

Short-term intravenous therapy with Neridronate in Paget's disease

S. Adami¹, M. Bevilacqua²,
M. Brogginì³, P. Filipponi⁴,
S. Ortolani⁵, E. Palummeri⁶,
F. Ulivieri⁷, F. Nannipieri⁸,
V. Braga¹

¹Department of Rheumatology, Valeggio S/M, University of Verona; ²Hospital L. Sacco, Milan; ³Hospital F. Del Ponte, Varese; ⁴Hospital of Montelucre, Perugia; ⁵Centro Auxologico Italiano, Milan; ⁶Hospitals Galliera, Genoa; ⁷Ospedale Maggiore, Milan; ⁸Abiogen, Pisa, Italy.

Please address correspondence and reprint requests to: Silvano Adami, MD, University Hospital, 37067 Valeggio, Verona, Italy.

E-mail: adami@borgoroma.univr.it

Received on October 13, 2000; accepted in revised form on June 19, 2001.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2001.

Key words: Paget's disease of bone, bisphosphonates, neridronate.

ABSTRACT

Aims: To describe the effects of two consecutive intravenous infusions of aminohexane bisphosphonate (Neridronate) in patients with active Paget's disease of bone.

Methods: The study population included 83 patients, aged 41 to 85 years, randomized to 4 cumulative doses of Neridronate (25, 50, 100, 200 mg) given over 2 days, with a follow up of 180 days. The baseline serum alkaline phosphatase activity was at least 10% above the upper limit of the laboratory range. The response to treatment was assessed by changes in the serum total alkaline phosphatase (primary end point of the study), bone alkaline phosphatase and N-telopeptide urinary excretion.

Results: All Neridronate doses significantly suppressed the biochemical indices of disease activity. The nadir of total alkaline phosphatase levels ranged from -16 % to -57.5% of pre-treatment values in the four groups, with a dose-response relationship that was apparent even between the two highest doses. The proportion of patients still maintaining a partial response (decreases in serum total alkaline phosphatase > 25%) at the 6 month follow-up was also related to the dose: 98%, 67%, 57%, 21% in the patients given 200, 100, 50, 25 mg respectively. The proportion of responders in terms of bone alkaline phosphatase and N-telopeptide excretion changes was similar. Bone pain attributed to Paget's

disease was significantly reduced. A typical acute phase reaction (fever and/or arthromyalgia) occurred in 16 out of 83 patients.

Conclusions: We conclude that all of the Neridronate doses tested here were well tolerated and effective in decreasing, in a dose-related manner, the bone turnover parameters of Paget's disease. The highest dose (200 mg) resulted in the normalization of the markers of disease activity in more than 60% of the patients.

Introduction

Paget's disease of bone is characterized by a localized disorder of bone remodeling, starting with an abnormality in osteoclast-mediated bone resorption followed by an increase in formation, an event closely coupled to the increase in bone resorption (1). The newly formed bone is architecturally abnormal and prone to deformity and, less commonly, to fracture.

Bisphosphonates have been demonstrated to be potent inhibitors of bone resorption both *in vitro* and *in vivo* in animals and in humans, acting directly on the osteoclasts, the principal cell type responsible for bone resorption, and are considered the treatment of choice in Paget's disease (2).

The newest bisphosphonates, such as alendronate and risedronate, despite some preliminary experiences with IV administration (3, 4) have been developed for oral use (5-8), but this formulation is not appropriate for patients

Table I. Baseline characteristics of the study population (mean \pm SD or median with range) divided according the cumulative I.V. dose of Neridronate.

	25 mg	50 mg	100 mg	200 mg
No.	21	21	20	21
Sex (m/f)	11/10	6/15	8/12	13/8
Age	65.7 \pm 1.8	69.0 \pm 1.7	68.1 \pm 2.1	64.8 \pm 2.5
Weight (Kg)	73.5 \pm 3.0	66.5 \pm 2.8	70.0 \pm 2.6	71.5 \pm 2.9
Height (cm)	165.0 \pm 2.1	163.4 \pm 1.8	164.8 \pm 1.7	166.2 \pm 2.4
Total alkaline phosphatase (53-185 IU/L)	262 192-357	270 230-318	326 247-431	372 290-478
Bone alkaline phosphatase (12-41 IU/L)	62 40-94	74 59-91	90 64-125	104 77-140
N-telopeptide (5-65 nmol BCE/Mmol Cr)	265 186-376	306 237-395	385 255-583	361 254-512

with the severe form of the disease, in whom a prompt suppression of disease activity is warranted or in patients who do not tolerate oral bisphosphonates (9).

