



The Use of Bisphosphonate Therapy for Osteoporosis in Childhood and Adolescence

Position	Paper	Authors
JA Batch, FRACP	Dept. of Endocrinology and Diabetes, Royal Children's Hospital, Brisbane, Queensland.	
JJ Couper, FRACP	Dept. of Endocrinology and Diabetes, Women's and Children's Hospital, Adelaide, South Australia.	
C Rodda, PhD, FRACP	Dept. of Endocrinology and Diabetes, Monash Medical Centre, Melbourne, Victoria.	
CT Cowell, FRACP	Institute of Endocrinology, The Children's Hospital at Westmead, Sydney, New South Wales	
M Zacharin, FRACP	Dept. of Endocrinology and Diabetes, Royal Children's Hospital, Melbourne, Victoria.	

Abstract:

Congenital and acquired forms of osteoporosis in childhood and adolescence can result in morbidity from fracture and pain in childhood, and place an individual at significant risk for problems in adult life. A range of therapies exist for the prevention and treatment of osteoporosis, including optimization of daily calcium intake, adequate vitamin D status, weight-bearing exercise, treatment with sex steroids where delayed puberty is a problem and, more recently, use of bisphosphonate therapy. Intravenous pamidronate therapy (a bisphosphonate) has been shown to reduce fractures and improve bone density in children with osteogenesis imperfecta, and might prove to be of benefit in other osteoporotic conditions in childhood. However, a number of issues regarding the optimal use of bisphosphonate therapy in children and adolescents remain to be resolved, including total annual dose and frequency and duration of administration. Bisphosphonate therapy should, therefore, be used only in the context of a well-run clinical programme with specialist knowledge in the management of osteopenic disorders in childhood.

Osteoporosis is being recognized increasingly in childhood and adolescence, with heightened awareness of the potential adverse effect of chronic disease and glucocorticoid use on the attainment of peak bone mass. Broadly, osteoporosis can result from decreased bone formation or increased bone resorption. Osteoporosis occurs where there is reduced bone mass, reduced microarchitectural bone structure, perforation within trabecular plates and loss of trabeculae. There can be defects in bone-forming cells, leading to defective matrix formation or abnormalities of coupling of bone formation, resorption and mineralization. The largest group of children and adolescents with osteoporosis are those who have an associated chronic disease where osteoporosis can be exacerbated by the concurrent need for systemic glucocorticoid treatment and by nutritional



deficiencies, including vitamin D deficiency. Examples of this and other causes of osteoporosis in children are shown in [Table 1](#).

The definition of osteoporosis in adults is based on areal dual energy X-ray absorptiometry (DXA) measurements and a standard deviation score of < -2.5 compared with healthy young adults. The definition in children and adolescents still accruing areal bone density, particularly with pubertal delay, is less clearly defined. [\(1\)](#) It is important to compare an individual's DXA data to a paediatric reference range.

The female skeleton has a higher lifetime risk of osteoporotic fractures than the male, predominantly because of a smaller skeletal size and menopause, together with the added burden imposed on the skeleton by pregnancy and lactation. For girls and women with an inherent low bone density (e.g. osteogenesis imperfecta), the impact on bone density can be even more severe. As peak bone mass is attained in the adolescent years and provides a basis for bone strength and integrity in later life, the prevention and treatment of osteoporosis in childhood and adolescence is a priority for prevention of the long-term morbidity and expense associated with osteoporosis in adult life. [\(2\)](#)

Therapeutic interventions for osteoporosis target either increased bone formation or decreased bone resorption. The action of bisphosphonates is predominantly to decrease bone resorption.

