Rheumatology 2001;40:1394–1397

Treatment of reflex sympathetic dystrophy with pamidronate: 29 cases

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Abstract

Objective. To evaluate the efficacy of treatment with pamidronate in reflex sympathetic dystrophy (RSD) refractory to previous treatment.

Methods. We studied the response (disappearance of pain and functional improvement) to pamidronate (60 mg/day for 3 days) in 29 patients with RSD refractory to previous treatment for at least 14 days.

Results. On day 45, complete pain disappearance was observed in 86.2% of patients and functional improvement in 70%. The mean delay until the pain disappeared was 20 ± 14 days and the delay until functional improvement was observed was 29 ± 18 days. The mean delay of functional improvement was shorter in patients with post-traumatic RSD. Multivariate analysis did not reveal any factor predictive of response to treatment. Six (20.7%) patients suffered from side-effects (fever, diarrhoea).

Conclusion. Pamidronate appeared to be effective in the treatment of refractory RSD; however, these results need to be confirmed by a controlled placebo study.

KEY WORDS: Pamidronate, Bisphosphonates, Reflex sympathetic dystrophy, Algodystrophy, Complex regional pain syndrome (CRPS) type I.

Reflex sympathetic dystrophy (RSD), also called complex regional pain syndrome type I, is a lengthy and painful affection with a protracted course and chronic sequelae in 20–40% of patients, represented by functional impairment and/or debilitating pain [1–4]. The classical medical treatments (calcitonin, physical treatment, sympathetic blockade, etc.) are not always effective and new therapies must be evaluated. Accelerated and enhanced bone resorption and turnover play a central pathophysiological role in RSD [5–10]. Bisphosphonates were proposed in the treatment of RSD due to their action as potent osteoclast-blocking agents [9–14]. Another property of bisphosphonates is the ability to inhibit afferent nerve fibres, from whose endings various neuropeptides are released following disease and trauma; these neuropeptides may contribute to the pain and trophic changes observed in RSD [7]. Pamidronate, a second-generation bisphosphonate, has shown efficacy in diverse pathological situations (hypercalcaemia, bone metastasis, Paget's disease) and also appears to be effective at various doses in RSD [11, 12, 14, 15]. The aims of our study were to evaluate the effectiveness of a standard dose of intravenous pamidronate in the treatment of RSD, and to find factors predictive of response to treatment.

Submitted 6 June 2000; revised version accepted 14 June 2001.
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Patients and methods

We included all patients affected by RSD who were seen at our consultations or hospitalized in our Department of Internal Medicine between 1 January 1993 and 30 June 1999. All patients were treated with pamidronate, with their verbal consent, after failure of classical medical treatment for at least 14 days. Diagnosis of RSD was based on Doury's criteria [4]. All patients complained of pain associated with allodynia and/or hyperpathia, tenderness and reduced range of motion, symptoms in an area much larger than the primary injury, and symptoms aggravated by physical activity of the affected extremity [2]. Swelling and changed skin temperature and skin colour were not always present, especially in the shoulder. All patients had a bone scintigraph suggestive of reflex sympathetic dystrophy. The use of non-steroidal anti-inflammatory drugs (NSAID), calcitonin, steroids and infiltrations was not authorized during the study. Twenty-nine cases of RSD were studied, comprising 10 men (34.5%) and 19 women (65.5%); the average age was 53.0 ± 14.0 yr (range 14–81 yr), without significant difference between the sexes [men 53.6 ± 11.6 yr; women 52.6 ± 12.4 yr].

The duration of the disease before treatment with pamidronate, was on average 41.89 ± 38.90 weeks (range 2–163). For 20 patients [shoulder (16), knee (3) and wrist (1)], the quantification of the reduction in amplitude was on average $45.25^\circ \pm 15.0^\circ$ (range 30–70). The RSD was localized in the upper limb in 58.6% of cases, and in the lower limb in 41.4% (Tables 1 and 2). A secondary aetiology was found in 93.2% of patients ($n = 27$) (Tables 1 and 2). The treatments carried out before the use of pamidronate are mentioned in Tables 1 and 2. Pamidronate was administered intravenously in 500 ml of glucose 5% over 4 h with a daily dose of 60 mg over a period of 3 consecutive days (a cumulative dose of 180 mg). The treatment was evaluated on days 15 and 45 after the beginning of pamidronate treatment. The treatment was considered to be effective if the pain disappeared completely (stopping of analgesics). The functional improvement was judged to be favourable if the increase in range of movement was more than 20° compared with the range of movement prior to treatment. The measurements of the delay in pain disappearance and the delay in functional improvement were analysed as continuous variables. Side-effects of pamidronate were noted.

