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Short-term Efficacy of Monthly Pamidronate Infusion in Patients with Osteogenesis Imperfecta

We evaluated the efficacy of a monthly infusion of pamidronate on the frequency of fractures, biochemical effects, and bone mineral density in children with osteogenesis imperfecta. Eleven patients from 0.9 to 13.8 yr of age were included in this study. The patients were administered pamidronate intravenously (30 mg/m^2) over a 4-hr period monthly for a period ranging from 6 to 37 months. Height and weight Z-scores did not change significantly. The frequency of fractures was decreased from 2.3±1.01 times per year before treatment to 0.6±0.69 times per year during treatment. There were no long-term changes in biochemical markers during pamidronate therapy. The mean bone mineral density of the spine and femur increased significantly. Monthly intravenous pamidronate therapy decreased frequencies of fracture and increased bone mineral density without significant adverse events in Korean patients with osteogenesis imperfecta.

Key Words : *Osteogenesis Imperfecta; Pamidronate*

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INTRODUCTION

Osteogenesis imperfecta (OI) (MIM# 166200, 166220, and 259420) is an autosomal dominantly or recessively inherited disorder primarily caused by mutations of type I collagen genes; *COL1A1* on chromosome 17 and *COL1A2* on chromosome 7 (1). OI is characterized by osteopenia, multiple bone fractures, dentinogenesis imperfecta, kyphoscoliosis, joint hyperlaxity, easily bruised skin, blue sclerae, conductive hearing loss, inguinal hernia, mitral valve prolapse, and aortic insufficiency (2). Therefore, a thorough evaluation of the ear, skin, teeth, cardiovascular, and orthopedic systems is needed. Bone deformities and recurrent bone fractures are the major concerns for patients with OI. The disease is classified into seven types by phenotype and mode of inheritance (2, 3). In the milder autosomal dominant form (Type I), the patient shows minimal bone deformities, occasional fractures before puberty, blue sclerae, dentinogenesis imperfecta, and normal height. In type II autosomal dominant form, fractures in utero and perinatal death occur. Type III, an autosomal dominant or recessive form, causes a high frequency of fractures and severe progressive deformities. In type IV autosomal dominant form, normal sclerae, dentinogenesis imperfecta, and less severe deformities are present. Type V OI is characterized by moderate to severe bone fragility, dislocation of radial head, mineralized interosseous membrane, hyperplastic callus, short stature, and white sclerae. Type VI OI is also a moderate to severe form of the disorder with disordered mineralization of bone tissue, white sclerae, and scoliosis. Type VII OI, an autosomal recessive disorder localized to chromosome 3p22-24.1, is characterized by bone fragility, rhizomelia, and coax vara (4).

Recurrent bone fractures and deformities due to generalized osteopenia are the major complication of OI. A variety of agents have been used to increase bone mass and to reduce the frequency of fractures, such as anabolic steroids, sodium fluoride, growth hormone, magnesium oxide, and calcitonin. However, none have reduced the complications of the disease (4). Bisphosphonates, synthetic analogues of naturally occurring inorganic pyrophosphate, have been commonly used and considered to be the treatment of choice for moderate to severe OI in several studies (5-14). In most studies, pamidronate (3-amino-1-hydroxypropylidene-bisphosphonate) is infused slowly for 3 consecutive days every 4 months (8-11, 13).

The aim of the present study was to evaluate the short-term efficacy and safety of monthly infusion of pamidronate on the frequency of fractures, biochemical effects, and bone mineral density (BMD) in Korean patients with OI.

MATERIALS AND METHODS

Eleven patients showing clinical features of OI such as recurrent fractures to minor trauma, blue sclerae, and/or dentinogenesis imperfecta were included in this uncontrolled prospective study (Table 1). Eight patients were classified as type IA, two patients as type IB, and one patient as type III. All patients had generalized osteopenia observable by simple radiography and dual energy radiography absorptiometry, and suffered from recurrent fractures 2.3±1.01 times per year before treatment.

After obtaining informed consent, the patients were administered 30 mg/m^2 of pamidronate monthly for a period ranging from 6 to 37 months (20.8±8.11 months) (6). Pamidronate was diluted in isotonic saline at a concentration less than 0.1 mg/mL and administered by intravenous infusion over 4 hr. The patients received 200 mg of elemental calcium and 0.25 μg of 1,25-dihydroxycholecalciferol (1,25 $[OH]_2D_3$) daily for 7 days concurrently. Patients' age at the initiation of therapy ranged from 0.9 to 13.8 yr.

