The Use of Bisphosphonates in Pediatrics

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Key Words

Adverse effects · Bisphosphonates · Hypercalcemia · Osteoporosis · Pharmacokinetics

Abstract

Bisphosphonates are widely used for the prevention and treatment of osteoporosis in adulthood. In the last years, bisphosphonates have been increasingly used in pediatric patients for the treatment of a growing number of disorders associated with osteoporosis, resistant hypercalcemia or heterotopic calcifications. The use of bisphosphonates in pediatric patients has been proven safe; however, the risk of potential severe consequences into adulthood should be kept in mind. Well-defined criteria for bisphosphonates treatment in pediatric patients are not specified, therefore an accurate selection of patients who could benefit from bisphosphonates is mandatory. A strict follow-up of pediatric patients receiving long-term bisphosphonate therapy is strongly recommended. The purpose of this mini review is to provide a summary of current knowledge on some main general aspects of the structure, mechanisms of action, pharmacokinetics, and bioavailability of bisphosphonates, and to focus on the latest advances of bisphosphonate treatment in pediatric patients. Particular attention has been paid to the common and potential adverse effects of bisphosphonate treatment, and some suggestions concerning the clinical approach and general measures for bisphosphonate treatment in pediatric patients are reported.

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Introduction

Bisphosphonates have been used extensively to treat some bone disorders such as postmenopausal and glucocorticoid-induced osteoporosis, malignancy-induced hypercalcemia and Paget's disease. The potential adverse effects of bisphosphonates on the growing skeleton have been the main limiting factor to their use in pediatric patients. However, experience in recent years has suggested that bisphosphonates treatment is safe in pediatric patients, even though potential consequences into adulthood are not well defined yet.

The aims of this mini review were to summarize some general aspects on the pharmacokinetics of bisphosphonates that are relevant for their clinical application, and to report the main pediatric bone disorders in which a positive effect on the outcome of the disease has been demonstrated. Furthermore, potential adverse effects related to bisphosphonate treatment and some general measures for proper and safe use are discussed.

Mini Review Criteria

Studies for this mini review were identified by searching the PubMed database using terms including 'bisphosphonates', 'children', 'pediatrics', 'osteoporosis', 'hypercalcemia', 'heterotopic calcifications', and 'adverse effects', alone and in combination, as well as by searching for selected diseases. Priority was given to full-text papers.

Papers were selected for inclusion according to the author's opinion of their relevance to the subject, with a general preference given to review publications.

Structure and Mechanisms of Action of Bisphosphonates

Bisphosphonates differ from pyrophosphates in that there is a carbon rather than an oxygen atom attached to the two phosphate residues (fig. 1). The P-C-P motif is responsible for the strong affinity of bisphosphonates for bone tissue; the hydroxyl group on the R1 side chain imparts high affinity to calcium hydroxyapatite crystal, allowing rapid and efficient targeting of bisphosphonates to bone mineral surfaces. The structure and 3-dimensional conformation of the R2 side chain is the major determinant of antiresorptive potency [1, 2]. Based on the R2 chain, bisphosphonates can be subdivided into two main groups, nonnitrogen-containing moiety and nitrogen-containing moiety [1, 3]. Nitrogen-containing moiety bisphosphonates have higher antiresorptive potency in vitro than nonnitrogen moiety bisphosphonates. In any case, antiresorptive potency and binding affinity to hydroxyapatite are not necessarily parallel with one another [3]. The effect of bisphosphonates on osteoclast activity is the result of their potency as inhibitors of the enzyme farnesyl pyrophosphate synthase, a key branch point enzyme in the mevalonate pathway. Farnesyl pyrophosphate synthase generates isoprenoid lipids utilized in sterol synthesis and for the posttranslational modification of small GTP-binding proteins essential for osteoclast function. As a consequence of the inhibition of osteoclast activity, recruitment and apoptosis, suppression of bone turnover occurs [3].

Recent studies have demonstrated that some beneficial effects of bisphosphonates on the skeleton could be due to the prevention of osteoblast and osteocyte apoptosis [4]; this prosurvival effect is strictly dependent on the expression of connexin-43 [3, 4]. A schematic representation of bisphosphonate effects on bone cells is depicted in figure 2. The positive effect of bisphosphonates on bone formation, even in the face of reduced overall bone remodeling, could explain part of the antifracture efficacy and bone mass recovery in patients with idiopathic juvenile osteoporosis (IJO) during pamidronate treatment [5]. Table 1 shows the chemical structure, route of administration, dose range, and potency relative to etidronate of the main bisphosphonates used in pediatric patients.

