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POSITION PAPER

Consensus guidelines on the use of bisphosphonate therapy in children and adolescents

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Abstract: Bisphosphonate therapy is the mainstay of pharmacological intervention in young people with skeletal fragility. The evidence of its use in a variety of conditions remains limited despite over three decades of clinical experience. On behalf of the Australasian Paediatric Endocrine Group, this evidence-based consensus guideline presents recommendations and discusses the graded evidence (using the GRADE system) for these recommendations. Primary bone fragility disorders such as osteogenesis imperfecta are considered separately from osteoporosis second-ary to other clinical conditions (such as cerebral palsy, Duchenne muscular dystrophy). The use of bisphosphonates in non-fragility conditions, such as fibrous dysplasia, avascular necrosis, bone cysts and hypercalcaemia, is also discussed. While these guidelines provide an evidence-based approach where possible, further research is required in all clinical applications in order to strengthen the recommendations made.

Key words: bone health; fracture; skeletal fragility.

Introduction

Bone health is an important but often underappreciated issue in childhood. Altogether, primary and secondary paediatric bone fragility disorders are relatively common, cause significant morbidity and have the potential to reduce long-term bone strength.² Unlike the vast majority of adult osteoporotic disorders, which result from bone loss in later life,¹ paediatric osteoporosis results from a failure of normal bone development. The greatest contributors to optimal bone mass accrual and development are genetic factors, and there has been a rapid expansion in the understanding of genetic forms of skeletal fragility over recent decades.²

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The growing skeleton changes size and shape, with cortical accrual and trabecular bone development (bone modelling) that is maximal at the time of puberty. Understanding these changes is essential to the assessment of paediatric bone health and to choosing an appropriate management strategy.

Paediatric secondary osteoporosis, where bone fragility is associated with an underlying medical disorder or its treatment, often has multiple factors contributing to reduced bone strength, including immobility with reduced muscle pull and reduced mechanical loading on bone, poor growth, pubertal delay, elevated cytokines, nutritional deficiency, inadequate daily calcium intake, vitamin D deficiency and use of osteotoxic medications. Each of these factors needs to be considered in turn and managed to optimise outcomes.

It is recognised that recurrent long-bone fractures can occur with normal bone mineral density (BMD).³ Consensus guidelines state that a diagnosis of osteoporosis in children requires a dual energy X-ray absorptiometry (DXA) BMD *z* score lower than -2 (using age-, gender- and height-matched norms on the DXA measure), as well as the presence of recurrent long-bone fractures.³ In addition, a diagnosis of paediatric osteoporosis can be made in the presence of vertebral compression fractures alone,

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independent of a DXA measurement, because outside of severe trauma, all vertebral compression fractures in children are considered pathological.³

Pharmacological treatment of paediatric osteoporosis has largely been confined to bisphosphonate therapy. Despite widespread use of bisphosphonate therapy for over three decades, significant controversy remains regarding its use in children.⁴

This is a consensus guideline for the use of bisphosphonates in children and adolescents, drawn from current evidence and clinical practice, with reference to published literature on the subject. The GRADE system of assessing evidence and making recommendations is utilised.⁵ Recommendations are listed as 1 (strong recommendation) or 2 (weak recommendation) – evidence for that recommendation is graded as per Table 1.

What Are Bisphosphonates?

Bisphosphonates are pyrophosphate-derived medications that inhibit osteoclastic function. This guideline predominantly discusses nitrogen-containing bisphosphonates, whose mechanism of action is due to the disruption of the mevalonate pathway involved primarily in osteoclastogenesis. Histomorphometric studies in children show that bisphosphonates significantly reduce bone remodelling.⁶ They do not, however, reduce bone growth, trabecular bone formation or periosteal bone formation (modelling), with increases in both trabecular number (metaphyseal bone) and cortical width. Reduced bone resorption and ongoing bone growth and modelling results in the significant increase in bone mass and strength observed when bisphosphonates are administered to the growing child. Bisphosphonates are retained in the skeleton, with evidence of renal excretion 8 years after the cessation of a nitrogen-containing bisphosphonate, pamidronate, in young people.7

Some inflammatory or neoplastic conditions involving bone, such as chronic recurrent multifocal osteomyelitis (CRMO) or bone cysts, may also be modified by the use of these agents, with the mechanism for these effects still unclear.

