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ORIGINAL STUDY

Cyclic administration of pamidronate to treat osteoporosis in children with cerebral palsy or a neuromuscular disorder : a clinical study

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Eighteen osteoporotic (Z-score at or below 2.5) non-ambulatory children with cerebral palsy or a neuromuscular disorder received cyclic intravenous administration of pamidronate.

One year after treatment, bone densitometry showed an improvement in all patients : a mean increase of 13% +/- 15% standard deviation (SD) ($p < 10^{-5}$) on the global data, and a mean increase of 27% +/- 15% ($p < 10^{-5}$) on the most significant area for each individual patient.

Clinical improvement was found in all patients, with a decrease in pain on manipulation, and no new fractures. No major adverse effects were reported.

Cyclic intravenous administration of pamidronate is a useful tool in the treatment of osteoporosis in these children.

INTRODUCTION

Osteoporosis is a common finding in severe neuromuscular or cerebral palsy patients. It contributes to pathological fractures, "bone" pain and thus difficulty in everyday care and physical therapy (*13, 14, 16, 23*).

The classical therapeutic strategies including physical therapy, weight bearing, appropriate diet and supplementation with calcium and vitamin D are not always efficient in reducing the loss of bone mass in these patients.

Biphosphonates have been used for several years in the treatment of osteoporosis in different conditions in adults (*2, 24*), and more recently in children (*1, 4, 7-10, 18-21, 25, 26, 28-30, 32-34, 36, 37*). Much less has been published on their use in neuromuscular conditions (*17, 31*).

In the present prospective study, the clinical aspects and changes in bone densitometry were studied in 18 non-ambulatory osteoporotic children with cerebral palsy or a neuromuscular disorder, after they received cyclic treatment with pamidronate.

The results show that cyclic intravenous administration of pamidronate is a useful adjuvant in the difficult management of osteoporosis in these children.

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Table I. — Patients' clinical data

Patient	Sex	Age	Diagnosis	Fractures	Type of fracture	"Bone" pain	First Z-score	"special region"
1	F	8 y 3 m	CP- Like *	Yes	Proximal femur	Yes	-2.5	Pelvis
2	F	9 y	CP- Like	Yes	Proximal femur	Yes	-3.1	Pelvis
3	M	15 y	CP**	Yes	Multiple. Tibia	Yes	-4	Lumbar Spine
4	M	10 y 8 m	DUCHENNE	No		Yes	-3	Spine
5	M	11 y 8 m	CP	Yes	Multiple. Tibia	Yes	-5.9	Spine
6	F	9 y	SMA***	Yes	Proximal Femur	Yes	-2.5	Lumbar Spine
7	M	12 y 5 m	DUCHENNE	Yes	Distal femur	No	-2.5	Subtotal
8	F	12 y 8 m	CP	No		Yes	-2.5	Spine
9	F	9 y 10 m	MYOPATHY	Yes	Distal femur	Yes	-2.5	Subtotal
10	F	5 y 10 m	CP	Yes	Multiple. Proximal femur	Yes	-2.5	Pelvis
11	M	11 y 10 m	DUCHENNE	Yes	Humerus	Yes	-2.5	Spine
12	M	11 y 10 m	DUCHENNE	No		Yes	-2.5	Subtotal
13	M	18 y 2 m	CP-Like	Yes	Multiple. Tibia	Yes	-7.7	Lumbar Spine
14	M	9 y 8 m	DUCHENNE	Yes	Humerus	No	-2.5	Spine
15	M	14 y 4 m	CP	Yes	Multiple. Tibia	Yes	-4.3	Lumbar Spine
16	F	9 y 5 m	CP	No		Yes	-3.5	Lumbar Spine
17	M	13 y 2 m	CP-Like	Yes	Distal femur	Yes	-2.5	Subtotal
18	M	16 y 1 m	CP	Yes	Multiple. Tibia	Yes	-4.3	Lumbar Spine

**CP : Cerebral Palsy, *CP-Like : Cerebral palsy like syndrome, ***SMA : Spinal muscular atrophy.

PATIENTS AND METHODS

To be included in the present prospective study, the children had to be diagnosed with non-ambulatory cerebral palsy or neuromuscular disorder (spinal muscular atrophy, Duchenne muscular dystrophy, other severe myopathy) and to suffer from osteoporosis.

