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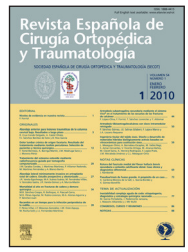

UPDATE

Bisphosphonate applications in children's orthopaedics

M. Salom, [a,b,*] **S. Vidal,** [c] **L. Miranda** [a]

[a] *Unidad de Ortopedia Infantil, Hospital Universitario La Fe, Valencia, Spain*
[b] *Miembro del Grupo de Estudio e Investigación en Osteoporosis (GEIOS), Spain*
[c] *Servicio de Pediatría, Hospital Universitario La Fe, Valencia, Spain*

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Abstract. Bisphosphonates are chemical compounds which mainly act on bone metabolism by inhibiting bone resorption. Their main indication is currently the treatment of post-menopausal osteoporosis, but they can also be used in other diseases that involve an increase in bone resorption.

They have been shown to be beneficial in some paediatric diseases, such as osteogenesis imperfecta, particularly in the more severe forms, polyostotic fibrous dysplasia, patients with severe neuromuscular involvement, and corticosteroid-induced osteoporosis. New indications are also being studied experimentally, such as in Perthes disease or bone lengthening by distraction osteogenesis.

Although experience with bisphosphonates in these diseases is limited, and there is also little consensus as regards the most suitable type of bisphosphonate, the dose to use, the form of administration and on the duration of treatment.

The long-term secondary effects are still not well known, so caution must be used when using them in growing patients and particularly in girls when reaching fertile age.

PALABRAS CLAVE
Bifosfonatos;
Osteoporosis;
Osteogénesis imperfecta;
Displasia fibrosa

Aplicaciones de los bifosfonatos en la ortopedia infantil

Resumen. Los bifosfonatos son compuestos químicos cuya principal acción sobre el metabolismo óseo es la inhibición de la reabsorción ósea. Su principal indicación médica, actualmente, es el tratamiento de la osteoporosis postmenopáusica, pero también puede administrarse en otras patologías que cursan con aumento de la reabsorción ósea.

Dentro de las patologías pediátricas han demostrado ser beneficiosos en la osteogénesis imperfecta (OI), especialmente, en las formas más graves, displasia fibrosa poliostótica, pacientes con grave afectación neuromuscular, osteoporosis secundaria al tratamiento con corticoides y también de forma experimental se están estudiando nuevas

*Corresponding author.
E-mail: salom_martav@gva.es (M. Salom).

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indicaciones como en la enfermedad de Perthes o en los alargamientos por distracción-osteogénesis.

La experiencia con estos fármacos en este tipo de patología aún es pequeña y existe todavía poco consenso en cuanto al tipo de bifosfonato, dosis, forma de administración más adecuada y duración del tratamiento.

Los efectos secundarios a largo plazo aún no son totalmente conocidos, por lo que debemos ser cautos a la hora de utilizarlos en este tipo de pacientes en crecimiento y sobre todo en las niñas al llegar a la edad fértil.

Introduction

Bisphosphonates are chemical compounds that have been used for various industrial purposes. The first bisphosphonate used in humans was etidronate, and it was synthesised more than 100 years ago.[1,2]

Chemically, these compounds are characterised by 2 carbon-phosphate chains (P-C-P) located on a single carbon atom. In addition, the bisphosphonates have 2 radical groups named R1 and R2 on their molecules that are bonded to the carbon atom (fig. 1). The presence of these R groups permit numerous substitutions resulting in synthesis of a great number of compounds with different properties. Because each bisphosphonate has its own unique chemical, physico-chemical, and biological characteristics, it may be difficult to extrapolate the results of one compound's action to those of the others.[3-5]

Their in vivo effects are inhibition of mineralisation and inhibition of bone resorption. Chemical groups in the R1 position determine its affinity for bone mineral, and those in the R2 position determine the strength of its anti-resorption action.[5]

The first bisphosphonates used in humans were etidronate and clodronate, both having the same power to inhibit mineralisation and to inhibit bone resorption. In contrast, the new bisphosphonates (tiludronate, alendronate, pamidronate, risedronate, ibandronate, and zoledronate) have a hydroxyl group (OH) at the R1 position, which gives the molecule a stronger affinity for bone, and an amine group on the R2 chain, which confers an increase of up to 1,000 times more anti-resorption activity but with no great inhibition of bone mineralisation. This group is called the aminobisphosphonates.[4]

Their principal pharmacological properties are their incorporation by the skeleton, their strong bond to hydroxyapatite crystals, their suppression of osteoclast-mediated bone resorption, their prolonged skeletal retention, and their excretion unmetabolised in urine.[5]

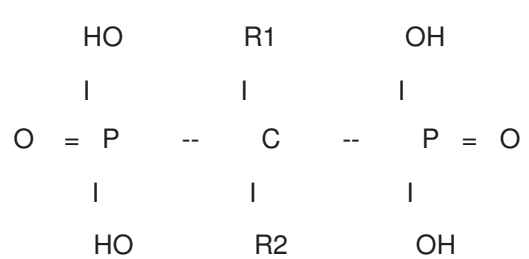

Figure 1 Chemical formula for the bisphosphonates.