Recommendations for the Use of Bisphosphonates in Children

Primary bone fragility disorders

Osteogenesis imperfecta

Recommendation

Intravenous bisphosphonates should be considered for use in children with severe osteogenesis imperfecta (OI) (e.g. type III), children with vertebral compression fractures or children who have had two or more long-bone fractures per year. Oral bisphosphonates should only be considered for those with mild to moderate OI in the absence of vertebral compression fractures $(1, \oplus \oplus \oplus O)$.

As outlined below, we would not recommend that children with severe OI cease therapy once BMD improves; rather, they should continue on a long-term lower dose of bisphosphonate to preserve bone strength during growth.

The annual dose of intravenous bisphosphonate can be halved once the height-adjusted BMD z score falls within the range of -2-0.

Once the BMD z score > 0, the dose can be reduced further and treatment continued at this lower dose until the cessation of growth.

In children with less severe OI, it may be possible to stop bisphosphonate therapy during childhood without deterioration in clinical status or BMD.

Once a child with OI stops growing, it is recommended that therapy be suspended and the child monitored $(1, \oplus OOO)$.

Evidence

OI is a heterogeneous group of bone fragility disorders characterised by low bone mass, recurrent fractures and chronic disability, with a broad spectrum of clinical severity. It can also be associated with other clinical features, including scoliosis, blue sclerae, deafness, easy bruising, wormian bones and dentin hypoplasia (the cited reviews provide a good summary of diagnosis, classification and multidisciplinary management of OI).^{8,9}

The management of OI should involve a multidisciplinary team of medical, surgical and allied health-care professionals at specialised centres experienced in managing such patients. Bisphosphonate treatment should be overseen by a paediatrician with expertise in genetic bone disease.

A recent Cochrane review of 819 participants from 14 trials (2003–2013) showed a universal improvement in bone density, but data on growth, bone pain, fracture incidence and function were incomplete.¹⁰ The studies included in this review were insufficiently powered to appropriately assess these secondary outcomes. Intravenous bisphosphonate treatment is associated with improvement in the number of vertebral fractures in the growing skeleton and modelling,¹¹ and some studies have shown a significant reduction in the incidence of long-bone fractures.¹² In mild OI, oral bisphosphonates have been shown to reduce fracture rates to a degree similar to that of intravenous agents¹² but have neither been associated with improvements in spinal morphology nor reduction in bone pain.¹³

Choice of regime

Not all children with OI require intravenous bisphosphonates. Treatment should be instigated in children with severe OI

Table 1 Grade system of	evidence (from Swiglo <i>et al</i> .) ⁵		
$\oplus 000$ (very low quality)	$\oplus \oplus OO$ (low quality)	$\oplus \oplus \oplus O$ (moderate quality)	$\oplus \oplus \oplus \oplus$ (high quality)
Unsystematic clinical observations, very indirect evidence	At least one observational study, RCTs with flaws, indirect evidence	RCTs with limitations, strong unbiased observational studies	Well-performed RCTs, exceptionally strong unbisaed observational studies

RCTs, randomised controlled trials.

(e.g. type III) and strongly considered in children with two or more long-bone fractures per year or children with vertebral compression fractures. Most data in OI pertain to the use of pamidronate, with increasing data accumulating on the use of other bisphosphonates, primarily zoledronate. The best agent, dose or frequency is yet to be determined. Treatment approaches vary according to resources available and experience of the treating clinician. Pamidronate is often used in children vounger than 2 years of age, followed by switching to zoledronate in older children with moderate to severe OI. A typical treatment approach is shown in Figure 1. Pamidronate doses vary from 9 to 12 mg/kg/ year, and zoledronate is commenced at 0.1 mg/kg/year in two divided doses. Many centres reduce the first ever dose of pamidronate (0.5 mg/kg) or zoledronate (0.0125 mg/kg or 0.025 mg/ kg) in bisphosphonate-naïve patients to minimise acute phase reactions and hypocalcaemia. When bisphosphonate treatment is ceased, there is no measurable effect on any subsequent bones formed.14 Ongoing treatment at reduced doses (as per recommendation above and Fig. 1) is determined by a combination of fracture history, bone pain, bone mineral densitometry and growth.⁹ In general, once the height-adjusted z score is >0, therapy should be reduced to 0.025 mg/kg/year of zoledronic acid



