Bisphosphonates for the Treatment of Charcot Neuroarthropathy

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*Excess osteoclastic activity is believed to be responsible for the destruction in Charcot neuropathic joint disease. By intervening early in the destructive process, it may be possible to halt the progression toward the devastating bone and joint deformity responsible for morbidity in Charcot feet. This retrospective study evaluated the effects of the bisphosphonate pamidronate on associated signs of Charcot. The 13 study patients (14 infusions) administered pamidronate were compared with 10 control patients who were treated with traditional immobilization methods. Limb temperature and alkaline phosphatase levels were measured as markers of the Charcot process. After pamidronate infusion, limb temperature decreased a mean 2.8°F by 48 hours and 7.4°F by 2 weeks. The alkaline phosphatase levels also decreased an average 53% 2 weeks after infusion. The control group showed no reduction in limb temperature at 48 hours, and had an average limb temperature reduction of 2.3°F at 2 to 3 weeks. This was significantly less than the temperature reduction in the treated group (*P = .008 *at 48 hours and* P = .001 *at 2 weeks). Mean alkaline phosphatase levels declined only 9% in the control group, a significantly smaller decline than in the pamidronate-infusion group (*P = .001*). These results suggest that pamidronate may be useful in halting the acute phase of Charcot neuroarthropathy.* (The Journal of Foot & Ankle Surgery 43(5):285-289, 2004)

Key words: Charcot, bisphosphonate, neuroarthropathy, pamidronate

In 1868, Jean Charcot defined a destructive process more appropriately termed neuroarthropathy (1, 2). In today's population, Charcot neuroarthropathy has become commonly associated with diabetes because of diabetic neuropathy. The destruction caused by Charcot neuroarthropathy has a complex cause in which joint destruction physiology consists of 3 main elements: hyperemia, neuropathy, and inflammation. The combination of hyperemia and trauma produces a chronic inflammatory cycle. This cycle includes recruitment of tissue macrophages and osteoclasts, with the osteoclasts removing and replacing injured osteoblasts and chondrocytes with underlying bone. At the cellular level, the deformation results in a demineralization of the hydroxyapatite latticework of bone, predisposing the bone to pathologic fracture and dislocation. This cyclic process of bone and cartilage damage creates what is visualized clinically and radiographically as exostosis formation and severe bone resorption, leading to the permanent joint deformity of the Charcot foot (1, 3–7).

Immobilization has been the cornerstone of treatment for Charcot neuroarthropathy. By impeding joint movement, the cycle of inflammation, bone destruction, fracture, and deformity is interrupted. The harmful effects of trauma are controlled in part by immobilization. However, bone destruction continues because of osteoclast activity. Simply stated, one may be able to slow down Charcot deformity by immobilization, but the damage posed by overactive osteoclasts still continues (1, 5, 7).

A very promising adjunctive therapy is the use of bisphosphonates. A rapidly growing body of literature supports bisphosphonates for the treatment of diseases of osteoclast overactivity (8–15). For example, pamidronate, a second-generation bisphosphonate, was originally used for patients with hypercalcemic states. Currently, its other uses include Paget's disease, osteoporosis, and neoplastic bone disease with hypertrophic ossification. However, the use of these drugs in Charcot neuroarthropathy has been limited to a few reports consisting of a total of 51 patients, with less than 10 of these patients in the United States (8, 13–15).

If bisphosphonate therapy has been proven to control osteoclastic activity in multiple conditions of bone, it is reasonable to believe that it may have a role in controlling osteoclastic activity in Charcot neuroarthropathy. The purpose of this study was to see if 1 infusion of pamidronate

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could stop or slow down the acute phase of Charcot neuroarthropathy.

Materials and Methods

This study included 33 patients who were diagnosed with acute Charcot neuroarthropathy from the period of October 1997 to January of 2001. These patients presented to Forest Park Hospital in St. Louis, MO, and Scripps Mercy Hospital in San Diego, CA. The diagnosis was formed from the patient's medical history and physical examination and from blood work, radiographs, and ancillary imaging. The only inclusion criterion for this study was a diagnosis of Charcot neuroarthropathy. Patients were excluded from the study if they did not present for follow-up evaluations, showed a bilateral Charcot process, or had a concurrent infection. Two study groups were created from these patients: group 1, which received pamidronate infusion, and group 2, which did not. Both groups also received traditional immobilization treatment.

