Delayed Osteotomy but Not Fracture Healing in Pediatric Osteogenesis Imperfecta Patients Receiving Pamidronate

Craig FJ Munns,1 Frank Rauch,1 Leonid Zeitlin,1,2 François Fassier,3 and Francis H Glorieux1

ABSTRACT: This study evaluated factors influencing fracture (n = 197) and osteotomy (n = 200) healing in children with moderate to severe OI. Pamidronate treatment was associated with delayed healing after osteotomy, but not after fracture. The data suggest that both pamidronate and mechanical factors influence bone healing in this cohort.

Introduction: Intravenous pamidronate is widely used to treat children with moderate to severe osteogenesis imperfecta (OI). However, the effect of this treatment on bone healing is not well characterized. We therefore retrospectively analyzed the healing of lower limb fractures and osteotomies in children with moderate to severe OI, both before and after the start of pamidronate treatment.

Materials and Methods: Bone healing was evaluated on standard radiographs after 197 lower limb fractures (132 femur and 65 tibia) in 82 patients (age at fracture, 0.0–19.9 years) and 200 intramedullary rodding procedures in 79 patients (age at surgery, 1.2–19.8 years). Delayed healing was diagnosed when a fracture or osteotomy line was at least partially visible 12 months after the event.

Results: Delayed fracture healing was observed more frequently during than before pamidronate treatment. However, the effect of pamidronate was no longer significant when age differences were taken into account (odds ratio [OR], 1.76; 95% CI, 0.61–5.10). Better mobility status was a strong independent predictor of delayed healing after fractures that occurred during pamidronate treatment. After osteotomies, delayed healing was more frequent when pamidronate had been started before surgery (OR, 7.29; 95% CI, 2.62–20.3), and this effect persisted after adjustment for multiple confounders. During pamidronate treatment, older age (OR per year of age, 1.25; 95% CI, 1.06–1.47) and osteotomy of the tibia (OR, 3.51; 95% CI, 1.57–7.82) were independent predictors of delayed healing.

Conclusions: This study suggests that pamidronate therapy is associated with delayed healing of osteotomy sites after intramedullary rodding procedures. Better mobility status, but not pamidronate treatment, seems to be predictive of delayed healing after fractures.


Key words: fracture healing, intramedullary rodding, osteogenesis imperfecta, osteotomy, pamidronate

INTRODUCTION

OSTEOGENESIS IMPERFECTA (OI) is a heritable bone disorder characterized by bone fragility, short stature, and bone deformities.(1) Intravenous infusions of pamidronate, a nitrogen-containing bisphosphonate, have been reported to be beneficial in children with moderate to severe OI, resulting in increased vertebral bone mass and size, muscle force, and growth rate, and reduced bone pain and fracture rates.(1)

The primary mechanism of action of bisphosphonates is to suppress osteoclastic bone resorption by reducing the number and activity of osteoclasts on the bone surface.(2) In children with OI, histomorphometric analysis of iliac bone biopsy specimens has shown that cyclical pamidronate markedly reduces trabecular remodeling activity, reducing both bone resorption and formation.(3)

Fracture healing requires coordinated bone resorption and formation.(4) Because bisphosphonates decrease both of these parameters and have a half-life of many years, concern has been raised that these medications may have a negative effect on fracture and osteotomy healing.(5,6) A number of animal experiments have shown that bisphosphonates can affect bone healing, resulting in increased callus size and a retardation of callus remodeling.(6–10) In contrast, studies in adults have found no evidence that bisphosphonates interfere with fracture healing in a clinically relevant manner.(6,11,12)

The effect of bisphosphonates on fracture healing in children with moderate and severe OI has not been studied systematically, although various investigators have reported...
the impression that fracture healing proceeded normally during intravenous pamidronate therapy.\(^{13–15}\) To address this issue in detail, we evaluated the incidence of delayed healing of femur and tibia fractures and osteotomy sites in children with moderate and severe OI, both before and after the start of cyclical intravenous pamidronate therapy.

**MATERIALS AND METHODS**

**Subjects**

This study was comprised of 131 patients (65 girls and 66 boys) with moderate to severe OI that were treated at the Shriners Hospital for Children in Montreal between 1984 and 2003. The distribution of OI types was as follows: type I, \(N = 15\); type III, \(N = 39\); type IV, \(N = 58\); type V, \(N = 8\); type VI, \(N = 7\); type VII, \(N = 3\); unclassified, \(N = 1\). After 1992, an increasing number of OI patients received cyclical intravenous pamidronate therapy. Pamidronate was initiated in patients who had long bone deformities, had sustained more than two fractures per year during the previous 2 years, or had vertebral compression fractures.