Fig. 1. Chemical structure of pyrophosphate compared with the basic structure of bisphosphonate. R1 side chain determines the binding to hydroxyapatite. R2 side chain determines the potency of bisphosphonate.

Fig. 2. Schematic description of the main bisphosphonate effects on bone cells. Inhibition of osteoclast activity reduces bone resorption, and prevention of osteoblast and osteocyte apoptosis increases their survival. Both mechanisms may improve BMD and fracture outcome.

Table 1. Chemical structure, route of administration, dose range, and potency relative to etidronate of the main bisphosphonates used in pediatric patients (relative potency order)

Name	R1	R2	Oral	Parenteral	Dose	Relative potency
Etidronate	OH	CH ₃	+	+	5–40 mg/kg per day 400 mg per day per 2 weeks, every 3 months	1
Clodronate	C	Cl	+	+	1,200 mg per day (subdivided into 3 doses) 2 mg/kg per day (200–250 ml ISS 2–3 h, every 3–6 months)	10
Pamidronate	OH	CH ₂ CH ₂ NH ₂		+	0.5–1.5 mg/kg per day for 3 days (200–250 ml ISS 3 h, every 2–6 months)	100
Neridronate	OH	(CH ₂) ₅ NH ₂		+	1–2 mg/kg per day (250 ml ISS/25 mg 3 h, every 3–6 months)	100
Alendronate	OH	(CH ₂) ₃ NH ₂	+		1–2 mg/kg per week 5 (<20 kg) to 10 (>20 kg) mg per day 70 mg per week	100–1,000
Ibandronate	OH	CH ₂ CH ₂ N(CH ₃)(pentyl)		+	2 mg (250 ml ISS 2 h, every 3 months)	1,000–10,000
Risedronate	OH	CH ₂ -3-pyridine	+		15 mg per week (<40 kg) 30 mg per week (>40 kg) 2 mg/kg per week	1,000–10,000
Zoledronate	OH	CH ₂ -(imidazole)		+	0.015–0.05 mg/kg (50 ml ISS 30–45 min, every 3–6 months)	>10,000

R1: when an OH group binding to hydroxyapatite is enhanced. R2: it exerts a pharmacological effect (potency) on osteoclasts [1]. ISS = Isotonic saline solution. Note: the most widely used bisphosphonates in pediatric patients are alendronate, pamidronate and zoledronate.

Pharmacokinetics and Bioavailability of Bisphosphonates

Pharmacokinetics and differences among the bisphosphonates are essential for optimal clinical outcomes and minimalization of the risk of adverse effects.

Absorption and Tissue Distribution

Bisphosphonates are poorly absorbed in humans. They are absorbed throughout the entire gastrointestinal tract by paracellular transport, with better absorption from segments of the tract with larger surface areas [6]. There are small differences in absorption among bisphosphonates. Nitrogen-containing bisphosphonates have an absorption of about 0.7%, whereas bisphosphonates without a nitrogen atom in their side chain have a slightly higher gastrointestinal absorption of 2–2.5% [6]. The poor absorption of bisphosphonates has been attributed to their very poor lipophilicity, which may prevent transcellular transport across the epithelial barriers.

Bisphosphonates are distributed widely throughout the body – primarily in bone, but also in soft tissues such as the liver, kidney and spleen [6]. Bisphosphonates bind preferentially to bones with high turnover rates but their distribution in bones is not homogeneous.

Elimination from Plasma and Bone, and Renal Excretion

Intravenous bisphosphonates disappear from plasma rapidly, showing a half-life of 1–2 h, according to the renal clearance and bone uptake. Once taken up by the bone, bisphosphonates are desorbed from the hydroxyapatite during bone resorption and are taken up by osteoclasts, but they can also be taken up again by the skeleton or can be released in the circulation. The amount of bisphosphonates in the skeleton can be further embedded in the bone during continuing bone formation [6]. Renal excretion is the main mechanism by which bisphosphonates are excreted by the body. It is correlated with renal function, so that their dose should be corrected by creati-

nine clearance. Bisphosphonates are excreted unchanged in urine; a very small percentage is excreted in the bile [6]. A terminal half-life of 10 years has been estimated for alendronate in the longest pharmacokinetic study in humans, up to 1.5 years, after intravenous administration [7]. Pamidronate urinary excretion after the cessation of long-term treatment with daily oral administration was detectable up to 8 years after the cessation of treatment [8]. This may be a crucial issue in pediatric patients.