We performed the statistical analysis using SPSS. All P values were two-sided, with a value of <0.05 considered to be statistically significant. The tests used in the univariate analysis were the Wilcoxon non-parametric test for comparison of averages, the Fisher exact test for comparison of percentages and the Pearson non-parametric test for correlations between variables. Logistic regression was used for multivariate analysis of categorical variables (functional improvement and disappearance of pain).

Table 1. Characteristics of 29 patients treated with pamidronate

Patient	Sex	Age (yr)	Site	Aetiology	Disease duration (weeks)	Treatment before pamidronate	Pain on day 45
1	F	34	Shoulder	Trauma	24	C, I, N	Yes
2	M	58	Hand	Trauma	52	N	No
3	F	48	Shoulder	Cancer	8	C, I, N	No
4	M	27	Knee	Trauma	52	C, N	Yes
5	F	48	Shoulder	Diabetes	36	C, N	No
6	F	62	Shoulder	Idiopathic	32	C, I, N	No
7	F	68	Foot	Cancer	10	N, S	No
8	F	59	Knee	Trauma	163	C	No
9	M	46	Shoulder	Drugs	52	C, N, I	No
10	M	41	Knee	Idiopathic	2	C, N	No
11	F	40	Foot	Trauma	24	N	No
12	F	51	Foot	Trauma	24	C, N, B, G	No
13	M	53	Knee	Diabetes	24	C, N	No
14	F	56	Shoulder	Diabetes	24	C, N, S	No
15	F	68	Foot	Diabetes	24	N, I	No
16	F	44	Shoulder	Stroke	40	N	No
17	F	53	Foot	Trauma	12	C, N	No
18	F	81	Foot	Diabetes	38	N	No
19	F	71	Shoulder	Cancer	60	N, S	No
20	F	49	Shoulder	Hyperthyroiditis	52	N	No
21	M	59	Shoulder	Diabetes	32	C, N, I, S	Yes
22	M	69	Foot	Diabetes	108	N	Yes
23	F	51	Foot	Diabetes	26	C, N	No
24	F	14	Foot	Trauma	12	C, G	No
25	M	56	Shoulder	Diabetes	108	C, N, I, B	No
26	M	60	Shoulder	Drugs	12	C, N, I	No
27	M	68	Shoulder + hand	Diabetes	24	C, I, N	No
28	F	43	Shoulder	Drugs	20	C, N	No
29	F	61	Shoulder	Trauma	120	C, N	No

C, calcitonin; N, non-steroidal anti-inflammatory drugs; S, steroids; I, infiltration; B, β- blockers; G, griseofulvin.

Table 2. Characteristics of the 29 patients treated with pamidronate

Localization		Aetiology		Previous treatment	
Shoulder	51.7%	Stroke	3.4%	Calcitonin	69%
Hand	6.9%	Diabetes	34.5%	NSAID	93.1%
Knee	13.8%	Trauma	31%	Steroids	13.8%
Foot	31%	Hyperthyroidism	3.4%	Griseofulvin	6.9%
		Drugs	10.3%	β-blockers	6.9%
		Cancer	10.3%	Infiltration	32%
		Idiopathic	6.9%	Physical	55.2%

Results

On day 15 after the beginning of the treatment, total pain disappearance was obtained in 17 patients (58.6%) and functional improvement was observed in nine cases (45% of 20). On the 45th day after the beginning of the treatment, total disappearance of pain was obtained in 25 patients (86.2%) and functional improvement was obtained in 14 out of 20 patients (70%) (Table 3). The mean delay before pain disappearance was 19.96 ± 14.4 days, without significant difference between the sexes (men 15 ± 0 days, women 10 ± 4.3 days; $P = 0.079$). The mean delay until functional improvement was 28.95 ± 18.26 days, without significant difference between the sexes (men 32 ± 11 days, women 28 ± 20 days; $P = 0.154$). Functional improvement was faster in younger patients ($\rho = -0.460$; $P = 0.0031$). The aetiology of RSD varied according to age: trauma was more frequent in younger people ($\rho = -0.459$; $P = 0.012$). The mean delay until functional improvement was shorter in patients with post-traumatic RSD (16.9 ± 9.7 days) than in the other patients (34.5 ± 18.4 days; $P = 0.04$). No correlation was found between age and disappearance of pain. Localization in the lower limb did not seem to be associated with faster functional improvement ($\rho = -0.285$; $P = 0.14$) and the disappearance of pain was not significantly related to its localization ($\rho = -0.112$; $P = 0.58$). Multivariate analysis did not reveal any factor predictive of response to treatment. Side-effects were observed in 20.7% ($n = 6$) of cases [fever 20.7% ($n = 6$), shivers 17.2% ($n = 5$) and diarrhoea 10.7% ($n = 3$)].

