

Clinical use of bisphosphonates in children

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Background: Bisphosphonates are being increasingly and successfully used to prevent bone fractures and treat bone pain in children with severe osteoporosis from different origins. The purpose of this article is to update the clinical use of bisphosphonates in pediatric patients and to present the authors' experience with the intravenous administration of pamidronate in osteopenic children.

Data sources: PubMed database was used to collect publications reporting the utilization of bisphosphonates in children. The medical records of five pediatric patients treated in our unit with bisphosphonates were also reviewed.

Results: A growing experience is accumulating with the cyclical intravenous administration of pamidronate in children with osteogenesis imperfecta. Bisphosphonates may also be useful in the prevention and treatment of vascular calcification in patients with chronic renal failure, although no data on children in this clinical setting are available.

Conclusions: Intravenous bisphosphonates are well tolerated, even in infants and small children, and represent a promising therapeutic tool to prevent the development of bone fractures and to improve the well-being of osteoporotic children. A number of questions about the precise clinical indications for bisphosphonates' administration, the duration of the treatment, the best way to monitor its effectiveness and to early detect toxic effects remain to be answered.

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Structure and mechanism of action

Bisphosphonates are analogues of pyrophosphate that contains two phosphonic acids directly attached to a central carbon atom, from which two side chains, denominated R¹ and R²,^[1] also extend (Fig. 1). Bisphosphonates bind avidly to the hydroxyapatite of bone surfaces and are subsequently accumulated in the osteoclasts by endocytosis. The R¹ chain determines the affinity of this binding, whereas the R² chain determines the potency of inhibiting bone resorption, which varies between different bisphosphonates up to 5000-fold, and the intrinsic mechanism of action on osteoclasts (Table 1). Bisphosphonates lead to osteoclasts' apoptosis by interfering with prenylation (transfer of fatty acid chains) of small guanosinotriphosphate (GTP) binding proteins. Failure of prenylation causes inability of these proteins to translocate into cell membranes and results in apoptosis.^[2] Older non-containing nitrogen bisphosphonates cause osteoclasts' apoptosis by forming toxic adenosinotriphosphate (ATP) analogues. In addition to the bone resorption inhibition mediated by their effects on osteoclasts, bisphosphonates given in large doses inhibit normal and ectopic mineralization as a result of a direct chemical mechanism since they bind to solid phase calcium-phosphate and limit crystal growth.^[1]

Pharmacokinetics

Bisphosphonate compounds are available as intravenous or oral preparations (Table 1).^[3] Digestive tolerability of oral bisphosphonates is poor and the experience with its use in children is really limited. To facilitate the absorption, which is less than 1% of the administered dose, bisphosphonates must be given in fasting conditions with enough amount of water. Absorption is negligible in the presence of divalent ions which chelate the bisphosphonates. Bisphosphonates circulate in the blood freely or weakly bind to plasma proteins. Unbound bisphosphonates are actively taken up by bone within 12-24 hours. Bisphosphonates bind preferentially

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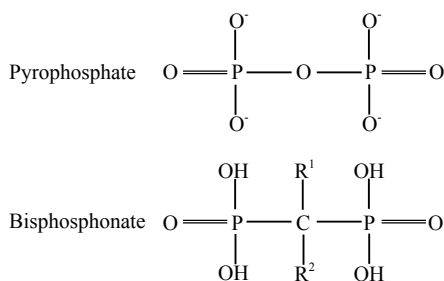


Fig. 1. Chemical structure of bisphosphonates.

Table 1. Relative potency to inhibit bone reabsorption and side chain features of various bisphosphonates used in humans

Bisphosphonates	Antiresorptive potency	R ¹	R ²
Etidronate	1	OH	CH ₃
Clodronate	10	Cl	Cl
Tiludronate	10	H	S-CH ₂ Cl
Pamidronate	100	OH	Contains nitrogen
Neridronate	100	OH	Contains nitrogen
Olpadronate	200–500	OH	Contains nitrogen
Ibandronate	500–1000	OH	Contains nitrogen
Alendronate	1000–2000	OH	Contains nitrogen
Risedronate	2000	OH	Contains nitrogen
Zoledronate	10000	OH	Contains nitrogen