Osteoporosis was suspected because of fracture(s) with minor or absent trauma or multifocal "bone" pain on manipulations with no other obvious reasons.

Osteoporosis was then quantified by bone densitometry (Dexa : Dual X-ray Absorptiometry using Hologic QDR 4500A) and a Z-score at or below 2.5 standard deviations was considered for treatment (*34*). The Z-score was used to confirm osteoporosis before starting the treatment, but the actual bone densitometry (g/cm^2) was used for analysis of the final results .

Standard laboratory tests (renal function, ionogram, ...) as well as radiographs were done when deemed necessary for each particular patient but are not the object of review in this study.

Eighteen children (7 girls and 11 boys) fitted those criteria and had appropriate follow-up to be included in the study. There were 11 patients with severe quadriplegic cerebral palsy (or cerebral palsy like syndrome), 5 patients with Duchenne muscular dystrophy, one patient with another severe myopathy and one patient with spinal muscular atrophy.

The mean age was 11 years and 4 months (range, 5 years and 10 months to 18 years and 2 months) at the start of treatment. The two older children included were physically completely "prepubertal" and suffered from cerebral palsy like syndromes.

Fourteen of the 18 children suffered at least one pathological fracture : six had multiple fractures. The lower extremities were involved in 12 patients and the humerus in two. In the lower extremities, 8 patients had at least one femur fracture (four proximal fractures, one diaphyseal fracture and three distal fractures), 5 patients had a tibia fracture and two a humerus fracture. Four patients had no obvious fractures, but obvious discomfort on manipulations.

Sixteen of the 18 patients had pain on manipulations and transfers. They received the treatment as described by Glorieux *et al* in 1998 (*8*) : pamidronate disodium diluted in 250 to 500 ml isotonic saline and administered by slow intravenous infusion over a four-hour period on each day for three consecutive days. The dose was 3.0 mg per kg body weight per infusion cycle (thus 1.0 mg per kg body weight per day). This dose had to be decreased in the 5 patients with Duchenne muscular dystrophy because of high persistent temperature and the perfusion had to be slowed down to a six-hour period. These measures solved the problem in these 5 patients. Three-day infusions were given every four months.

Supplemental intake of calcium and vitamine D appropriate for age and weight was given continuously.

Table I summarizes the clinical data of the 18 patients.

After one year, patients (when possible) and/or parents/caretaker were questioned about their perception of the treatment results on general comfort.

Bone densitometry of the whole skeleton was performed again after one year of treatment. The exact bone densitometry values in gr/cm^2 were used to analyse the data.

Data of all the areas of the body were available for interpretation for 8 patients. Three patients had orthopaedic surgeries with the hardware still in place, and the "regions" with hardware were therefore excluded. In 7 patients, despite all efforts and patience, contractures and difficulty in positioning resulted in part of the data being unavailable.

All patients had overall osteoporosis, but one (or several) particular region(s) could be more affected than others, and special attention was then also drawn to that or those specific region(s) : the spine in 9 patients in whom surgery for scoliosis was planned, the pelvis in two patients with proximal femur fractures.

Total bone mass, "subtotal" bone mass, selected area(s) (lumbar spine, pelvis...), spine, were reviewed. Moderately involved and severely involved patients were also studied, as well as the patients with cerebral palsy versus those with a neuromuscular disorder.

Descriptive statistical analysis was applied to the data with means, standard deviations and p-values for comparisons.

Statistical analysis with a mathematical model was also applied to the actual BMD (Bone Mineral Density) values using a two factors repeated measures design with repeated measures on both factors. The first factor (further called "treatment" factor) is of binary type (before/after one year treatment) and the second factor is represented by a categorical variable whose categories are the various regions where BMD was measured. A "treatment" by "region" interaction is also included in the model.

Results of the statistical test are expressed by its p-value and estimation of a parameter is given by its (model) estimation +/- its standard error.

RESULTS

After one year of treatment, all patients had a positive clinical response.

No new fractures were observed, and pain on manipulation improved in all 16 patients with "bone" pain. Six patients already had a positive response on pain after one infusion cycle and the 10 others after the second cycle. This was reported by the patient (when possible) and/or parents/caretaker. Table II summarises the clinical results.

One year after treatment, descriptive statistical analysis of the change in bone densitometry showed an improvement in all patients : a mean increase of 13% +/- 15% ($p < 10^{-5}$) on the raw global data was found.