The clinical status of height, body weight, growth velocity, frequency of fractures, and adverse events were evaluated at each visit for pamidronate infusion. Height for each child was translated into Z-scores according to the standard height table for Korean children (15). The fracture incidence was annualized 2 yr prior to treatment and throughout the treatment period of 6-37 months except in patient 5, who started treatment at the age of 0.9 yr. Fractures were confirmed by simple radiographs. Vertebral compression fractures were excluded in the analysis. The level of ambulation was assessed according to the modified criteria of Bleck with a 4-point scale as follows: non walker, score=0; therapeutic walker with or without the use of crutches, canes, or walker, score=1; household walker with or without the use of crutches, canes, or walker, score=2; neighborhood or community walker with or without the use of crutches, canes, or walker, score=3 (16). Biochemical markers reflecting bone and mineral metabolism (serum calcium, phosphate, alkaline phosphatase, osteocalcin, and parathyroid hormone [PTH]), and BMD were assessed at 6-month intervals immediately before the application of pamidronate. Simple radiography of thoracolumbar spine was taken with BMD for the evaluation of vertebral compression fractures. BMD of the lumbar spine (L2-4) and femur neck was measured by dual energy radiography absorptiometry (Lunar Corp., Madison, WI, U.S.A.). Age- and sex-matched BMD Z-scores for Korean children were used for comparisons of BMD during treatment (17). The children did not receive any physiotherapy, occupational therapy or surgical intervention during the time of the pamidronate therapy.

Statistical analyses were performed with SPSS version 11.0. Changes before and after treatment were analyzed by a Wilcoxon signed rank test. Differences of biochemical parameters at more than two treatment time points were analyzed for significance using repeated measures ANOVA. *p*-values less than 0.05 were considered statistically significant.

RESULTS

Linear growth of patients was not significantly delayed.

Table 1. Clinical characteristics, bone mineral density, and fracture frequency of patients with osteogenesis imperfecta before and during the pamidronate therapy

Patient No.	Type	Sex	Age at initiation of treatment (yr)	Duration of treatment (months)	Height (Z-score)*		Spine BMD (g/cm^2)*			Femur BMD (g/cm^2)*			Fracture rate per year*	
					Initial	Final	Initial	Final	Annual % increase	Initial	Final	Annual % increase	Before treatment	During treatment
1	1A	F	7.7	37	0.18	-0.03	0.440	0.722	32.0	0.302	0.622	52.9	1.5	1.0
2	1B	M	6.9	26	-0.75	-0.20	0.478	0.667	19.8	0.557	0.725	15.1	1.0	1.0
3	1B	F	5.9	26	-1.02	-0.97	0.462	0.765	24.0	0.474	0.726	26.6	3.0	0
4	1A	M	12.0	18	-1.22	-1.07	0.554	0.672	10.6	0.568	0.682	10.0	2.0	0
5	1A	F	0.9	12	0.12	-0.32	0.342	0.545	59.4	0.496	0.520	2.4	2.0	0
6	1A	M	4.4	18	0.02	-0.71	0.458	0.542	19.0	0.479	0.634	39.7	4.0	2.0
7	3	M	2.4	24	-1.37	-1.20	0.290	0.571	48.4	0.372	0.853	64.7	4.0	0
8	1A	M	2.7	24	-0.45	-1.20	0.374	0.657	37.8	0.278	0.633	63.8	1.5	0
9	1A	M	5.8	18	-1.53	-0.26	0.440	0.598	7.3	0.485	0.656	17.0	1.5	0
10	1A	M	13.8	6	-1.42	-0.69	0.626	0.804	14.2	0.659	0.782	9.4	2.5	1.0
11	1A	M	2.5	20	-1.76	0.37	0.440	0.545	15.9	0.505	0.660	20.5	2.0	1.0
Mean±SD			5.9± 8.11	20.8± 0.71	-0.8± 0.52	-0.6± 0.09	0.446± 0.06	0.644± 16.47	26.2± 0.11	0.471± 0.09	0.681± 22.45	29.3± 1.01	2.3± 0.69	0.6± 4.06

*p values represent the significance of difference of results at the two time points (initial vs. final) (p<0.05).
BMD, bone mineral density.

During treatment, no significant differences were noted in height and weight Z-scores although height Z-scores of patients 1, 5, 6, and 8 were slightly deteriorated. All patients showed a normal growth velocity although their ages were variable for the assessment of growth (Table 1). No patients showed aggravation of long bone deformity and progression of scoliosis. The ambulation scores were grade 3 before treatment in all patients. There was no change in the level of ambulation in patients with OI during treatment. Low-grade fever developed in 4 patients at the first infusion. No other side effects were notified during pamidronate therapy.

Baseline levels of serum calcium, phosphorus, alkaline phosphatase, PTH, and osteocalcin were normal. There were no significant differences between age groups. No patients showed long-term changes in biochemical markers during the treatment period.