to bones which have high turnover rates, and their distribution in bone is not homogeneous. After bone uptake, the bisphosphonates are liberated again only when the bone in which they are deposited is reabsorbed. Thus, the half-life of bisphosphonates in bone is very long, ranging among different species from 1 to 10 years, depending largely on the rate of bone turnover.^[3] However, current data suggest that bisphosphonates are active only while binding to the bone surface, and become biologically inactive once the drug gets buried in bone tissue.^[1] Bisphosphonates are eliminated unchanged in the urine and the doses should be adjusted in the case of renal insufficiency. In general, it is recommended to avoid the use of the majority of bisphosphonates when the glomerular filtration rate is below 30 ml/min/1.73 m². The kinetics of bisphosphonates in children and patients with renal diseases is largely unknown.^[4]

Clinical use in children

In adults, the potent ability of bisphosphonates to inhibit bone reabsorption has been extensively used over the last three decades to treat osteoporosis, Paget's disease, hypercalcemia of malignancy, tumor-induced bone disease, and hyperparathyroidism. More preliminary experimental and clinical data indicate that intravenous bisphosphonates may be useful in the treatment and prevention of atherosclerosis because they reduce

arterial calcification and improve the serum lipoprotein profile. This beneficial effect on the concentrations of serum lipoprotein is related to the ability of aminobisphosphonates to inhibit the mevalonate pathway and so to interfere with cholesterol synthesis. A shift in circulating cholesterol from low-density lipoprotein cholesterol to high-density lipoprotein cholesterol and marginal decrease in total serum cholesterol and triglycerides has been found in postmenopausal women with osteoporosis^[5] and patients with Paget's disease^[6] treated with aminobisphosphonates.

The experience with bisphosphonates in children is limited although there are a growing number of publications showing their usefulness in several bone and metabolic diseases. The largest population of pediatric patients treated with bisphosphonates corresponds to children with osteogenesis imperfecta. In 1998, Glorieux et al^[7] reported that intravenous administration of pamidronate at 4 to 6-month intervals improved bone mineral density, mobility, incidence of bone fractures and reduced chronic bone pain and biochemical markers of bone resorption in 30 children with severe osteogenesis imperfecta. This study indicated the beneficial effects of bisphosphonates in this disease as demonstrated by former clinical observations,^[8-10] and prompted the increasing use of this therapy in children with moderate and severe osteogenesis imperfecta.^[11-46] In these studies, the vast majority coming from the same group,^[7,13,16-20,29,36,37,41,44,45] cyclical intravenous administration of pamidronate was given most frequently, although a few studies have reported the effects of other bisphosphonates such as oral alendronate,^[26-28,33] oral olpadronate,^[24] or intravenous neridronate.^[32,38]

Nowadays, the frequently recommended dosage of pamidronate in children with osteogenesis imperfecta is 1 mg/kg per day, infused intravenously with 0.9% saline solution in a 4-hour period for three consecutive days every 4 months.^[45] In infants, lower dose of pamidronate is recommended at shorter intervals, such as 0.5 mg/kg per day in 3-day cycles every 6-8 weeks^[20,29] because of the shorter duration of the clinical effects in this age group. To test the tolerance to the medication, the dose used in the first cycle must be lower than those of the above in all patients.^[45]

The experience with the use of bisphosphonates in pediatric patients with diseases other than osteogenesis imperfecta is mostly based on small series or single clinical cases. Thus bisphosphonates have been used in the treatment of hypercalcemia induced by such conditions as cancer,^[47-56] bone marrow transplantation for osteopetrosis,^[57] prolonged immobilization,^[58-60] vitamin A toxicity,^[61] total parenteral nutrition,^[62-64] Williams syndrome,^[65] vitamin D intoxication,^[66-70] or

hyperparathyroidism.^[59]

