Intravenous pamidronate in juvenile osteoporosis

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Abstract

***Aims*—To investigate the use of the aminobisphosphonate, disodium pamidronate, in children with vertebral osteoporosis.**

***Methods*—Five children (aged 10–15 years) with vertebral osteoporosis who developed compression fractures in the thoracic and/or lumbar spine as a consequence of five different conditions, received treatment with intravenous disodium pamidronate in doses ranging from 0.5 to 12 mg/kg/y.**

***Results*—Each child had rapid pain relief following the first treatment, followed by large increments in lumbar spine bone density over one year; the change in bone density standard deviation score ranged from 0.5 to 2.5 with percentage increments of 26% to 54%.**

***Conclusion*—Intravenous pamidronate appears to be a useful therapeutic option in childhood osteoporosis, but its use in children must still be regarded as experimental and therefore closely monitored.**

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Although osteoporosis is uncommon in children, when it is present it can cause severe pain and lead to short and long term disability. There are currently limited therapeutic options for osteoporotic fractures, with most children being treated symptomatically with analgesia. The bisphosphonates are a class of drugs used in adults for the management of postmenopausal and corticosteroid induced osteoporosis.[1 2] They act by inhibiting the action of osteoclasts and therefore bone resorption. None of the currently available bisphosphonates have a product licence for children and there have been concerns about potential adverse effects in the growing skeleton regarding bone mineralisation and longitudinal bone growth. We document our experience of using intravenous pamidronate in five children with vertebral osteoporosis.

Patients and methods

The patients presented between 1992 and 1998 at Birmingham Children's Hospital, UK, being referred to one of the authors (NJS) with symptoms and signs of vertebral osteoporosis. Table 1 lists details of the patients, their conditions, duration of symptoms, and presentation. Patient 1 presented one month postoperatively following bilateral adrenalectomy for Cushing's syndrome. Patient 2, who had osteogenesis imperfecta type III and had never walked because of repeated fractures, presented with progressive vertebral collapse over four years. Patient 3 presented following a second liver transplant for cirrhosis and portal hypertension subsequent to a Kasai procedure in infancy for biliary atresia. She had received large doses of oral and intravenous corticosteroids for rejection episodes after the first transplant and was receiving prednisolone 15 mg daily at the time of presentation. Patient 4 developed progressive symptoms of back pain and difficulty walking over several months and had been referred to an orthopaedic surgeon with a thoracic kyphosis. The clinical picture and results of investigations were consistent with idiopathic juvenile osteoporosis. Patient 5 had suffered from systemic juvenile chronic arthritis for seven years and was receiving oral prednisolone at the time of her presentation; she had also been receiving growth hormone treatment for 18 months because of growth retardation.

Thus, in three of these patients, the effect of corticosteroids, either endogenous or exogenous, were contributing to the development of osteoporosis. Severe back pain was the main symptom leading to recognition of an osteoporotic fracture. At the time of initial treatment, three patients (patients 1, 3, and 5) required regular analgesia of whom two received oral opiate preparations. All but one patient (patient 3) had fractures in both the thoracic and lumbar spine.

After discussion about the potential benefits and possible risks of bisphosphonates, each patient received treatment with the aminobisphosphonate, disodium pamidronate given as an intravenous infusion in 0.9% normal saline over four to six hours. Bone density at the lumbar spine L2–L4 was quantified by dual energy *x* ray absorptiometry (DXA) using a Lunar DPX-L scanner prior to and one year after commencement of treatment. The radiation dose from a DXA scan is approximately 5 mRem and typically has an accuracy and precision of 1–2%. The absolute values were converted into standard deviation scores (SDS) by comparison with mean and standard deviation reference values for age supplied by the manufacturer.