The first bisphosphonates' mechanism of action involved being metabolised to cytotoxic, non-hydrolysable analogues of adenosine triphosphate (ATP) that, accumulating intracellularly, inhibited the function of and induced apoptosis in the osteoclasts.[4,5] However, the aminobisphosphonates have a direct effect on the osteoclasts in that they interfere in the intracellular metabolic pathway for mevalonate, inducing apoptosis in the osteoclasts. They also have an effect on other bone cells, hindering the formation of osteoclasts by regulating their precursors, and inhibiting bone resorption by stimulating osteoblasts to produce an osteoclast inhibiting factor.[5]

Owing to their mechanism of action, the bisphosphonates may be used in any bone pathology in which osteoclasts play a featured role. Within the metabolic bone diseases, their primary indication was Paget's disease, which is characterised by focal areas of increased bone turnover. Administration of bisphosphonates translates to a rapid suppression of bone resorption followed by a reduction in bone formation so that bone turnover is closer to normal.[1]

Their chief indication, due to its high incidence, is postmenopausal osteoporosis, for which they are the treatment of choice. They have been proven effective in reducing the number of vertebral and non-vertebral fractures and in increasing bone mineral density.[6] Because of the good results achieved with these drugs in this type of pathology, the indications have been extended to the treatment of osteoporosis secondary to corticosteroids and to organ transplants; they are also the drug of choice in the treatment of osteoporosis in men.[4]

The bisphosphonates are also used in the majority of malignant tumours with bony metastases and in malignant hypercalcemia.[4]

In recent years, the effect of these drugs in other pathologies involving increased bone resorption has been studied, for example, in avascular necrosis of the femoral head,[7] aseptic loosening of prosthesis,[8] and giant cell tumours.[9]

In paediatric diseases, we will see the efficacy of the bisphosphonates in osteogenesis imperfecta (OI), fibrous dysplasia, osteoporosis secondary to immobilisation in neuromuscular diseases, corticosteroid-induced osteoporosis, and in other pathologies on an experimental basis. We will also

discuss their possible side effects and the precautions that must be taken into consideration prior to using these drugs in children.

Diagnosing osteoporosis in children

Before going into the paediatric indications for the bisphosphonates, we must speak about diagnosing osteoporosis in the paediatric age group.

In adults, osteoporosis is defined as a low bone mineral density (BMD), with changes in the bone microarchitecture that result in an increased bone fragility and an increased risk of fractures.[10] Nowadays, the only objective way we have of measuring a low BMD is with densitometry, and we speak of osteoporosis when T-score values are below –2.5 standard deviations.[11]

However, these criteria are not readily applicable to the paediatric age group because the BMD is constantly changing during growth depending on body mass, bone mass, sex, age at onset of puberty, skeletal maturation, and race.[12,13]

Although simple x-rays are the first tests we obtain on children with suspicion of osteoporosis, they do not afford us a precise quantitative determination of the BMD. Mineral must be reduced by 30%-40% before it is evident on an x-ray.[14] Densitometry is currently the test most widely used to quantify skeletal mass because it is safe, precise, and relatively economical.[12-14] Agreement has been reached at the international level as to the definition of osteoporosis in the paediatric age group (fig. 2). We must remember, however, that it is best to personalize each case by taking into account the important variables we have already mentioned.[15]

Z-score < -2

(adjusted for age, sex, height, and race)

+

History of Fracture

(2 upper extremity fractures, a vertebral wedging, or a lower extremity fracture)

Figure 2 Definition of osteoporosis in the paediatric age group.[15]

Osteogenesis imperfecta

OI is a genetic disorder caused by a mutation in 1 of the genes for bone tissue collagen, which leads to improper bone development resulting in increased bone fragility and low bone mass. The severity varies across a very wide range from intrauterine fractures and perinatal mortality to mild forms with no fractures.[16-22]

The Sillence et al classification described in 1979 is the one most used, and 3 new groups have been added to it.[16,20,23] The different types, from most to least severe, are as follows: type II > type III > types IV, V, VI, VII > type I (table 1). OI type I includes patients who have mild disease with no serious deformities; however, vertebral fractures are common and may result in a moderate scoliosis. Type II is fatal, usually from respiratory failure due to multiple rib fractures. Patients with type III are extremely short-statured and also have deformities of the back and extremities secondary to multiple fractures. Type IV patients have moderate bony deformities and a variable short stature.