Fig. 1 Flow chart of the use of bisphosphonates in a young person with severe osteogenesis imperfecta. Note: Optimise bone health – Optimise dietary calcium intake, ensure vitamin D is sufficient, maximise weightbearing exercise. Other factors assessed at 12 months: Fracture rate, bone pain, mobility and other medications. BMD, bone mineral density; DXA, dual energy X-ray absorptiometry.

and 1.5 mg/kg every 6 months of pamidronate until the end of growth. It may be possible to cease treatment in children with OI type 1; however, there remains no clear evidence with which to assist in these decisions, and this remains a controversial topic.

If the decision is made to cease at some point, re-institution of bisphosphonate can be considered when BMD starts to fall.

Idiopathic juvenile osteoporosis

Recommendation

We recommend consideration of the use of bisphosphonates in severe forms of idiopathic juvenile osteoporosis (IJO) (as evidenced by two or more long-bone fragility fractures or vertebral fractures, consistent with the diagnosis of osteoporosis in paediatrics) $(1,\oplus OO)$.

Evidence

IJO is a primary bone disorder of unknown aetiology. It tends to affect young people in late childhood/early adolescence, and while it can result in recurrent long-bone and vertebral compression fractures, it is classically self-limiting. Residual long-bone and vertebral deformities can be disabling, even once the bone mass has recovered. Given this, the use of bisphosphonates has been reported in this condition, with one randomised controlled trial (RCT) using pamidronate. This study was limited by small sample size (n = 5 in treatment group), but a reduction in fracture rate and bone pain in the treatment group was reported.¹⁵ There is no evidence to guide the duration of treatment; therefore, we recommend that the dose of bisphosphonate should be reduced after 2 years if height-adjusted DXA scores are normalsing, as per the recommendations for OI outlined in Figure 1.

Secondary osteoporosis

There are many causes of secondary osteoporosis in childhood (Table 2).

Recommendations

Children with vertebral fracture(s) and/or low BMD and two or more long-bone fractures should be considered for intravenous bisphosphonate therapy (see Fig. 2) $(1, \oplus \oplus OO)$.

Appropriate management of secondary osteoporosis also involves adequately addressing the underlying condition, together with the consideration for reducing or ceasing osteotoxic medications where possible.

Bisphosphonates should only be used after attention to vitamin D status; calcium intake; physical therapies to maximise mobility; and gonadal hormone treatment of absent, delayed or arrested puberty or late-presenting hypogonadism $(1, \oplus \oplus OO)$.

In general, prophylactic bisphosphonate therapy (i.e. treating a low bone density z score in the absence of fracture) is not recommended.

Evidence for bisphosphonate use in secondary osteoporosis

Cerebral palsy

Many factors result in low BMD and increased fractures in patients with cerebral palsy (CP), including reduced mobility, poor nutrition, anticonvulsant use, limited sun exposure, later pubertal onset, pubertal arrest and late hypogonadism (Tables 3,4).^{18,24,25} Low-trauma lower limb fractures

Inflammatory	Immobility	latrogenic	Nutritional	Endocrine	Haematological/ Inflitrative
Inflammatory bowel disease Juvenile idiopathic arthropathy	Cerebral palsy Neuromuscular dystrophy	Glucocorticoid therapy Anti-epileptic drugs	Anorexia nervosa Coeliac disease	Hypogonadism Hyperthyroidism	Malignancy Haemaglobinopathies
Other systemic inflammatory disorders	Spinal cord injury	GnRH agonist therapy	Protein calorie malnutrition (e.g. in elite athletes)	Cushing's syndrome/ disease	
	Spina bifida	Warfarin	Cystic fibrosis	Growth hormone deficiency	
	Spinal-muscular atrophy		Other malabsorptive disorders	Hyperparathyroidism	

GnRH, gonadotropin releasing hormone agonist therapy.



