The clinical and radiological assessment of cyclic intravenous pamidronate administration in children with osteogenesis imperfecta

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Over the past 20 years, orally administered biphosphonates have been used extensively in the management of a number of common skeletal disorders of different etiology. Recently, in clinical practice, in a number of cases in whom oral therapy is insufficient or contraindicated, intravenous administration of pamidronate presents an alternative therapeutic option.

In order to investigate the clinical and radiological effects of cyclic intravenous pamidronate administration in children with osteogenesis imperfecta, a prospective open study of pamidronate treatment was undertaken in a cohort of eight bed-bounded (3.6-13.8 years) patients with severe osteoporosis and vertebral deformities. Pamidronate was administered at a dose of 0.5 mg/kg/day for three days. Tri-monthly cyclic intravenous infusions were performed over-one year. Bone density, verebral corpus heights, estimated volumetric bone density and biochemical measurements were analyzed. Side effects of the therapy were determined via questionnaire.

Significant reductions in the number of bone fractures and pain were observed in all patients. Ambulation scores were significantly altered and seven of eight patients became independent. Serum alkaline phosphatase levels decreased significantly. Lumbar X-ray and densitometry showed a striking improvement by the end of the treatment period. Even spaced dense lines corresponding to infusion periods were observed on roentgenograms of the radio-ulnar region. Pubertal progression and growth velocity were not affected inversely during therapy. Although we did not observe any severe side effect, one patient's blood urea nitrogen level was altered slightly.

In conclusion, one year cyclical pamidronate treatment seems to be effective and safe in improving bone mineralization and in reducing fracture incidence in severe osteoporosis.

Key words: intravenous pamidronate, osteogenesis imperfecta, clinical and radiological improvement.

Over the past 20 years, biphosphonates, synthetic compounds that suppress bone resorption and reduce bone turnover, have been used extensively in the management of a number of common skeletal disorders of different etiology, including osteoporosis, metastatic bone disease, osteogenesis imperfecta and Paget's disease of bone[1-9]. For whatever reason, the clinical symptoms range from only a slightly to a greatly increased frequency of fractures with extreme shortness, skeletal disproportions, frequent skeletal pain and confinement to a wheelchair. The patient's quality of life also worsens with time. Severe forms of osteogenesis imperfecta (OI) are characterized by generalized osteoporosis with

multiple fractures, chronic bone pain, progressive loss of mobility and deformity, which increase with time, particularly in childhood. Disability in these patients has remained severe[5]. Orally administered biphosphonates have a very low bioavailability (0.3-6%) and may induce gastrointestinal disturbances during the treatment period[10]. Recently, in clinical practice, in a number of cases in whom oral therapy is insufficient or contraindicated, intravenous (IV) administration of biphosphonates presents an alternative therapeutic option in OI[4,5,10-15]. In the skeleton, biphosphonates bind strongly to hydroxyapatite crystals, are locally released and are taken up by bone cells, remain embedded in bone for a long period, and can be released again slowly during bone remodelling. About 50% of an IV administered therapeutic dose concentrates selectively in the skeleton, while the rest is excreted unchanged in urine[16]. Determination of the serum concentrations of pamidronate over a sufficiently long period to fully characterize its disposition remains difficult. The long-lasting retention in the body results in low serum concentrations. Consequently, the design of therapeutic regimens is mainly based on clinical data. Although there is extensive experience with their use in adults, there is very little experience with their use in children. This study was designed to assess the clinical and radiological effect of cyclic IV administration of pamidronate treatment for on year in eight children with osteogenesis imperfecta.

Material and Methods

Since January 2000, this prospective pilot, open study has recruited eight children with osteogenesis imperfecta (OI) who have completed at least one year of treatment. There were five girls and three boys, age range 3.62-13.8 years. Five had type III and three had type IV OI. All children had severe osteoporosis with a history of multiple fractures and all were below the 3rd percentile in height for age. All had severe restriction of ambulation with confinement to a wheelchair or to being carried at all times prior to treatment and chronic bone pain with sleep disturbance. Two patients had undergone previous surgical instrumentation procedures. One patient had intramedullary rod insertion in the long bones. The other patient had severe skeletal deformities indicating she needs more reconstructive orthopedic surgery. Before starting the therapy, expected effects of pamidronate infusion and probable side effects were explained in detail to all patients' legal guardians. Written consent was obtained from them and from the child where appropriate.