Neridronate (6-amino-1-hydroxyhexilidene-1,1-bisphosphonate monosodium) is a third generation aminobisphosphonate. Several pharmacological and clinical studies are already available in the literature, indicating that Neridronate is very well tolerated even at high doses (10-14). Its use in a limited number of patients with Paget's disease has shown that Neridronate in oral and intravenous (IV) preparations decreases serum alkaline phosphatase as well as other markers of disease activity (10, 13, 14). Bone histological examination showed that Neridronate is not associated with osteomalacia and does not impair bone mineralization (10, 11).

This multicenter, open, randomized study was conducted in patients with Paget's disease of bone to assess the safety, tolerability and efficacy of IV Neridronate and to determine the dose-response relationship, following present European registration guidelines.

Materials and methods

Patient population and study design

Eighty-three patients, aged 41 to 85 years, with active Paget's disease of bone diagnosed by radiographic methods together with bone scintiscans when a total body X-ray evaluation was not carried out, were enrolled in six centers. Patients were required to have increased serum activity of alkaline phosphatase. Fifteen of the patients had been treated in the past, but were excluded if they had received bisphosphonates within 12 months or calcitonin within 6 months preceding the study. They were also ineligible if they had severe cardiovascular, renal, hepatic or pulmonary disease, or other metabolic bone diseases that could interfere with the interpretation of the results. The baseline characteristics of the study population are shown in Table I.

Patients satisfying the entry criteria were randomly assigned to receive one of the following four neridronate (Abiogen, Pisa, Italy) regimens: 12.5 mg

(group 1), 25 mg (group 2), 50 mg (group 3), or 100 mg (group 4), administered once a day for two consecutive days. The study drug was diluted in 250 ml of saline and given intravenously over a period of at least 1 hour. At baseline and 7, 30, 60, 90 and 180 days after the treatment course, blood and urine samples were collected for bone turnover evaluation and safety assessment. At the same visits, a physical examination was also performed.

Biochemical parameters

Serum and urine samples were collected after an overnight fast and stored at -20°C for the evaluation of serum total and bone alkaline phosphatase (total and bone AP) and of urinary N-telopeptide of type I collagen to creatinine ratio (NTX).

Bone turnover markers were measured in a single laboratory. Total AP was assayed by a colorimetric kinetic method (Chema Diagnostica; normal range 53-185 IU/L). The intra- and inter-assay coefficients of variation (CVs) were below 1.6%. Bone AP was measured using the EIA method "Alk-phase-B" (Metra Biosystem; normal range 11.6-41.3 IU/L). Intra- and inter-assay CVs were 3.9% and 7.6%, respectively. NTX evaluation was carried out using an EIA (Osteomark, Ostex), and the results were expressed as Bone Collagen Equivalents (BCE; normal range 5-65 nmol BCE/mmol creatinine). Intra- and inter-assay CVs were less than 10%.

Efficacy assessment

The changes in total AP were considered as the primary end point, and changes in serum bone AP and NTX urinary excretion were considered secondary end points. The changes in total AP were clinically classified as follow: (a) the nadir total AP was defined as the mean of the 3 lowest consecutive values reached after treatment; (b) "complete response" was a reduction in the nadir total AP within the normal range; (c) a "partial response" to the treatment was defined as a decrease of 25% or more from the baseline value of total AP on 3 consecutive visits; and (d) a "partial response at 6 months" was a >

25% decrease at the 6th month of observation.

The primary goals of the trial were:

- To assess the safety and tolerability of Neridronate at the 4 different doses;
- To determine whether I.V. Neridronate induced a partial response in over 90% of patients and a complete response in over 50% for total AP;
- To determine if there is a dose-effect relationship.

At each visit a physical examination (including brief cardiac, respiratory, abdominal and musculoskeletal examinations, pulse rate and blood pressure) was carried out. Bone pain at skeletal sites with X-rays or bone scan evidence of Pagetic involvement was assessed using a body map and a linear visual analogue scale (VAS). The VAS was scored in millimeters from the left margin (0 = no pain) to the right (100 = most pain ever). Analgesic consumption was also recorded to indirectly assess the effect of treatment on pain.

The axillary temperature (morning and evening) was measured during the first 5 days, and the incidence of patients showing fever (temperature >37°C) was recorded.