Fig. 2 Flow chart of the use of bisphosphonates in a young person with secondary osteoporosis. Note: Optimise bone health – Optimise dietary calcium intake, ensure vitamin D is sufficient, maximise weight-bearing exercise. Other factors assessed at 12 months: Fracture rate, bone pain, mobility and other medications. BMD, bone mineral density; CP, cerebral palsy; DXA, dual energy X-ray absorptiometry.

predominate.²⁶ The annual fracture rate in patients with CP is approximately 5%, double that of a normal age-matched population.^{18,27}

Bisphosphonates increase BMD in children with CP,^{2816,20,21} but there is a paucity of randomised controlled trials^{18,19} and very

limited data on the effect of bisphosphonates in reducing fracture risk.^{17,29} A recent review concluded that bisphosphonates were probably effective at raising BMD and possibly effective at decreasing the fracture rate in this cohort.³⁰

Prophylactic bisphosphonate therapy (i.e. treating a low BMD *z* score in the absence of fracture) is difficult to justify in young people with CP, with no evidence supporting its use, and would rarely be considered outside the setting of severe pain presumed to be of bone origin.

There are limited data to guide recommendations for the duration of treatment in children with CP. Twelve months of intravenous pamidronate has been shown to reduce fracture rates by almost 70% 4 years after ceasing therapy and despite a return in BMD to pre-treatment values.¹⁷ After treatment cessation, it is also worth considering that a continuing increase in BMD without treatment (such as during puberty) should be reassuring, and re-institution of bisphosphonate should be considered when BMD starts to fall. In general, BMD assessment is problematic in this patient group and may not always be clinically useful. Given these factors and the clinical experience of the authors, we would recommend yearly evaluation of bone density where possible and treatment beyond 2 years only if there is an ongoing fracture or bone pain (Fig. 2). This is, however, an area in need of further research.

Other forms of secondary osteoporosis

The published evidence in non-CP-related secondary osteoporosis is limited by the few RCTs and heterogeneous groups studied. However, there are reports of improved BMD and vertebral morphology in these groups, even if there is no clear evidence for reduction in fractures.

Several RCTs have been published for a number of conditions with risks for osteoporosis, including: juvenile arthritis³¹, postrenal transplant³², nephropathy/glucocorticoids³³, Crohn's disease³⁴ and mixed cohorts of inflammatory disorders.³⁵ All show some improvement in BMD using different bisphosphonates (oral and intravenous), but most only have a short duration of followup, and none were powered to explore the key outcome measure of fracture rate. Further small case–control studies, with limited follow-up, of bisphosphonate use in inflammatory conditions,

Reference	Study	Participants, n	Bisphosphonate	Supplements
Allington <i>et al.</i> ¹⁶	Prospective case series	11 (CP)	Pamidronate i/v: 1 mg/kg for 3 days, every 4 months, for 1 year	Calcium and vitamin D, dose not reported
Bachrach <i>et al</i> . ¹⁷	Retrospective case analysis	25 (treated) 79 (non-treated comparison group)	Pamidronate i/v: 1 mg/kg/dose (maximum 35 mg) for three consecutive days every 3–4 months	Vitamin D supplementation if 25(OH)D < 30 ng/dL
Henderson <i>et al</i> . ¹⁸	Double-blind, placebo-controlled RCT	14 (7 intervention, 7 placebo)	Pamidronate i/v: 1 mg/kg for 3 days, every 4 months for 1 year (not <15 mg or >30 mg per dose)	Calcium 1000 mg, vitamin D 400 IU per day
Iwasaki <i>et al</i> . ¹⁹	Double-blind RCT	10 (vitamin D) 10 (vitamin D and risedronate)	Risedronate p/o for 6 months (dosage not reported)	Vitamin D dosage not reported
Plotkin <i>et al.</i> ²⁰	Prospective case series	23	Pamidronate i/v: 0.75 mg/day for 2 days every 4 months for 1 year	Calcium and vitamin D 1 week prior to infusion as required
Shaw <i>et al.</i> ²¹	Case series	1 (etidronate) 2 (pamidronate)	Etidronate p/o: 7.5 mg/kg for 2 days every 3 months for 1 year Pamidronate i/v: 0.4 mg/kg every 3 months for 1 year	Calcium 400 mg (elemental), vitamin D 400 IU/day
Paksu <i>et al.</i> ²²	Prospective case study	26	Aledronate p/o: 1 mg/kg/week for 1 year	Calcium 600 mg, vitamin D 400 IU/day

Table 3 Studies of bisphosphonate usage children with CP: Study description

CP, cerebral palsy; i/v, intravenous therapy; p/o, oral therapy; RCT, randomised controlled trial.