Table 1 Sillence classification of osteogenesis imperfecta

Type	Severity	Characteristics	Mutations
I	Mild	Normal stature or somewhat short. Blue sclera. No DI	Premature stop codon COL_1A_1
II	Perinatally fatal	Multiple rib and long bone fractures at birth. Significant deformities. Long bones widened. Dark sclera	Glycine substitution at COL_1A_1 or COL_1A_2
III	Very deforming	Very short stature. Triangular face. Severe scoliosis. Greyish sclera. DI	Glycine substitution at COL_1A_1 or COL_1A_2
IV	Moderately deforming	Short stature. Moderate to severe scoliosis. Greyish or white sclera. DI	Glycine substitution at COL_1A_1 or COL_1A_2
V	Moderately deforming	Medium or short stature. Radial head dislocation. Mineralised interosseous membrane. Hyperplastic calluses. White sclera. No DI	Unknown
VI	Moderately to severely deforming	Medium stature. Scoliosis. Osteoid accumulation in bone tissue. White sclera. No DI	Unknown
VII	Moderately deforming	Somewhat short stature. Short humerus and femur. Coxa vara. White sclera. No DI	Unknown

Taken from Rauch F et al and modified.[16]
DI: dentinogenesis imperfecta.

Among the new OI types we have type V, which is a dominant autonomic disorder with moderate to severe bone fragility. There is ossification of the interosseous membrane in the forearm and a predisposition to develop hypertrophic calluses. Type VI is also a moderate to severe form diagnosed on the basis of the anatomical pathology study of the bone with an increased amount of osteoid and an abnormal bone pattern. Type VII is a recessive disorder that has been seen only in a community of Native Americans in the north of Quebec. Besides bone fragility, they evidence rhizomelia and coxa vara at young ages.[16,20]

In OI, the treatment objectives are to achieve the best mobility and functional ability possible by preventing bone fractures and deformities. To meet these objectives, we have physical rehabilitation programs designed to prevent contractures and loss of bone mass due to immobilisation without increasing the risk of fractures and surgery to correct and prevent deformities via osteotomies and intramedullary fixations to achieve standing position and ambulation.[16,21] This does not improve the extreme bone fragility, however, so medical treatments have been sought to increase bone quantity and quality.

Over many years, different medical treatments were attempted with calcitonin, growth hormone, steroid hormones, vitamins C and D, and various minerals, but the results were not very encouraging.[16,17,19,21-23]

In 1998, the Glorieux group became the first to publish an important series on children with OI who were treated with bisphosphonates with good results.[17] In this work, the authors presented 30 children from 3 to 16 years of age with severe OI types III, IV, and V with marked osteopenia who were treated with pamidronate IV at dosages of 1.5-3 mg/kg every 4-6 months for 1.3-5 years. They observed an increase in lumbar BMD, the absence of any new collapsed vertebrae–some even recovered their height–and an increase of cortical thickness in the long bones. The earliest response was the reduction in chronic bone pain with improved functional status in 16 of the 30 patients. The incidence of fractures dropped from 2.3/year to 0.6/year. They encountered no delayed fracture healing.[17]

Since this work, many others have appeared in the medical literature, and the use of bisphosphonates in these patients is a routine practice in Centres where this disease is treated. The results observed by the majority of authors are a rapid and marked improvement in chronic back pain with an enhanced sense of well-being; a reduction in the number of fractures with a rapid increase in lumbar BMD; and recovery of morphology and normal size in the collapsed vertebral bodies.[16,19,21,23-26] The 2 longest series showed, in addition, improved mobility in more than 50% of the patients treated.[17,18] It is still unknown whether bisphosphonate therapy prevents long bone deformities or the progression of scoliosis. To obtain the best results, this medical treatment should be combined with physical therapy and surgical intervention.

In those patients who underwent iliac bone biopsy, histomorphometry studies show that the primary effect is an increase in cortical thickness as well as an increase in the amount of trabecular bone, where the trabeculae are greater in number but not thicker.[16,21,23,27]

In terms of the evidence from the use of bisphosphonates in treating children with OI, 2 meta-analyses have been published. This type of study is problematic because, although much has been published on the effect of the bisphosphonates in children with OI, these have most often been descriptive studies of cases with very little power of evidence and multiple factors to take into account such as age, type of bisphosphonate, treatment dosage and duration, surgical interventions, physical therapy, and the use of braces. Phillipi published a Cochrane review, presenting 8 randomised studies covering 403 patients. Of these studies, only 1 achieved a significant reduction in the risk of fracture and in the number of fractures, but all achieved an increase in BMD.[28] Castillo and Samson-Fang found only 8 studies with sufficient evidence level. In all the studies, improved bone density and a 30%-60% reduction in fracture risk was confirmed.[22]