The clinical trial protocol was approved by the Italian Health Authorities and afterwards was submitted for evaluation to the local Ethical Committees for the authorization. All patients provided their informed consent and the study was conducted in accordance with the declaration of Helsinki (Hong Kong revision, 1989).

Statistical analysis

The biochemical efficacy parameters total AP, bone AP and NTX were log-transformed to normalise their distribution and all analyses were carried out on the transformed values. Mean values and 95% confidence intervals were antilogged for presentation. Baseline homogeneity was checked by means of one-way analysis of variance (ANOVA). Percent changes from baseline within each group were evaluated by Student's t-test for paired samples. Between group comparisons at each visit and the changes from baseline to nadir values were analysed using one-way ANOVA; in cases of significance of the overall test,

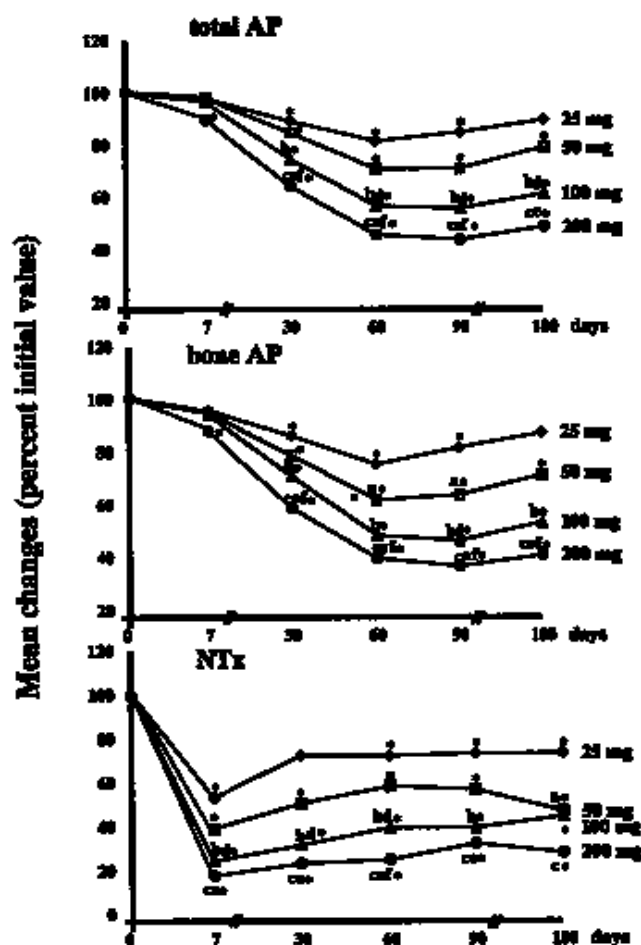


Fig. 1. Percent changes from baseline in total alkaline phosphatase (total AP), bone alkaline phosphatase (bone AP) and N-telopeptide excretion (NTX/Cr) (mean and 95% C.I.).

Between-group comparisons: ^a $p < 0.05$ 50 mg vs. 25 mg; ^b $p < 0.05$ 100 mg vs. 25 mg; ^c $p < 0.05$ 200 mg vs. 25 mg; ^d $p < 0.05$ 100 mg vs. 50 mg; ^e $p < 0.05$ 200 mg vs. 50 mg; ^f $p < 0.05$ 200 mg vs. 100 mg.

Within-group test of change from baseline: * $p < 0.05$.

pairwise treatment comparisons were carried out by the Newman-Keuls test. The proportions of patients showing either a partial or complete response, or a partial response at the 6th month were compared by means of the chi-square test. The extended Mantel-Haenszel test was used to determine if a trend in the response occurred over the 25 mg to 200 mg cumulative dose range. Statistical analysis was performed using the SPSS statistical package (SPSS Inc., Chicago, IL). All tests were two-tailed and significance was defined as $p < 0.05$.

Results

At baseline the indices of disease activity were somewhat higher in the patients given 100 or 200 mg, but these differences were not significantly different (Table I). The proportion of patients with polyostotic disease (38%) or previously treated with bisphosphonates was virtually identical among the four groups. All patients completed the

planned follow-up. Percent changes from baseline in the total AP (main efficacy parameter) showed a significant decrease over time in all treatment groups (Fig. 1). One month after the treatment course, the percent decrease in group 4 (200 mg) was statistically greater ($p < 0.05$) compared to the other treatment doses, with statistical significance maintained over most of the study points. At month 6 the AP changes found in groups 3 and 4 were not statistically different. The proportion of patients showing partial and complete responses in group 4 was 94.7% and 64.7%, respectively (Table II). The highest percentage of patients still showing a partial response at the end of the six-month period was also obtained with the highest dose ($p < 0.001$) (Table II). In group 4 the percent change to nadir was -56.5%. This decrease was statistically different ($p < 0.05$) from that observed in the other groups, indicating that the dose response relationship did not reach a plateau.

