

Usefulness of Pamidronate in the Treatment of Charcot's Arthropathy

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Objective: To investigate the usefulness of pamidronate in the management of active Charcot's arthropathy.

Material and methods: Open prospective study with a follow-up of 12 months, including patients with active neuroarthropathy seen over a period of 3 years in our rheumatology unit. Patients received 3 pamidronate infusions at 0, 2, and 4 months. Clinical assessment, serum, and urine bone turnover markers, radiological exam, and scyntigraphy were performed before and after treatment.

Results: Seven patients were included (4F/3M), mean age, 51.3 years (30-64). The underlying disease was diabetes mellitus in 4 cases, syringomyelia in 2, and sensory and autonomic neuropathy in 1. The joints affected were shoulder, ankle, tarsians, metacarpophalangeal, and metatarsophalangeal. All patients showed a rapid resolution of clinical symptoms, with a clear reduction of all bone remodeling markers that achieved statistical significance for urine NTX and urinary pyridoline ($P=.04$ and $P=.03$, respectively). Six of 7 patients disclosed at the end of follow-up a radiological healing. Quantitative scyntigraphy showed a clear reduction of the bone ^{99m}Tm uptake. No important side effects were reported.

Conclusions: Pamidronate appears as a useful treatment for neuroarthropathy independently of the underlying disease. A rapid diagnosis and early pamidronate treatment could avoid severe articular consequences.

Key words: Charcot. Bisphosphonates. Neuroarthropathy. Pamidronate.

Utilidad del pamidronato en el tratamiento de la artropatía de Charcot

Objetivo: Investigar la utilidad del pamidronato en el tratamiento de la neuroartropatía en fase activa.

Material y métodos: Estudio prospectivo, abierto, con un seguimiento de 12 meses. En un período de 3 años todos los pacientes con neuroartropatía activa visitados en la unidad de reumatología recibieron tres infusiones de pamidronato a los 0, 2 y 4 meses. Se realizó valoración clínica, de marcadores de remodelado óseo en sangre y orina, radiografía simple y gammagrafía ósea cuantitativa antes y después del tratamiento.

Resultados: Se incluyó a 7 pacientes (4 varones y 3 mujeres), con una media de edad de 51,3 (30-64) años. La enfermedad de base fue diabetes mellitus en 4 casos, siringomielia en 2 y neuropatía sensitiva autonómica en 1. Las articulaciones afectadas fueron hombro, tobillo, tarsianas, metatarsofalángicas y metacarpofalángicas. Todos los pacientes mostraron una rápida resolución de los síntomas, con una clara reducción de todos los marcadores de remodelado óseo siendo estadísticamente significativa en el caso del NTX y piridolina en orina ($p = 0,04$ y $p = 0,03$, respectivamente). Seis de los 7 pacientes mostraron una mejoría radiológica. La gammagrafía cuantitativa mostró una reducción evidente de la captación. No se observaron efectos adversos importantes.

Conclusiones: El pamidronato parece un tratamiento útil para la artropatía de Charcot independientemente de la enfermedad de base. El diagnóstico precoz y la administración rápida del tratamiento puede evitar complicaciones articulares graves.

Palabras clave: Charcot. Bisfosfonatos. Neuroartropatía. Pamidronato.

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Introduction

Charcot's arthropathy is a devastating and incapacitating complication that appears in patients with sensitive neuropathy due to diseases such as diabetes mellitus,

syringomyelia, and others. Its physiopathogeny is poorly known. There probably is a predisposing factor such as sensitive neuropathy over which a triggering factor, such as trauma or infection, exerts some effect, activating the start of an inflammatory cascade led by an increase in the osteoclastic activity. It typically presents as an inflammatory process with heat, pain, swelling, and erythema, commonly being sent to rheumatology departments for evaluation, constituting a therapeutic challenge given the poor results that have been obtained with conventional treatment, especially in advanced cases.