There is no clear protocol as to which bisphosphonate should be used,[22] although the majority of authors used intravenous pamidronate at a dosage of 1 mg/kg on 3 consecutive days every 4 months, following the Glorieux group's guidelines.[16,17,19,24,29]

Other intravenous bisphosphonates have also been used, such as zoledronate, administered annually,[30,31] and neridronate, similar to pamidronate, which has been used in adults, with a significant increase in BMD achieved,[16] and in children with OI type III, at birth and at 6 months of age, with good results.[23] Oral alendronate has also shown its capacity to increase BMD, reduce the frequency of fractures, restore vertebral body morphology, and improve mobility in school-age patients.[16,25,32] Olpadronate, also given orally, has been used in a placebo-controlled study; after 2 years, there was an increase in lumbar BMD and a reduced incidence of long bone fractures, with no difference observed in terms of mobility or muscle strength.[33]

There is not enough evidence to recommend a specific bisphosphonate because there are no placebo-controlled studies comparing different dosages, dose schedules, and intervals, but it does appear that IV pamidronate is the one that has a more marked effect on bone pain.[16,18,19,23] It also appears that, with children, it is difficult to get compliance with the oral bisphosphonates.

There is also no clear answer as to what type of patient should be treated. In the majority of series, the patients treated had severe involvement–that is, with long bone deformities, compression fractures of the vertebrae, and frequent fractures–regardless of the type of OI, genetic changes, or BMD, although they were usually patients with OI type III, IV, V, and VI.[16,19,23,26]

The use of bisphosphonates in treating the moderate forms–that is, with no more than 2 fractures per year, no vertebral compression fractures, and no long bone deformities–is under discussion.[16,21] All authors argue that isolated BMD values should not be the only criterion for treating a patient.[16]

There is also no general agreement as to the age at which treatment should be started, but the earlier the better, it seems, when it is a congenital disease. In fact, small children benefit more than adults from the treatment.[16,18,19,21,24]

Perhaps the most controversial point is determining when treatment should be suspended. In the absence of a solid

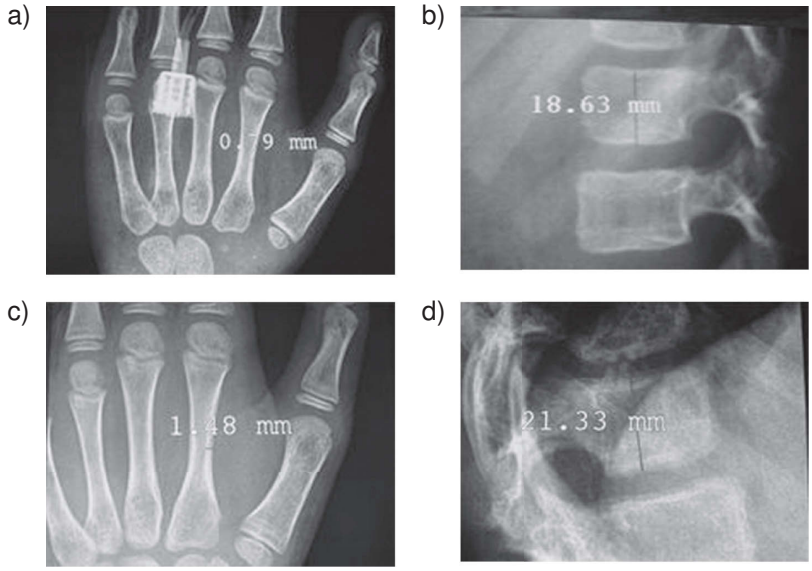

Figure 3 X-ray Images showing measurement of the effect of bisphosphonates on children with OI treated with pamidronate. a) and b): x-ray of left hand with measurement of cortical thickness in the 2nd metacarpal (a) and height of the first lumbar vertebra (b) prior to bisphosphonate therapy. c) and d): the same measurements after treatment, where increased cortical thickness (d) and increased height of the first lumbar vertebra (e) are noted.

consensus, treatment is usually suspended when BMD reaches normal levels.[16,29] As Land et al and Shapiro et al suggest, in terms of quality of life and reducing the number of fractures, it appears that, after 4 years, continuing pamidronate therapy does not yield much more benefit.[23,34] However, Ward[29] presented a case of OI type IV where, after 2.5 years of pamidronate therapy, BMD values were normalised and there were no further fractures, so the treatment was suspended. One year after treatment was suspended, the patient again suffered fractures and a marked drop in BMD values for the distal radius. Therefore, these authors use a maintenance protocol of 1 mg/kg, 1 day every 3 months, until growth is complete. Glorieux also recommends intermittent treatment until skeletal maturation.[35] The oral bisphosphonates may be another alternative.