Patients were evaluated and treated in both outpatient and inpatient settings. Limb temperature and blood alkaline phosphatase levels were measured in all study patients on the day of the infusion, and at 24 to 48 hours and 2 to 3 weeks after infusion. Limb temperatures were measured by using a dual temperature monitor with dermal sensors (Omnitherm, St. Louis, MO). The authors measured limb temperatures for each patient by placing the dermal sensor on the involved dorsal midfoot. The temperature was taken 5 to 10 minutes after removal of the dressing, cast, or walking boot from the extremity.

Group 1 (Pamidronate-Infusion Group)

All group 1 patients received pamidronate infusion. The patients presented to Forest Park Hospital from October 1997 to September 1999. All patients with a diagnosis of acute Charcot neuroarthropathy were considered for pamidronate infusion. Patients were excluded from consideration if they did not consent to the treatment, had a bilateral Charcot process, or had a concurrent infection. Data collected from these patients included complete blood count, serum electrolytes, liver function tests, alkaline phosphatase level, erythrocyte sedimentation rate, blood urea nitrogen level, and creatinine level. If abnormalities in blood-work values were noted, patients were excluded from consideration for pamidronate infusion. However, if the blood urea nitrogen/creatinine level ratio indicated impaired renal function, consideration was not rescinded. Pamidronate was still administered, but the dose was adjusted. No specific formula was used for adjustment.

The limb temperatures were recorded at presentation, 24 to 48 hours after pamidronate infusion, and 2 weeks after infusion ($\pm$36 hours). Serum alkaline phosphatase levels were measured at presentation and at 2 weeks after infusion therapy.

Each patient was kept nonweightbearing in a cast or removable boot for 6 weeks ($\pm$2 weeks). Side effects of pamidronate infusion were recorded when present.

Group 2 (Control Group: No Pamidronate)

Group 2 patients did not receive pamidronate infusion. This group consisted of 15 patients who presented to Scripps Mercy Hospital from August 1999 to January 2001 with acute Charcot neuroarthropathy. All patients with this diagnosis were considered for the study. The patients were excluded from the study if they did not consent to treatment, had a bilateral Charcot process occurring, or had a concurrent infection.

These patients were treated with traditional offloading means and were nonweightbearing from 12 to 39 weeks. The limb temperatures were recorded at presentation and at 24 to 48 hours and 2 weeks after presentation ($\pm$36 hours). Alkaline phosphatase levels were measured at presentation and at 2 weeks after presentation.

Statistical Analysis

Group 1 and group 2 findings, specifically limb temperature values and blood alkaline phosphatase levels, were compared. To determine whether the patient groups were similar before initiation of treatment, baseline temperatures and alkaline phosphatase levels at initial presentation were compared by using the Wilcoxon 2-sample rank-sum test. To determine if pamidronate improved the signs of Charcot neuroarthropathy, or if immobilization alone was responsible, the reduction in temperature and in alkaline phosphatase level in groups 1 and 2 were then compared. The Wilcoxon test was used to compare the reduction in temperature at 2 days and at 2 weeks after initial presentation. Similarly, the Wilcoxon test was also used to compare the reduction in alkaline phosphatase levels at 2 weeks after presentation. A confidence level of .05 was selected.

Results

There were 18 patients with 19 episodes of Charcot neuroarthropathy initially eligible for group 1 (the pamidronate-infusion group). Four patients were not included in the study because they were treated at the same time for Charcot and open wounds and osteomyelitis could not be excluded distinctly. One patient was excluded because of a

TABLE 1 Limb temperature and alkaline phosphatase levels

Patient	T 0 h (°)	T 24 to 48 h (°)	T 2 week (°)	Alkaline Phosphatase	
				0 h	2–3 weeks
Group 1[a]					
1	100.3	98.9	93.8	165	75
2	101.5	n/a	94.1	185	71
3	100.8	98.1	92	195	100
4	101.4	95.5	n/a	191	n/a
5	102.1	100	93.7	188	96
6	99.7	n/a	91.5	211	82
7	100.9	n/a	94.8	177	59
8	98.7	95.4	92.8	166	68
9	98.9	99.9	n/a	119	n/a
10	101.8	98.6	92.1	149	77
11	102.9	103	97.4	248	109
12	101.7	97.1	92.6	298	165
13	103.7	98.4	95.7	311	181
14	101	98.5	94.4	170	79
Group 2[b]					
1	100	99.8	97.2	199	172
2	99.8	100.2	100	222	203
3	101.4	102	101.1	255	237
4	102.3	102.3	98	182	169
5	98.8	99.3	95.5	168	173
6	101	101.7	99.1	149	111
7	102.6	102.2	99.9	189	157
8	100.2	101.2	98.1	234	202
9	100.3	100.9	96.5	256	254
10	99.2	100	97.2	190	182

Abbreviations: n/a, not applicable; T, temperature.
[a]Pamidronate infusion group.
[b]Control group (no pamidronate).

bilateral Charcot process. This left a study group of 13 patients, with 14 infusions.