Interestingly, bisphosphonates are administered to prevent the development of fractures in children with osteoporosis secondary to prolonged immobilization caused by neurological or muscular diseases. Allington et al^[71] treated 18 osteoporotic children with non-ambulatory cerebral palsy and other neuromuscular disorders with intravenous administration of pamidronate in cycles of 3 mg/kg every four months. They found improvement in bone densitometry, particularly in the lumbar spine, as well as beneficial clinical effects such as decrease of pain on manipulation and absence of new fractures after one year of treatment. Similar results were observed after the cyclical intravenous administration of pamidronate in children with cerebral palsy^[34] and of pamidronate or olpadronate in children with different symptomatic osteoporosis and multiple fractures.^[72] A positive response to oral alendronate of total body and spine bone mineral density was found in 16 deflazacort-treated boys with Duchenne muscular dystrophy.^[73] Moreover, the administration of alendronate markedly decreased the incidence of fractures in 10 non-ambulatory children with disuse osteopenia secondary to either static brain injury or spina bifida.^[74] Once-weekly oral alendronate has been shown to increase the volumetric bone density of the lumbar spine and reduce urine N-telopeptide excretion as a biochemical marker of bone resorption in children treated persistently with glucocorticoids.^[75] In a group of 17 osteopenic or osteoporotic children, administration of pamidronate or zoledronic acid (1 mg of pamidronate

= 0.025 mg of zoledronic acid) for 6-43 months showed a beneficial effect on bone mineral density and, more importantly, the effect maintained for 18-44 months after withholding the treatment.^[76]

Bisphosphonates have been used in the treatment of calcinosis and heterotopic ossification in children with dermatomyositis,^[77-80] myositis ossificans,^[81-84] and fibrodysplasia ossificans progressiva.^[85-87] The majority of these studies are based on the administration of etidronate disodium in a single center with few clinical cases, and the results are variable. Recent reports have shown rapid and marked improvement of calcinosis in two children with dermatomyositis treated with alendronate.^[79,80]

The intravenous administration of pamidronate in children in our institute is analyzed (Table 2). Five osteoporotic patients, 3 male, aged 2 to 14 years at the beginning of treatment, received intravenous pamidronate at 2-3 mg/kg per cycle for 3-day cycles. Four of them had presented fractures caused by minor or absent trauma. Immediately before each cycle, serum concentrations of calcium, phosphate, alkaline phosphatase, blood urea nitrogen, creatinine, osteocalcin, PTH and vitamin D metabolites were measured as well as blood acid-base equilibrium. Elemental uroanalysis as well as measurement of the concentrations of cross-linked N telopeptide type I collagen, hydroxiprolin, calcium, and creatinine were performed in the second urine sample collected in the morning after fasting the first day of each cycle. Bone mineral density was measured before the treatment

Table 2. Clinical features of five osteoporotic children treated with intravenous cycles of pamidronate

Patient	1	2	3	4	5
Sex	Male	Male	Female	Male	Female
Age (y)	7	14	12	2	9
Primary diagnosis	Osteogenesis imperfecta type III	Cerebral palsy	Idiopathic osteoporosis	Spinal muscular atrophy	Severe myopathy
Associated diagnosis	Urolithiasis	Epilepsy, vesicoureteral reflux	Asthma	Chronic respiratory insufficiency	Chronic respiratory insufficiency, malnutrition
Follow up	7 y	6 mon	5 y	2.5 y	7 mon
Cycles of pamidronate	27	2	7	11	3
Fractures before treatment	14	2	6	0	2
Fractures during follow-up	0	0	0	0	0
Initial weight (kg) (SDS)	11.3 (-2.9)	28 (-2.3)	55 (+1.5)	10.7 (-1.5)	14.0 (-2.7)
Final weight (kg) (SDS)	25.5 (-2.5)	29 (-2.2)	70 (+2.5)	20 (+1.5)	16 (-2.6)
Initial height (cm) (SDS)	84 (-)	134 (-3.6)	157 (+0.8)	86.5 (-0.06)	120 (-2.4)
Final height (cm) (SDS)	141 (-)	Not available	162 (+0.9)	100 (-0.6)	Not available
Initial BMD (g/cm ²) (SDS)	180 (-)	0.455 (-5.9)	0.666 (-3.4)	0.326 (-3.0)	0.459 (-2.4)
Final BMD (g/cm ²) (SDS)	400 (-)	Not available	0.969 (-1.2)	0.541 (+0.45)	Not available
Side effects	Fever	Fever	None	Fever	None
Clinical outcome	Improvement	Improvement	Improvement	Not available	Improvement

BMD: bone mineral density; SDS: standard deviation score. Lumbar spine BMD was measured by DEXA, except for patient 1 in whom it was measured on forearm because of calcium nephrolithiasis. For patient 1, SDS of height and BMD were not provided because of the lack of adequate normal reference values.