Subsequent to the initial radiograph, which was taken at the time of fracture or osteotomy, follow-up radiographs were taken as clinically indicated to assess healing and/or annually as part of a skeletal survey to evaluate pamidronate therapy.

**Fracture study**

The dates of femoral and tibial fractures were obtained from patient records. Only fractures confirmed radiographically were included in this study. Most fracture management occurred at the child’s primary health care facility.

Femur and tibia fractures were included in this analysis if they occurred either \(>12\) months before (to eliminate those fractures where pamidronate was started during the 12-month evaluation period) or at any time after the start of pamidronate therapy. Radiographs from the first 10 subjects were evaluated by all authors. Subsequent radiographs were evaluated by a single observer (CM). Radiographs taken after 390 fractures in 112 patients were assessed (Fig. 1). In 193 of these fractures, radiographic follow-up was insufficient to judge whether or not the fracture site had completely healed within 12 months. Thus, the analysis was comprised of a total of 197 fractures (Fig. 1; Table 1).

**Osteotomy study**

The dates of femoral and tibial rodding procedures were obtained from the patients’ medical records. Femoral and tibial osteotomies were performed by orthopedic surgeons of the Shriners Hospital for Children, Montreal, to facilitate the straightening of lower limb deformities for intramedullary rod placement. Femoral and tibial osteotomies were performed by standard techniques\(^{16}\) using an oscillating power saw. Fibula osteoclasis was performed by applying direct force to the bone after completion of the tibial osteotomy.

Intramedullary rodding procedures of the lower limbs were included in this analysis if they occurred either \(>12\) months before or at any time after the start of pamidronate therapy. Radiographs from the first 10 subjects were evaluated by all authors. Subsequent radiographs were evaluated by a single observer (CM). Radiographs after 317 interventions were assessed (Fig. 2). In 117 interventions, radiographic follow-up was insufficient to judge whether or not osteotomy sites had completely healed within 12 months. Thus, the final analysis was comprised of a total of 200 intramedullary rodding surgeries (Fig. 2; Table 1).

**Outcome analyses**

Delayed healing was diagnosed when a fracture or osteotomy line was at least partially visible 12 months after the event (Figs. 3 and 4). This definition corresponds to grade 3 of the Hammer classification of fracture healing.\(^{17}\)

The long-term outcome of the fractures and osteotomies with delayed healing at 12 months was assessed by evaluating subsequent radiographs for healing, angulation, or fracture through the site or the requirement for surgical intervention (Fig. 5).

At each pamidronate treatment cycle, physiotherapists experienced in the care of children with OI evaluated patient mobility on a four-point scale as follows: 0 (does not walk), 1 (able to walk during therapy sessions only), 2 (walking only within the house), and 3 (able to walk within the community).\(^{18}\) For this analysis, the maximal mobility score between 90 and 365 days after the fracture or osteotomy event was used.

**Treatments**

The period of immobilization was minimized after fracture or osteotomy to reduce disuse osteoporosis. If there was radiological evidence of callus formation, active physiotherapy and weight bearing with the aid of orthoses were commenced 5–8 weeks after a fracture and 3 weeks after intramedullary rod placement.

Pamidronate was administered intravenously on 3 consecutive days in all patients, as described.\(^{11}\) The total annual pamidronate dose was 9 mg/kg in all children, although timing and dosage of the 3-day cycles varied with age.
Children <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 of subsequent cycles. Cycles were repeated every 2 months. 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 3 months. 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 consecutive days. Cycles were repeated every 4 months. Each dose was diluted in 0.9% saline solution and administered slowly over 4 h.

All patients were advised to maintain adequate calcium intake according to the recommended daily allowance at all times before and during pamidronate treatment. All patients underwent physiotherapy and occupational therapy evaluation and support, including exercises and design of special devices for transportation and sitting.

**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.\(^{(19)}\)

Urine creatinine concentration was determined colorimetrically. Urinary cross-linked N-telopeptides of type I collagen (NTX) were quantified by enzyme-linked immunoabsorbent assay (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.\(^{(20)}\) Patients were fasting at the time of urine sampling.

