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| Paediatric guideline for the administration of zoledronic acid. | | | |
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| **Target Audience:** | Medical, nursing and pharmacy staff involved in the prescribing and administration of zoledronic acid infusions to paediatric patients. | | |
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1. Purpose

To provide guidance to those involved in the prescribing and/or administration of zoledronic acid infusions to children and young people.

1. Scope

The guideline will be used by medical and nursing staff involved in the prescribing and administration of zoledronic acid infusions to paediatric patients. This will generally be those based in Dirleton ward at RHCYP or occasionally other paediatric in-patient wards.

The decision to commence bisphosphonate therapy will primarily be made by consultants in the paediatric endocrinology team who are managing patients with metabolic bone disease.

1. Definitions

Metabolic bone disease is a loss of bone mass for body size, and may be caused by a variety of congenital and acquired causes such as osteomalacia, rickets or osteoporosis (which may be dietary or drug induced e.g. consequence of chemotherapy, radiotherapy or long-term steroid use), osteogenesis imperfecta and other conditions leading to reduced bone mineral density.

Zoledronic acid, also known as zoledronate, is a bisphosphonate drug. This group of drugs binds strongly to bone mineral and interferes with bone remodelling by slowing the process of osteoclastic bone resorption and bone turnover.

Zoledronic acid is not licensed for use in children but is currently used off-label for a number of conditions associated with increased bone fragility. The advantage of zoledronic acid is that it can be given on a single day as a thirty to forty-five minute infusion every three to six months compared to pamidronate which must be given over several days. To date, evidence suggests no difference in the desired treatment effect, or side effects, between pamidronate disodium and zoledronic acid.

1. Roles and responsibilities

The decision to proceed with bisphosphonate therapy will generally be made by a consultant endocrinologist. The pre-treatment preparation should be completed by the prescribing clinician or team.

1. Main content

**5.1. In advance of the first planned admission for a zoledronic acid infusion**

1. Children and young people should always have an adequate Vitamin D level (>50 nmol/l) prior to receiving their first infusion. This must be checked and reviewed following clinic consultation, prior to booking the admission for infusion.
2. The patient should be booked for the infusion in Dirleton ward. An overnight admission to a paediatric medical ward should be arranged following the FIRST infusion to monitor ionised calcium levels – see below. This is not required for subsequent infusions.
3. All patients require oral calcium supplements for three days before, the day of, and three days after every infusion (i.e. seven days total). This should be documented in the patient’s clinic letter alongside a request for the GP to prescribe.

**Calcium dose is 1 mmol/kg/day, divided into two or three doses depending on convenience of preparation** (see BNFc for available preparations).

The dose should be revised according to patient’s weight, as required.

1. Prescribe the zoledronic acid on the patient’s fluid prescription chart. Prior to the first infusion, the post-infusion calcium supplementation and paracetamol as required should also be prescribed on the patient’s medication prescription and administration record, in preparation for their overnight stay.

**5.2. At first admission**

Children and young people should have a medical review at admission, including plotting on a growth chart of their height, weight and occipito-frontal circumference (OFC) for children under the age of two years. Ensure that enteral calcium supplements have been taken for the three days prior to and the day of admission.

An intravenous cannula will be inserted and bloods taken for U&Es and creatinine, LFTs, PTH, calcium, magnesium and phosphate. A blood gas for ionised calcium should also be taken prior to first infusion as a baseline, in order to compare results post-infusion. A vitamin D level should be checked not more than annually.

**Bloods should be sent urgently to the laboratory and the results reviewed prior to commencement of infusion** **– this is to ensure normal renal function prior to receiving zoledronic acid - unless normal renal function has been confirmed in the preceding four weeks.**

As a side effect of the infusion, some children and young people will experience ‘flu-like symptoms’ with fever, musculoskeletal aches and pains and occasionally vomiting. Most symptoms respond to paracetamol and usually only occur on the occasion of the first infusion.

Following the first infusion, patients require four-hourly observations of heart rate, respirations, blood pressure and temperature which should be documented on the patient’s PEWS (Paediatric Early Warning Score) chart.

Please ensure enteral calcium supplementation is prescribed on the patient’s medication prescription and administration record for three days post-infusion, as per dosing schedule above.