An average temperature reduction of 2.8° F was noted 48 hours after administration of pamidronate as compared with the temperature at presentation. Temperature was also measured at 2 weeks after infusion, with an average reduction of 7.4° F (Table 1; Fig 1). There was also a mean 53% reduction in alkaline phosphatase levels, as compared with presenting values.

Side effects of pamidronate infusion were evaluated. Six of 14 infusions resulted in a drug fever. However, 4 of 13 patients were not evaluated for a postinfusion fever. Three of the evaluated patients recorded no fever. The exact values for drug-infusion fevers were not included. When a fever did occur, it subsided within 24 hours in all cases (Table 2). Five of 14 infusions resulted in mild gastrointestinal upset without emesis, which was transient (<24 hours' duration). None of the patients experienced an increase in pain after the infusion. None of the side effects resulted in a discontinuation of therapy or other complications.

TABLE 2 Side effects for group 1 (infusion group)

Patient No.	Drug Fever	GI Upset
1	Yes	Transient
2	n/a	None
3	No	None
4	No	Transient
5	Yes	Transient
6	n/a	None
7	n/a	Transient
8	No	None
9	n/a	None
10	Yes	None
11	Yes	Transient
12	Yes	None
13	No	None
14	Yes	None

Abbreviations: GI, gastrointestinal; n/a, not applicable.

Group 2, the control group, did not receive pamidronate infusion. This group consisted of 10 patients. In group 2, the average limb temperature increased by 0.4° F at 24 to 48 hours after presentation. At 2 weeks, there was 2.3° F average reduction in temperature after traditional nonweightbearing therapy alone. The alkaline

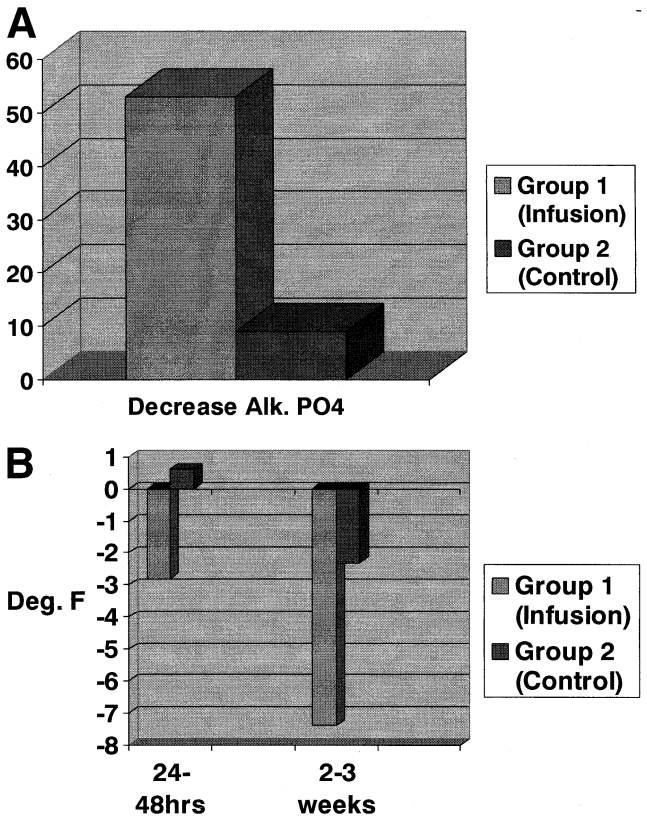

FIGURE 1 (*A*) Percent decrease in alkaline phosphatase. Alk., alkaline. (*B*) Limb temperature reduction.

phosphatase levels decreased a mean 9% 2 weeks after presentation (Table 1).

Statistical analysis, using the Wilcoxon 2-sample rank-sum test, showed no significant difference between the 2 patient groups at presentation ($P = .358$ for temperature and $P = .454$ for alkaline phosphatase levels). Reduction in temperature at 2 days and at 2 weeks was significantly greater for group 1 compared with group 2 ($P = .008$ and $P = .001$, respectively). Similarly, reduction in alkaline phosphatase levels at 2 weeks was significantly greater for group1 than for group 2 ($P = .001$).