Bisphosphonate Use in Pediatric Patients

Many genetic and acquired disorders of children may be associated with osteoporosis. It has been shown that bisphosphonates may improve the acquisition of bone mass, reducing fracture rate in some primary or secondary forms of osteoporosis. Bisphosphonates have also been effective in treating severe hypercalcemia caused by excessive bone resorption or increased intestinal calcium absorption. Moreover, treatment with bisphosphonates has shown a reduction of existing calcifications and the disappearance of new ectopic ossifications in some disorders associated with heterotopic calcifications. Furthermore, bisphosphonates may be useful in reducing osteolytic lesions and bone pain in patients with fibrous dysplasia of bone, chronic recurrent multifocal osteomyelitis and osteonecrosis-related chemotherapy. Table 2 summarizes the main disorders for which bisphosphonates have shown positive effects on the outcome of disease in pediatric patients.

Primary Forms of Osteoporosis

Primary forms of osteoporosis are due to an intrinsic alteration of bone structure. They are relatively rare, and some of them are familial or genetically determined. Osteogenesis imperfecta may be considered the prototype of a genetic disease associated with low bone mass and fragility fractures. Osteogenesis imperfecta is a clinically heterogeneous collection of disorders primarily affecting the production of normal amounts of correctly formed type I collagen. Approximately 90% of infants and children with the osteogenesis imperfecta phenotype will have a mutation in one of the two type I collagen genes with dominant inheritance, whereas a small number will have mutations in genes that are involved in collagen protein assembly with recessive inheritance [9–11].

Many studies have demonstrated the positive effects of bisphosphonates on bone health in patients with osteogenesis imperfecta, so that this therapy has rapidly be-

Table 2. Main disorders for which bisphosphonates have shown positive effects on the outcome of disease in pediatric patients

<i>Osteoporosis</i>
Primary forms
Osteogenesis imperfecta
IJO
Other genetic diseases ¹
Osteoporosis pseudoglioma syndrome
Neurofibromatosis
Gaucher's disease
Hajdu-Cheney syndrome
Familial idiopathic hyperphosphatasia
Secondary forms
Glucocorticoid-induced osteoporosis (diffuse connective tissue diseases, chronic kidney diseases, inflammatory bowel diseases, posttransplantation) ²
Disuse osteoporosis (neurological diseases with palsy and muscular dystrophies)
<i>Hypercalcemic disorders</i>
Vitamin D intoxication
Malignancy-induced hypercalcemia
Subcutaneous fat necrosis
Idiopathic infantile hypercalcemia
Neonatal severe primary hyperparathyroidism
Immobilization hypercalcemia
<i>Heterotopic calcification¹</i>
Fibrodysplasia ossificans progressiva
Generalized arterial calcification
Juvenile dermatomyositis
<i>Other</i>
Fibrous dysplasia of bone/McCune-Albright syndrome
Chronic recurrent multifocal osteomyelitis
Osteonecrosis-related chemotherapy

¹ Few studies are available.

² Etiology of osteoporosis is multifactorial in the majority of disorders.

come established as a standard of care [9–13]. Intravenous pamidronate, neridronate or zoledronate are the treatment of choice in patients with moderate-to-severe osteogenesis imperfecta, whereas, bisphosphonate treatment is discussed in patients with mild forms of osteogenesis imperfecta [2, 11–13]. An important concern is whether oral bisphosphonate treatment is just as effective as intravenous use in patients with osteogenesis imperfecta. A randomized, placebo-controlled study by oral alendronate (5 and 10 mg) for 2 years showed decreased bone turnover and increased lumbar bone mineral density (BMD) but unchanged fracture outcomes [14]. In children with a mild form of osteogenesis imperfecta oral

risedronate treatment for 2 years increased lumbar BMD, whereas this was not evident in the placebo group. However, histomorphometric analysis of transiliac bone biopsies did not show a significant treatment difference in cortical width, trabecular bone volume or parameters of bone turnover [15]. These results suggested that the skeletal effects of oral risedronate were weaker than those that are commonly observed with intravenous pamidronate but still lead to an increase in lumbar BMD. A recent randomized, double-blind, placebo-controlled trial showed that oral risedronate increased BMD and reduced the risk of first and recurrent fractures, so that it should be regarded as a treatment option for pediatric patients with osteogenesis imperfecta [16].