and every one to two years afterwards. All children had a positive response to the treatment, with rapid and marked clinical improvement in their mobility and strength. Moreover, one patient who was confined to bed before treatment became able to walk. After receiving two or three cycles of pamidronate, no new fractures occurred during follow-up of 6-7 months in two children who subsequently died from primary disease related complications. Patients' tolerance to treatment was excellent, fever was noted in 3 of the 5 patients after administration of the first dose of pamidronate for the first cycle. Consistent and significant changes in the above mentioned biochemical variables were not found except the level of urine N telopeptide type I collagen. In patients followed up for more than one year, the levels of N telopeptide type I collagen decreased to 40% of the initial levels after the third cycle of pamidronate and were still between 30% to 40% of the pre-treatment levels at the last follow-up. Hypocalcemia and proteinuria were not detected in any patient. Bone mineral density was improved in the 3 patients, in whom it could be repeatedly measured.

Bisphosphonates in kidney diseases

The potent inhibitory effect of bisphosphonates on bone reabsorption has been implicated in renal transplanted adults to prevent or treat bone loss induced by persistent administration of glucocorticoids.^[88-102] Two randomized controlled trials on bisphosphonates in kidney transplant recipients^[99,100] revealed that the treatment with bisphosphonates has a beneficial effect on bone mineral density although the trials were inadequately powered to show a reduction in the risk for fracture. The experience with the use of bisphosphonates in transplanted children is very limited. In 15 osteopenic or osteoporotic patients transplanted at the age of 17 years or less, the T-score of bone mineral density at the lumbar spine changed from -2.3 to -1.9 after 12 months of oral treatment with alendronate at a dose of 5 mg/day, whereas the density fell from -2.4 to -2.8 in untreated transplanted controls and improved from -2.3 to -0.5 and from -2.3 to 1.0 in patients receiving either alphacalcidol (0.25 mcg/day) or nasal spray calcitonin (200 IU/day).^[103] In pediatric patients with nephropathies receiving high doses of corticosteroids, administration of 125 mg of pamidronate for 3 months prevented the loss of lumbar spine bone mineral density induced by the steroid treatment.^[104]

Because of their inhibitory activity of bone resorption and ability to interfere with mineralization and calcium phosphate crystallization,^[105] bisphosphonates might be useful in the management of selected hypercalciuric patients with urolithiasis.^[106] A 2-year therapy with etidronate increased bone mineral density in lumbar spine

of young male patients with idiopathic hypercalciuria and osteopenia.^[107] Alendronate has been shown to decrease urine calcium and super-saturation of urine with respect to calcium oxalate and calcium hydrogen phosphate in genetic hypercalciuric stone-forming rats^[108] and adult humans subjected to bed rest immobilization.^[109]

Bisphosphonates are given to adult patients with severe hyperparathyroidism secondary to end-stage renal failure in an attempt to reduce hypercalcemia caused by increased bone reabsorption and therapy with vitamin D analogues and/or calcium containing phosphate binders.^[110-116] The results of the studies, always based on a small number of patients, do not support the use of bisphosphonates in the treatment of secondary hyperparathyroidism because of the lack of uniformity in the effects on serum calcium concentration, the presence of mineralization defects, and changes in the bone histological structure, such as increase of both fibrous tissue and the number of osteoclasts,^[111,114] and even worsening of serum parathyroid hormone.^[110,116] However, in the experimental model of chronic renal failure induced by subtotal nephrectomy, ibandronate^[117] and olpadronate^[118] have been shown to increase bone volume and prevent the osseous lesions of hyperparathyroidism.

More interestingly, bisphosphonates are potentially used to inhibit ectopic mineralization for the prevention and treatment of vascular calcifications in patients with end-stage renal failure. Several experimental studies have been carried out on rats with acute uremia,^[119] rats with normal renal function receiving a toxic dose of vitamin D,^[120] subtotally nephrectomized rats treated with calcitriol for three weeks,^[121] and rats made uremic by administration of a synthetic diet containing 0.75% of adenine for 4 weeks.^[122] In those studies, all the animals treated with bisphosphonates demonstrated a lower calcium content in the aorta. In a diabetic woman with chronic renal failure, intravenous administration of pamidronate improved dramatically calciphylaxis, a condition characterized by medial calcification of the small arteries and ischemia of the subcutaneous tissue, often leading to necrosis of subcutaneous fat and skin.^[123] Likewise, oral treatment with etidronate for 3 cycles given for 14 days every three months ameliorated the progression of coronary artery calcification, as assessed by multidetector spiral computed tomography in 26 of 36 adult patients receiving frequent hemodialysis.^[124]