Simple radiography of thoracolumbar spine and both femur revealed osteopenia and/or compression fractures of spine in all patients. The frequency of fractures decreased from 2.3±1.01 times per year before treatment to 0.6±0.69 times per year during treatment ($p<0.05$). Pretreatment BMD was at the low limit of the reference range in all patients. The mean BMD measured in both the lumbar spine and femur neck has significantly increased in all patients after treatment ($p<0.05$) (Table 1). The average annualized increment in BMD was 26.2±16.47% in lumbar spine and 29.3±22.45% in femur neck. The mean BMD Z-scores of spine were significantly improved from -2.5±1.75 to 1.5±3.06 ($p<0.05$), and those of femur neck also increased from -3.7±0.90 to -1.77±0.89 ($p<0.05$).

DISCUSSION

Infusion of pamidronate for three consecutive days, using a 4-month interval protocol, is widely used as a therapy for patients with OI (8-11, 14). Glorieux et al. (9) reported a safe and favorable outcome when the mean dose was about 6-9 mg/kg per year. Although it is significantly effective, pamidronate infusions for three consecutive days every four months take much time and interfere with patients' daily life. Two previous studies in Korea also suggested that pamidronate therapy in OI using the 3 consecutive days every 2-4 months protocol increased BMD and decreased fracture rates (18, 19). Single-day, monthly infusion protocols of pamidronate were also shown to be efficacious (6, 7). A simplified protocol of single-day infusion of pamidronate every 3 months was tried and turned out to be efficacious and well tolerated with pediatric patients with osteoporosis. This report supports the findings of other studies that showed pamidronate has beneficial effects in patients with OI although a small cohort population was enrolled in this study.

Height Z-scores decreased during pamidronate treatment in some patients. However, changes in height Z-scores were statistically not significant, and their growth velocity was normal. Zeitlin et al. (13) reported long-term pamidronate therapy at least four years led to a significant height gain in moderately to severely affected OI patients.

No significant adverse events were encountered during pamidronate therapy except low-grade fever. Self-limited flu-like symptoms such as decreased appetite, myalgia, irritability, low-grade fever, and decreased energy could be associated with pamidronate therapy (8).

Serum calcium, phosphorus, PTH, and vitamin D metabolites are generally normal in patients with OI. Subtle changes in parameters of bone metabolism during pamidronate therapy, such as serum calcium, phosphorus, PTH, and vitamin D metabolites, have been reported (11). Serum calcium levels transiently decreased with a transitory increase in PTH levels during pamidronate therapy (10, 11). Although serum calcium levels could be decreased, none of the patients showed symptomatic hypocalcemia (9). The OI patients showed reduced levels of serum alkaline phosphatase, osteocalcin, and urinary excretion of calcium, which are suggestive of slowed bone turnover (6, 9, 11). The biochemical parameters including calcium, phosphorus, alkaline phosphatase, PTH, and osteocalcin levels did not altered significantly in this study. Presumably, calcium and vitamin D supplement might contribute to the normalization of the biochemical parameters.

Bisphosphonates are a class of drug that are potent inhibitors of osteoclastic bone resorption (20, 21), and known to result in a net effect of increased bone mass and reduced risk of fractures in patients with OI (22, 23). The increase in BMD following therapy results from a reduction in remodeling space due to both decreased activation of new remodeling cycles by reducing the population of cells committed to becoming mature osteoclasts (20). Osteoblasts may have a role in the inhibition of bone resorption by bisphosphonates. Bisphosphonates have been postulated to induce osteoblasts to secrete an inhibitor of osteoclastic resorption (24). Numerous preliminary studies described that cyclic administration of bisphosphonates increased BMD and decreased the frequency of fractures (5-14). There was no correlation between phenotype severity, age at the start of treatment, and treatment response (14). In the present study, pamidronate therapy increased BMD in all patients. Significant improvement in BMD causes beneficial clinical effects such as significant reduction in fracture frequency, decreased bone pain, and increased mobility (9, 10). Dual energy radiography absorptiometry provides the assessment of areal BMD (g/cm^2), which is calculated by dividing the bone mineral content by the projected bone area of the scanned skeletal region. Since the volume of the scanned bone is not measured, areal BMD fails to distinguish between changes in the BMD and bone size in growing children. Increased bone mass after pamidronate therapy can be demonstrated by bone biopsy, showing the influence of the treatment on cortical modeling and enchondral ossification (12). However, bone deformities prior to therapy did not improve

during and after pamidronate therapy. The sclerotic lines observed in the metaphyses during treatment indicated no significant functional impairment (25).

In summary, monthly pamidronate treatment was safe and effective in Korean patients with OI. Although the period of treatment and the age of the subjects varied considerably making it difficult to draw a definitive conciusion, monthly intravenous pamidronate therapy in patients with OI improved clinical symptoms, decreased the frequency of fractures, and increased BMD without significant adverse events. The chronic effects of pamidronate on bone metabolism in OI patients are not yet known. Therefore, randomized, well-controlled studies are needed for the evaluation of the efficacy, adverse effects, appropriate treatment interval, optimal duration, and dosage of pamidronate.

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