IJO is a rare primary form of osteoporosis of unknown etiology that develops in a previously healthy child. Diagnosis of IJO is based on the exclusion of known causes of osteoporosis in childhood, mainly the mild forms of osteogenesis imperfecta. Typical features of patients with IJO are fractures of the metaphyses and vertebral bodies after minimal trauma, pain in the back and extremities and difficulty in walking. A gradual remission 1–5 years after the onset of puberty usually occurs in patients with IJO. However, permanent disabilities such as scoliosis, kyphosis, rib and spine deformities, and fractures may occur in young adulthood [17]. Although there is no reliable treatment in patients with IJO, bisphosphonates would seem to be the most effective therapy for improving painful symptoms and bone mass accumulation [17]. A study showed that intravenous pamidronate stimulated the onset of recovery phase, improving bone mineral status, reducing fracture rate and preventing skeletal deformities [5].

Secondary Forms of Osteoporosis

Many disorders may be associated with secondary osteoporosis in childhood. Reduced motility, sarcopenia, vitamin D deficiency, reduced nutrient intake, abnormal endocrine function, chronic inflammation, bone marrow expansion, some medications including glucocorticoids and chemotherapies, and cranial irradiation may affect bone health [18–20].

Glucocorticoid-induced osteoporosis is a common form of secondary osteoporosis in both adults and children. It frequently affects children with diffuse connective tissue diseases [21, 22], inflammatory bowel diseases [23], chronic renal diseases [24, 25], hematological malignancies [26–29], or solid tumors [30]. Systemic glucocorticoid treatment is associated with an initial increase in bone resorption and a subsequent reduction of bone formation, leading to decreased peak bone mass, microar-

chitectural deterioration and increased fracture risk [31–34]. There is good evidence that oral glucocorticoids, mainly when used for more than 3 months and at doses greater than 5–7.5 mg/day of prednisone (or equivalent), increase the risk of fragility fractures [31–33]. A recent systematic review and meta-analysis of glucocorticoid-induced osteoporosis in children reported incident clinical fracture rates from 2 to 33%. Morphometric vertebral fracture incidence ranged from 6 to 10%, and prevalence was 29–45% [34].

Disuse osteoporosis is a severe complication in patients with acute and chronic neurogenic diseases with palsy or severely handicapped children with cerebral damage, myelomeningoceles and muscular dystrophies [35, 36]. Prevalence rates for fragility fractures have been estimated at 20% in nonambulatory children [37].

Table 3 summarizes some controlled studies in pediatric patients with secondary osteoporosis associated with glucocorticoid treatment or chronic disuse treated with bisphosphonates. The majority of subjects showed increased BMD or reduced bone pain [21, 38–48]; a reduced fracture rate was reported in patients with quadriplegic cerebral palsy [48].

Increased survival of patients with thalassemia major allowed for many complications, including osteoporosis in young adulthood. Bone marrow expansion, iron overload and iron chelation by deferoxamine, endocrine dysfunctions (including growth hormone and IGF-1 deficiency and hypogonadism), vitamin D deficiency, diabetes, and reduced physical activity due to the complications of the disease are primary causes of osteoporosis in these patients [49, 50]. A recent review in randomized controlled trials in thalassemic young adults with established osteoporosis showed that bisphosphonates treatment may prevent bone loss and improve BMD [51].

Hypercalcemic Disorders

Symptomatic hypercalcemia requires an aggressive treatment due to its cardiotoxicity. The main causes of severe hypercalcemia (serum calcium levels >14 mg/dl) in infants and children are vitamin D intoxication and malignancy-induced hypercalcemia due to the invasion of the skeleton by malignant cells releasing bone-resorbing cytokines or related to the production of parathyroid hormone-related peptide [2]. Glucocorticoid treatment (prednisone, 1–2 mg/kg per day) is the treatment of choice for vitamin D-induced hypercalcemia. In patients who do not respond promptly to glucocorticoid treatment, bisphosphonates may be effective [52, 53]. Alendronate treatment was able to restore normocalcemia 4

Table 3. Some controlled studies in pediatric patients treated with bisphosphonates for secondary osteoporosis associated with glucocorticoid treatment or chronic disease

