusions. Nevertheless, the mean BMD changes in response to the regimen used was similar to what has been reported with oral bisphosphonate therapy *(2–10),* with mean increments in the spine of 3.2–4.3% and in the hip of 0.3–3.8%, depending on the gender and specific hip site. We further evaluated BMD response in each individual based on BMD reproducibility data obtained in our laboratory. A sig-

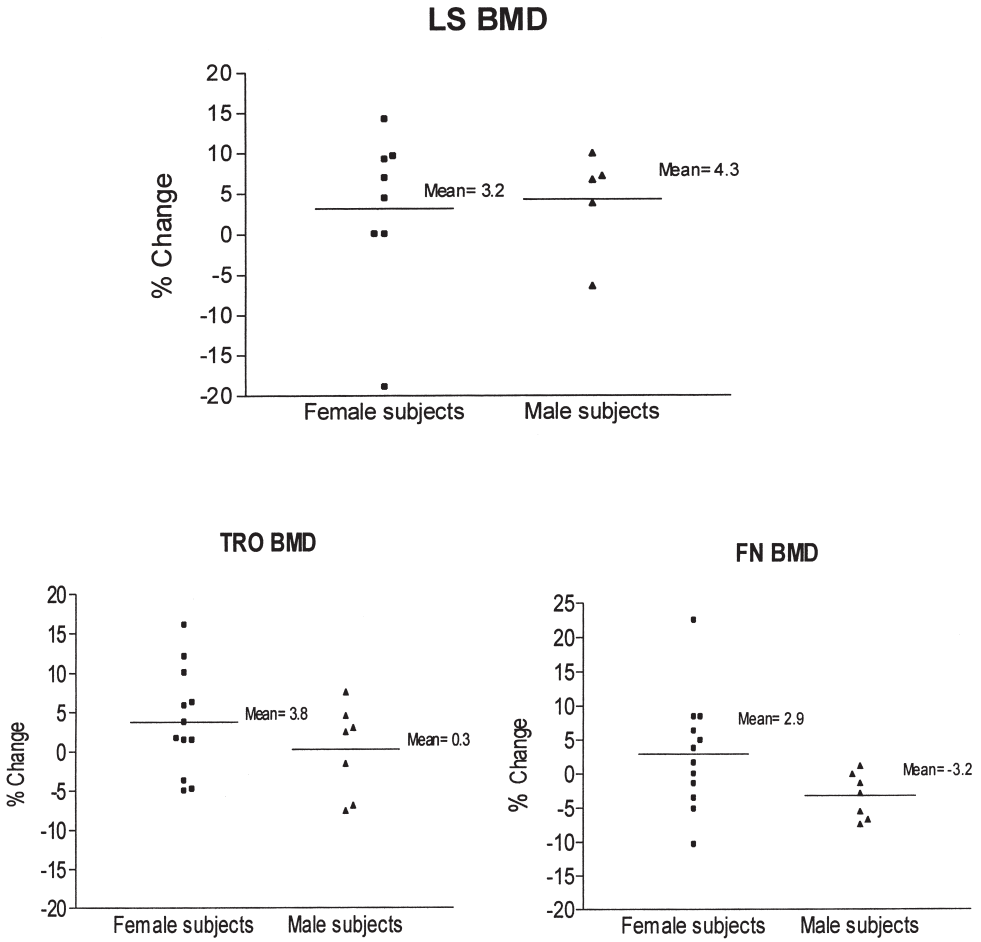

Fig. 1. Lumbar spine (LS), femoral neck (FN), and trochanter (TRO) BMDs percent change in response to pamidronate in male and female subjects. Thirteen postmenopausal women were in the study: seven patients had BMD of the spine and hip, five patients had BMD of the hip only, and one patient had BMD of the spine only.

Table 3
Side Effects with Pamidronate Infusion as 30 mg over 2 h

Side effect	Frequency *(N)*	Percent
Subjective fever	3	15
Myalgia	3	15
Arthralgia	1	5
Increased blood pressure	1	5
Dizziness	1	5
More than one of the above	3	15

nificant increase (i.e., BMD percent change that exceeded 4%) (see Methods section for full details) was achieved in two-thirds of subjects at either the spine or hip. However, a significant increment was more likely to occur at the lumbar spine, whereas maintenance was more likely to occur at the hip, as has been observed with most antiresorptive agents, including bisphosphonates *(2–10)*. Furthermore, the number of "nonresponders" (i.e., patients with BMD loss) varied between 1 and 2 patients out of the 13 female subjects (i.e., 13–17%). These numbers are higher than those obtained from the Fracture Intevention Trial and the Multiple Outcomes Raloxifene Evaluation Trial. Indeed, in those two trials, 1% and 8% of woman in each study lost more than 4% BMD at the total hip, respectively *(23)*. In our study, there was a trend for a less positive BMD response in male subjects, both at the lumbar spine

and hip, which did not, however, reach significance, possibly because of to the small sample size. This observation may be reflective of the dose used, which may need to be higher in the male subjects, in view of their larger size and body weight.

Pamidronate given every 3 mo was well tolerated except in five subjects (25%) experiencing side effects, findings that are slightly less frequent than previous observations, where these rates varied but ranged up to 40% *(25).* This lower incidence of side effects may be the result of potential recall bias of patients for side effects. In our study, the most common side effects were fever and myalgia, occurring in three (15%) of patients. Gallacher et al. reported a 41% incidence of pyrexia in osteoporotic patients receiving intravenous pamidronate *(26).* The lower incidence of pyrexia in our study may be the result of the routine use of acetaminophen for the first 24 h of the infusion. The underlying mechanism for the acute-phase response (pyrexia, leukopenia, fever) observed with pamidronate and other amino-bisphosphonates is unclear; this adverse event is mostly seen with the first infusion *(27, 28).* Other side effects with pamidronate include bone pain, mostly in patients with Paget's disease, and generalized malaise (in up to 7% of patients), which may last up to several weeks after administration *(26).* One patient did not enter the study because of severe prolonged bony pain after the first infusion.

In conclusion, pamidronate administered as 30 mg intravenously every 3 mo was overall well tolerated and stabilized bone mineral density in the majority of patients. Intravenous cyclical pamidronate is an attractive option for patients who are unable to take oral bisphosphonates.

Acknowledgments

The authors thank Sami Azar, MD, for referring a patient for inclusion in the analyses and nurse Yester Arslanian for diligently administering the pamidronate infusions.

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