Table 4	Studies of	f bisphosphonate	usage children	with CP: Out	tcomes of studies	from Table 3
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Reference	BMD on DXA in mean SDS (SD or SE) – before and after treatment						Clinical
	Lumbar-spine		P value	Femur		P value	
	n	z score		n	z score		
Allington <i>et al</i> . ¹⁶	18	Positive z score improvement statistically signific	ant				Pain improved
Bachrach et al. ²³	7	-4(0.4) to -2.8(0.3)	0.03	9	-3.6(0.4) to -1.7(0.9)	0.03	NA
Bachrach <i>et al</i> . ¹⁷	25	No specific data. BMD returned to baseline within 2 years	0.02, fracture reduced by 13%				
Henderson et al. ¹⁸	6	-3.4(0.4) to -2.2(0.4)	0.005	6	-4(0.6) to -1.8(1)	0.01	NA
Iwasaki <i>et al</i> . ¹⁹	20	Significant improvement in BMD	NA				
Plotkin <i>et al.</i> ²⁰	19	-3.8(1.4) to -2.3(1.2)	<0.01	23	-4.5(1.2) to -2.6(0.9)	<0.01	NA
Shaw et al. ²¹	3	Improvement in BMD z scores	NA				
Paksu et al. ²²	26	-3.45(1) to -2.4(0.9)	<0.001	ND	ND	ND	NA

Bachrach *et al.*'s study from Table 3 had two cohorts and therefore two outcomes as per References 17 and 23. BMD, bone mineral density; CP, cerebral palsy; DXA, dual energy X-ray absorptiometry; NA, not applicable; ND, no data; SD, standard deviation; SDS, standard deviation score; SE, standard error.

while heterogeneous, all support the positive effect of treatment.^{36–39}

All published studies on Duchenne muscular dystrophy are observational in nature, with a recent Cochrane review concluding that there was no high-quality RCT evidence to guide management.⁴⁰ Although limited in number and design, studies have shown maintenance/improvement in BMD,^{41,42} increased survival,⁴³ improved vertebral body shape and reduced pain.⁴⁴ However, there is some evidence that bone quality may be affected, with a reduction in the trabecular number on bone biopsy.⁴⁵ Further studies are required to strengthen the evidence base, but we would recommend therapy in the presence of fractures, particularly vertebral fractures, which are very common in this patient group. If glucocorticoid therapy is accompanied by poor growth, it may be possible to reduce the frequency of bisphosphonate therapy. There are, however, no data to support this recommendation. Consideration in DMD should be given to ongoing bisphosphonate treatment for longer periods than

recommended in other conditions whilst high-dose corticosteroids continue to be administered.

The vast majority of corticosteroid-treated boys with DMD do not enter puberty spontaneously, and we would recommend consideration of pubertal induction by age 14.

Limited case–control data in bone marrow transplant patients with graft versus host disease showed increased BMD using bisphosphonates,⁴⁶ while in a group with haematological malignancies, bisphosphonates reduced bone pain and increased BMD compared to a control group.⁴⁷

Other studies have also shown improvements in vertebral body shape with bisphosphonate therapy in young people, including a mixed cohort of patients with low BMD and fracture⁴⁸ and a cohort with congenital neutropenia.⁴⁹

Use of bisphosphonates in conditions other than skeletal fragility

Bisphosphonates have been trialled with varying effects in a wide range of conditions beyond skeletal fragility, including fibrous dysplasia (FD), avascular necrosis (AVN), bone cysts/tumour/ metastases, inflammatory conditions and generalised arterial calcification of infancy (GACI). Available evidence and recommendations are highlighted below.