BISPHOSPHONATE THERAPY FOR OSTEOPOROSIS

Bisphosphonates are analogous in structure to the naturally occurring pyrophosphates, but with a carbon atom bridging two phosphate residues forming a P-C-P moiety. Bisphosphonates have been used clinically for more than 30 years. Bisphosphonates decrease bone turnover by decreasing bone resorption. They have a direct effect on decreased recruitment and function of osteoclasts and an indirect effect by stimulating osteoblasts to produce an inhibitor of osteoclast formation. Bisphosphonate effect is complex, with inhibition of the mevalonate enzyme pathway in osteoclasts and binding to hydroxyapatite crystals in bone. By decreasing osteoclastic activity without impairing bone architecture and mechanical strength, bisphosphonates have a cumulative inhibitory effect on bone loss and, thus, lead to increased vertebral bone mass and bone density. [\(3-5\)](#)

Bisphosphonate therapy is available in oral or intravenous forms, with the biological action varying widely, being dependent on the chemical structure of the side chains. The first generation bisphosphonates are the least potent and include etidronate and clodronate. Second generation aminobisphosphonates contain a nitrogen group, such as alendronate and pamidronate, and are 10-100-fold more potent than first generation bisphosphonates. Third generation bisphosphonates, such as risedronate and zoledronic acid, contain a nitrogen atom within a heterocyclic ring, and are up to 10 000-fold more potent. [\(5\)](#)

The oral form has not been widely used in children or adolescents, although trials are underway. [\(6\)](#) If given orally, only a small proportion (approximately 2%) is absorbed; the rest remains in the bowel lumen. The amount absorbed is dependent on the time of administration in relation to food, with the usual recommendation being that food is avoided for 2 hours after oral administration. Gastrointestinal symptoms with alendronate have been reported in adults, with the possibility of oesophageal irritation and ulceration. Maintaining an upright posture for 30 min after the dose can reduce the likelihood of this occurring. Oral forms of bisphosphonates that have been used include etidronate, clodronate, pamidronate and alendronate. Use of the intravenous form, pamidronate has been studied extensively in adults.

Bisphosphonate therapy is established as beneficial in postmenopausal osteoporosis and steroid-induced osteoporosis. [\(7,8\)](#) It is also first-line therapy for Paget's disease of bone, [\(9\)](#) for management



of renal osteodystrophy and for management of bone pain and hypercalcaemia associated with disseminated malignancy in bone.(10) Recent studies in adults also suggest that bisphosphonates may could have an important role in the acute and medium-term management of severe immobilization that is the result of problems such as spinal cord lesions.(11,12) Bisphosphonate use as an anticancer drug has been reported increasingly, including its use in metastatic breast cancer, multiple myeloma, giant cell tumour of bone and inhibition of osteogenic sarcoma cell lines *in vitro*. (13-17)

BISPHOSPHONATE USE IN CHILDREN AND ADOLESCENTS

Although bisphosphonates have been used in children for 25 years, the systematic use of bisphosphonates in children has been limited, with most reports being single cases or being based on small numbers of patients. The established uses of bisphosphonates in adults are for postmenopausal osteoporosis, steroid-induced osteoporosis, Paget's disease and hypercalcaemia due to malignancy. However the conditions for which bisphosphonates have been used successfully in children are more diverse than those in adults and can be broadly divided into the following groups:

1. Primary structural defects in type I collagen and other structural bone proteins (e.g. osteogenesis imperfecta).(18)
2. Fibrous dysplasia of bone (e.g. McCune-Albright syndrome).
3. Bone abnormalities resulting from systemic disease or the effects of systemic treatment (e.g. steroid treatment of chronic disease or immobilization).
4. Bone matrix abnormalities (e.g. osteoporosis pseudoglioma syndrome).
5. Conditions with a primary defect in bone mineralization (e.g. idiopathic juvenile osteoporosis).
6. Malignancy associated hypercalcaemia.

Many other conditions have been treated with bisphosphonate therapy in children and adolescents; these include Gaucher's disease, Rett's syndrome and osteoporosis pseudoglioma syndrome. (19)

The aim of bisphosphonate therapy is to improve bone mineral density in osteoporosis by 0.5-1.0 SD score/year, with no evidence of a cessation of effect with time. The only reported trial of pamidronate use for a moderate number of children (30 osteogenesis imperfecta subjects) was an open, uncontrolled observational trial. Clinically and statistically, significant improvements in bone mineral density, reduction in fracture rate and bone pain, and improved mobility were documented.(20) Loss of bone pain has been noted to be a reliable clinical indicator of effect. Recently the successful use of intravenous pamidronate in children less than 3 years of age with osteogenesis imperfecta has also been reported.(21) Many cases of individuals or small numbers of patients with osteogenesis imperfecta have also been reported.(22) Successful treatment with pamidronate of patients with idiopathic juvenile osteoporosis has been reported.(23,24) There are no literature reports of randomized trials in osteogenesis imperfecta, although the Shriner's Hospital group in USA is currently undertaking a randomized trial of alendronate use.