Treatment

Disodium pamidronate (Aredia, Novartis Pharma AG, Basle, Switzerland) was diluted in 150-250 ml of isotonic saline and administered by slow intravenous infusion over a two-hour period on each of three consecutive days. The dose was 0.5 mg/kg per day and 1.5 mg/kg per cycle. Overall they received four cycles at a cumulative total dose of 6 mg/kg per year. The dose given was based on that used previously in other pediatric reports of treatment of osteogenesis imperfecta. The duration of therapy was thus far one year for all patients. The patient's calcium intake was regularly evaluated and was maintained at 600 to 800 mg per day through diet and supplementation. Their vitamin D intake was at least 4000 IU per day.

Measurements

Clinical Evaluation

Clinical evaluation, including assessment of anthropometric variables and pubertal development, was performed at each admission for pamidronate infusion. Accurate records were used in evaluating the growth rate before treatment. The subjects' mobility and ambulation were assessed using a five paint scale as follows: 0 (bed- or wheelchair-bound), 1 (standing with aids, but not functionally mobile), 2 (able to take a few steps with or without aids), 3 (able to walk short distances with or without aids), 4 (independent walking)[17]. Fracture data were collected as recounted by the subjects and confirmed by review of radiographs. Annual fracture rate was determined at 0, 6 and 12 months. Patients were monitored closely for clinical side effects and skeletal pain at every cycle.

Biochemical Measurements

Immediately prior to each infusion of disodium pamidronate, complete blood count (CBC), electrolytes, BUN, creatinine, calcium, phosphate, ALT, AST, alkaline phosphatase (AP), full urine analyses and urine calcium and creatinine levels were analyzed and repeated after 1, 2, 3 and 7 days. In order to evaluate hypercalciuria, calcium/creatinine ratio was analyzed.

Radiology

Roentgenogram of the upper and lower limbs, hand-wrist and spine (lateral views) were obtained at the beginning and at 6th and 12th months. All roentgenograms were examined on an ongoing basis by a radiologist at Ankara University, Faculty of Medicine, Department of Radiology, and he was unaware of the treatment status of the children.

Bone Density

Areal bone mineral density (BMD) (g/cm^2) of the second to fourth lumbar spine (L_2-L_4) was assessed by dual energy X-ray absorptiometry (Norland DEXA model XR-36; 394 A040; coefficient of variation 1%). Standard deviation scores (Z score) were calculated with our unpublished gender- and age-matched data. Estimated volumetric BMD (g/cm^3), a function of bone mineral content (g) per volume of bone (cm^3), was calculated assuming that the spine is cylindrical (π x radius^2 x height)[14,18-20]. The radius was derived from the width of the vertebra as measured by dual energy X-ray absorptiometry software.

Statistical Analyses

Analysis of data was performed using the SPSS 9.0 software (SPSS Inc., Chicago, IL). Differences in mean values were assessed by the Mann-Whitney rank-sum test.

Results

The clinical and biochemical characteristics of the patients are shown in Table I.

Clinical Outcome

Bone pain ceased in all patients after the first cycle. This was the first positive clinical outcome observed. While fracture rate was 3.80±1.21 per year at the onset of therapy, none of the patients had new fractures during this one-year therapy period. All of these eight patients were immobile and bed bounded with score 0 at the beginning of the therapy. Five patients had score 2 at the end of second cycle and progressed to score 4 by the end of year. Two of them showed slower progression compared to others and scored 3 at the end of the year. One patient was score 1 after the last infusion. This patient was the oldest patient (aged 12.8 at the onset of therapy) and she had fixed flexion deformities at hip, knees and ankles prior to treatment. She still needs reconstructive surgery for these deformities. These deformities did not alter during therapy and at the end of the year she was hardly able to bear weight.

Seven patients were prepubertal and the oldest patient was at Tanner stage 2 before treatment. At the end of one year this patient's pubertal stage was at Tanner 3 and the others were still prepubertal. The growth rate was not affected inversely during this therapy. Their height standard deviation score (HSDS) was increased by a mean of –5.60±3.30 to –4.40±3.20 ($p<0.01$). A positive HSDS gain was obtained during this therapy (0.62±0.25).