**Radiological technique**

Radiographs were performed using the Siemens Multix H radiological unit (Siemens AG, Erlangen, Germany) onto

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<table>
<thead>
<tr>
<th>TABLE 1. CLINICAL CHARACTERISTICS AT THE TIME OF FRACTURE OR AT INTRAMEDULLARY RODDING SURGERY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture study</td>
</tr>
<tr>
<td>(N = 42)</td>
</tr>
<tr>
<td>Bone involved (femur/tibia)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Gender (male/female)</td>
</tr>
<tr>
<td>OI type (II/III/IV/V–VII)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Height (z score)</td>
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<tr>
<td>Weight (z score)</td>
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</table>

Values represent N or median (range).

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**FIG. 2.** Rodding count. Number of evaluated rodding procedures and their outcome before and after pamidronate therapy (fx, fractures; pat., patients).

**FIG. 3.** Delayed fracture healing of the right tibia in a boy with OI type IV who received pamidronate from 1.2 years of age. (A) Initial fracture (arrow) at the age of 4.2 years. (B) Persistent fracture line (arrow) 2 years later. The fracture gap is bridged only on the posterior (compressive) surface of the tibia.
Kodak medical film (Eastman Kodak, Rochester, NY, USA). Where possible, both the anterior-posterior and lateral radiographs were taken with the patient in the standing position. Unless requested otherwise by the treating physician, femora and tibias were included on a single cassette (lower extremity radiograph).

Statistical analyses

Logistic regression analysis was used to evaluate the relationship between clinical characteristics and the presence of delayed fracture or osteotomy healing. Results were expressed as odds ratios (ORs) with 95% CI. The effect of potential predictor variables was initially assessed in univariate models and in multivariate models (all variables entered). To assess the effect of pamidronate therapy, pamidronate treatment status was included as a dichotomous variable (no/yes). OI types V, VI, and VII were coded as one group, because the number of subjects of individual groups was insufficient for the analysis. OI type III was selected as the reference category, because this group of patients constitutes one end of the spectrum of disease severity.

Healing of fractures and osteotomy sites might be influenced by the duration and timing of prior and subsequent pamidronate treatment, patient mobility, and the suppression of bone turnover during therapy (as expressed by urinary NTX levels). Therefore, a second logistic regression analysis including these variables was performed, including only fractures or osteotomies that had occurred while patients were receiving pamidronate treatment. Differences in the incidence of complications after delayed healing were tested for significance using the $\chi^2$ test only, because the number of events was too small for multivariate analysis.

All tests were two-tailed. In the logistic regression analysis, the association with delayed healing was considered to be significant, when the 95% CI of an independent variable did not include 1.00. Otherwise, $p$ values $<0.05$ were considered significant. These calculations were performed using the SPSS software, version 12.0 for Windows (SPSS, Chicago, IL, USA).

**FIG. 4.** Delayed osteotomy healing of the right tibia in a girl with OI type III who received pamidronate from 0.2 years of age. (A) Radiograph taken immediately after tibial rodding using a K-wire at 3.2 years of age. One osteotomy site is indicated by an arrow. (B) This site remained unhealed 2 years later (arrow).

**FIG. 5.** Complication of delayed osteotomy healing in a girl with OI type III who received pamidronate from 0.8 years of age. (A) Radiograph of the right tibia taken at 3.6 years of age, 3 weeks after a K-wire had been inserted. (B) The osteotomy site (arrow) remained unhealed 3.5 years later and now has an anterior angulation of 25°.
RESULTS

Fracture study

Forty-two fractures with informative follow-up occurred >1 year before the start of pamidronate therapy, and 155 fractures were sustained after the start of pamidronate treatment. Fractures that occurred before pamidronate therapy on average happened at a younger age than fractures that were sustained during pamidronate treatment (Table 1).

Twelve months after fracture, delayed healing was observed in 47 of these 197 fractures (Table 2). According to univariate analysis, delayed fracture healing was associated with increasing age and was significantly more frequent during pamidronate treatment. However, multivariate analysis indicated that pamidronate treatment was no longer significantly associated with delayed fracture healing when differences in age were accounted for (Table 2). Neither univariate nor multivariate analyses yielded significant associations of delayed healing with gender, fractured bone, OI type, height, and weight.

Next we attempted to elucidate factors that were associated with delayed fracture healing during pamidronate treatment. Compared with fractures that healed normally, fractures with delayed healing occurred at an older age, after a longer duration of pamidronate treatment, and after a longer interval following the most recent pamidronate treatment (Table 3). Although all of these factors were significantly associated with delayed healing in the univariate analysis, only age remained a significant predictor of delayed healing in the multivariate analysis (Table 3).