Pamidronate treatment has been used to treat the fibrous dysplasia of McCune-Albright syndrome and has shown radiological and clinical improvement of the bony lesions.(25,26) In addition, pamidronate has been used successfully in children with bone abnormalities secondary to systemic disease. These include hypercalcaemia with or without malignancy or immobilization.(27,28) Lepore *et al.* reported the successful treatment of osteoporosis in association with juvenile chronic arthritis.(29) Bisphosphonates have also been used in the paediatric age group in situations involving soft tissue calcification, such as myositis ossificans, although the therapeutic efficacy has been limited.(30)



SAFETY OF BISPHOSPHONATE THERAPY IN CHILDREN

Short-term side effects of pamidronate infusion are common and consist of an acute phase reaction (influenza-like symptoms) 24-48h following the first treatment. Such symptoms might be ameliorated by prophylactic use of paracetamol or ibuprofen. Hypocalcaemia is an uncommon problem in the 72h following the first infusion, but can be prevented by ensuring a dietary intake of 1-1.5g calcium daily. Bone pain after infusion in adult cystic fibrosis patients has been reported and could also occur in children.(31-33) Subsequent infusions of pamidronate are not usually associated with the influenza-like symptoms, and bone pain is attenuated.

Brumsen *et al.* reported on experience with bisphosphonate use in 12 children followed from 2.5 to 12 years.(6) They received treatment for periods ranging from 2 to 8 years. All the children grew normally and bone biopsies on six of the children showed normal lamellar bone. Glorieux *et al.* in their report of 30 children with osteogenesis imperfecta, treated for 1.3-5 years, found no adverse effects on fracture healing, linear growth rate or the appearance of the growth plates.(20) Although no adverse effects on growth have been seen in children, bisphosphonate treatment was associated with diminished longitudinal growth in one experimental study on animals.(34)

Thus, bisphosphonate treatment currently appears to be relatively safe even when used for quite long periods. However, bisphosphonates are incorporated into bone and can remain in the skeleton for up to 10 years.(24)

There are two reports of impaired mineralization in children receiving bisphosphonate therapy, (35,36) although the radiologically diagnosed demineralization was said to heal spontaneously during treatment. This might have been related to the doses used, and furthermore, etidronate has a relatively greater effect on demineralization compared with second and third generation bisphosphonates. Mineralization defects have been seen in adults with Paget's disease following treatment with pamidronate.(37) Nephrocalcinosis can also occur with long-term use. There have been no reports of bone or other abnormalities in children of adolescents or young women who have received previous bisphosphonate therapy. The use of bisphosphonate therapy during pregnancy is clearly contraindicated.(38) The side effects of bisphosphonate therapy in childhood are summarized in [Table 2](#).

ISSUES TO BE RESOLVED

Pamidronate has been successfully and safely used in children with a range of conditions, but in limited numbers in observational studies - there are no reports of randomized controlled studies, but one is underway for the indication of osteogenesis imperfecta. Information on the most effective drug dose (total annual dose), frequency (e.g. monthly vs quarterly) and duration of treatment is currently lacking. In addition, pamidronate treatment has been given only to children with significant morbidity from recurrent fracture, pain and immobility (e.g. osteogenesis imperfecta). A large group of children with suboptimal bone density exists across a range of conditions including osteogenesis imperfecta. It is impractical and probably unnecessary to treat these children with pamidronate therapy, but, at present, suitable alternative therapies (e.g. oral bisphosphonate) are not available, could have side effects (e.g. gastrointestinal symptoms) and have not been studied in children and adolescents. Recently, a once-weekly preparation of oral alendronate has been developed. Studies are required to determine the usefulness of this preparation for children and adolescents. Risedronate, a new bisphosphonate has been reported to have fewer gastrointestinal side effects than alendronate in adults, and could prove to be of use in children and adolescents. The most appropriate preventive measures for osteoporosis in at-risk groups (e.g. glucocorticoid treatment of chronic disease) remain uncertain, with the place of oral or intravenous bisphosphonates undefined in children. Bisphosphonates might also have a paradoxical effect on stimulating osteoblasts and provide a useful

adjunctive therapy for orthopaedic procedures performed in an attempt to produce limb lengthening.(39) Potential uses for bisphosphonates in children and adolescents are summarized in [Table 3](#).

