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Date Created: May 2011
Reviewed by: Dr C DeVile, Dr J Allgrove, Dr B Crowe, M Heathfield, S Mahal
Date Reviewed: July 2016, July 2021
Date for next review: Jul 2022
Version: 4
DTC Ref No.: IN00055

Drug Monograph for Osteogenesis Imperfecta: Use of Intravenous Pamidronate Disodium

Osteogenesis Imperfecta (OI) encompasses a group of disorders characterised by increased fragility of bone. In the most severe form, fractures are present at birth and continue to occur, often several times a year in response to minimal trauma. In milder forms, fractures may only occur occasionally and the symptoms e.g. back pain, may be more subtle. Generalised osteoporosis is usually also present and may be accompanied by vertebral collapse and severe long bone deformity.

Management of OI should be undertaken as a multidisciplinary team and consists of appropriate physiotherapy and occupational therapy, orthopaedic surgery and family support. Medical treatment to try to strengthen bone and reduce the number of fractures and bone deformity has been tried with some success. The most promising of these approaches has been the use of bisphosphonates to increase bone density and redress the imbalance between bone resorption and bone formation, which occurs in OI.

Bisphosphonates have been used for a variety of conditions in childhood where there is bone pain and immobility in association with osteoporosis and/or abnormal bone formation. The most commonly used bisphosphonate in the UK is pamidronate, which has been used with considerable success in several conditions in which generalised osteoporosis occurs, although the longer-acting and more potent zoledronic acid is being increasingly used in children over the age of five years (see separate protocol). Apart from OI, conditions treated include Idiopathic Juvenile Osteoporosis, Osteoporosis Pseudoglioma Syndrome, Polyostotic Fibrous Dysplasia and Steroid Induced Osteoporosis. In all cases an increase in bone density was seen with vertebral body remodelling, an early reduction in pain and improved mobility.

As patients with these conditions are rare, they are likely to be under the care of specialist paediatricians in the UK and it is proposed to use a common protocol for the administration of intravenous pamidronate, so as to gather uniform data for subsequent audit and research.

Mechanism of Action

The principal pharmacological action of pamidronate disodium is inhibition of bone resorption.

Indications

- Severe phenotype
- Bone pain requiring regular analgesia
- Recurrent fractures and/or vertebral insufficiency fractures
- Severe bone deformity
- Reduced mobility and function

Baseline Investigations

Radiology:
Lateral X-ray of whole spine to quantify any evidence of vertebral insufficiency fractures (this will have been done as part of the diagnostic / monitoring process).
Anterior Posterior (AP) spine only if scoliosis present/suspected.

- DEXA scan (bone densitometry) if not already performed.
  This is a lumbar spine DEXA. There are no normative data below 5 years of age but can be done in younger children (≥ 10 kg), to act as own control.
- GOSH data-set also includes a BMAD Z-score, a 3-dimensional measurement, which adjusts for body size. In cases where spinal fusion or growth rod surgery has been performed, a DEXA

scan of hips will take place prior to surgery and be completed thereafter in place of lumbar spine DEXA as metalwork may affect the bone density readings.
- Urinary tract ultrasound scan (monitoring for nephrocalcinosis).

Biochemistry:
- Plasma calcium, phosphate, urea and electrolytes, alkaline phosphatase and albumin, serum intact PTH and 25-OH vitamin D.

Dosage and Administration Details

Vitamin D: All children with OI should be taking 400 units (10 µg), 800 units (20 µg) or 1,000 units (25 µg) of oral, over-the-counter purchased vitamin D as a daily dose for maintenance depending on age and as directed by the specialist team.

If baseline 25-OH vitamin D is low (<50 nmol/L), give supplemental vitamin D daily (3000 units/day) for 3 months and check levels again in 2 months.
Defer treatment until 25-OH vitamin D levels are ≥ 50 nmol/L.

Calcium: Calcium levels should be checked before each infusion and a clinical decision made if supplementation is required.

Pamidronate: Pamidronate disodium can be used from birth, up to and beyond adolescence but frequently is substituted with zoledronic acid over the age of five years. Doses are listed below according to age, although the child's medical records should be **always** checked before prescribing, as doses may be modified following clinical review. A full cycle consists of 3 infusions over 3 days.

On first infusion (day 1) of first treatment cycle, half the usual dose should be given to minimise an acute phase reaction (see below). Doses should not exceed a total of 12 mg/kg/year (i.e.1 mg/kg/month).

A maximum schedule of 1 mg/kg/dose, unless specifically directed by OI specialist, and maximum dose of 60 mg as a single infusion should not be exceeded.

Age / years	1st Cycle 1st dose	1st Cycle 2nd dose	1st Cycle, 3rd dose	2nd Cycle 1st dose	2nd Cycle 2nd dose	2nd Cycle 3rd dose	Frequency
0-2	0.25mg/kg	0.5mg/kg	0.5mg/kg	0.5mg/kg	0.5mg/kg	0.5mg/kg	6 weekly
2-3	0.33mg/kg	0.66mg/kg	0.66mg/kg	0.66mg/kg	0.66mg/kg	0.66mg/kg	8 weekly
≥3	0.5mg/kg	1mg/kg	1mg/kg	1mg/kg	1mg/kg	1mg/kg	3 monthly

For each infusion make up in sodium chloride 0.9% or glucose 5% to a concentration not greater than 240 micrograms per 1mL and infuse over four to six hours (rate not exceeding 60 mg/hour). In infants with severe OI the infusion rate may be slowed to six to eight hours to minimise risk of potential respiratory symptoms associated with an acute phase reaction.