Mobility scores were available after 136 fracture events during pamidronate treatment. Delayed healing was seen after 7 of 62 (11%) fractures in patients with a mobility score of 0 or 1 and after 31 of 74 (42%) fractures in patients with a mobility score of 2 or 3 (OR, 5.66; 95% CI, 2.28, 14.1). When mobility score was added to the multivariate

### Table 2. Clinical Characteristics at the Time of Fracture

<table>
<thead>
<tr>
<th></th>
<th>Normal healing*</th>
<th>Delayed healing*</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 150)</td>
<td>(N = 47)</td>
<td>univariate</td>
<td>multivariate</td>
</tr>
<tr>
<td>Bone involved</td>
<td>98/52</td>
<td>34/13</td>
<td>0.72 (0.35, 1.48)</td>
<td>0.74 (0.34, 1.63)</td>
</tr>
<tr>
<td>Gender</td>
<td>75/75</td>
<td>23/24</td>
<td>1.04 (0.54, 2.01)</td>
<td>1.01 (0.47, 2.16)</td>
</tr>
<tr>
<td>OI type (I/III/IV/V–VII)</td>
<td>15/57/47</td>
<td>51/14/20</td>
<td>0.71 (0.35, 1.58)</td>
<td>0.75 (0.36, 1.62)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>3.9 (0.0, 19.2)</td>
<td>7.8 (1.1, 19.9)</td>
<td>1.18 (1.10, 1.27)</td>
<td>1.19 (1.07, 1.32)</td>
</tr>
<tr>
<td>Height (z score)</td>
<td>3.4 (-1.2, 11.0)</td>
<td>3.8 (-12.2, -1.2)</td>
<td>0.94 (0.84, 1.05)</td>
<td>1.06 (0.83, 1.35)</td>
</tr>
<tr>
<td>Weight (z score)</td>
<td>2.1 (-5.3, 0.8)</td>
<td>-1.8 (-5.6, 1.1)</td>
<td>1.11 (0.89, 1.39)</td>
<td>1.03 (0.71, 1.50)</td>
</tr>
</tbody>
</table>

All patients are included in the analysis. Comparison of sites that did (“normal healing”) or did not heal completely within 12 months (“delayed healing”).

*Values represent n or median (range).

### Table 3. Analysis of Fracture Healing during Pamidronate Treatment

<table>
<thead>
<tr>
<th></th>
<th>Normal healing*</th>
<th>Delayed healing*</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 113)</td>
<td>(N = 42)</td>
<td>univariate</td>
<td>multivariate</td>
</tr>
<tr>
<td>Bone involved</td>
<td>72/41</td>
<td>29/13</td>
<td>0.79 (0.37, 1.68)</td>
<td>1.20 (0.48, 3.00)</td>
</tr>
<tr>
<td>Gender</td>
<td>54/59</td>
<td>21/21</td>
<td>0.92 (0.45, 1.86)</td>
<td>0.76 (0.30, 1.88)</td>
</tr>
<tr>
<td>OI type (I/III/IV/V–VII)</td>
<td>11/46/35</td>
<td>5/11/19</td>
<td>0.79 (0.37, 1.72)</td>
<td>1.00 (0.49, 2.07)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>4.3 (0.5, 19.2)</td>
<td>8.1 (2.2, 19.9)</td>
<td>1.20 (1.10, 1.31)</td>
<td>1.17 (1.01, 1.36)</td>
</tr>
<tr>
<td>Height (z score)</td>
<td>-4.2 (-11.0, 0.9)</td>
<td>-3.8 (-10.1, -1.2)</td>
<td>0.98 (0.86, 1.10)</td>
<td>0.96 (0.71, 1.30)</td>
</tr>
<tr>
<td>Weight (z score)</td>
<td>-2.2 (-4.8, 0.8)</td>
<td>-1.7 (-4.3, 1.1)</td>
<td>1.20 (0.95, 1.52)</td>
<td>1.01 (0.65, 1.56)</td>
</tr>
<tr>
<td>Years of pamidronate treatment</td>
<td>1.1 (0.0, 6.8)</td>
<td>2.1 (0.1, 7.4)</td>
<td>1.39 (1.14, 1.70)</td>
<td>1.06 (0.81, 1.40)</td>
</tr>
<tr>
<td>Weeks since last pamidronate infusion</td>
<td>5.1 (0.0, 19.6)</td>
<td>9.9 (0.0, 22.0)</td>
<td>1.09 (1.02, 1.17)</td>
<td>1.10 (0.96, 1.26)</td>
</tr>
<tr>
<td>Weeks until next pamidronate infusion</td>
<td>6.6 (0.1, 19.6)</td>
<td>5.8 (0.0, 18.6)</td>
<td>1.00 (0.93, 1.07)</td>
<td>1.04 (0.92, 1.18)</td>
</tr>
<tr>
<td>NTX/creatinine (% of healthy mean)</td>
<td>64 (22, 337)</td>
<td>58 (33, 203)</td>
<td>0.98 (0.91, 1.05)</td>
<td>0.92 (0.83, 1.02)</td>
</tr>
</tbody>
</table>