Discussion

The natural course of RSD is lengthy and varies from 3 to 9 months [1–4] with chronic sequelae in about 30% of cases. This study, although imperfect because of the absence of a control group, gives objective evidence for the effectiveness of pamidronate in the treatment of RSD, as regards both pain disappearance and functional improvement. This series is comparable to published studies of the treatment of RSD with bisphosphonates (Table 4) as regards the age and sex ratio of the patients and the duration of the RSD. In contrast to the cases reported in other publications, 93.2% of the cases of RSD were secondary,

TABLE 3. Clinical evolution after pamidronate treatment

	Pain disappearance on day 45		Delay of pain disappearance (days)		Functional improvement on day 45		Delay of functional improvement (days)	
	(%)	*P*	(mean ± S.D.)	*P*	(%)	*P*	(mean ± S.D.)	*P*
Sex								
Men	66.7		27.8 ± 16		50		32.5 ± 11.3	
Women	94.4	NS	17 ± 12.1	NS	77.8	NS	27.8 ± 20.4	NS
Localization								
Upper limb	85.7		21 ± 14.4		64.3		29.5 ± 21.6	
Lower limb	86.7	NS	19 ± 14.9	NS	71.4	NS	28.3 ± 14.2	NS
Aetiology								
Post-traumatic	77.8		16.9 ± 13.5		77.8		16.9 ± 9.7	
Other	88.9	NS	21.3 ± 16.7	NS	65	NS	34.9 ± 18.1	0.04
Total	86.2		19.96 ± 14.4		70		28.9 ± 18.3	

TABLE 4. Treatment of reflex sympathetic dystrophy with bisphosphonates in the literature

	Number of patients	Characteristics of RSD	Characteristics of study	Bisphosphonate	Dose	Evaluation		
						Criteria	Day	Positive response
Maillefert *et al.*, 1995 [15]	11	Refractory	Open	Pamidronate i.v.	30 mg/day 3 days	Pain	90	55%
Cortet *et al.*, 1997 [14]	23	Refractory	Open	Pamidronate i.v.	Variable 1 mg/kg/day 1–3 days	Pain	30 60 90	58.8% 41% 38.8%
Adami *et al.*, 1997 [17]	20	10 naive + 10 refractory	Double-blind and open	Alendronate i.v.	7.5 mg/day 3 days	Pain, swelling, BMD	30	62%
Varenna *et al.*, 2000 [18]	32	16 naive + 16 refractory	Randomized double-blind	Clodronate i.v.	300 mg/day 10 days	Pain, CGA	40 90 180	72% 75% 93.2%

i.v., intravenous; CGA, clinical global assessment; BMD, Bone mineral density.

and an aetiological agent was usually found in only 50–75% of the cases [14–16]. This is probably due to the fact that patients were seen in a department of internal medicine. Our study only considered cases of refractory RSD, and is the only one that has taken into account the total disappearance of pain and improvement in the range of movement. It provides evidence of a satisfactory response on day 45 (86.2% for pain and 70% for functional improvement). As in our series, no factor predictive of response to pamidronate was found in the study (11 patients) of Maillefert *et al*. [15]. Cortet *et al*. [14] have already demonstrated, in a series of 23 patients, significant effectiveness of intravenous pamidronate on pain, expressed as a reduction in the scores of pain scales on the 30th, 60th and 90th days after the beginning of the treatment; however, pamidronate was given in variable doses (60–180 mg). Maillefert *et al*. [15] noted an improvement in six of 11 cases with a dose of 30 mg of intravenous pamidronate per day for 3 days (a cumulative dose of 90 mg), expressed as a significant pain reduction on day 90. A recent article on the pooled data of these two studies is similar in its conclusions [16]. Adami *et al*. [17] reported, in an open, controlled factorial trial *vs* placebo, a very significant reduction in pain and local oedema in 62% of patients treated with intravenous alendronate at a daily dose of 7.5 mg on 3 non-consecutive days (days 0, 15 and 30). They also noted an increase in bone mass 6 weeks after the beginning of the treatment. Varenna *et al*. [18] observed a significant decrease in pain and clinical global improvement in 15 patients treated with clodronate compared with the placebo group (17 patients). Pamidronate appeared to be effective and well tolerated in the treatment of refractory RSD. However, a randomized, double-blind, controlled placebo study is necessary to confirm this. Use of pamidronate as the first-intention treatment for RSD can be proposed. However, there are two limiting factors: the cost of pamidronate and the need for intravenous administration.

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