Table 1 Details of patients

Patient	*Condition*	*Age (y)*	*Sex*	*Duration*	*Presentation*	*HtSDS*
1	Cushing's syndrome	11	M	2 wk	Back pain	+1.1
2	Osteogenesis imperfecta	12	F	4 y	Immobility	−10.7
3	Liver transplant	15	F	2 wk	Back pain	+0.8
4	Idiopathic juvenile osteoporosis	11	F	11 mth	Back pain	−0.2
5	Juvenile arthritis	10	F	3 wk	Back pain	−4.5

HtSDS, height standard deviation score.

Results

Table 2 lists the details of the treatment courses received by each patient, the effect on pain relief, and the presence of an acute phase reaction following the first infusion. The number of

Table 2 Details of treatment courses

Patient	No. of treatments	Onset of pain relief	Acute phase reaction
1	2	1 wk	+
2	12	1 mth	+
3	12	1 wk	−
4	3	2 wk	+
5	12	1 wk	−

Table 3 Change in lumbar spine bone mineral density (BMD) after one year

	Baseline BMD		1 y BMD		
Patient	g/cm²	SDS	g/cm²	SDS	% change in BMD
1	0.638	−2.1	0.834	−0.25	31
2	0.246	−6.8	0.378	−6.2	54
3	0.810	−3.7	1.08	−1.2	33
4	0.403	−4.6	0.564	−3.6	40
5	0.444	−3.5	0.556	−3.0	26

treatments given ranged from two to 12, with two patients (1 and 4) receiving two and three treatments respectively over one week, while the other three patients were treated for one year with courses of treatment being given every three months. As a consequence of the number of treatments given, the total dose of pamidronate received by the patients over one year ranged from 0.5 to 12 mg/kg. Pain relief was seen in all patients and occurred within one week in the three requiring regular analgesia, which was then discontinued. There was no recurrence of pain during follow up. Three patients experienced an acute phase reaction following the first infusion. This consisted of flu like symptoms of fever and generalised aches and pains. This settled within 24 hours and was treated symptomatically.

Table 3 shows the lumbar spine bone density measurements at baseline and after one year. Each patient had a bone density more than two standard deviations below the mean at baseline ranging from −2.1 to −6.8 SDS. The growth retardation seen in two patients (2 and 5) will have exacerbated the reduction in bone density in comparison to age related reference data because of the influence of body size on bone density in children. After treatment all patients showed significant increments in bone density standard deviation score (mean change in SDS, $p = 0.014$, 95% confidence interval −2.4 to −0.22, Student's paired *t* test) ranging from 0.5 to 2.5 SDS with the percentage increments in bone density ranging from 26% to 54%. In two patients bone density entered the normal range following one year of treatment, while three patients (2, 4, and 5) still had measurements more than two standard deviations below the age related mean. No relation was found between the total dose and number of treatments received and the change in bone density. No patient sustained a further vertebral fracture following treatment during one to five years follow up, and there were general improvements in activity and mobility. After six months' treatment, the girl with osteogenesis imperfecta began to walk for the first time (using a rollator).

Discussion

Childhood osteoporosis is uncommon and may present as a complication of several different conditions and their treatment, including prolonged immobilisation and the effect of inflammatory cytokines and corticosteroids. In osteogenesis imperfecta, abnormalities in the production of type 1 collagen lead to defective bone formation with evidence of increased bone resorption in many individuals.[3] Idiopathic juvenile osteoporosis is a rare form of primary osteoporosis that typically presents in early puberty and often produces vertebral osteoporosis and characteristic metaphyseal fractures.[4] There are currently no guidelines for the investigation and management of osteoporosis in children, unlike adults.[5]

There are individual reports suggesting benefit from the use of treatments such as calcitriol[6] and calcitonin[7] in children with osteoporosis, but no large series studying these agents. Spontaneous recovery may also occur, particularly if a child is still growing.[4] The bisphosphonates have been used for the past 25 years for the management of osteoporosis in adults, particularly when postmenopausal[1] or steroid induced.[2] They can be administered orally or intravenously and their biological action varies widely, being dependent on the chemical structure of the side chains. The aminobisphosphonates such as pamidronate and alendronate are felt to be 100 times more potent than etidronate,[8] which was the first bisphosphonate to be commercially available. Because they inhibit bone resorption they are likely to be most effective where there is evidence of increased bone resorption.