Biphosphonates are potent inhibitors of osteoclastic activity and as such, they should be a good therapeutic alternative if one takes into account the accepted etiopathogenic theories of this process.¹ There are few studies that indicate the usefulness of biphosphonates in neuroarthropathy and no series has ever been published in a rheumatology journal. On the other hand, none of the publications have investigated the joint clinical, radiologic, scyntigraphic, and the effect on bone remodeling markers of biphosphonates. For this reason we have decided to analyze the effect of intravenous pamidronate on all of these parameters in patients with Charcot's arthropathy.

Material and Methods

Study Design

The study consists of an open, prospective therapeutic protocol with a 12-month follow-up. We include all consecutive patients with the diagnosis of active Charcot's arthropathy who were evaluated in our rheumatology department during 3 years (November 2002 to September 2005). The ethics committee of our hospital approved the protocol and all patients gave informed consent. Patients included in this protocol received 3 intravenous infusions of pamidronate at 0, 2, and 4 months. The dose was 60 or 90 mg depending on the patient's weight (<70 or >70 kg, respectively). In addition, all of the patients underwent traditional immobilization therapy. Active neuroarthropathy was defined according to the patients' clinical and imaging (simple x-ray and/or bone scyntigraphy) presentation. The clinical criteria were based on the presence of heat, pain, joint swelling with or without erythema, and the radiologic criteria in the presence of resorption of the joint surfaces. The scyntigraphic criteria were based on the presence of an increased uptake in the affected joint. All of the included patients had a normal kidney function (creatinine, 0.7-1.2 mg/dL for males and 0.5-0.9 mg/dL for females) and had peripheral sensitive neuropathy, which was diagnosed by a neurologist and confirmed by electromyography (EMG).

All patients were controlled for a year. The clinical evaluation was performed on each patient visit (0, 2, 4, 6,

and 12 months) and the bone remodeling markers, simple x-ray (2 simple radiologic projections of the affected joint), and bone scyntigraphic study (3 phase quantitative bone scyntigraphy with technesium-99) done at the beginning of treatment and at the end of follow-up (12 months). The study of bone remodeling markers included the determination of serum alkaline phosphatase (AF, 40-129 U/L, colorimetry, Roche; Mannheim, Germany), bone alkaline phosphatase (BAP, 5.5-21.9 µg/L, enzymatic immunoassay EIA, Beckman Coulter; Fullerton, California), and type I collagen N-telopeptide in the second urine voiding of the morning and under fasting (NTX, 3-63 nmol/mmol, EIA; Wampole, Princeton, New Jersey, United States), pyridoline (26-91 nmol/mmol, HPLC, CromSystems; Munich, Germany), and desoxypyridoline (3-21 nmol/mmol, HPLC, CromSystems; Munich, Germany).

Results

The study included 7 patients (Table 1) with a mean age of 51.3 (30-64) years. Baseline disease was diabetes mellitus in 4 cases, syringomyelia in 2 cases, and autonomic sensitive neuropathy in 1 case. The affected joints were tarso/metatarsal and/or intertarsal in 3 cases; metatarsophalangeal in 1 case; ankle in 1 case; metacarpophalangeal in 1 case; and shoulder in 1 case. Two of the diabetic patients (cases 4 and 6) presented a concomitant form of septic arthritis in the intertarsal joints. The diagnosis of concomitant septic arthritis was done upon finding an active foot ulcer and a culture positive for *Pseudomonas aeruginosa* in case 4 and for *Staphylococcus aureus* in case 6. In these 2 patients, specific antibiotics were started in addition to treatment with pamidronate.