Cause	Disease(s)	n	Treatment duration	Bisphosphonate treatment regimen	Effects on bone health
<i>Glucorticoid-induced osteoporosis</i>					
Bianchi et al. [21]	Diffuse connective tissue diseases	38	12 months	Oral alendronate, 5 mg per day for body weight ≤20 kg, 10 mg per day for >20 kg	Lumbar spine BMD↑ in treated group; BMD unchanged or ↓ in the untreated group (n = 38)
Lepore et al. [38]	Systemic or polyarticular juvenile chronic arthritis	7	12 months	Oral disodium clodronate, 1,200 mg per day for 1 year	D13–L3 BMD↑ in treated group and BMD↓ in the untreated group (n = 6)
El-Husseini et al. [39]	Renal transplant recipients	15	12 months	Oral alendronate, 5 mg per day	Lumbar spine BMD in comparison with placebo group (n = 15)
Rudge et al. [40]	Chronic illnesses	11	12 months	Oral alendronate, 1–2 mg/kg for body weight once weekly	Lumbar spine BMAD↑ in treated group; BMD unchanged in the placebo group (n = 11)
Acott et al. [41]	Renal or rheumatic diseases	17	36 months	Intravenous pamidronate, 1 mg/kg/dose (max. 90 mg) once every 2 months for 1 (n = 15) or 2 (n = 2) years	Lumbar spine BMD↑ with resolution of bone pain in treated group; BMD unchanged in the untreated group (n = 17)
Kim et al. [42]	Nephropathies	22	3 months	Oral pamidronate, 125 mg per day	Lumbar spine BMD unchanged in treated group; BMD↓ in the control group (n = 22)
Carpenter et al. [43]	Hematopoietic cell transplantation	18	351 days ²	Intravenous pamidronate, 1 mg/kg monthly	Standardized ¹ lumbar or femoral BMD↑ in treated group in comparison with the untreated group (n = 48)
Sbrocchi et al. [44]	Crohn's disease	7	6 and 12 months	Intravenous zoledronate, 0.066 mg/kg/dose (max. 4 mg)	Lumbar spine BMD↑ and lumbar spine BMAD↑ in comparison with the placebo group (n = 6)
Lee et al. [45]	Acute lymphoblastic leukemia and non-Hodgkin lymphoma	24	12 cycles ² (range 6–30)	Intravenous pamidronate, 1 mg/kg per day for 3 days at 1- to 4-month intervals	Lumbar spine BMD↑ and reduction of bone pain in comparison with the untreated group (n = 10)
<i>Disuse osteoporosis</i>					
Henderson et al. [46]	Nonambulatory cerebral palsy	6	12 months	Intravenous pamidronate, 1 mg/kg per day for 3 days at 3-month intervals (total 15 doses)	Lumbar spine BMD↑ and lateral distal femur BMD in comparison with the placebo group (n = 6)
Iwasaki et al. [47]	Nonambulatory cerebral palsy	10	6 months	Oral risedronate combined with calcitriol (doses not reported)	Lumbar spine or distal radius ΔBMD increased more in treated patients in comparison with the control group receiving only calcitriol (n = 10)
Bachrach et al. [48]	Quadriplegic cerebral palsy	25	13.6 months	Intravenous pamidronate, 1 mg/kg per day (max. 35 mg) for 3 days at 3- to 4-month intervals (total 15 doses)	Fracture rate↓ in treated group; fracture rate↑ in comparison group (n = 79)

BMAD = Bone mineral adjusted density, measured by DXA and calculated by extrapolating volumetric BMD by a mathematical formula.

¹ Calculated by mathematical formulae to account for the 12% reproducible variability in BMD when DXA devices were used from different manufacturers.² Median of bisphosphonate therapy expressed as time or number of cycles.

times earlier than prednisolone in infants with vitamin D intoxication [53].

In addition to the beneficial effects in reducing hypercalcemia in patients with malignancy-induced hypercalcemia, bisphosphonate treatment may be an important option for patients with relapsed or refractory disease that includes metastatic bone disease in combination with chemotherapies [54, 55].