GENERAL MEASURES TO OPTIMIZE BONE HEALTH

Before considering bisphosphonate or any other treatment, it is important to ensure that general measures promoting bone mass are optimized. Daily calcium intake should be equivalent to the recommended daily intake, 25 OH vitamin D status should be adequate, weight-bearing exercise should be maximized and medications, such as glucocorticoids, known to interfere with bone mass accumulation should be minimized or withdrawn where possible.

RECOMMENDATIONS

Children and adolescents with symptomatic osteoporosis (bone pain, recurrent fractures and vertebral crush fractures) should be considered for pamidronate therapy.

Until results are available from further studies of bisphosphonate use in children, which clarify the most appropriate dose, frequency and duration of treatment, all children receiving bisphosphonate therapy should be treated as part of a well-run clinical programme with specialist knowledge in the management of osteopenic disorders in childhood. Informed parental and/or patient consent for treatment is essential. Appropriate data on safety parameters, linear growth and long-term bone structure and function need to be collected to augment the current knowledge, which has been gained from recently published trials. As there is no current animal or human evidence of adverse effects on the fetus where a mother has previously received bisphosphonate therapy, withholding treatment from a woman of child-bearing age might not be justified. However, bisphosphonate use during pregnancy is contraindicated(38) and its use in females of reproductive age should only occur if contraception is ensured during therapy. The skeletal health of children of mothers previously treated with bisphosphonate will require ongoing surveillance. Indiscriminate use of this apparently safe and effective therapy must be avoided in children and adolescents until the outstanding issues have been resolved. For each child or adolescent where this treatment is being considered, an assessment of the potential risks and benefits should be made).

CONCLUSION

Pamidronate therapy has undoubtedly improved the quality of life and medical morbidity (fracture rate, pain and immobility) of many children with symptomatic osteoporosis, particularly those with osteogenesis imperfecta and fibrous bone dysplasia. Improved understanding of the use of bisphosphonate therapy promises to be a powerful addition to the current strategies (nutrition, exercise, vitamin D, calcium and hormonal therapy) for optimization of bone mass and treatment of established osteoporosis in children and adolescents.

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Table 1 : Differential diagnosis of osteoporosis in children

Primary

- Osteogenesis imperfecta
- Idiopathic juvenile osteoporosis
- Calcium deficiency

Secondary

Endocrine

- hypogonadism
- vitamin D deficiency
- endogenous and exogenous steroids
- diabetes mellitus

Chronic disease

- inflammatory bowel disease
- protein malnutrition
- juvenile arthritis
- cystic fibrosis

Syndromes

- homocystinuria
- hyper-immunoglobulin E syndrome
- lysosomal storage disorders
- osteoporosis pseudoglioma syndrome
- thalassaemia

Miscellaneous

- Immobilization
 - Childhood malignancy and its therapy
-

Table 2: Potential adverse effects of bisphosphonates

Short-term

- Acute phase reaction (fever, chills, myalgia) with first infusion
- Hypocalcaemia (uncommon)
- Bone pain
- Transient iritis and/or uveitis (uncommon; suspect if photophobic)

Longer-term

- Impaired mineralization of bone
 - Impaired linear growth (not reported)
 - Unknown effects from long-term deposition in bone
 - Nephrocalcinosis
-



Table 3
Potential uses of bisphosphonates in children and adolescents

- Prevention of glucocorticoid-induced osteoporosis
- Prevention of immobilization-induced osteoporosis (e.g. cerebral palsy)
- Prevention of chronic-disease-associated osteoporosis (e.g. inflammatory bowel disease, childhood malignancy, cystic fibrosis)
- Rare disorders associated with high bone turnover (e.g. osteoporosis pseudoglioma syndrome, Gaucher's disease, hyper-immunoglobulin E syndrome)
- Regional osteoporosis (e.g. distraction osteogenesis (limb lengthening))