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Zoledronic acid (zoledronate) in children with osteogenesis imperfecta (OI)

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Abstract

Introduction: *Zoledronic acid or zoledronate is a potent bisphosphonate that recently has been used in children with osteoporosis and osteogenesis imperfecta (OI), so it could be an option in the treatment of children with this terrible disease that virtually condemns them to a life of pain and prostration. The aim of this study was to evaluate the clinical and biochemical conditions of pediatric patients with OI before and after treatment with zoledronate.* **Results***: We included 14 patients, median age six years (6 months to 14 years), eight (57.1%) males and six (42.9%) females, weight 19 kg (5.8-45 kg). According to the type of OI, six (42.9%) were type I, six (42.9%) type III, and two (14.2%) type IV. The functional score (Bleck) previous to treatment was 4 (1-9) and 6 (2-9) after treatment (p = 0.001). Pain intensity prior to zoledronate was 2 (1-9) and 0 (0-2) after (p = 0.008). Previous fractures five (1-15) and post-treatment one (0-2) (p = 0.001). There were no significant differences in calcium, phosphorus, alkaline phosphatase, and parathyroid hormone.* **Conclusions:** *Zoledronic acid decreases the number of bone fractures and pain in children with osteogenesis imperfecta and improves functional status. The most common side effects were fever and bone pain within five days after the infusion, which disappear with paracetamol. No adverse long-term effects such as hypocalcemia or hypoparathyroidism were reported.* (Gac Med Mex. 2015;151:152-6)

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Introduction

Osteogenesis imperfecta (OI), also known as "brittle bone disease", is characterized by a dysfunction of the connective tissue due to mutations in the genes *COL1A and COL1A2* that codify for the type I collagen chains[1,2]. Sillence et al. determined four types of OI: type I, with minimal or no deformity; type II, lethal in the perinatal period; type III, severely deforming, and type IV, moderately deforming[3]. In recent years, other 4 types have been added: type V refers to moderate or severe disease that frequently causes deformity and short stature, with normal teeth and sclerae; type VI is a moderate disease with spinal compression, blue or white sclerae and normal teeth; type VII is very similar to II, but with smaller head, and sclerae can be white or slightly bluish, and type VIII is similar to III, but with rounded face, normal sclerae and barrel-shaped rib cage[4]. The prognosis is determined by the degree if bone fragility; type II is the most severe, since children die in the prenatal period or within the first weeks of life, with multiple fractures[5-7].

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Treatment goals are oriented towards solving OI most frequent problems, to increase bone mass, to reduce the number of fractures, maintain normal height and enable for the child to have a life as close as possible to normal[8-10].

Bisphosphonates are potent inhibitors of bone resorption by decreasing the number and activity of osteoclasts; this results in an improvement in vertebrae form and density, cortical diameter increase, increased bone volume, etc.[11-13]. Some oral and parenteral bisphosphonates have been used in an attempt to treat children with OI, with varying results[14-18]. Intravenous pamidronate has been the most widely used, and has been proven to reduce the incidence of fractures, as well as bone resorption, thus increasing bone density and improving the size of vertebral bodies[19]. However, some hospitals have no access to this drug.

Zoledronate is a potent bisphosphonate for which improvement in bone density and bone remodelling has been reported[21,21]. This drug was created for adult patients with multiple myeloma and other severe osteopenias, as well as malignant hypercalcemia, but, recently, some studies in children have started to be conducted. There are new publications reporting on the efficacy and safety of this drug in pediatric patients with osteoporosis and in OI[21-23]. The purpose of this study was to assess the clinical and biological evolution of children with OI before and after receiving a treatment with zoledronate, since this medication could be a new management option in children with OI, and thus prevent a life of pain, suffering and disability.

Material and methods

An interventional study was conducted, where children with OI attending the Specialties Hospital of Monterrey, Nuevo León, in the years 2011 to 2013, and who decided to participate by means of informed consent, were included. Prior to the treatment, sociodemographic variables, type of OI, number of fractures, pain scale and Bleck functional score were assessed. Serum calcium, alkaline phosphatase, phosphorus and parathyroid hormone were determined.

Zoledronic acid (zoledronate) was administered at 0.05 mg/kg in a 1-2 h infusion every 6 months. Patients were monitorized every 3-6 months, with number of fractures, pain, functionality and biochemical and imaging test-results being recorded.

The analysis was performed using descriptive statistics and the Wilcoxson test to assess before and after zoledronate treatment.