Biochemical Measurements and Side Effects

Before the treatment all patients' biochemical analyses were in normal range except for high AP levels, After the one-year treatment period,

Table I. Clinical and Biochemical Characteristics of the Patients at the Onset and at the End of Pamidronate Therapy

	Onset of therapy	At the end of one year	Significance
Annual fracture rate	3.80+/-1.21	0	P<0.01
Height SDS	-5.60+/-3.30	-4.40+/-3.20	P<0.01
Increment of HSDS	–	0.58+/-0.26	–
Ambulation score	8 cases: 0	5 cases:4; 2 cases:3, 1 case: 1	–
Bone pain	8 cases	None	–
Ca (mg/dl)	9.63+/-0.44	9.81+/-0.34	p>0.05
P (mg/dl)	5.15+/-0.44	5.16+/-0.53	p>0.05
Serum AP (IU/I)	331.50+/-113.39	258.83+/-75.68	P<0.05
BMD (L2-L4)	0.350+/-0.120	0.470+/-0.200	P<0.05
BMD Z score	-3.825+/-1.54	-1.482+/-1.676	P<0.05
Increment of BMD Z score	–	1.87+/-2.27	–
Vertebral corpus height (mm; L2)	14.80+/-9.01	23.40+/-8.29	P<0.05

SDS: standart deviation score; BMD: bone mineral density; HSDS: height SDS.

mean AP was decreased from 331.50±113.39 to 258.83±75.68 (U/I) ($p<0.05$). Urea and electrolytes, CBC, and liver function tests remained normal in all patients except one throughout the study. Her urea was increased slightly at the last cycle but it came to within normal range with hydration. Her renal function and renal ultrasound examinations remained normal.

One patient had symptomatic hypocalcemia at the second cycle and he required IV calcium replacement. None of the patients had hypercalciuria throughout the treatment period.

The most common side effect was a transient low grade fever (<38°C) which occurred during and immediately after the first infusion. Some of the patients complained of back and lower limb pain but these flu-like syndrome manifestations were controlled with standard doses of acetaminophen. These side effects did not occur with subsequent infusions.

Radiological Changes

At the onset of therapy 1/8 had wedge type, 1/8 had biconcave type and 6/8 had both wedge and biconcave vertebral deformities at lumbar vertebral site. No new crush fractures were seen during therapy; instead a significant increase was noted in vertebral height ($p<0.05$) (Fig. 1).

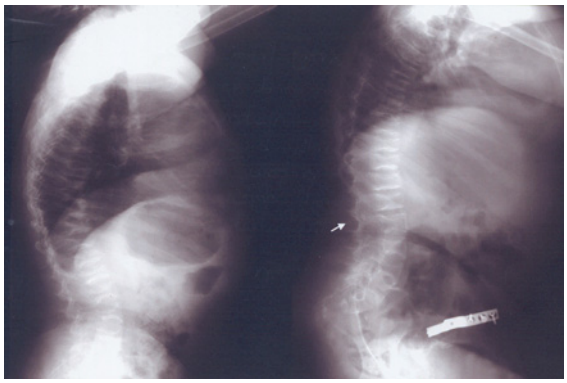

Fig. 1. Lateral X-ray film of the lumbar spine of a patient before and after one-year cyclic pamidronate treatment. Collapsed vertebral bodies with biconcave deformities are shown with arrow. A remarkable increase in vertebral corpus height and density was demonstrated.

Characteristic dense lines appeared under the growth plates, particularly in the distal forearms (Figs. 2, 3). There were regular spaces between these lines. It was interesting that these lines corresponded with the intervals of cycles, and that in every cycle, one lines appeared (Figs. 2, 3). Systematic surveys of the epiphyses showed no evidence of widening or rachitism. Bone age was not affected inversely and was associated with the growth rate and not with the change of metaphysis.