We have treated 20 cases, all of them with moderate to severe involvement, types I, III, and IV. We used intravenous pamidronate at the dosages described by Glorieux.[16] In all cases, we obtained a reduction in the number of fractures and improvement in lumbar pain. On control densitometries, an increase in BMD values in the lumbar spine was observed. We also found positive results on follow-up x-rays, measuring the cortex on the 2nd metacarpal of the left hand and the height of the first lumbar vertebra (fig. 3). Patients with collapsed vertebrae showed improvement on x-ray from the treatment (fig. 4).

Zebra lines could be seen on follow-up x-rays of the children treated; these are dense, metaphyseal lines parallel to the growth plate (fig. 5), each line representing 1 treatment cycle. They are formed from calcified cartilage that, due to the action of the bisphosphonates, is not resorbed, and calcified bone.[21] Over time, these lines move away from the growth plate, which shows that bone growth continues, despite the treatment.

Fibrous dysplasia

Fibrous dysplasia is a rare, benign bone lesion with a broad spectrum of involvement in which normal medullary bone is replaced by fibrous tissue, resulting in increased bone fragility.[36]

If it is a single lesion, it is called monostotic fibrous dysplasia; if it affects various bones, it is referred to as polyostotic; and if it is also associated with café-au-lait patches on the skin and some endocrine disturbance, such as precocious puberty, hyperthyroidism, excess growth hormone, or osteomalacia, then it is known as McCune-Albright syndrome.[36]

Its aetiology is a mutation of the somatic activation of subunit (a) of the protein GS (GSa). The gene that codes for this protein is located on chromosome 20q1337.

The symptoms include pain, pathological fractures, and deformities; therefore, the treatment objectives are prevention of deformities and prevention of pathological fractures. We use surgery for this, intramedullary implants being the ones of choice.[37]

In terms of medical treatment, bisphosphonates have been used with variable results. The longest series are those published by the Chapulart et al group[38] and the Plotkin et al group.[39] Chapulart et al published a series of 58 patients with fibrous dysplasia treated with intravenous pamidronate; 17 of these patients were under 18 years of age. They obtained a significant reduction in pain, in all cases where it was present; a significant reduction in the biochemical markers for bone turnover; and, in 50% of cases, improvement in the bone lesions was noted on x-ray, with increased cortical bone and increased filling of the lytic areas.[38] The Chapulart et al group presented 18 children with polyostotic fibrous dysplasia who were also treated with IV pamidronate at the same dosages. These authors also observed a