Results

Fourteen OI-diagnosed patients were included, with a median age of 6 years (from 6 months to 14 years), out of which 8 (57.1%) were males and 6 (42.9%) were females, and with median weight of 19 kg (5.8-45). With regard to the type of OI, 6 (42.9%) were type I, 6 (42.9%), type III and 2 (14.2%), type IV. All patients received treatment with zoledronate at a dose of 0.05 mg/kg body weight diluted in physiological saline deivered in a 1 or 2 h intravenous infusion every 6 months, with acetaminophen and single-dose diphenhydramine as premedication. Eight patients (57.1%) received two doses, 4 (28.6%), three doses, and 2 (14.3%), four doses. Seven patients (50%) experienced adverse reactions, out of which 5 had bone pain and fever for 2 to 4 days after the drug adminstration and two had fever and headache. No patients experienced rash, nausea, vomiting or other adverse effects immediately or later after zoledronate was applied. Supportive treatment with calcium was given to 4 patients, with calcitriol to 4, and a combined therapy with both medications was given to other 4. Acetaminophen was given to all patients with the instruction of taking it within the first five days following the infusion in case of fever or pain, but only 9 patients reported having required it, especially after the first dose; in the following doses, they referred less discomfort and no medications were required (Table 1).

Patients were assessed before and after treatment with zoledronate. The score in Bleck functional scale before the treatment was 4 (range: 1-9), and after, 6 (2-9) ($p = 0.001$). In the pain intensity evaluation, a pre value of 2 (0-9) and a post value of 0 (0-2) were found ($p = 0.008$). The number of fractures prior to the use of the medication was 5 (1-15) and after treatment, 1 (0-2) ($p = 0.001$). Previous serum calcium measurements were 9.5 ± 0.16 mg/dl and control values after the use of the drug were 9.7 ± 0.2 mg/dl ($p = 0.510$). Serum phosphorus levels before the treatment were 5.2 ± 0.3 mg/dl, and 5.3 ± 0.2 mg/dl afterwards ($p = 0.828$). Pre-treatment alakaline phosphatase was 242 ± 23.3 mg/dl vs. 219 ± 27.8 post-treatment ($p = 0.167$). Parathyroid hormone was 29.4 ± 7.9 pcg/dl before the management and 49.9 ± 16 afterwards ($p = 0.444$) (Table 2).

Discussion

OI is a genetic disease caused by a mutation in genes that codify for type I collagen chains *(COL1A,*

Table 1. Clinical characteristics and treatment of 14 children with OI treated with zoledronate in a tertiary care hospital*

Age (years)	6 (6 months-14 years)
Sex	
Males	8 (57.1%)
Females	6 (42.9%)
Weight (kg)	19 (5.8-45)
Type of osteogenesis	
I	6 (42.9%)
III	6 (42.9%)
IV	2 (14.2%)
Doses†	
2	8 (57.1%)
3	4 (28.6%)
4	2 (14.3%)
Adverse reactions†	
Bone pain and fever	7 (35.7%)
Headache and fever	2 (14.3%)
No adverse effects	5 (50%)
Suportive treatment†	
Calcium	4 (28.5%)
Calcitriol	4 (28.5%)
Acetaminophen	9 (57%)

*Values are expressed in means (ranges).
†Number of patients.

located in chromosome 17, and *COL1A2,* located in chromosome 7), which is characterized by connective tissue dysfunction. Its clinical presentation is very varied: affected individuals are susceptible to suffer fractures upon mild trauma, their bone mass is reduced, they have short height, progressive skeletal deformities, blue sclerae, dentinogenesis imperfecta, articular lassitude and deafness at adult age. Initially, Sillence et al. described four types of OI, but later, other 4 were added based on clinical characteristics. Classification of the disease depends on clinical and radiological data, on the age of fractures onset, deformities and sequels, as well as ambulatory capability, blue sclerae, etc.; due to the large heterogeneity of OI, sometimes it is difficult to determine its classification[1-5,25]. In a study conducted by Deike and Kok et al. with 37 patients, 13% had type I OI, 23.6%, type III OI, and 32.4%, type IV OI[24]. In other report from Colombia by Lazala and Solaque, where 33 patients with OI treated with pamidronate were studied, there were 9 (27.3%) type I, 1 (3%) type II, 9 (27.3%) type III and 14 (42.4%) type IV patients[26]. In this study, 14 patients were included: 42.9% type I, same percentage type III, and only 2 type IV, in contrast with reports in previous articles, where there were more type IV patients. Patients with type II, which is lethal during the first days or months of life, were not included.