The evolution over time of serum bone AP showed a profile similar to that reported for AP (Fig. 1). A statistically significant difference ($p < 0.05$) between the two highest dose groups was already apparent at the first month and persisted until the end of the follow-up. Urinary NTX decreased within 7 days after the start of treatment in all study groups (Fig. 1).

At baseline 62 out of 83 patients reported pain which could be linked to Pagetic disease. Although the results showed a global and significant decline in the pain scores over time for all groups (data not shown), no differences among the treatment doses were detected.

An increase in body temperature 1 to 2 days after the IV infusion, together with the presence of flu-like symptoms, was observed in 16 patients (1 patient in group 1, 6 patients in group 2, 4 patients in group 3, and 4 patients in group 4). The symptoms completely disappeared within 4 days and there was no statistical trend for a dose-response relationship.

All biochemical safety parameters (serum transaminases, haematocrit, serum creatinine) were within the normal reference range over the study period. Mean levels of serum calcium significantly decreased at day 7 and returned towards the baseline values at the subsequent visits (data not shown). Serum calcium levels fell below the normal range in 75% of the patients given 200 mg Neridronate and in a smaller proportion with the other doses, but hypocalcemia was never symptomatic (data not shown).

None of the patients violated the protocol during the follow-up. The intention-to-treat analysis was not pre-planned. All patients who received IV Neridronate finished the 6-month follow-up, but 3 refused to participate in the trial after randomization. These 3 patients had higher initial AP values, ranging from 582 to 878, and the assigned therapy (cumulative dose) was 25 mg in 2 patients and 50 mg in one. This could explain the lower baseline disease activity found in the patients who were actually given the 25 and 50 mg doses.

Table II. Percent of patients with a complete response (normalization of total alkaline phosphatase), a partial response and a partial response at six months (see text for details).

	Cumulative Neridronate dose			
	25 mg	50 mg	100 mg	200 mg
Complete response (%)	21.1	18.8	58.8	64.7
Partial response (%)	21.4	33.3	73.7	94.7
Partial response at 6 months (%)	21.1	28.6	57.9	89.5

Discussion

This study demonstrates that Neridronate administered by IV infusion is a well tolerated treatment for Paget's disease of bone. Previous studies (10-14) included a limited number of patients, were not carried out according to the "good clinical practice" criteria necessary for registration procedures and were not designed as dose-finding studies. The cumulative doses tested ranged here from 25 to 200 mg given in 2 infusions. There was a proportionality between the dose and the effect that tended to flatten out with the highest dose, although without reaching an obvious plateau. This suggests that an even better outcome in patients with extremely active disease might be expected with larger doses. However, the baseline disease activity was somewhat more severe in the patients given the highest dose and this might have lowered the proportion of these patients with both a partial and a complete response. In this regard, it should also be pointed out that most of the patients included in this study had moderately active disease; only 32% had serum total AP levels more than 3 times above the upper limit of normal. In such patients, in future phase 3 clinical trials repeated treatment courses with 200 mg Neridronate may be necessary in order to increase the proportion of complete suppression of disease activity. The inclusion in this study of patients with moderately active disease reflects the recent tendency to treat not just for symptoms or when Paget's disease is extremely active, but also to treat patients with active disease as assessed by turnover markers (15). This new attitude has undoubtedly been driven by the favorable cost/benefit ratio of bisphosphonate therapy, which is likely to reduce the risk of late complications

that can seriously impair both functioning and the quality of life (15).

For comparable cumulative doses, the effects observed here are comparable to those reported in other pilot studies where a single Neridronate IV dose was tested (10, 14).

Even though a head-to-head comparison has never been carried out, the potency of Neridronate IV seems to be close to that of Pamidronate (16) and 10 times less than that of IV Alendronate (3, 4). The effect on bone markers of two IV infusions of 100 mg Neridronate are comparable to those obtained with the newest aminobisphosphonates, Alendronate and Risedronate given orally over 3 and 6 months (5-8). The tolerability of IV Neridronate was excellent. The only relevant side effect was an acute phase response that occurred in ~20% of the patients. This effect is shared by all aminobisphosphonates given intravenously; usually it does not last for more than 2-3 days and it does not occur after subsequent IV administrations (17).