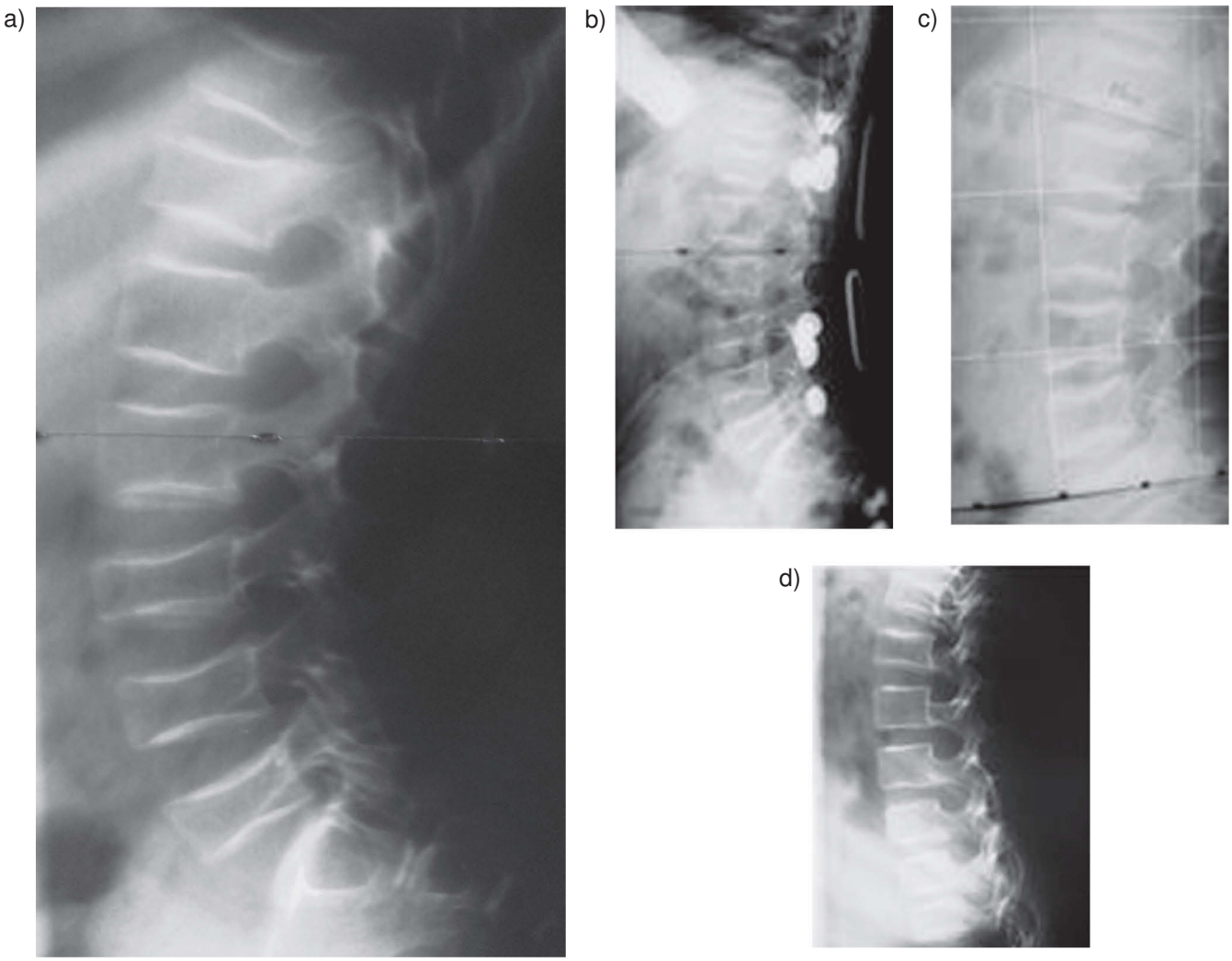

Figure 4 X-ray Images of the lumbar spine of a girl with osteogenesis imperfecta and multiple vertebral wedgings. Recovery of vertebral body morphology and height is noted following bisphosphonate therapy.

significant reduction in bone pain and in the biochemical markers, but they did not find improvement on x-ray.[39]

Therefore, it appears that pain relief is the clearest benefit of this treatment, and the majority of authors endorse this indication.[37] It is difficult to interpret the observed reduction in biochemical markers, and some authors believe that it results from the bisphosphonates having an effect on healthy bone, also.[37]

We have little experience with this pathology, having treated 2 children with polyostotic fibrous dysplasia. A subjective reduction in pain was seen in all of them, as well as a reduction in biochemical markers of resorption. On x-ray, we were able to see a thickening of cortical bone in only 1 case.

Osteoporosis secondary to immobilisation in neuromuscular diseases

We know that, in children with neuromuscular diseases, the incidence of pathological fractures is 5%40%[40] The most common location for these fractures is the long bones, primarily the femur.[40,41]

They are caused by minimal traumas or by stress due to a mechanical overload associated with gait changes in these patients. However, there are other associated factors, as well, such as a tendency to fall, poor balance, joint stiffness, gait impairment, and manipulations during physical therapy, personal hygiene, and even due to abuse.[40]

There are many factors that may contribute to the low BMD in these patients, such as mechanical factors, given that many of them do not walk; the immobilisations to which they are subjected after surgical procedures; nutritional factors, given that these patients usually have difficulty feeding themselves, and many receive parenteral nutrition and have gastro-oesophageal reflux, problems with inappetence, and inadequate dietary intake of calcium and vitamin D; and other factors such as being overweight.

However, there are also intrinsic factors such as hormonal disorders that favour low BMD, and these are usually low-