Heterotopic Calcifications

Fibrodysplasia ossificans progressiva is a rare and disabling genetic condition characterized by congenital malformations of the big toes and progressive heterotopic endochondral ossification, which is the most catastrophic of the heterotopic endochondral ossification disorders in humans. Heterozygous activating mutations in activin receptor IA/activin-like kinase-2, a bone morphogenetic protein type I receptor, have been found in all sporadic and familial cases of fibrodysplasia ossificans progressiva [56]. There are no effective medical treatment options to prevent the formation of heterotopic bone in this disease. Bisphosphonate treatment has shown improvement in ambulation, a reduction of existing calcifications and the disappearance of some new ectopic ossifications [57–59].

Generalized arterial calcification of infancy is a rare, potentially lethal condition characterized by diffuse and generalized calcification of large and medium-sized arteries caused by homozygous or compound heterozygous mutation in the ENPP1 gene on chromosome 6q23. Bisphosphonates were effective in reducing the progression of the disease in some children with generalized arterial calcification of infancy [60–62] but not in others [63]. Severe skeletal toxicity was observed in 1 patient [62]. Bisphosphonate treatment was associated with survival beyond infancy in 11 cases (65%), whereas 18 of 26 patients (69%) not treated with bisphosphonates died in infancy [64].

However, few data on bisphosphonates treatment in children with heterotopic calcifications are available and long-term efficacy and safety should be further examined.

Fibrous Dysplasia of Bone/McCune-Albright Syndrome

Fibrous dysplasia of bone is characterized by osteolytic lesions, mainly localized at long bones, skull and ribs, that may be associated with bone pain and fragility fractures. Neurological complications may develop as a consequence of hypertrophic bone [65]. McCune-Albright syndrome represents the association of fibrous dysplasia with multiple endocrinopathies due to an activating mutation of G_sα protein in the *GNAS1* gene, including preco-

cious puberty, hyperthyroidism, hypersecretion of growth hormone with increased production of IGF-1 with gigantism, hyperprolactinemia, hyperadrenocorticism with Cushing syndrome, gynecomastia, and hypophosphatemic rickets/osteomalacia. Bone turnover is increased [65]. Affected patients show a variable phenotype, including bone deformities and skin lesions (large café-au-lait spots with irregular margins) [65]. Bisphosphonates may have some beneficial effects on the osteolytic lesions, reducing bone pain, bone turnover and fracture rate [66]. Reduced bone turnover could reflect both the effect of bisphosphonate therapy on bone lesions and on unaffected bone; however, no deleterious effect of bisphosphonates on the unaffected bone and on longitudinal growth has been found [67].

Chronic Recurrent Multifocal Osteomyelitis

Chronic recurrent multifocal osteomyelitis is a rare inflammatory disorder of the skeleton of unknown etiology. It typically follows an intermittent course, often with involvement at multiple sites – classically the metaphyseal regions of long bones. The lesions can be asymptomatic, but can also be painful with a reduction of physical function and quality of life. Bisphosphonates may be a useful adjunctive treatment in patients with chronic recurrent multifocal osteomyelitis when simple therapies such as anti-inflammatory agents fail to control bone pain, in cases in which lesion expansion continues or in patients with spinal involvement [68].

Osteonecrosis-Related Chemotherapy

Nontraumatic osteonecrosis, resulting in infarction and necrosis of bone, is recognized as a potential complication in pediatric patients following chemotherapy for acute lymphoblastic leukemia, lymphoma or solid-tumor cancer. Glucocorticoids are associated with host-related risk factors and clearly linked to the development of osteonecrosis-related chemotherapy [69, 70]. Osteonecrosis-related chemotherapy is a major cause of severe bone pain, reduction in joint mobility and long-term disability; it can affect any or multiple joints but the hip and knee are most frequently involved. Bisphosphonate treatment does not seem to prevent progressive joint destruction and collapse in patients with hip joint involvement, but disease stabilization in knee joints with reduced bone pain and motor function recovery has been shown [69, 70]. A recent review in children with lymphoblastic leukemia suggested that osteonecrosis-related chemotherapy could be prevented by discontinuous glucocorticoid treatment [71].

Fig. 3. X-ray of hand and wrist of a male patient (age: 14.4 years) affected by IJO, showing typical multiple zebra lines at distal radius and ulna and at the proximal metaphysis of the first phalanx (white arrows) during intravenous pamidronate treatment.

Fig. 4. X-ray of distal femur and proximal tibia of a male patient (age: 15.2 years) affected by type IV osteogenesis imperfecta showing typical multiple zebra lines (white arrows) during intravenous pamidronate treatment. The femoral and tibial diaphysis is narrow and femoral metaphysis is wide due to bisphosphonate-associated impairment of bone modeling.