Following the first infusion, all patients require a blood gas to check ionised calcium **every twelve hours for twenty-four hours**. Post-zoledronate hypocalcaemia is usually mild, transient and asymptomatic. If hypocalcaemia occurs, give additional doses of oral calcium, in addition to pre-prescribed calcium, as per separate guideline ‘Guideline for Management of Hypocalcaemia in Children and Neonates admitted to RHCYP’. Alfacalcidol could also be considered if calcium remains low (doses as per BNFc).

Hypocalcaemia can be avoided in future by giving a higher dose of calcium supplementation prior to subsequent infusions and ensuring that the patient is not Vitamin D deficient.

All patients should continue oral calcium supplements for three days after each infusion.

**5.3. For subsequent admissions**

Ensure that calcium supplements have been taken for the three days prior to, and the day of admission.

Patients should have urgent bloods sent for U&Es and creatinine, LFTs, calcium, magnesium and phosphate, as well as vitamin D if not measured within the last year. **Results must be reviewed prior to commencement of infusion to ensure normal renal function - unless normal renal function has been confirmed in the preceding four weeks.**

Provided the infusion is well tolerated, patients can go home straight afterwards to continue their three further days of oral calcium.

**5.4. Zoledronic acid dosing**

The dose and frequency of zoledronic acid should always be discussed with a consultant endocrinologist. Starting doses are detailed below. Some children and young people will be on a reduced infusion frequency after the first two years.

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| **Age** | **Dose**  ***(maximum dosage)*** | **Volume of sodium chloride 0.9% infusion bag** | **Duration of infusion** | **Frequency of infusions** |
| < 2 years | 25micrograms/kg  (max. 2mg) | 50ml | 45 minutes | 3 monthly |
| 2-5 years | 35micrograms/kg  (max. 2mg) | 100ml | 45 minutes | 4 monthly |
| >5 years | 50micrograms/kg  (max. 4mg) | 100ml | 30 minutes | 6 monthly |

Preparation:

Zoledronic acid is available as a concentrate of 4mg/5ml.

This MUST be diluted prior to administration. To do this, withdraw the required volume of zoledronic acid from the vial. Add the dose to the infusion bag. Mix well and then infuse over the required time.

For doses less than 1mg, please prescribe in micrograms. For doses of 1mg or over, please prescribe in milligrams.

*Example 1: For a 6 year old patient weighing 11.8kg, the dose would be 50 micrograms/kg = 590 micrograms, rounded to 600 micrograms zoledronic acid. 4mg/5ml concentrate = 4000 micrograms in 5 millilitres = 800 micrograms in 1 ml solution. Therefore 0.75ml (= 600 ÷ 800 micrograms) of zoledronic acid 4mg/5ml concentrate should be withdrawn from the vial and added to a 100 ml infusion bag of sodium chloride 0.9%. This should be then infused over 30 minutes.*

*Example 2: For a 12 year old patient weighing 43 kg, the dose would be 50 micrograms/kg = 2,150 micrograms = 2.15 mg zoledronic acid. 4mg/5ml concentrate = 0.8 mg in 1 ml solution. Therefore 2.7 mls (= 2.15 ÷ 0.8 milligrams) of zoledronic acid 4mg/5ml concentrate should be withdrawn from the vial and added to a 100 ml infusion bag of sodium chloride 0.9%. This should be then infused over 30 minutes.*

1. Associated materials

N/A.

1. Evidence base

Munns CF et al. Acute phase response and mineral status following low dose intravenous zoledronic acid in children. *Bone* 2007; 41(3):366-70.

Shaw NJ, Bishop NJ. Bisphosphonate treatment of bone disease. *Arch Dis Child* 2005; 90:494-99.

Högler W et al. Short-term safety assessment in the use of zoledronic acid in children*. J Paediatr* 2004; 145:701-4.

Glorieux F et el. Intravenous zoledronic acid compared to pamidronate in children with severe osteogenesis imperfecta. *Abstract, 35th European Symposium on Calcified Tissues, Barcelona* 2008.

Vuorimies I et al. Zoledronic acid treatment in children with osteogenesis imperfecta. *Horm Res Paediatr* 2011; 75:346-53.

1. Stakeholder consultation

N/A.

1. Monitoring and review

This guideline will be updated if any significant new evidence or national guidance is published. Otherwise, it will be due for review in March 2024.