Bone Mass, Size, and Density in Children and Adolescents With Osteogenesis Imperfecta: Effect of Intravenous Pamidronate Therapy

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ABSTRACT
Cyclical intravenous therapy with pamidronate improves the clinical course in children and adolescents with osteogenesis imperfecta (OI). In this study, we evaluated the effect of this therapy on lumbar spine bone mass (bone mineral content [BMC]), size (bone volume [BV]), and density (volumetric bone mineral density [vBMD]). Results from 56 patients (age, 0.2-15.9 years; 25 girls) on long-term pamidronate treatment were compared with those of 167 patients who had not received pamidronate before densitometry. In all patients who received pamidronate, BMC, BV, and vBMD increased above levels expected for untreated patients ($p < 0.001$ in each case). After 4 years of treatment, BMC, BV, and vBMD were 154%, 44%, and 65% higher, respectively, in treated than in untreated patients who were matched for age and OI type. A multiple regression model showed that baseline BMC was negatively associated with the increase in BMC. In conclusion, the bone mass increase in pediatric OI patients receiving pamidronate is caused by increases in both bone size and density. Patients with larger deficits in bone mass at baseline have a more marked bone mass gain during therapy. (J Bone Miner Res 2003;18:610-614)

Key words: bisphosphonate; bone fragility; osteoporosis; pediatric

INTRODUCTION

OSTEOGENESIS IMPERFECTA (OI) is a genetic disorder with increased bone fragility and low bone mass. The most commonly used classification distinguishes four clinical types.((1)) OI type I comprises patients with absence of bone deformities. Type II is lethal in the perinatal period. OI type III is the most severe form in children surviving the neonatal period. These patients have extremely short stature and limb and spine deformities secondary to multiple fractures. Patients with less severe bone deformities and variable short stature are classified as OI type IV.

We and others have shown that cyclical intravenous therapy with the bisphosphonate pamidronate has a beneficial effect in children and adolescents with severe OI, resulting in decreased fracture rates and improved mobility.((2-5)) These positive clinical effects are thought to be at least partly caused by an increase in bone mass.((2-4)) However, it is currently unknown how much bone mass is actually gained compared with untreated patients.

The mass of any physical body (g) is determined by two propertiesits size and its average density (g/cm3). The relevant measure of size is the body's volume (cm3). Changes in mass can therefore occur through changes in volume or density. With regard to pamidronate treatment of children with OI, the relative contributions of size and density to the increase in bone mass are unknown at present. This is an important gap in our knowledge on this treatment, because the aim of therapy should be to make bones as "normal" as possible. In that respect, it would certainly be preferable to obtain an adequate bone mass by bringing both bone size and density as close to normal as possible, rather than to achieve the same bone mass through a combination of small bone size and very high density.

It is important to realize that this reasoning is based on the notion of density as established by Archimedes more than 2000 years ago (i.e., density equals mass divided by volume). More recently, this same measure has come to be called "volumetric density" in the field of bone densitometry. The commonly used areal bone mineral density (BMD) (g/cm2) reflects a mixture of bone size and (volumetric) density and therefore is not helpful in distinguishing between the two determinants of bone mass. The term "mass" also requires explanations, as it is inconsistently used in the bone densitometric literature. In this report, we follow the lead of basic physics and restrict it to measures that can be expressed in grams. The mass of mineral within a bone is called bone mineral content (BMC).

In this study, we analyzed changes in lumbar spine BMC in children with OI who received long-term pamidronate therapy. The aim of the study was 2-fold. First, we assessed the magnitude of the treatment effect by comparing BMC of treated and untreated patients. Second, we evaluated to what extent changes in bone volume (BV) and volumetric BMD (vBMD) contribute to the increase in BMC.

MATERIALS AND METHODS

Subjects

This study comprises patients with a diagnosis of OI type I, III, or IV who received pamidronate therapy at the Shriners Hospital for Children in Montreal, Canada. Patients were eligible for pamidronate treatment if they had long bone deformities or had suffered at least three fractures per year (including vertebrae) during the previous 2 years.((2,3)) This applies to all patients with OI types III and IV and generally to the more severe cases of OI type I. Between October 1992 and May 2002, a total of 167 such patients (age, 2 weeks to 17.9 years; 88 girls and 79 boys) received at least one course of pamidronate at our institution. Baseline results from these patients were used as "untreated" control data.

The type of OI was assigned using the Sillence criteria.((1)) However, some patients fulfilling the Sillence criteria for OI type IV were not included in this group because they could be further classified as having OI type V, VI, or VII based on our expanded classification.((6-8)) Classification is difficult in patients younger than 3 years of age. This is especially true when pamidronate therapy is started early in life, because the treatment markedly changes the natural evolution of the disease. Therefore, patients with unclassified OI who were under 3 years of age were also included in the present study. The diagnostic distribution was OI type I, n = 32; type III, n = 52; type IV, n = 47; and unclassified, n = 36.

56 patients (25 girls and 31 boys; mean age at baseline, 8.3 years; range, 0.2-15.9 years) received pamidronate for at least 4 years at our institution. Each of these patients could be assigned to one of the three types of OI that are considered here (OI type I, n = 17; type III, n = 18; type IV, n = 21).