Fig. 5. X-ray of the knees of a female patient (age: 15.3 years) affected by Lujan-Fryns syndrome showing typical multiple zebra lines (white arrows) during weekly oral alendronate treatment. The white circle indicates a coexisting nonossifying fibroma.

Adverse Effects of Bisphosphonates in Pediatric Patients

Bisphosphonates are usually well tolerated and safe both orally and intravenously. Sclerotic lines (zebra lines) in the metaphyses of long bones represent a typical manifestation of the administration of cyclic bisphosphonates before closure of the epiphyseal growth plate (fig. 3–5). The distance between the sclerotic lines is dependent on the patient's age, the rate of bone growth and the bisphosphonate dosing regimen. Zebra lines do not have negative consequences for bone growth and disappear progressively as they move into the diaphysis secondary to bone remodeling [72].

However, bisphosphonate treatment may decrease the speed of metaphyseal inwaisting by interfering with periosteal resorption, causing impaired bone modeling [73], as we observed in a patient with osteogenesis imperfecta during pamidronate treatment (fig. 4).

The main adverse effects of bisphosphonates treatment in pediatric patients are reported in table 4. Acute effects of intravenous bisphosphonates are common and consist of an acute phase reaction (flu-like symptoms) 1–2 days following the first and/or second course of treatment. Symptoms are self-limiting and resolve over hours to a few days by using paracetamol or other analgesic/antipyretics drugs. The cause(s) of the acute side effects are not clearly defined. Some studies have shown that these symptoms may be caused by a low vitamin D status, defined as serum 25-hydroxyvitamin D (25-OH-D) levels <30 ng/ml [74, 75].

Bisphosphonate-induced hypocalcemia may occur after intravenous administration and this is due to a failure to release calcium from the skeleton as a consequence of the osteoclast inhibition. It rarely occurs after oral bisphosphonate administration. Bisphosphonate-induced hypocalcemia may affect cardiac repolarization documented by a prolonged corrected QT

Table 4. Main adverse effects of bisphosphonates treatment in pediatric patients

Acute effects	Effects associated with long-term use	Potential side effects
Flu-like syndrome ¹ Hypocalcemia ²	Delay in bone healing ³ Drug-induced osteopetrosis ⁴ Gastrointestinal reflux ⁵	Atypical femur fractures ⁶ Osteonecrosis of the jaws ⁶ Orbital inflammation ⁶ Growth impairment ⁷ Teratogenicity ⁸

¹ Mild fever, malaise, nausea, diarrhea, myalgia, arthralgia, bone pain. ² May be symptomatic (tetany, prolongation of corrected QT interval) and may be associated with hypophosphatemia, hypomagnesemia. ³ After intramedullary rodding procedures but not after a fracture. ⁴ Related to cumulative overdoses. ⁵ By oral route: a severe but rare complication may be corrosive esophagitis (not reported in pediatric patients). ⁶ Only in adults, not reported in pediatric patients. ⁷ Unproven. ⁸ Significant fetal risks are not reported, but few data are available.

interval [76]. Moreover, a recent meta-analysis showed an increased risk of atrial fibrillation but no increase in the risk of stroke or cardiovascular mortality [77]. This adverse effect has not been observed in pediatric patients. Vitamin D deficiency, advanced renal disease and subclinical hypoparathyroidism may be contributing factors for bisphosphonate-induced hypocalcemia [78].

Bisphosphonate treatment may cause a delayed healing of osteotomies after intramedullary rodding procedures, but it does not affect the healing of fractures [79]. A recent review on upper limb fractures associated with bisphosphonate treatment did not show any differences in union time between bisphosphonate users and nonusers [80].

Bisphosphonate-induced osteopetrosis with pathological fractures is a rare adverse effect of bisphosphonate treatment and seems to be due to cumulative overdoses [81]. Bone modeling abnormalities as described in osteopetrosis have been reported in a patient, a 7-year-old boy, with generalized arterial calcification of infancy treated with etidronate [61].

Some studies in adult patients have shown that bisphosphonate treatment is a risk factor for atypical femur fractures, although most bisphosphonate users will not experience atypical fractures and some patients with atypical fractures have not used bisphosphonates. To date, atypical femur fractures are not reported in pediatric patients receiving bisphosphonates.