Clinical characteristics at the time of fracture are given. Comparison of sites that did (“normal healing”) or did not heal completely within 12 months (“delayed healing”).

*Values represent n or median (range).

†Per increase of 10%.
formative follow-up occurred

regression model shown in Table 3, it emerged as the strongest predictor of delayed fracture healing (Table 4). In addition, male gender and lower height z scores became significant predictors of delayed healing. However, time since the previous or until the subsequent pamidronate cycle was not significantly associated with delayed fracture healing, whether or not mobility score was taken into account.

To assess the clinical consequences of delayed fracture healing, information at the last available follow-up examination was considered. The median follow-up period was 1.9 years (range, 1.3–2.6 years) after fractures that occurred before pamidronate treatment and 1.7 years (range, 1.0–4.7 years) after fractures that occurred during pamidronate treatment. As shown in Fig. 1, refracture, angulation deformity, and eventually intramedullary rodding surgery occurred in both groups. The incidence of these complications was similar after fractures that occurred before pamidronate was started and after those that occurred during pamidronate treatment ($p > 0.2$ in each case; $\chi^2$ test).

Osteotomy study

Thirty-eight intramedullary rodding procedures with informative follow-up occurred $>1$ year before the start of pamidronate therapy, and 162 such interventions were done after the start of pamidronate treatment (Table 1). Rodding procedures performed before pamidronate therapy occurred at a slightly older age than interventions done during pamidronate treatment.

Twelve months after intramedullary rodding, delayed healing was observed after 103 of the 200 interventions where radiographic follow-up was sufficient for analysis (Table 5).

In univariate analysis, delayed osteotomy healing was significantly more frequent in patients who had received pamidronate, in patients with OI type IV (compared with OI type III), and in osteotomies involving the tibia. Delayed osteotomy healing was also associated with height and weight z scores (Table 5). In the multivariate analysis, only pamidronate treatment and osteotomy of the tibia remained significant predictors of delayed healing (Table 5).

Next we attempted to elucidate factors that were associated with delayed osteotomy healing during pamidronate treatment. Compared with osteotomies that healed normally, osteotomies with subsequent delayed healing were performed more frequently at the tibia, in OI type IV patients, at an older age, and at a higher height z score (Table 6). However, the multivariate analysis indicated that only tibia osteotomy and age remained significant predictors of delayed healing. Mobility score (available after 141 osteotomy procedures performed during pamidronate treatment) was not significantly associated with delayed osteotomy healing, neither in the univariate nor in the multivariate analysis (data not shown).

To assess the clinical consequences of delayed osteotomy healing, information at the last available follow-up examination was taken into account. The median follow-up period was 2.9 years (range, 1.3–7.4 years) in osteotomies that were performed before pamidronate treatment and 3.0 years (range, 1.0–5.9 years) in osteotomies that occurred during pamidronate treatment. In the former group, no complications were noted, whereas in osteotomies that were performed during pamidronate treatment, fractures through the osteotomy site and angulation of $>10^\circ$ occurred in 10 and 21 cases, respectively (Figs. 2 and 5). Further surgical intervention was performed in 20 of these unhealed osteotomy sites. This difference in complication rate between osteotomies before and during pamidronate treatment was statistically significant with regard to angulation of $>10^\circ$ and further surgical intervention ($p = 0.02$, $\chi^2$ test), but not for refracture ($p = 0.12$).

To correct deformities of the lower extremity a tibial osteotomy has to be combined with an osteoclasis (manual breaking) of the fibula. It was noted that in the 44 lower extremities with unhealed tibial osteotomies at last follow-up, only 5 of the adjacent fibulas remained unhealed ($p < 0.001$ for difference between the two bones; $\chi^2$ test).