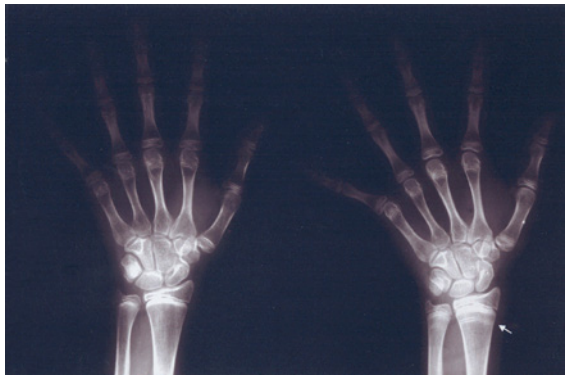

Fig. 2. A radioulnar roentgenogram of a patient who was administered two cycles of intravenous pamidronate treatment.

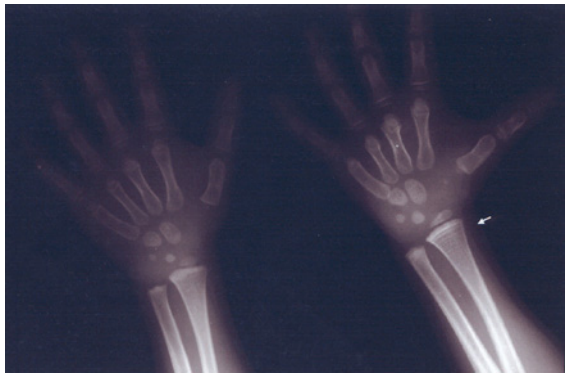

Fig. 3. A radioulnar roentgenogram of a patient at the end of four cycles of intravenous pamidronate treatment.

Bone Density

Dual-energy X-ray absorptiometry results are given in Table II. All patients had low bone mineral density at the beginning of therapy. During one year IV cyclic pamidronate therapy, BMD L_2-L_4 increased by a mean of 0.350±0.120 to 0.470±0.200 (g/cm^2) ($p<0.05$). An improvement in Z score from a mean of –3.825±1.540 to –1.482±1,676 was found ($p<0.05$). There was a significant increment in mean vertebral height (L_2) (14.80±9.01 to 23.40±8.29; $p<0.05$). An improvement in Z score from a mean of –3.825±1.540 to –1.482±1.676 was found ($p<0.05$). There was

Table II. Dual-energy X-ray Absorptiometry and Radiologic Measurements

Lumbar spine (L_2-L_4)	Month	Mean±SD (range)	Increment (%)
Bone area (cm^2)	0	21.37±10.34 (9.67-39.13)	–
	6	20.71±11.97 (10.67-37.90)	88.89±26.22 (50.67-110.34)
	12	25.04±10.30 (14.38-41.64)	121.82±14.28 (106.41-148.71)
Bone mineral content (g) (BMC)	0	8.46±7.28 (2.16-23.63)	–
	6	11.90±9.01 (2.69-23.91)	118.35±11.49 (101.18-125.23)
	12	13.26±11.51 (4.02-39.09)	159.50±21.38 (131.45-186.15)
Areal bone density (g/cm^2) (BMD)	0	0.350±0.120 (0.224-0.604)	–
	6	0.440±0.160 (0.252-0.631)	119.65±13.48 (104.50-133.62)
	12	0.470±0.200 (0.282-0.867)	131.38±15.37 (106.82-149.43)
Estimated bone volume (cm^3)	0	59.15±40.17 (20.29-140.78)	–
	6	58.82±50.44 (24.83-131.88)	89.38±36.23 (38.06-122.35)
	12	78.46±41.56 (36.17-149.36)	142.07±26.18 (123.53-178.27)
Estimated volumetric bone density (g/cm^3) (vBMD)	0	0.130±0.02 (0.107-0.168)	–
	6	0.240±0.180 (0.108-0.181)	163.31±106.53 (101.50-322.63)
	12	0.150±0.04 (0.110-0.242)	114.01±16.53 (97.73-143.96)

a significant increment in mean vertebral height (L_2) (14.80±9.01 to 23.40±8.29; $p<0.05$). During treatment BMD, estimated volumetric BMD and estimated bone volume showed a significant increment ($p<0.05$). There was a mean increase in vertebral length at L_2-L_4 of 110.07±8.13% (100-125%) and a mean increase in vertebral area of 121.82±14.82% (106.41-148.71%).