Treatment depends on the severity of the disease and age of the patient, but in all cases, it is oriented towards preserving the function and autonomy. Treatment goals are directed to increase bone mass, reduce the number of fractures, maintain a normal height and to enable for the child to live a life as close as possible to normal[7,8]. Bisphosphonates have been accepted as part of the treatment of children with OI. These compounds are pyrophosphate analogues that can be orally or parenterally administered and are characterized by their rapid binding to hydroxyapatite crystals in bone mineral. Some oral and parenteral bisphosphonates have been used in an attempt to treat

Table 2. Results obtained before and after treatment with zoledronate in 14 children with OI*

	Before	After	p
Bleck scale score	4 (1-9)	6 (2-9)	0.001
Pain analogue scale score	2 (1-9)	0 (0-2)	0.008
Previous fractures	5 (1-15)	1 (0-2)	0.001
Calcium	9.5 ± 0.16	9.7 ± 0.2	0.510
Phospohrus	5.2 ± 0.3	5.3 ± 0.2	0.828
Alkaline phosphatase	242 ± 23.3	219 ± 27.8	0.167
Parathyroid hormone	29.4 ± 7.9	49.9 ± 16	0.444

*Values expressed in medians (ranges) and means with standard deviation.

children with OI, with varying results. Alendronate, pamidronate, risedronate and olpadronate have been widely used in previous studies[14-18]. These medications are not available within the basic drug list of the Mexican Institute of Social Security (IMSS – *Instituto Mexicano del Seguro Social),* but since a few years, a bisphosphonate that was initially intended for the treatment of multiple myeloma in adults but that later was proven effective in other diseases with severe osteopenia, is available. Zoledronate belongs to the nitrogen-containing group of bisphosphonates, same as alendronate, pamidronate and risedronate. It is a potent bisphosphonate for which improvement in bone density and bone remodelling has been reported[20,21]. There are publications that report on the efficacy and safety of this drug in pediatric patients with osteoporosis and OI[21-23]. In this study, zoledronate was used according to the doses recommended by Vuorimies et al., who have demonstrated efficacy by reducing the number of fractures with few adverse events, such as hedache, nausea, rash, vomiting, fever and bone pain (flu-like)[23]. Based on this knowledge, the decision was made to premedicate the patients with diphenhydramine and acetaminophen prior to the zolendronate infusion, and after the infusion, acetaminophen was administered in case of drug-related symptoms. All patients received at least two doses, and half of them received up to 3 and 4 twice-yearly and, hence, the follow-up lasted 18-24 months. Most frequent adverse reactions were mild fever and bone pain within the first 5 days after the infusion, which were controlled with acetaminophen; in the following infusions, the patients referred less drug-related symptoms and even half of the children reported not having experienced any symptoms related to the medication.

In a Columbian study where pamidronate was used in patients with OI, a statistically significant reduction in the incidence of fractures was found ($p < 0.001$). Fifteen of the 33 treated patients (45.4%) did not have any fracture after starting pamidronate. Pain was also assessed using the verbal analogue scale: prior to the treatment, it was 3.97, and it decreased to 1.28, with a statistically significant difference ($p < 0.001$). Of 8 patients classified in the functional scale as Bleck, 3 modified it towards ambulation[26]. In the study conducted by Kok et al., in which the patients received olpadronate, differences in quality of life were found, which reflected in behavioral changes ($p < 0.05$), in addition to a significant decrease of pain and in the incidence of fractures ($p < 0.03$). In this study, which included 14 patients, an important improvement was found in Bleck functional scale, with a statistically significant differenece before and after zoledronate; even some patients who were not ambulatory achieved ambulation with help, and those previously ambulatory with help, managed to ambulate without support. There was an important decline in the number of fractures after the treatment, with a statistically significant difference, and we consider this to directly impact on pain, since there was also an important decrease in the analogue pain scale: with fewer fractures and less surgical procedures, children refer less pain and, therefore, their quality of life improves. Bisphosphonates long-term adverse effects include hypocalcemia, alkaline phosphatase elevation and hypoparathyroidism[21-23]; these parameters were monitorized, with no statistically significant differences being found before and after the medication, indicating that they were not modified, and no long-term adverse events were reported. Occasionally, the patients required calcium and vitamin D supplementation, especially the younger children, but not because they suffered any reduction in calcium or parathyroid hormone levels, but prophylactically; it was possible to withdraw them during follow-up, since normal levels of this ion were corroborateed during the outpatient control visits.

Over the last decade, different medical centers of the world have investigated the use of bisphosphonates in children with OI, with favorable results at increasing bone mass and reducing the incidence of fractures and pain. Zoledronic acid or zoledronate is a potent bisphosphonate that constitutes a treatment option for children who suffer from this terrible disease, whose frequent fractures condemn them to a life of suffering and disability. This is the first study conducted in Mexico assessing the efficacy of zoledronate in children with this disease, demonstrating this bisphosphonate's efficacy bin the reduction on pain and the number of fractures in children with OI, in addition to improving their functional class and quality of life.