The study was approved by the Shriners Hospital Institutional Review Board, and informed consent was obtained from parents or legal guardians.

Treatment

Pamidronate was administered intravenously on 3 consecutive days in all patients. As described earlier,((3)) the clinical effect of the infusions (suppression of bone pain, sense of well-being) was more short-lived in younger children. Therefore, the timing and dosage of these 3-day cycles varied with age. Children below 2 years of age received 0.25 mg/kg on the first day of the first cycle, 0.5 mg/kg on days 2 and 3 of the first cycle, and 0.5 mg/kg daily on all 3 days in subsequent cycles. Cycles were repeated every 8 weeks. Children from 2 to 3 years of age received 0.38 mg/kg on the first day of the first cycle, 0.75 mg/kg on days 2 and 3 of the first cycle, and 0.75 mg/kg daily on all 3 days of subsequent cycles. Cycles were repeated every 12 weeks. Above 3 years of age, the first 3-day cycle consisted of a dose of 0.5 mg/kg on the first day and 1 mg/kg on days 2 and 3. In subsequent cycles, the dose was 1 mg/kg daily for 3 days. Cycles were repeated every 16 weeks. Thus, the yearly dose of the drug was the same at all ages. Each dose was diluted in 0.9% saline solution and administered slowly over 4 h, as previously described.((2,3))

Calcium and vitamin D intake was maintained as adequate according to the recommended daily allowance in all patients. All patients underwent physiotherapy and occupational therapy evaluation and support, including exercises and design of special devices for transportation and sitting.

Bone densitometry

Bone densitometry was performed in the antero-posterior direction at the lumbar spine (L1-L4) using a Hologic QDR 2000W or 4500A device (Hologic Inc., Waltham, MA, USA). Areal BMD results were transformed to age-specific z-scores combining reference data from Salle et al.((9)) and data provided by the densitometer manufacturer. The latter data are based on the studies of Glastre et al.((10)) and Southard et al.,((11)) which were comprised of a total of 353 children and adolescents. Measures of BV and vBMD were derived from BMC and projection area as described by Carter et al.,((12)) using the following formulas:

BV, as calculated by this formula, is an estimate of the volume enclosed by the vertebral bodies' periosteum. It should not be confused with bone volume as used in histomorphometry, which reflects the relative amount of bone matrix in a tissue section.((13)) There is no relationship between the two types of bone volume.

Anthropometric and biochemical measurements

Weight and height measurements were converted to age- and sex-specific z-scores based on reference data published by the National Center for Health Statistics.((14))

Urinary cross-linked N-telopeptides of type I collagen (NTX) were measured by ELISA (Osteomark, Ostex, Seattle, WA, USA) using the second void sample of the morning. Results for urinary NTX/creatinine ratios in OI patients were expressed as a percentage of age-specific mean values using published reference data.((15))

Urine creatinine concentration was determined colorimetrically. Patients were fasting at the time of urine sampling.

Statistical analyses

Expected results for BMC, BV, and vBMD in untreated OI patients were calculated by simple regression analysis. Regression curves were fitted to the age-dependent data. Because there were no significant gender

differences, boys and girls were grouped together for this analysis. The points on the regression lines correspond to the expected results in untreated OI patients. BMC, BV, and vBMD of each patient at each time-point were converted to the percentage of the expected result.

Variables were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed data were expressed as mean and SD. Geometric means and geometric SD were calculated for non-normally distributed variables. These variables were log-transformed before performing tests that require normal distribution. The difference of densitometric results to the mean result expected in untreated OI patients (i.e., 100%) was tested for significance using the one-sample t-test. Changes during therapy were assessed using ANOVA for repeated measures. Differences between results at baseline and during therapy were tested for significance using Bonferroni's adjustment.

Associations are given as Pearson's correlation coefficient. All tests were two-tailed, and throughout the study, $p < 0.05$ was considered significant. These calculations were performed using the SPSS software, version 9.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

The effect of pamidronate therapy on bone mass, size, and density was assessed in two different ways. In the first approach, results of pretreatment measurements in all 167 patients were used to estimate the age dependency of lumbar spine BMC, BV, and vBMD in OI patients who fulfill our criteria for pamidronate therapy (Fig. 1). The curves fitted to these data represent the mean result that is expected in patients who do not receive pamidronate. These regression curves were used as a baseline for the subsequent assessment of treatment effects on densitometric parameters.

Individual results in the 56 patients who completed 4 years of pamidronate treatment are shown in Fig. 2. BMC, BV, and vBMD increased in all patients. After 4 years of treatment, all but two patients had a BMC above the value expected for untreated patients. In four patients, BMC was above the mean for healthy children. When analyzed as a group, the pretreatment mean results of these 56 patients were close to the values expected for untreated patients (Table 1). After 4 years of pamidronate therapy, BMC, BV, and vBMD had increased to levels that were well above the result expected for untreated patients. Table 1 also shows areal BMD z-scores, ensuring consistency with our previous reports.((2,3)) Areal BMD z-scores increased by an average of 2.6 SD during 4 years of pamidronate therapy.