Fibrous dysplasia

Recommendation

Intravenous bisphosphonates are effective to treat bone pain associated with FD (1, $\oplus\oplus$ OO). Twenty-four months of therapy (pamidronate or zoledronate) can result in long-term pain control. Treatment duration may be limited by an increase in BMD in the normal adjacent bone.

Bisphosphonates do not alter lesion size or expansion in long bones $(1,\oplus\oplus OO)$ but should be considered for progressive optic canal encroachment.

Evidence

There is no evidence to suggest that bisphosphonates alter the size or expansion of bony lesions in FD in children. Small observational studies,^{50–56} with no control group, show variable responses, although there is a good analgesic effect seen in most patients. One RCT using oral alendronate⁵⁷ showed variable results. When FD is part of McCune-Albright syndrome, untreated acromegaly has a major adverse effect on the expansion of craniofacial FD and needs to be managed separately.

Avascular necrosis

Recommendation

Bisphosphonates can be considered for pain control in AVN. There is no convincing evidence of its effect in the prevention of bony collapse $(2, \oplus OOO)$.

Evidence

AVN in children can be idiopathic, occur after trauma or follow corticosteroid administration. It may be confined to a single bone, such as Perthes' disease of the hip, or can occur at multiple sites. Small observational studies in children suggest improvement in pain and prevention of collapse of the femoral head following

Bone cysts, bone tumour, skeletal metastases

Recommendation

There is limited evidence to show that bisphosphonates reduce pain or slow lesion progression in benign bone cysts. However, they may be considered in large/rapidly expanding lesions if conventional therapies have failed or are not feasible $(2,\oplus OOO)$.

Evidence

Bisphosphonates have been used to treat aneurysmal bone cysts and benign bone tumours. A single case report⁶³ showed significant reduction in pain and lesion size after treating an aneurysmal bone cyst with zoledronate. Pain reduction was seen in five children with bone cysts,⁶⁴ with variable responses in lesion size. The rarity of these lesions reduces the likelihood of improving the evidence base for bisphosphonate use.

Bisphosphonate therapy is used in adults, across many varieties of bony metastatic disease, to reduce pain and other skeletal events, such as fractures (e.g. breast cancer⁶⁵). Observational evidence exists for the effect of zoledronic acid on pain relief of metastatic disease in neuroblastomas and hepatoblastomas.⁶⁶

Inflammatory bone conditions

Recommendation

Bisphosphonates are a potential second-line therapy to reduce pain in CRMO (1, \oplus OOO).

Evidence

The use of bisphosphonates as second-line agents in CRMO is limited to reports in four observational studies, with no control group. All showed reduced pain in the majority of patients,⁶⁷ with 12 months of bisphosphonate therapy often resulting in sustained pain relief. One study showed improved lesion size,⁶⁸ and two found improvement in vertebral morphology.^{69,70}

Generalised arterial calcification of infancy

Recommendation

Bisphosphonate therapy can be considered in severe cases of GACI $(1, \oplus OOO)$.

Evidence

GACI, if untreated, is a generally fatal condition often caused by a mutation in *ENPP1*. However, there is observational evidence supporting a survival benefit of bisphosphonate therapy, with a variety of first- and second-generation bisphosphonates used.⁷¹ There has been some longer-term evidence, given the propensity of a hypophospatemic rickets-type picture in this condition, that bisphosphonate use worsens skeletal outcomes.⁷² Newer targeted therapies are in development, such as an ENPP1-Fc fusion protein,⁷³ which would avoid these negative sequelae.

Hypercalcaemia

Recommendation

When hypercalcaemia is refractory to dietary manipulation and intravenous hydration, low-dose bisphosphonate can be considered (pamidronate at 0.25 mg/kg or zoledronate at 0.0125 mg/ kg), with at least 48 h between doses and serum calcium monitored closely for 72 h $(1,\oplus\oplus OO)$.