Discussion

Biphosphonate therapy is increasingly used for OI and other childhood osteoporotic conditions; however, the most optimal and practical dosing regimen has yet to be defined. This study used a practical and cost effective regimen consisting of two-hour infusions every three days in one cycle and four cyclic infusions per year, which minimized loss of school hours for children and work hours for the parent. Also the dose is the minumum dose that has been used in the literature[4,5,14].

Our study demonstrates that tri-monthly cyclic infusions of pamidronate for one year successfully reduced bone turnover and improved bone mineralization. The reduced bone turnover did not affect the bone growth. The pubertal progression of the patients was also not affected during this therapy. The significant improvement in BMD translates to direct clinical benefits with a significant reduction in fracture rates and an increase in the ambulation scores. These children were able to participate more actively during occupational therapy and to achieve independence in their daily activities. The reduction in pain permits more effective physiotherapy, which also positively affects the skeleton and improves the patient's mobility. These findings were consistent with other investigations[5,12-15]. Our oldest patient had the lowest ambulation score because of her flexion deformities. If pamidronate therapy had been initiated early in her life prior to the onset of deforming fractures, her clinical outcome and quality of life could have been significantly improved. We hope she will get better with reconstructive surgery combined with physiotherapy. All of the patients were bed bounded at the onset of pamidronate therapy. Caring for a bed-bounded child without any hope very difficult for parents to handle. At the end of the year, two mothers of six had returned to business.

Characteristic dense lines at anteroposterior radiographs reported previously also appeared under the growth plates of our cases[13,21]. These sclerotic evenly spaced bands corresponded to the intervals between treatment cycles. Glorieux et al.[13] reported that this finding demonstrates the continued growth of bone during therapy. Our patients' growth was not altered during therapy and this finding correlated with other reports[12-15]. Our patients' growth velocity was better than during the untreated period. We suggest that at least a part of this gain was due to the increment of vertebral corpus height.

Areal BMD (cm^2) is a size-dependent measure and is likely to be distorted by vertebral collapse. In a similar fashion, the validity of our estimates of bone volume would have been compromised by vertebral deformity. The six-month increment of volumetric BMD (vBMD) appeared exaggerated compared to one-year vBMD results. However, the improvements in vertebral morphology that were seen with biphosphonate therapy would have tended to minimize rather than exaggerate true improvements in volumetric BMD at one year. It was also interesting that estimated bone volume improved faster than bone area. It could be due to the significant increment in vertebral height. This finding paralleled results in the literature[8].

Although we did not observe severe life-threatening side effects, one of our patient's blood urea nitrogen was slightly altered. This side effect was not reported before. Although we do not have an explanation for this side effect it could have been due to renal excretion of pamidronate. This patient's renal functions and renal sonography remained normal. These findings highlight that patients should be followed up more closely for possible different side effects as they may occur due to individual differences. It was reported before that elimination of biphosphonates from the skeleton is extremely slow[10,22]. Cremers et al.[10] reported that the suppression of bone resorption was progressive with every cycle, and that it not only on the amount of biphosphonate attached to bone but also on the amount of biphosphonate buried in the bone. Plasma decline of pamidronate is highly correlated with renal clearance. Under these circumstances we suggest that it will be useful to follow the patients with BMD without continuing therapy

after the one-year period. While there is no doubt that pamidronate therapy can help children with severe osteoporosis, there are still insufficient long-term data on its safety in children. Giraud and Meunier's[23] study is one of the longest studies in literature. They found that there was a trend toward a decrease in the fracture rate as compared to the pretreatment period and also a significant annual increase at lumbar spine BMD. Although they followed up these patients for seven years, their study included only seven patients. Osteogenesis imperfecta is a relatively rare disorder. Multicenter studies can be done in order to increase the patient numbers. There is also no sufficient data about the cumulative effects of pamidronates. Further pharmacokinetic (PK) and pharmacodynamic (PD) studies could lead to a better understanding of the PKs and PDs of this drug and help in the design of more effective therapeutic strategies. We also believe that long-term follow-up with larger studies will be helpful to establish the exact role for pamidronate in this debilitating disease.

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