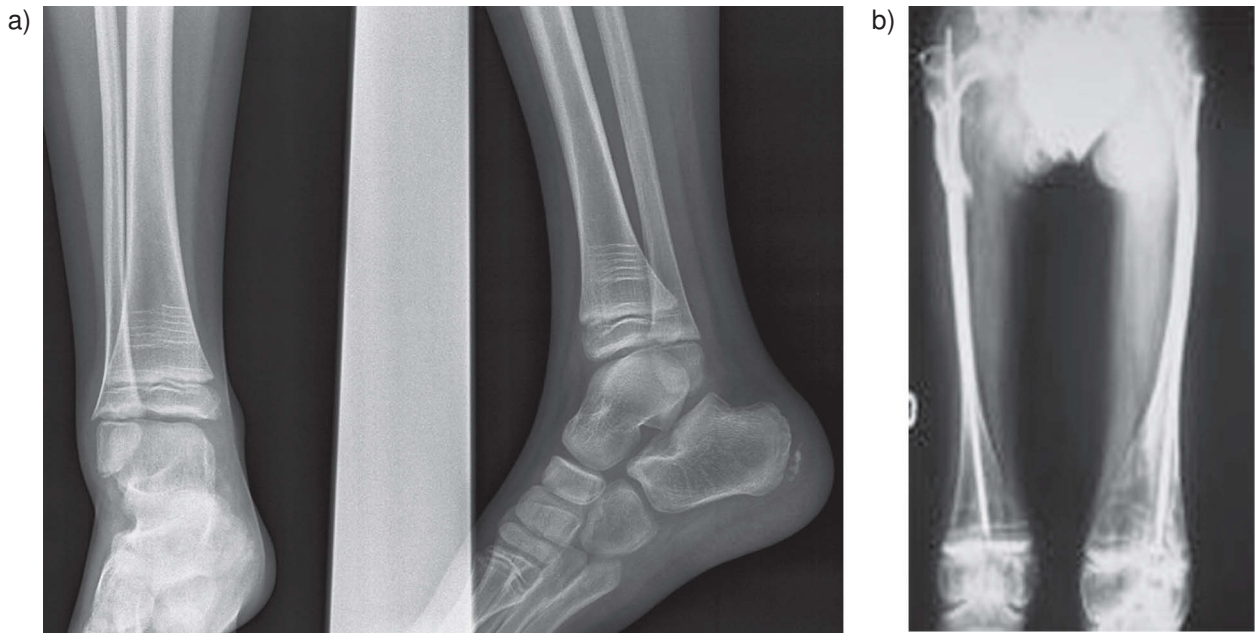

Figure 5 X-ray images of 2 children with OI Treated with bisphosphonates. Zebra lines may be seen in the metaphyseal region of the long bones. a), boy with moderate involvement, and b), boy with severe involvement.

birth-weight children who undergo less growth and frequently have genetic factors associated with their neurological disease. Other factors, such as low exposure to sunlight or medical treatment with anti-epileptics and corticosteroids, also contribute to the osteoporosis in these patients.[14,41]

Our approach as orthopaedic surgeons will be to correct those factors we can address, such as the imbalances, in a single surgical procedure; to immobilize for the time absolutely necessary; to recommend regular physical exercise, especially weight-bearing exercises; and to promote early weight-bearing post-operatively. We should also recommend that nutritional problems be corrected, ensuring that these children have an adequate intake of calcium (1,200-1,500 mg/day) and vitamin D (400 U.); that they are exposed to sunlight; and that anti-epileptics with the least impact on BMD are used.[41]

Currently, there are only 2 treatments that have been shown to significantly increase BMD in this type of patient: physical therapy with weight-bearing exercises[42] and the use of bisphosphonates.[43]

As is the case with the other indications for bisphosphonates we have reviewed, the bisphosphonate of choice, the dose, the frequency, the form of administration, and the long-term effects remain unknown.[41,44]

Our own experience is limited: we have treated 5 cases of children with severe involvement who were non-ambulatory GMFCS (Gross Motor Function Classification System) types IV and V, with very good results in that the number of fractures was reduced, facilitating physical therapy and the daily management of these patients. An increase in BMD, in cortical thickness of the 2nd metacarpal of the left hand, and in height of the first lumbar vertebra was achieved in all cases.

Osteoporosis secondary to corticosteroids

In recent years, survival rates have improved for children with chronic diseases, such as the autoimmune diseases (juvenile rheumatoid arthritis), lung diseases, kidney diseases, and neoplastic processes such as acute lymphocytic leukaemia where treatment is based largely on the use of corticosteroids.[13,14]

In these patients, the cause of the osteoporosis is not only the use of corticosteroid therapy but also a multi-factorial mechanism: generally, they are chronic processes involving a reduction in bone formation and an increase in bone resorption. These children also have reduced mobility, poor nutrition, and hormonal abnormalities.[13] The inflammatory cytokines produced in many of these processes have also been described as favouring the reduction in BMD.[13]

In these patients, the most common fractures are vertebral fractures.[13,14]

Indications for the use of bisphosphonate therapy are usually vertebral collapse or chronic bone pain in patients with low BMD.[13]

Other pathologies

Perthes disease

Bisphosphonate therapy is being used experimentally to maintain the morphology of the femoral head. The Little group created models for avascular necrosis of the femoral head in rats and observed how 6 weeks of zolendronate therapy could preserve the architecture in the femoral head in comparison with the non-treated group.[45] Kim et al

created an experimental model in the femoral head of pigs with open epiphyses and observed that, after an ischaemic necrosis occurred, the architecture in the femoral head was preserved with ibandronate therapy.[46]

Bone lengthening by distraction osteogenesis

Distraction osteogenesis is an effective technique used in the treatment of congenital and post-traumatic leg length discrepancy. In this technique, a long bone is separated by corticotomy and subjected to slow distraction using an external fixator. The distraction gap gradually fills in with new bone formed during the distraction, and then this bone is remodelled and cortical bone is formed. Different procedures, such as growth factors and morphogenetic protein, have been attempted to boost the anabolic process. However, catabolic agents such as the bisphosphonates may also be used to shift bone turnover in favour of bone formation.