The age distribution of the group that was used to construct the regression lines for untreated patients was skewed to the left, and therefore, results are less accurate in the older patients. For this reason, we opted to confirm these results using a different statistical approach. In this second analysis, pairs of treated and untreated patients were matched for age and OI type. Five of the patients in the treated group had to be excluded because no matching partner was available. Results of the remaining 51 patients are shown in Table 2. After 4 years of therapy, BMC, BV, and vBMD were 154%, 44%, and 65% higher, respectively, in the IO patients than in the untreated patients.

To elucidate factors that predict long-term response to therapy, pretreatment characteristics were compared with the increase in BMC after 4 years of therapy. For all of these calculations, BMC was expressed as a percentage of the result expected for untreated patients. There were significant differences in response between OI types, with the largest increase in OI type III ($p = 0.04$, ANOVA). However, the difference between OI types disappeared after adjustment for baseline BMC ($p = 0.21$). A multiple regression model using baseline age, height z-score, alkaline phosphatase activity, urinary NTX/creatinine ratios, and BMC as predictors showed that only age, height z-score, and BMC were independently associated with the increase in BMC. The regression equation was as follows ($r2 = 0.59$; $p < 0.001$):

DISCUSSION

The present group of patients showed an increase in lumbar spine areal BMD z-scores after the start of therapy that was similar to what we and others had observed previously in OI patients receiving pamidronate.((2-4)) It is noteworthy that the treatment effect could be observed in every single patient. Each of the 56 patients on long-term pamidronate treatment increased bone mineral mass faster than expected in untreated patients. Importantly, the increase in mineral mass was not simply the effect of higher vBMD. Indeed, changes in both bone size and vBMD contributed similarly to the increase in mineral mass. Although increased bone mass, size, and density cannot be simply equated with increased bone strength, it can be assumed that these changes contribute to decrease fracture rates in these patients.((2,4,5))

What is the structural correlate of the increase in vBMD? Whole bone vBMD reflects the mass of mineral per unit bone volume. As such, it depends on cortical thickness, the relative amount of bone tissue in the trabecular compartment, and the material density of bone tissue within both the cortical and trabecular compartment.((13)) All of these determinants of vBMD are likely to be affected by pamidronate therapy.

First, pamidronate treatment is associated with an increase in cortical thickness, as evidenced by both radiological and histomorphometric analyses.((2,16)) Second, the relative amount of trabecular bone tissue

within the trabecular compartment increases during pamidronate treatment because of an increase in trabecular number.((16)) Third, the material density of mineralized bone may increase during pamidronate therapy, as occurs in adults with postmenopausal osteoporosis.((17))

In addition, the increase in vBMD may be partly caused by an increased amount of calcified cartilage within trabecular bone tissue. Decreased bone turnover will delay the removal of primary bone that is synthesized at the growth plate/metaphyseal bone interface and that contains calcified cartilage cores. Indeed, iliac bone histology reveals that pamidronate therapy of growing OI patients is associated with a significant increase in the amount of calcified cartilage.((16)) This observation may explain why the radiographic density of vertebral bodies increases most at locations that are close to the growth cartilage (end plates).((2)) A more quantitative evaluation of this phenomenon might be gained from lateral lumbar spine DXA scans.

Why does pamidronate therapy increase the size of vertebral bones? The obvious explanation is that, in OI patients who receive pamidronate, bones are more stable and there are fewer or no vertebral compression fractures. In addition, pre-existing vertebral compressions seem to reshape in growing patients.((2-4)) It is also possible that that the increased mechanical stimulation caused by better mobility and higher muscle force gives rise to faster periosteal expansion. Finally, a direct growth stimulating effect of the drug cannot be excluded, although animal experiments do not provide evidence for this hypothesis.((18))

The search for predictors of therapeutic response showed that pretreatment BMC was negatively associated with the increase in BMC during treatment. Translated into clinical terms, this means that more severely affected patients can be expected to benefit the most from pamidronate therapy, at least as far as bone mineral mass is concerned. Similar observations have been made by others.((5)) Age was positively associated with the gain in BMC, suggesting that younger patients do not gain as much bone as older patients. However, when comparing the BMC regression lines of untreated patients with the BMC of healthy children (Fig. 2), it becomes obvious that younger OI patients have a smaller deficit in bone mineral mass. Consequently, they do not need to gain as much as older patients. Finally, our results show that baseline levels of serum alkaline phosphatase and urinary NTX cannot be used to make predictions on the gain in bone mineral mass. Thus, it remains unclear whether markers of bone metabolism can help to direct clinical decisions with regard to pamidronate treatment in OI.

In conclusion, this study shows that pamidronate therapy in children and adolescents with OI leads to a marked gain in bone mineral mass, which is caused by an increase in both bone size and density. Important unresolved questions concerning this form of treatment are as follows. How long should pamidronate be given? What are the criteria to stop the drug? How long is the treatment effect preserved after discontinuation of therapy? Careful long-term follow-up of a large number of patients will be required to answer these open questions.

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