Side effects and toxicity

Oral administration of bisphosphonates produces some degree of gastrointestinal intolerance, particularly the aminobisphosphonates. To minimize esophageal irritation, they must be given in fasting conditions and

with large amounts of water which limit their use in young children and patients with swallowing difficulties or obliged to remain in decubitus. Administration of risendronate or alendronate once a week facilitates the oral tolerance. Etidronate does not contain nitrogen and is usually well tolerated, causing mild diarrhea.

In children, pamidronate is given cyclically by intravenous infusion, giving few serious adverse events. After the first dose for the first cycle, one third of patients may undergo an immediate reaction characterized by high fever, malaise, musculoskeletal aches and lymphocytopenia. The reaction usually does not recur in further cycles, and can be prevented by pre-treatment with acetaminophen and ibuprofen,^[125] and may also be occasionally observed with oral administration of bisphosphonates in a milder intensity.^[126]

Given the potent effect of pamidronate on osseous metabolism, several studies have analyzed whether the repeated administration of this drug might adversely impair growth or bone structure. Each cycle of pamidronate leaves a radiologically visible metaphyseal band (Fig. 2). Sclerotic lines are formed by trabeculae rich in calcified cartilage, and the percentage of calcified cartilage decreases as the band goes away from the growth plate.^[127] The trabeculae undergo remodeling and disappear within 2 to 8 years, and likely represent a non-specific effect resulting from temporary interruption of growth plate cartilage resorption at the time of pamidronate infusion.^[127,128] A widening of the distal femoral metaphyses was seen on radiographs of children with osteogenesis imperfecta who had received pamidronate therapy for 2-4 years.^[128] This change in the metaphyses is attributable to the interference of pamidronate with the physiological process of periosteal resorption. In spite of these radiological findings,



Fig. 2. Methaphyseal bands, each corresponding to a cycle of pamidronate, are visible in the wrist X-ray of a patient with osteogenesis imperfecta.

longitudinal growth rate is not adversely affected by pamidronate treatment in osteoporotic children.^[72] As to the bone structure, mineralization defects have not been observed in patients with osteoporosis^[72] or osteogenesis imperfecta^[13] treated with pamidronate. Histomorphometric analysis of iliac bone of infants, children and adolescents with osteogenesis imperfecta indicates that pamidronate increases cortical width and the volume of cancellous bone and suppresses bone turnover markedly.^[13,29] Excessive amounts of pamidronate may lead to oversuppression of bone resorption and osteopetrosis, whereby monitoring of biochemical markers of skeletal turnover is mandatory in children treated with bisphosphonates.^[129]

Hypocalcemia may result from pamidronate administration. It is usually mild and asymptomatic,^[45,65] and the occurrence of more severe hypocalcemia must suggest unrecognized hypoparathyroidism, impaired renal function, or vitamin D deficiency as underlying conditions.^[130]

Adverse effects of pamidronate found in adult patients such as osteonecrosis of the jaw in patients with cancer,^[131] collapsing focal segmental glomerulosclerosis leading to nephrotic syndrome,^[132] and acute tubular necrosis^[133,134] have not been reported in children so far.

In summary, a growing number of publications support the use of bisphosphonates in children with different bone disorders to improve bone mineral density, reduce the risk of fracture and ameliorate bone related clinical symptoms. Osteogenesis imperfecta is the disease for which bisphosphonates are extensively used and intravenous pamidronate is often employed cyclically. The metabolism of calcium, phosphate, vitamin D and parathyroid hormone as well as biochemical markers of bone turnover, particularly bone resorption, should be closely monitored before and during the administration of bisphosphonates. Some questions concerning the clinical use of bisphosphonates remain to be answered. Should osteoporotic children receive bisphosphonates in a prophylactic way to prevent the development of fractures? When should the treatment be started and for how long? Which protocol and drug should be recommended in the different clinical settings? Which are the long-term effects of bisphosphonates' administration? Which is the best way to monitor the effectiveness of treatment?

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