All of the clinical parameters (pain, swelling, erythema) improved rapidly after the first infusion and these were the earliest effect seen after pamidronate administration. Bone remodeling markers were collected in a complete form in 5 of the 7 patients. In spite of the fact that not all of the markers were increased over the normal range in the baseline measurement, all of them decreased after therapy, which was statistically significant in the case of NTX in urine and pyridoline in urine (Table 2). All of the patients except 1 showed radiologic improvement with a marked sclerosis and reconstruction of the bone cortex (Figures 1 and 2). Only the patient with syringomyelia and shoulder affection due to neuropathy did not show radiologic improvement (case 1).

In the 3 cases in which a quantitative scyntigraphy was performed there was a reduction in the uptake of ⁹⁹Tc after treatment (Table 1); this reduction was superior to 40% in 2 of the patients.

Treatment was well tolerated and only 2 patients presented mild adverse events, nausea and fever, which did not lead to treatment interruption in any case.

TABLE 1. Clinical and Epidemiologic Characteristics of Patients With Charcot's Arthropathy^a

Case	Gender	Etiologic Diagnosis	Affected Joint	X-ray Simple		Bone Scyntygraphy ^b
				Before Treatment	After Treatment	
1	Female	Syringomyelia	Shoulder I	Normal	Joint destruction	Yes (40.71%)
2	Male	Diabetes mellitus	Ankle I	Fragmentation, subluxation, eburnation	Deformity, sclerosis	Yes (43.46%)
3	Female	Syringomyelia	1-3 MCP R	Normal	Normal	Yes (14.35%)
4	Female	Diabetes mellitus	Tarsus I	Fragmentation, subluxation, loss of defined contours, eburnation	Sclerosis, defined contours, deformity	NR
5	Male	Diabetes mellitus	Tarsus I	Fragmentation, eburnation, soft tissue increase	Sclerosis	NR
6	Male	Diabetes mellitus	Tarsus R, ankle R, MTP R	Fragmentation, subluxation, loss of defined contours, eburnation	Sclerosis, defined contours, deformity	NR
7	Female	Autonomic neuropathy	MTP 2-3-4 R	Resorption of the MTP	Sclerosis, defined contours	NR

^aR indicates right; L, left; MCP, metacarpophalangeal; MTP, metatarsophalangeal; NR, not realized.

^bQuantitative bone scyntygraphy with technesium-99; data represent percentage of change in total counts after treatment.

TABLE 2. Bone Mineral Metabolism Markers^a

	AP Before/After	Bone AP Before/After	U-NTX Before/After	U-Pyr Before/After	U-D-Pyr Before/After
Case 1	88/67	16/9.9	50.6/9.4	146/86	19/8.5
Case 4 + inf	94/81	ND	77.3/36.1	110.4/68	13.8/5.9
Case 5	91/95	10.1/9.5	36.5/48.5	74.5/50.8	7.7/6.3
Case 6 + inf	1034/238	106/38.8	136/81.9	186/126	331/10.9
Case 7	63/48	ND	64/26	37/37	6.3/7.9
MD (95% CI)/P	-168 (-604 to 267)/NS	-24 (-115 to 66.6)/NS	-32 (-64 to -1.46)/.04	-37 (-68 to -5.4)/.03	-67 (-242 to 107)/NS

^aAP indicates alkaline phosphatase (40-129 U/L); Bone AP, bone alkaline phosphatase (5.5-21.9 µg/L); U-NTX, Cross-linked type I collagen N-telopeptides in urine (3-63 nmol/mmol); U-Pyr, pyridinoline in urine (26-91 nmol/mmol); U-D-Pyr, deoxypyridinoline in urine (3-21 nmol/mmol); Before/after, before and after treatment with pamidronate; ND, no data; + inf, with an added infection; MD, mean difference; CI, confidence interval; NS, not significant. Distributions analyzed through the Wilcoxon method.

Discussion

The exposed results show that intravenous pamidronate does not only improve symptoms of neuroarthropathy but, in most cases, also halts progression of the disease, as shown by the radiologic results.