A mean increase of 27% +/- 15% ($p < 10^{-5}$) was found on the most significant area for each individual 18 patients (spine, proximal femur ...).

Total or subtotal change of bone densitometry could be studied in 11 patients and showed an increase of 12% +/- 7% ($p = 0.0004$).

The 10 patients with moderate osteoporosis (Z-score 2.5) showed a mean increase of 11% +/- 13% ($p = 0.03$) whereas the patients with severe osteoporosis showed an increase of 15% +/- 17% ($p = 0.04$).

The 14 lumbar spines with appropriate data showed an improvement of 31% +/- 15% ($p < 10^{-4}$).

Table II. — Clinical results after treatment

Patient	Patient /caretaker's opinion	New Fractures	Treatment
1	+	No	Stopped
2	+	No	Ongoing
3	+	No	Ongoing
4	+	No	Ongoing
5	+	No	Ongoing
6	+	No	Stopped
7	+	No	Stopped
8	+	No	Ongoing
9	+	No	Ongoing
10	+	No	Stopped
11	+	No	Ongoing
12	+	No	Stopped
13	+	No	Stopped
14	+	No	Ongoing
15	+	No	Ongoing
16	+	No	Ongoing
17	+	No	Ongoing
18	+	No	Ongoing

Table III. — Descriptive statistical results of change in bone densitometry

	Raw Data	**Specific region**	**2.5 Initial Z-score**	**<< 2.5 Initial Z-score**	**Lumbar spine**
Number of patients	18	18	10	8	14
Mean	13%	27%	11%	15%	31%
SD	15%	15%	13%	17%	14%
p value	$< 10^{-5}$	$< 10^{-5}$	0.03	0.04	$< 10^{-4}$

Table IV. — Global results statistics (mathematical model)

	Mean	Standard error	P-value
Before treatment	0.596	0.0125	$< 10^{-5}$
After treatment	0.665	0.0125	$< 10^{-5}$

Table III summarizes the descriptive statistical results of the bone densitometry.

The statistical analysis of data using the (incomplete) two factors repeated measures design lead to the following results : the "treatment" factor was found to be highly significant ($p < 10^{-5}$) indicating a positive effect of treatment (table IV).

The "region" factor is also significant ($p < 10^{-5}$) indicating substantial differences between various regions.

The treatment effect on the various regions is summarised in table V. The lumbar spine was the region with the most positive effect. Several regions (arms, legs) have no significant improvement with this mathematical model. They consist of more cortical bone. Besides, areas other than the spine are also more difficult to delineate with precision in these children, because of the retractions.

DISCUSSION

Osteoporosis affects a wide range of patients. Normal values for bone densitometry have been studied less extensively in children than in the adult, but they are becoming more and more available (*11, 12, 15*).

Bone markers have been reviewed by several authors (*5, 6*) but are not the subject of the present clinical study.

Since a long term study, by Brumsen *et al* (*3*), on the effects of biphosphonates concluded to the innocuity of pamidronate for the growth plate, its use in different osteoporotic conditions in children has grown. Other authors also noted that there were no adverse effects on the growth rate or growth plate appearance (*9*). One controversial publication by Whyte *et al* in 2003 described a biphosphonate-induced osteopetrosis, but the patient received four times the amount of pamidronate given by other authors (*27, 35*). In the present study, follow-up is not sufficient but up to know no major side effect has been observed.

A well-documented study of 30 children with osteogenesis imperfecta by Glorieux *et al* (*8*) showed effective results on pain relief, reduction in

Table V. — Statistical results (mathematical model) of treatment effect on different regions of the body

Region	Number of patients	Before treatment	After treatment	P-value
Left arm	11	0.439	0.465	0.47
Right arm	11	0.432	0.484	0.14
Left Thorax	11	0.430	0.479	0.17
Right Thorax	11	0.440	0.477	0.30
Thoracic Spine	8	0.478	0.565	0.04
Lumbar Spine	15	0.528	0.658	0.000003
Pelvis	8	0.518	0.622	0.01
Left Leg	10	0.620	0.667	0.21
Right Leg	8	0.633	0.652	0.65

fractures and improved Z- scores. Their treatment protocol was applied to the patients in the present study, where a positive response to the treatment was also found in these osteoporotic children with neuromuscular disease. Other treatment protocols are found in the literature (*33*) and also give encouraging results.