Various work groups have studied the effect of different bisphosphonates, such as alendronate,[47,48] pamidronate,[49] and zoledronate,[50] using models of bone lengthening by distraction osteogenesis in skeletally immature rabbits.

Little et al examined the effect of IV pamidronate on distraction osteogenesis in immature rabbits, observing an increased BMD in the bone formed. The histological study showed increased bone formation and reduced bone resorption.[49] Omi et al studied the effect of alendronate using a distraction osteogenesis model in rabbits, and it appeared that bone formation improved when BMD increased.[48]

These authors demonstrated that, during distraction osteogenesis, there is increased bone turnover, in terms of both bone formation and bone resorption. Bisphosphonates reduce resorption, thereby improving mineralisation and mechanical properties, which shortens the lengthening process.[47-50]

Side effects

It is important to remember that there are currently no approved indications for using bisphosphonates in children for any of the pathologies mentioned above; therefore, we should always obtain a consent for utilisation of medication for compassionate use, and we should inform the parents of this circumstance.

In terms of the short-term side effects of the bisphosphonates in children, the acute phase reaction has been described; this resembles flu symptoms and occurs following the first intravenous administration of the drug. The symptoms are self-limited and are treated with antipyretics; it is not necessary to discontinue the treatment.[16-24,26,27,30]

It is more difficult to speak of the long-term side effects, for experience with these drugs has not been very extensive. Although the bisphosphonates are known to have a cumulative effect and to remain strongly bound to the bone for a long time after treatment has been discontinued, based on 10 years of using these drugs, it seems we can affirm that the bisphosphonates do not impact fracture healing, do not affect the epiphyses, do not reduce the rate of growth, and do not impact the onset of puberty.[13] Histological studies have shown no changes in bone structure or cellularity–only a reduction in resorption.[16,21,23,27]

In animals, it has been noted that the bisphosphonates cross the placenta.[51] They have a low molecular weight, so they cross the placenta easily. Bone turnover is quite rapid in the developing foetus, so any agent that interferes with bone formation may interfere with resorption or mineralisation. In studies done with rats, alendronate has been noted to cross the placenta and accumulate in the foetal skeleton, increasing bone mass most likely by reducing bone resorption, affecting bone growth, and reducing overall foetal growth. Some authors call attention to the risk of giving these drugs to women of child-bearing age and point out that they should discontinue treatment long before planning a pregnancy because the bisphosphonates remain in bone for a long time.[13,51]

On the other hand, cases have been appearing in the literature of girls treated with bisphosphonates for OI or fibrous dysplasia who, upon reaching child-bearing age, have given birth, and the children born to them had no complications; in the cases of OI, it has even been beneficial for them.[52,53] It is important to remember, however, that these are only anecdotal cases, and we should still expect that it will be some years before the safety of these drugs is known.

Another long-term side effect that has been described is the appearance of a clinical picture resembling osteopetrosis due to the excessive suppression of bone resorption. Whyte described the case of a boy who, following pamidronate therapy at 4 times the recommended dosage, developed a picture of bisphosphonate-induced osteopetrosis over a period of 3 years. The indication for this drug in this patient was not very clear, however. It appears that the boy did not have an impairment of bone metabolism; that the doses administered were much higher than those normally used; and that, as a result, resorption was probably much more severely suppressed than in cases treated properly and at the correct dosages.[54] Using bone biopsies, micro CT, and bone markers, these authors are researching whether there is some predisposing factor for excessive suppression of resorption as a complication of bisphosphonate therapy, as occurred in the case of the boy they described.

Although bisphosphonate-related mandibular necrosis has been described in adults, no case of this in children has been published. Authors who reviewed the literature to evaluate this possible complication found no cases in children treated with intravenous pamidronate and zoledronate over an average of 6 years, even in those who underwent invasive dental treatments.[55]

Conclusions

The bisphosphonates are drugs that can alter bone metabolism, and we can use them when there is increased bone resorption. These drugs are safe for children in the short term, but we will have to wait to find out their long-term impact. They are effective in paediatric diseases involving increased bone fragility, the best results being obtained in severe OI. It is recommended that they be used

in specialised Centres that have experience with this type of drug.

Protection of human and animal subjects

The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of data

The authors will declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

Right to privacy and informed consent

The authors must have obtained the informed consent of the patients and / or subjects mentioned in the article. The author for correspondence must be in possession of this document.

Evidence level

Evidence level: V.

Conflict of interest

The authors declare no conflict of interest.

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