References

1. Rauch F, Glorieux FH. Osteogenesis imperfecta. Lancet. 2004;363(9418): 1377-85.
2. Cheung MS, Glorieux FH. Osteogenesis imperfecta: update on presentation and management. Rev Endocr Metab Disord. 2008;9(2):153-60.
3. Sillence DO, Senn A, Danks DM. Genetic heterogenecity in osteogenesis imperfecta. J Med Genet. 1979;16(2):101-16.
4. Van Dijik FS, Pals G, Van Rijn RR, et al. Classification of ostegenesis imperfecta revisited. Eur J Med Genet. 2010;53(1):1-5.
5. Rauch F, Lalic L, Glorieux FH. Relationship between genotype and skeletal phenotype in children and adolescents with osteogenesis imperfecta. J Bone Miner Res. 2009;9999 (999A):1-30.

7. Antoniazzi F, Mottes M, Fraschini P, Tato L. Osteogenesis imperfecta: practical treatment guidelines. Paedriatr Drugs. 2000;2(6):465-88.
8. Davie MW, Haddaway MJ. Bone mineral content and density in healthy subjects and in osteogenesis impefecta. Arch Dis Child. 1994;70(4): 331-4.
9. Gloriueux FG. Treatment of osteogenesis imperfecta: who, why, what? Horm Res. 2007;68 Suppl 5:8-11.
10. Engelbert RH, Pruijis HE, Beemer FA. Osteogenesis imperfecta in childhood: treatment strategies. Arch Phys Med Rehabil. 1998;79(12):1590-4.
11. Bleck EE. Non operative treatment of osteogenesis impefecta: orthotic and mobility management. Clin Orth Rel Res. 1981;(159):111-22.
12. Esposito P, Plotkin H. Surgical treatment of osteogenesis imperfecta: current Concepts. Curr Opin Pediatr. 2008;20(1):52-7.
13. Rusell RG. Biophophonates: mode of action and pharmacology. Pediatrics. 2007;119 Suppl 2:S150-62.
14. Allgrove J. Biphosphonates. Arch Dis Child. 1997;76(1):73-5.
15. Munns CF, Rausch F, Travers R, Glorieux FH. Effects of intravenous pamidronate treatment in infants with osteogenesis imperfecta: clinical and histomorphometric outcome. J Bone Miner Res. 2005;20(7):1235-43.
16. Phillipi CA, Remington T, Steiner RD. Bisphosphonate therapy for osteogenesis imperfecta. Cochrane Database Syst Rev. 2008;(4):CD005088.
17. Landsmeer-Beker EA, Massa GG, Maaswinkel-Mooy PD, van de Kamp JJ, Papapoulos SE. Treatment of osteogenesis imperfecta with olpadronate. Eur J Pediatr. 1997;156(10):792-4.
18. Sakkers R, Kok D, Engelbert R, et al. Skeletal effects and functional outcome with olpadronate in children with osteogenesis imperfecta: 2 year randomsed placebo-controled study. Lancet. 2004;363(9419): 1427-31.
19. Glorieux FH. Experience with bisphosphonates in osteogenesis imperfecta. Pediatrics. 2007;119 Suppl 2:S163-5.
20. Brown JJ, Zacharin MR. Safety and efficacy of intravenous zoledronic acid in paediatric osteoporosis. J Pediatr Endrocrinol Metab. 2009;22(1):55-63.
21. Almeida M, Uenis T, Guarniero R. The effect of zoledronate Turing bone Ealing. J Orthopaed Traumatol. 2010;11(1):7-12.
22. Panigrahi I, Das RR, Sharda S, Marwaha RK, Khandelwal N. Response to zoledronic acid in children with type III osteogenesis impefecta. J Bone Miner Metab. 2010;28(4):451-5.
23. Vuorimies I, Toivainen-Salo S, Hero M. Zoledronic acid in children with osteogenesis impefecta. Horm Res Peadiatr. 2011;75(5):546-53.
24. Kok D, Sakkers R, Janse A, et al. Quality of life in children with osteogenesis imperfecta treated with oral bisphosphonates (Olpadronate): a 2-year randomized placebo-controled trial. Eur J Pediatr. 2007;166(11): 1155-61.
25. Herreros F, Ascurra M. Las osteogenesis imperfectas: revisión del tema. Pediatr (Asuncion). 2008;35(1):33-7.
26. Lazala O, Solaque H. Terapia con bisfosfonatos en osteogenesis imperfecta. Rev Col Or Tra. 2009;23(2):109-14.