Cerebral palsy children, especially those severely involved, suffer from osteoporosis which contributes to pathological fractures and discomfort. Besides the suffering of these children, the treatment of these fractures is quite costly (*14, 16, 17, 23*).

Shaw *et al* in 1994 (*31*) treated 9 children with cerebral palsy and osteoporosis and found a good clinical result and improvement on DEXA studies.

Henderson *et al* in 2002 (*17*) evaluated in a double blind placebo controlled clinical trial 6 pairs of children, the efficacy of biphosphonate to treat osteopenia in non ambulatory quadriplegic children and reported good improvement.

The present study confirms these good results : all patients had improvement in bone densitometry, decrease of pain on manipulation, and no new fractures were observed.

In this study population, total body or specific regions were studied for assessing bone mineral density and obtaining good bone densitometry studies was the major difficulty because of orthopaedic hardware, spasticity and contractures.

Other authors have encountered the same difficulties : Henderson *et al* in 1997 (*17*) trying to find an area of reference for bone densitometry showed that there was a poor correlation, in the pathological range, between the lumbar spine and the whole body, and thus suggested not to use the spine data for extrapolation.

More studies (*11, 12, 15*) deal with the difficulty of obtaining good reproducible bone densitometry studies in these patients and elected to study the distal femur. This gives indeed more reproducible and accessible data, but in the present study total body bone densitometry measurements were performed. In the present study, a statistically significant increase in bone densitometry was found on the global data (13% +/- 15% ($p < 10^{-5}$), on the most significant area of each individual 18 patients (spine, proximal femur…) (27% +/- 15% ($p < 10^{-5}$). Total or subtotal increase in bone densitometry was also statistically significant in the 11 patients with sufficient data (12% +/- 7% ($p = 0.0004$)).

The lumbar spine was available for study as a specific area in 14 children and showed an impressive improvement of 31% +/- 15% ($p < 10^{-4}$). This was also confirmed by the statistical analysis using the mathematical model (table V). Data relative to the lumbar spine should therefore not be used for extrapolation to total body or other parts of the body.

Several regions (arms, legs) showed no significant improvement in the mathematical model. These regions are more difficult to delineate on regular BMD. We would thus recommend to use either the global data of the patients or a specifically affected region of the patient, as was done in the present study, or to select a well predefined zone as suggested by other authors (*11, 12, 15*).

We found no difference between the 10 patients with moderate osteoporosis (Z-score 2.5) (11% +/- 13% ($p = 0.03$)) and those more severely affected (15% +/- 17% ($p = 0.04$)).

Larson *et al* in 2000 (*22*) studied a population of 41 boys with Duchenne muscular dystrophy and found that their bone mineral density decreased rapidly once they lost ambulation, but also that their bone loss already started before loss of ambulation. They concluded than the use of biphosphonates should be attempted in these children at a young age, even before bone loss occurs.

In this study we noted improvement in the 6 patients with Duchenne muscular dystrophy, with no degradation of their bone density. These encouraging results corroborate the conclusions of Larsen as to preventive administration of biphosphonates, in patients with Duchenne muscular dystrophy.

Special attention has to be drawn to these patients with Duchenne muscular dystrophy since more difficulties were encountered in applying the treatment than in the other patients : all had high fever with the intravenous injection and the treatment protocol had to be adapted.

Treatment modalities vary among authors but all show a positive effect on osteoporosis : single-

day injection (*33*), three-day cycle every three months (*17*), every four months (*8, 9, this study*), every 6 months (*10*) and other variations (*7, 24*).

CONCLUSION

Biphosphonates are a useful tool in the treatment of osteoporosis associated with neuromuscular conditions in children, and the present study corroborates the promising results of the other studies on this particular subject (*17, 31*).

All patients in this study had a positive response clinically, and statistically significant improvement was seen on bone densitometry.

Nevertheless future studies could further divide this patient population : the severely osteoporotic non-ambulatory cerebral palsy or neuromuscular patients, and the specific group of patients with Duchenne muscular dystrophy who could receive the treatment preventively, even before they loose ambulation (*22*).

Future studies could also better define the treatment modalities : single-day injection, three-day cycle, oral treatment versus intravenous injections.

Other promising future possibilities would be the use of even more potent biphosphonates which could be given once a year in a single injection.

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