**DISCUSSION**

This study suggests that the administration of cyclical intravenous pamidronate in children with OI is associated with delayed bone healing after osteotomy but not after fracture. Delayed osteotomy healing led to clinically relevant complications, such as angulation deformity and fracture, which necessitated further surgical intervention.

A number of previous studies have examined fracture and osteotomy healing in children with OI not receiving medical therapy. However, the findings of these reports cannot be directly compared with the present observations, because they differ considerably with regard to case selection and surgical technique. In addition, comparisons between studies are complicated by the fact that there is no generally accepted definition of delayed fracture union within the orthopedic surgical community. The criteria used in this study (total or partial persistence of a fracture or osteotomy line 12 months after the event) represent a conservative approach to the diagnosis of delayed bone healing.
It may come as a surprise that pamidronate should have a differential effect on osteotomy and fracture healing, as was observed in this study. However, similar observations have been made in both animal and clinical studies. In fracture healing studies, bisphosphonates did not have a major effect irrespective of the type of bisphosphonate and dosing regimen used. (11,12,25,26) In contrast, bisphosphonate application after osteotomy has been reported to interfere with callus remodeling and to lead to the persistence of the osteotomy line on radiographs. (7,9,10) Our data showing a difference between the healing of fibulas and tibias after tibial rodding further support a discrepancy between fracture and osteotomy repair. Fibulas, which are broken manually by osteoclasis when lower limb deformities are corrected, had a much lower rate of delayed healing than adjacent tibias, which undergo osteotomy with an oscillating saw and receive the intramedullary rod.

The reasons for the discrepancy between fracture and osteotomy healing are not clear. Possibly, the presence of the rod may affect the healing process when at the same time the bone is exposed to pamidronate. It is also possible that the use of an oscillating saw for osteotomies interferes with bone healing by cauterizing bone ends, whereas osteoclasis neither disrupts the periosteum nor alters the bone ends. In addition, the more rapid healing of the fibula may have further delayed tibial osteotomy healing by acting as a splint, thus disturbing apposition of the tibial bone ends. Thus, the etiology of delayed osteotomy healing after the start of pamidronate therapy may be multifactorial, with interplay between drug, mechanical, and surgical factors. This topic clearly warrants further investigation.

In this study, neither the duration of pamidronate therapy nor the timing of drug administration in relation to the osteotomy influenced outcome. This observation is in con-
trast to animal studies,(8,9) which suggested that there is a critical period after an osteotomy when bisphosphonates are more likely to delay bone healing. Our observations may indicate that the timing of pamidronate administration does not play a significant role in osteotomy healing in children withOI. However, it must be noted that, in this study, pamidronate was given every 4 months, regardless of surgical interventions. It is therefore also possible that any administration of pamidronate within the 4-month cycle interval is sufficient to interfere with healing.

With regard to fracture healing, we found that better mobility status increased the risk for delayed healing during pamidronate treatment, whereas pamidronate by itself had no independent effect. This suggests that weight bearing on abnormal OI bone adversely affected healing.

Limitations of this study include the fact that this is an uncontrolled observational trial, and therefore, comparisons are limited to historical controls. Details in clinical management other than medical treatment may therefore have differed between the pre-pamidronate and the pamidronate-treated groups. Also, follow-up radiographs were not obtained systematically, but mostly as required for clinical management. This may have introduced bias, because normal healing is less likely to lead to radiographic studies than delayed bone healing.

Despite these limitations, it seems prudent to devise strategies that minimize the chances of delayed healing in OI patients receiving pamidronate. A longer pamidronate-free period around the time of intramedullary rodding procedures may be required. Altering surgical and rehabilitative techniques by avoiding the use of oscillating saws for osteotomies and extending the non–weight-bearing period after a fracture/osteotomy might also prove beneficial in improving bone healing. However, it must be acknowledged that there are no data to show that any of these proposed measures are effective in reducing the risk of delayed healing.

In summary, this report suggests that pamidronate is associated with delayed osteotomy healing in children and adolescents with moderate to severe OI and that better mobility is associated with a higher risk of having a delay in fracture healing.

REFERENCES


Address reprint requests to:
Francis H Glorieux, MD, PhD
Genetics Unit
Shriners Hospital for Children
1529 Cedar Avenue
Montreal, Quebec H3G 1A6, Canada
E-mail: glorieux@shriners.mcgill.ca

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