It is interesting to point out that our study does not exclusively include diabetic patients with Charcot's arthropathy, making it possible that these results reflect the fact that intravenous pamidronate could be useful as treatment of Charcot independently of the baseline disease. Our results coincide with those of previous studies in which different biphosphantes and treatment protocols

were employed.²⁻⁶ We decided on the use of intravenous pamidronate because of its known prolonged antiresorptive activity. The treatment protocol was chosen taking into account the different modalities in treatment previously used by published studies and the modalities of treatment used in Paget's disease, which is another disease characterized by an increase in osteoclastic activity.^{7,8} After treatment with pamidronate we saw a rapid clinical improvement, followed by a reduction in bone remodeling markers, especially those related to bone resorption, indicating that the inhibition of osteoclasts plays an important role in the clinical improvement of these patients. The observed data coincides with previous studies⁵⁻⁹ and

Figure 1. Left tarsus with active Charcot's arthropathy before treatment with pamidronate. Fragmentation, subluxation, resorption, and a loss of defined contours can be seen.

reinforces the etiopathogenic theories on Charcot's arthropathy which hold that the osteoclastic activity plays a key role in the severity and destruction of the disease.¹⁻¹⁰ In 1 of the cases (case 3), treatment with pamidronate was administered very early in the course of the disease, halting the process before this could lead to radiologic damage. This finding indicates that the treatment is more effective in relation to how rapidly it is installed in order to prevent bone destruction. But, unfortunately, most of the patients included in this study were in an advanced stage of Charcot's disease with bone destruction evident in simple x-rays, a common fact in a disease that is under diagnosed. However, even in these cases, pamidronate seemed to halt the progression of the disease, as shown in the follow-up x-rays, in all cases except 1: 1 case (case 1)

Figure 2. Left tarsus of the same patient appearing in Figure 1, after treatment with pamidronate. Radiologic improvement can be seen in the form of sclerosis and contour definition.

with localized arthropathy of the shoulder and secondary to syringomyelia, which showed progression in bone destruction in spite of evident clinical improvement and an improvement in the bone remodeling markers. In this sense, we must accept the fact that treatment with pamidronate can be ineffective or only partially effective in some cases of Charcot's arthropathy. It is likely that the osteoclastic activity in the larger joints is more difficult to stop and which may require a more potent drug or a larger dose for its treatment.

Our series included 2 patients (cases 2 and 5) with a concomitant infection. In both cases, the combination of pamidronate with antibiotic treatment had excellent therapeutic results. Though a beneficial effect of the antibiotic cannot be excluded, it leads us to think that the

combination of antibiotics and biphosphonates is the best option in these cases because it leads to the eradication the possible triggering factor in the process and inhibits osteoclastic activity simultaneously; in this way, posterior complications which may be severe and incapacitating are avoided.

Quantitative bone scintigraphy with ^{99}Tc done in 3 phases is a technique which is normally employed for diagnosis of the disease but not for its follow-up. Our study shows a clear reduction in the activity after treatment with pamidronate in those cases in which we had analyzable data, though none showed normalization in uptake. The observed results coincide with those exposed previously regarding Charcot's arthropathy.¹¹

The study has some limitations such as: *a*) the number of patients included and the design of the study (open therapeutic protocol): in this sense, though all patients combined traditional immobilization and biphosphonates, the possibility that the larger beneficial effect was due to immobilization is remote because these patients were sent to our department after starting teatmnt with immobilization without showing an adequate response. On the other hand, the variables which were used to evaluate the therapeutic response (biochemical markers and, especially, radiologic findings) are objective variables with no influence on the placebo effect; and *b*) the short follow-up period does not allow us to exclude the reactivation of the disease or the loss of drug efficacy and the need for retreatment in the future.

In conclusion, our data shows that intravenous pamidronate is a useful treatment for Charcot's arthropathy independently of the baseline disease. In these cases, an early diagnosis

and a rapid administration of the drug could prevent severe and irreversible joint damage.

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