Evidence

Bisphosphonates have been used in a wide variety of conditions that cause severe hypercalcaemia,⁷⁴ with case series/observational data of its use in vitamin D toxicity,^{75,76} immobilisation hypercalcaemia⁷⁷ and severe neonatal hyperparathyroidism.⁷⁸ In addition, case reports are published for its use in subcutaneous fat necrosis,⁷⁹ parathyroid hormone related peptide (PTHrP)-associated hypercalcaemia of infancy⁸⁰ and Williams syndrome.⁸¹ Bisphosphonate use has also been reported in paediatric cancer patients with hypercalcaemia,^{82,83} with a case–control study showing improvement in patients treated with pamidronate.⁸⁴ Prior to administration, it is important to make sure the child is rehydrated to limit the possibility of bisphosphonate-induced renal damage.

With this limited evidence base in mind, we recommend that consideration for the initial use of low-dose 0.0125 mg/kg zoledronic acid or 0.25 mg/kg pamidronate therapy should be given due to the risk of rebound hypocalcaemia. Repeated dosing can be given at 1–2 weekly intervals if needed until the underlying condition is controlled, with reports of doses of pamidronate up to 2 mg/kg⁷⁵ being used.

Side Effects and Monitoring for Bisphosphonate Therapy

First dose effects

Recommendation

To minimise the risk of hypocalcaemia, the serum vitamin D level should be >50 nmol/L prior to the first infusion, and adequate calcium intake should be maintained post-infusion. Paracetamol and anti-nausea medication can be used to manage the acute phase symptoms. Administration of a reduced first-ever dose of bisphosphonate may reduce these side effects $(1, \oplus \oplus OO)$.

Evidence

Acute phase response

Up to 80% of patients develop a self-limiting acute phase response with flu-like symptoms (fever, bone pains, myalgia, nausea/ vomiting) within 24–48 h after the first infusion, lasting up to several days⁸⁵ and resolving with simple analgesia and fluids.⁸⁶

Hypocalcaemia/hypophosphatemia

Bisphosphonate-induced hypocalcaemia occurs due to osteoclast inhibition of bone resorption. Contributing factors are vitamin D deficiency,⁸⁶ advanced renal disease, prolonged glucocorticoid use and subclinical hypoparathyroidism. Severe symptomatic hypocalcaemia is rare.⁸⁷ Calcitriol use for 3 days post-first dose may reduce the severity of hypocalcaemia and can be considered.⁸⁵ Encouraging an adequate dietary intake of calcium, with supplement use if this is not possible, is also advised. Hypophosphatemia may also occur, although routine supplementation of phosphate is not recommended in this setting.

Rare but serious postulated side effects of bisphosphonate therapy

Iritis

Recommendation

Any child with a red or painful eye should undergo an ophthalmological examination to exclude iritis, especially in the presence of an underlying rheumatological condition $(1,\oplus OOO)$.

Evidence

Iritis has been reported in anecdotal case reports.

Atypical femoral fractures

Recommendation

So called 'atypical' femoral fractures in young people in bisphosphonates may not be drug-related $(1, \oplus \oplus OO)$, and therefore, such fractures are not necessarily an indication for treatment cessation.

Evidence

The adult literature reports an association of long-term use of bisphosphonates with atypical subtrochanteric femoral fractures.⁸⁸ There are very few reports of similar lesions in the paediatric skeleton.^{89,90} Two recent reviews of cohorts of young people with OI call into question the possibility of 'atypical' femoral fractures.^{91,92}

Bisphosphonate-induced osteonecrosis of the jaw

Recommendation

Dental review should be undertaken prior to the first dose of bisphosphonate, with any invasive dental work completed before a first dose. A 6–12-monthly dental review while on bisphosphonate is $dvisable^{93}$ (1, $\oplus\oplus$ OO).

Evidence

A published guideline has recommended 6–12-monthly dental review while on bisphosphonates.⁹³ There are no published reports of osteonecrosis of the jaw (ONJ) occurring in childhood.^{94,95}

Teratogenic effects

Recommendation

Pregnancy should be avoided for 12 months after a dose of bisphosphonate. All post-menarcheal girls should have a pregnancy test prior to bisphosphonate administration $(1,\oplus OOO)$.