Bisphosphonate-related osteonecrosis of the jaws has been detailed extensively in adults but to date there have been no similar cases in children, suggesting that pediatric patients are likely to have a different dental risk profile compared with adults [82].

Bisphosphonate-associated orbital inflammation, including uveitis and scleritis, is reported in adults [83] but not in pediatric patients.

Bisphosphonate treatment does not appear to have a detrimental effect on linear growth in children, regardless of the severity of the condition. In patients with osteogenesis imperfecta, improved or no effect on linear growth is reported [84]. In patients with IJO, a normal pattern of linear growth during long-term intravenous pamidronate treatment was found [5].

Potential teratogenic effects of bisphosphonates could occur during pregnancy, but few data are available on this issue. Some cases of shortened gestational age, low neonatal birth weight and transient hypocalcemia of the newborns have been shown, while the few reported cases of spontaneous abortions and congenital anomalies probably resulted from maternal underlying diseases and concomitant medication [85, 86]. However, it would be prudent to prescribe effective means of birth control to adolescent girls during bisphosphonate treatment and to consider performing a pregnancy test before each bisphosphonate infusion. Moreover, the safety of bisphosphonate therapy beyond 10 years has not been established.

Clinical Approach and General Measures for Bisphosphonate Treatment in Pediatric Patients

There are no international guidelines for bisphosphonate treatment in pediatric patients. Their use remains controversial because of insufficient long-term efficacy and safety data. In our pediatric unit, as a general guide, bisphosphonate treatment is taken into consideration in

Table 5. Main clinical, biochemical and imaging assessments suggested in pediatric patients treated with bisphosphonates

Clinical assessments

General clinical examination including measurement of linear growth
Dental and parodontal examination (by an odontologist)
Complete eye examination (by an ophthalmologist)
Calcium intake estimation

Biochemical measurements

Complete blood count
Electrolytes
Total alkaline phosphatase and biochemical markers of bone turnover
Hepatic and renal functional tests
Vitamin D status and parathyroid hormone
Standard urine analysis and urinary calcium excretion

Imaging examinations

X-ray of the wrist and knees
Bone mineral status by densitometric techniques

Note: general clinical and dental-parodontal examination, as well as biochemical assessments should be performed approximately every 4–6 months, even in the absence of symptoms. Complete eye examination should be performed if ocular symptoms are referred or detected. Imaging examinations could be performed approximately every 1–2 years, according to the disorder and severity of disease in order to assess the occurrence of abnormal bone modelling, to examine bone structure and to estimate bone age according to skeletal growth.

children suffering from osteoporosis, diagnosed according to the pediatric guidelines of the International Society for Clinical Densitometry [87], in the presence of therapeutic failure with maximum doses of vitamin D and calcium. Moreover, compassionate use of bisphosphonates should be considered in severely affected pediatric patients with fragility fractures and extremely reduced quality of life [88, 89]. In addition, there is no consensus regarding the optimal bisphosphonate agent in children, dosage or duration of therapy [89]. Bisphosphonates are usually discontinued when the targets of the planned treatment are achieved or if adverse effects occur [2]. The main problem is when to discontinue the bisphosphonate treatment should the targets not be reached, considering the potential side effects related to long-term treatment. A discontinuation of treatment could be considered after 5 years of therapy for adult patients at low risk of fracture, although there is no official recommendation regarding this to guide clinicians [86]. However, no specific limits on the duration of treatment are imposed.

A normal vitamin D status (serum 25-OH-D levels ≥ 20 ng/ml) and a calcium intake according to RDAs [90] should be maintained before and after bisphosphonate treatment, mainly if intravenous administration is employed. In order to reduce the risk of hypocalcemia the patients could receive an intravenous 10% calcium gluconate infusion after each bisphosphonate intravenous infusion [5]. Although there are no official recommendations, some clinical, biochemical and imaging assessments may be suggested in pediatric patients receiving bisphosphonate therapy (table 5).

Conclusions

Bisphosphonate treatment has shown beneficial effects in some disorders associated with fragility fractures or severe hypercalcemia. The use of bisphosphonates in pediatric patients should be carefully weighed to ensure that the potential benefits to bone health outweigh any potential risks. At present there is insufficient evidence for the routine use of bisphosphonates in clinical care, therefore bisphosphonate treatment should be regulated by specialists with knowledge in the management of bone disease in pediatric patients.

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