Discussion

The exact mechanisms by which bisphosphonates inhibit bone resorption are not known. It is known that pamidronate is taken up extensively by bone, bound to the hydroxyapatite crystal of the bone matrix, and then acts to prevent osteoclast precursors from attaching to bone. Pamidronate also directly inhibits mature, already active, osteoclasts, and promotes osteoclast apoptosis. Finally, pamidronate decreases osteoblast-mediated osteoclast activation. Although pamidronate inhibits osteoclasts via several mechanisms, it has not been shown to impair mineralization (8, 9, 11, 13, 14, 16).

Dosing of pamidronate is usually performed intravenously because, similar to other bisphosphonates, it has poor oral absorption. When administered intravenously, 50% localizes to bone and 50% is excreted via the kidneys within 72 hours. The half-life of pamidronate is 30 minutes to 2 hours in circulation and up to 1 year in bone. It is dosed as 30 mg intravenously administered over 2 hours, 60 mg over 4 to 6 hours, or 90 mg over 4 to 24 hours. It is usually necessary to wait 7 days between treatments. Dosing adjustments based on the patients' renal function have been recommended because the renal clearance of pamidronate has been found to closely correlate with creatinine clearance. Generally, dosages should be reduced, or the time of infusion increased, for patients with renal impairment. Major reported adverse reactions are nausea, vomiting, diarrhea, electrolyte loss, infusion fever, and transient leukopenia. The average daily cost is approximately $575 for a 90-mg dose, not including the cost of hospitalization or administration. Most drug interactions involving pamidronate are seen with drugs that concomitantly lower calcium or those that interfere with the activity of calcium in protein binding or renal excretion (8, 9, 11, 12, 16).

Despite this study being somewhat abbreviated, its results give promise to pamidronate being used for treatment of acute Charcot neuroarthropathy. This study showed a decrease in the clinical signs of Charcot in a patient group receiving pamidronate infusion compared with a control group not receiving pamidronate. A 60- to 90-mg dose gave positive results for patients. In concurrence with other studies, temperature reduction correlated clinically with a decrease in inflammation and the acute process of Charcot (5, 8, 13–15, 17, 18). There was also a net reduction of alkaline phosphatase in all infusion patients, which has been correlated with a decrease in osteoclast hyperactivity in patients with healthy liver function (7, 8, 14, 15).

This study found that many patients exhibited a postadministration systemic fever of 1° to 3°F, which lasted only hours and subsided within 24 hours after the slow infusion. Obviously, the complete clinical picture must be appreciated so as to not mistake a drug-infusion fever for an underlying infectious process. Transient nausea and gastrointestinal upset during the pamidronate infusion was also observed, but this was also short lived. There were no major side effects related to pamidronate treatment in any of the study patients. Of note, bone pain has been reported as a side effect of pamidronate infusion. Interestingly, pamidronate is also used to treat bone-associated pain for many conditions (9, 11, 12). In this study, no increase in pain was noted after pamidronate infusion.

This study has several limitations. First, the patient cohorts were not randomized. In addition, the control group and infusion group were in different institutions and were not concurrent. Second, the obvious subjectivity of the examiners in different locations may have modified the results in some unknown fashion. Third, we also did not calibrate the sensor devices used. Because the tool was actually a different one at each site, some variability may have existed. Lastly, the number of patients enrolled in each arm was small. Larger trials would be necessary to show sufficient power of the results.

With an understanding of bone healing and the known and theorized mechanisms of the Charcot process, one can appreciate that cast immobilization alone may not always be sufficient. Many of these patients will be immobilized for more than 4 months (1, 4). If the loss of bone from cast immobilization is countered by a medical treatment, the benefits may be much greater than those seen with either therapy alone. The bisphosphonates, by inhibition of osteoclasts on a cellular level, may be one part of the solution.

It is even conceivable that pamidronate could be used prophylactically for patients at high risk of Charcot disease or for those with established Charcot disease who are undergoing surgical procedures. However, use of the drug in these situations has not been determined or defined. Also, cycles of multiple infusions over a longer time period may also be beneficial once the acute process has been halted by initial therapy. The promising results of this study suggest that further studies with a larger group of patients are warranted.

Conclusion

A brief trial of pamidronate therapy in Charcot neuroarthropathy has been presented. Improvement in signs of the acute destructive process has been documented. However, the true efficacy of bisphosphonate therapy for Charcot neuroarthropathy has yet to be established.

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