Evidence

Concerns have been raised in animal models regarding the potential teratogenicity of bisphosphonates^{96,97} due to their ability to cross the placenta and, potentially, disrupt skeletal development. In the small number of reports where bisphosphonates have been used prior to conception, no significant effects on the fetus have been noted.^{98,99}

Oesophagitis

Recommendation

As per the above recommendations, the only indication where there is any evidence to support even the consideration of oral bisphosphonates is mild to moderate OI. Care should be taken when using oral bisphosphonates in young people due to the risk of erosive oesophagitis. They should only be used in children who can reliably swallow a whole tablet with a glass of water and who do not have gastro-oesophageal reflux disease $(1,\oplus OOO)$.

Evidence

This recommendation is based on the adult literature where this is well described; however, it seems to be an uncommon finding in paediatric studies.¹³

Delayed bone healing in children with OI

Recommendation

Where possible, bisphosphonate therapy should be withheld until there is evidence of callus formation at a site of fracture or osteotomy in children with OI (1, \oplus OOO).

Evidence

A case–control study has shown delayed osteotomy healing in children with OI following the commencement of intravenous pamidronate therapy.¹⁰⁰ A more recent study did not show a delay in healing, which was attributed to a change in surgical technique and the use of zoledronic acid.¹⁰¹ Further studies are required to clarify the risk of delayed bone healing in this cohort of children.

Contraindications for bisphosphonate therapy

Recommendation

Avoidance of bisphosphonates in the following circumstances:

- During pregnancy as discussed above
- Renal impairment Given the renal excretion of bisphosphonates, extreme caution should be taken
- Conditions where the underlying nature of the disorder means that an impairment of resorption will only further increase skeletal fragility, such as hypophosphatasia or with sclerotic lesions and high bone mass disorders
- Active rickets, where attention to the mineral deficits is required

Contraindication to further doses of bisphosphonates

Recommendation

Bisphosphonate therapy is ceased when the height-adjusted BMD *z* score exceeds +2 SD $(1, \oplus \oplus OO)$.

Evidence

An osteopetrosis-like picture is reported to develop where excessive doses of bisphosphonates have been administered.^{72,102} Appropriate monitoring and judicious use, as outlined in Figure 1, would serve to avoid this complication.

Assessments during Bisphosphonate Use

Recommendation: See Table 5 (1, \oplus OOO).

While there has been no proven teratogenicity in humans, we recommend performing a urinary or serum qualitative hCG prior to every dose in post-menarcheal females given the limited evidence base and the concerns raised in animal models.

Table 5 Assessment to be undertaken before first dose of bisphosphonates
Full blood count
Urea and electrolytes
Liver function tests
25-hydroxy vitamin D
Parathyroid hormone
Calcium, magnesium, phosphate
Dental review

Bone turnover markers, such as osteocalcin, collagen crosslinking studies, procollagen type 1 intact N terminal (P1NP) and deoxypyridinoline, are still predominantly research tools, although reference ranges are improving for paediatric-age patients.

BMD using DXA scanning is the only available surrogate measure of bone accrual and should be undertaken prior to first dose and at annual intervals in order to assess response to treatment (Fig. 1). However, there are issues with the availability of reference data in <3-year-olds, and also technical issues in patients with significant contractures and/or internal fixation.

Peripheral quantitative computerised tomography (pQCT) is another method of assessing bone density. It has been primarily used in the research setting, and the clinical utility of these scans is yet to be fully elucidated. The ability to generate a true volumetric density, as well as assessing skeletal geometric parameters, means that it can complement DXA scanning in centres with experience in its use.

Imaging of the lateral thoraco-lumbar spine by X-ray or vertebral morphology assessment by DXA is important to assess for compression fractures. This is an integral part of bone fragility assessment and should be performed at baseline and as clinically indicated.

Regular clinical monitoring for those on bisphosphonates should include annual BMD assessment where feasible, vitamin D assessment and general biochemistry.

Conclusion

Bisphosphonates remain the main therapeutic agent for young people with significant skeletal fragility and are also useful in a small but important number of other clinical settings. Use of these agents should be undertaken in centres with sufficient expertise and with ongoing monitoring by a physician experienced in their effects. Further evidence is still required to strengthen many of the recommendations made in this guideline.

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