There was no difference between the 12.5, 25, 50 and 100 mg daily infusions in terms of tolerability. It has been shown that the effect is equal whether the same cumulative dose of aminobisphosphonate is given over one or two infusions (16). Thus, in terms of convenience to the patient and cost a single or double 100 mg Neridronate infusion, depending on the disease severity, should be preferred to lower doses. At these doses significant suppression of disease activity may be achieved in a large proportion of patients with a single IV infusion that could be repeated a few months later if the improvement is not considered adequate.

References

1. SIRIS ES: Paget's disease of bone. In: FAVUS

MJ (Ed.): *Primer on the Metabolic Bone Disease and disorders of Bone Metabolism*. New York, Raven Press 1993: 375-84.

- FLEISCH H: Bisphosphonates in osteoporosis: An introduction. *Osteoporos Int* 1993; 3 (Suppl.): S3-S5.
- ADAMI S, SALVAGNO G, GUARRERA G *et al.*: Treatment of Paget's disease of bone with intravenous 4-amino-1-hydroxybutylidene-1,1-bisphosphonate. *Calcif Tissue Int* 1986; 39: 226-9.
- O'DOHERTY DP, MCCLOSKEY EV, VASIKARAN S, KHAN S, KANIS JA: The effects of intravenous alendronate in Paget's disease of bone. *J Bone Miner Res* 1995; 10: 1094-100.
- SIRIS ES, WEINSTEIN RS, ALTMAN R *et al.*: Comparative study of alendronate versus etidronate for the treatment of Paget's disease of bone. *J Clin Endocrinol Metab* 1996; 81: 961-7.
- SIRIS ES, CHINES AA, ALTMAN RD *et al.*: Risedronate in the treatment of Paget's disease of bone: An open label, multicenter study. *J Bone Miner Res* 1998; 13: 1032-8.
- MILLER PD, BROWN JP, SIRIS ES, HOSEYNI MS, AXELROD DW, BEKKER PJ: A randomized, double-blind comparison of risedronate and etidronate in the treatment of Paget's disease of bone. *Am J Med* 1999; 106: 513-20.
- BROWN JP, HOSKING DJ, STE-MARIE L-G *et al.*: Risedronate, a highly effective, short-term oral treatment for Paget's disease: A dose-response study. *Calcif Tissue Int* 1999; 64: 93-9.
- ADAMI S, ZAMBERLAN N: Adverse effects of bisphosphonates. *Drug Saf* 1996; 14: 158-70.
- ATKINS RM, YATES APJ, GRAY RES *et al.*: Aminoheptane diphosphonate in the treatment of Paget's disease of bone. *J Bone Miner Res* 1987; 2: 273-9.
- DELMAS PD, CAPUY MC, EDOUARD C, MEUNIER PJ: Beneficial effects of aminoheptane diphosphonate in patients with Paget's disease of bone resistant to sodium etidronate. *Am J Med* 1987; 83: 276-82.
- MCCLOSKEY EV, YATES AJP, BENÉTON MNC, GALLOWAY J, HARRIS S, KANIS JA: Comparative effects of intravenous diphosphonates on calcium and skeletal metabolism in man. *Bone* 1987; 8 (Suppl. 1): 35-41.
- COULTON LA, PRESTON CJ, COUCH M, KANIS JA: An evaluation of serum osteocalcin in Paget's disease of bone and its response to diphosphonate treatment. *Arthritis Rheum* 1988; 31: 1142-7.
- FILIPPONI P, CRISTALLINI S, POLICANI G, CASCIARI C, GREGORIO F: Paget's disease of bone: benefits of neridronate as a first treatment and in cases of relapse after clodronate. *Bone* 1998; 23: 543-8.
- SIRIS ES: Paget's disease of bone: Treatment philosophy for the twenty-first century. *Bone* 1999; 24: 55S-56S.
- GUTTERIDGE DH, RETALLACK RW, WARD LC *et al.*: Clinical, biochemical, hematologic, and radiographic responses in Paget's disease following intravenous pamidronate disodium: A 2-year study. *Bone* 1996; 19: 387-94.
- ADAMI S, BHALLA AK, DORIZZI R *et al.*: The acute phase response after bisphosphonate administration. *Calcif Tissue Int* 1987; 41: 326-31.