As a minimum the first two infusion cycles are given at the tertiary unit in order to monitor for side-effects (see below). Once these settle satisfactorily, and in liaison with the local referring hospital, subsequent infusions may be given as an outpatient, for 3 sequential days.

In the younger children, and those with a severe phenotype in particular, central access (central venous port insertion) may be necessary before commencement of treatment (performed by Interventional Radiologists at Great Ormond Street Hospital).

Monitoring during Treatment

- Prior to each treatment cycle day 1:
  Plasma calcium, phosphate, urea and electrolytes, alkaline phosphatase, albumin, serum PTH and 25-OH vitamin D.

- Only monitor blood pressure if there are clinical concerns. “Routine” 4-hourly blood pressures should **not** be performed due to risk of fracture. In rare cases where blood pressure measurements are required, they should be taken manually with a sphygmomanometer and doppler / stethoscope and not with an automated device such as a Dinomap. All other observations should be completed in line with Trust policy. This may vary across centres.

- Daily before treatment cycle days 2 and 3:
  Plasma calcium, phosphate and albumin daily prior to each infusion. This is to ensure that calcium levels have not dropped too low in between daily infusions. If corrected calcium falls below 2.1 mmol/L, or the patient is symptomatic, additional oral calcium supplements should be given such as Cacit D3 or Calcichew D3 Forte - please contact the CNS or Consultant for the OI team if corrected calcium is low.

- Corrected calcium should be above 2.1 mmol/L. To calculate corrected calcium the following formula may be used;
  (40 – serum albumin level g/L) x 0.02 + plasma calcium mmol/L.

  Therefore corrected calcium for an uncorrected calcium of 2.25 mmol/L and albumin of 35 g/L would be calculated as 40 – 35 = 5 x 0.02 = 0.1 + 2.25 = 2.35 mmol/L.

- It is **not** necessary to repeat 25-OH vitamin D once known that baseline level is replete; a 6-monthly check is sufficient. Isoenzyme monitoring is not required. 1,25-OH vitamin D is not required for monitoring purposes.

- At the end of one year of treatment and at subsequent annual monitoring:
  Repeat baseline investigations. The DEXA scan should be performed on the same machine as previously. This will be usually undertaken at the tertiary centre.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Renal failure (GFR<30ml/min/1.73m2)
- Pregnancy
- Vitamin D deficiency

Precautions for Use

- Vitamin D deficiency – do not give pamidronate until the level is replete.
- It is strongly recommended that such treatment be undertaken in conjunction with a paediatric metabolic bone disease specialist, although it will be up to individual clinicians to decide where treatment should take place.
- Pamidronate disodium is a viscous drug that if given in too small a volume or too rapidly can lead to venous irritation and tracking marks along the vein.

Adverse Effects

An acute phase reaction (fever and flu-like symptoms, such as pyrexia, generalised aches and pains, vomiting) can occur following the first treatment. This happens in the majority of children and usually only lasts 24 to 48 hours and can be treated symptomatically. It usually only occurs with the first infusions (commonly days 2 and 3) and does not usually stop further treatment courses, although, if severe, the third dose of the first cycle may be delayed by a month or omitted.

In neonates, the acute phase reaction may include respiratory distress, especially if there is pre-existing respiratory difficulty. Management is with appropriate supportive care.

Hypocalcaemia: This is rarely symptomatic. If it occurs, double calcium supplements for 5 days. Plasma calcium to be measured daily during the infusion period and the infusion should not be given until the results are available.

There may be a potential risk of delayed bone healing (non-union) after orthopaedic procedures, such as osteotomy, or after prolonged treatment. If a patient requires surgery, then we would usually advise not giving pamidronate within 2-4 weeks of surgery, although there is limited evidence to support this timing and variance in practice across OI centres. Post-operatively we would advise to withhold pamidronate until there is evidence of bone healing confirmed on X-ray (usually confirmed by the orthopaedic team who conducted the surgery at around 6 weeks but may be longer).

In the event of an acute long bone fracture (not requiring surgical management), occurring at the time pamidronate is due, then in children with severe OI, treatment should proceed unless specified by the OI specialist. In children with milder OI, the decision or not to delay treatment is usually made on an individual basis in consultation with the OI specialist and review of radiographs of the fracture.

We recommend continuing pamidronate treatment, once started throughout childhood until completion of growth, reducing either dose per cycle, or frequency of cycles depending on monitoring investigations (stopping treatment may potentially increase risk of fracture at juncture of treated and non-treated bone). However, once children reach the age of five years, consideration may be given to changing to zoledronic acid. Any changes to treatment regimen will be directed by the OI team, usually following clinical assessment and review of an up-to-date DEXA scan.

It has been suggested that there is a risk of osteonecrosis of the jaw (ONJ) in association with bisphosphonate treatment. Whilst this may occur in adults, usually those who have been treated for some form of cancer, ONJ has **never** been described in children with OI and is not regarded as a risk.

Note:

- Paracetamol should be prescribed as a PRN medication.
- In female patients of childbearing potential, it is important to ask whether there is any chance of them being pregnant. If there is any doubt or suspicion, then obtain a pregnancy test and, if positive, withhold treatment and inform the consultant.

Points of Contact

Role	Preferred Contact Method
CNS (MH)	Email, Ext 5824 or EPIC
Lead OI Consultant (CDV)	Ext 8191 or Bleep 0120
OI Consultant (BC)	Ext 1501 PA Ext 5293/1198
Endocrine Consultant (JA)	07779 823 573

For fuller details of adverse effects see Summary of Product Characteristics for pamidronate disodium. For zoledronic acid guidelines, please see separate guidelines.

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