One of us originally used bisphosphonates in three children with spastic cerebral palsy[9] who suffered recurrent long bone fractures as a consequence of osteoporosis. Increments of lumbar spine bone density of 20–40% were seen after one year to 18 months of treatment. Although the five children we report had vertebral osteoporosis from different causes, similar large increments in bone density were seen one year after starting treatment. This is in comparison to the expected change in lumbar spine bone density over one year which would range from 3% to 15% for children of these ages.[10] The percentage changes of between 26% to 54% and the improvement in the SDS indicate a positive effect of treatment beyond that expected to occur with growth. As spontaneous improvement in bone density would be expected in the boy with Cushing's syndrome and may also occur in idiopathic juvenile osteoporosis, we can only claim a definite effect of the treatment in three of the patients. However, a previous report showed an increment of only 0.3 SDS at the lumbar spine one year after surgery in a 15 year old girl[11] with Cushing's syndrome in comparison to the increase of 1.85 SDS seen in our patient. The fact that no correlation was seen between the dose of pamidronate received and the change in bone density is not surprising considering the small sample size and that different conditions were being treated. The rapid pain relief seen in all patients significantly aided their management

and is a little reported benefit of pamidronate, the mechanism for which remains unclear. This was the primary indication for treatment in the two patients who only received treatment for one week.

There have been a number of reports of the use of bisphosphonates in children with osteoporosis following the first report in 1985 of the treatment of a child with idiopathic osteoporosis.[12] The majority of these have been single case reports, which were reviewed by Allgrove in 1997.[13] Since then there have been two larger series reported. Brumsen *et al* published their experience of the use of oral pamidronate or olpadronate in 12 children with osteoporosis followed up for 2.5–12 years.[14] They received treatment for periods ranging from two to eight years and showed a change in the mean bone density SDS from −3.8 to −1.9 over five years with early evidence of a decline in bone resorption. All the children grew normally and bone biopsies on six of the children showed normal lamellar bone. The most extensive report to date[15] documented the use of intravenous pamidronate given as repeated courses every four to six months in a group of 30 children with severe osteogenesis imperfecta for periods of 1.3–5 years. The mean annual increase in bone density was 41% with the lumbar spine bone density SDS increasing from −5.3 to −3.4. The incidence of fractures fell by an average of 1.7 per year and no adverse effects were seen on fracture healing, growth rate, or the appearance of the growth plates.

Thus, there is increasing evidence that bisphosphonates may be a treatment option for osteoporosis in children, although as yet there has only been one small randomised study published.[16] There are two reports of impaired mineralisation[17 18] occurring in children receiving bisphosphonates, and mineralisation defects have been seen in adults with Paget's disease following treatment with pamidronate.[19] Metaphyseal undertubulation of long bones was also noted in five children receiving bisphosphonates in one study.[20] It is important to be cautious in their use in children, as it is well known that the drugs remain in the skeleton for up to 10 years.[9] Information on the minimum effective drug dosage and duration of treatment is also lacking.

Our patients and most of those previously reported were experiencing fractures at the time that treatment was instituted, so we believe their use is justified on the basis of potential benefit compared to risk. As yet there is little justification to use prophylactic bisphosphonates in children with low bone density unless conducted in the context of a randomised controlled study. This is particularly pertinent where bone density measurements in children may be artefactually low in those who are small for their age, because of the failure of techniques such as dual energy *x* ray absorptiometry to correct for body size.[21] As a consequence of the influence of growth, it is currently not possible to define osteoporosis in children on the basis of bone density measurements alone. It is important that any child with osteoporosis is appropriately investigated in order to correctly identify the aetiology and advise appropriate management. As commented in a recent editorial,[22] children receiving bisphosphonates should be followed up by paediatricians with special interest in growth and skeletal disease, and detailed patient monitoring is critical.

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