Use of Bisphosphonates in paediatric patients
Policy Title: Paediatric Bisphosphonate Protocol

Executive Summary: Bisphosphonates such as pamidronate and zoledronic acid are occasionally recommended for children by the endocrinologists at Royal Manchester Children’s hospital (RMCH). This policy is their guidance on the treatment of children with bisphosphonates.

Supersedes: New policy

Description of Amendment(s): Extra information regarding risk of dental extractions and the need for ongoing preventative dental treatment – recommended by Dental services.

This policy will impact on: Children’s Services

Financial Implications: Operative procedure In patient care

Policy Area: Children’s Services Document Reference: Paediatric Bisphosphonates

Version Number: 1.1 Effective Date: May 2014

Issued By: Family and Wellbeing Business Unit Review Date: May 2017

Author: Adapted from Royal Manchester Children’s Hospital policy (Dr Raja Padidela, Consultant Endocrinologist, Hong Thoong, Pharmacist) by Sally Chartres, pharmacist. Impact Assessment Date: May 2014

APPROVAL RECORD

Committees / Group | Date
--- | ---
Consultation Phase: Paediatric consultants Pharmacy representative | Jan 2014
Paediatric Lead Dr Gail Whitehead Date | 
Received for information: IT Dept & Legal Services | 


1.1 Introduction
Bisphosphonates are widely used for management of children with Osteogenesis Imperfecta (OI), fragility fracture secondary to immobility; steroid induced osteoporosis; chronic inflammatory condition such as inflammatory bowel disease; neurofibromatosis type 1 and idiopathic osteopenia/osteoporosis of unknown origin. Bisphosphonates inhibit osteoclasts and therefore prevents excessive bone resorption and have a cumulative inhibitory effect on pathological bone loss.

Pamidronate is a second-generation intravenous bisphosphonate. Studies have confirmed reduced fracture rate and increase in bone mass in children with OI [1]. We have more than 20 years of experience of using pamidronate and we have found it to be safe and beneficial in a wide range of primary and secondary childhood bone disorders.

Zoledronic acid is a third generation amino bisphosphonates with significantly greater potency and affinity for bone (100- to 1,000-fold) compared to pamidronate, resulting in a prolonged action from a single dose, lasting 6-12 months in adult studies. Zoledronic acid reduces the risk of fracture or skeletal complications in children with osteoporosis and increases bone density [2-7].

The advantage of Zoledronic Acid is that it can be given as an infusion over 30-45min, every 4-6 months (i.e. 2-3 day case admissions/year). Pamidronate infusions are currently given as a 4-hour infusion on 2/3 consecutive days, 3-monthly (8-12 days/year).

Pamidronate infusions will be reserved for use in infants less than 1 years of age.

1.2 Pamidronate infusion

1.2.1 Preparations for treatment with intravenous pamidronate

1.2.1.1 Check serum Calcium, Phosphate, Urea, Creatinine, Alkaline Phosphatase, 25 hydroxycholecalciferol (25OH Vitamin D) and Parathyroid hormone before commencing treatment. Pamidronate can only be infused if the results of these biochemical parameters are within the normal limit within three months of planned infusion. These measurements will be routinely undertaken during clinic appointments (3 monthly).

1.2.1.2 Maintain serum 25OH Vitamin D >50nmol/l before commencing infusion. If 25OH Vitamin D is <50 nmol/l, ensure that loading dose/maintenance therapy with colecalciferol have been administered/commenced, within three months of infusion.

1.2.1.3 Ensure dental assessment and management of dental hygiene through the local community dentist or paediatric dentist at Royal Manchester Children’s Hospital has been arranged. Ongoing preventative dental care is advisable for all patients receiving these infusions.

1.2.2 On the day of infusion (prior to infusion)

1.2.2.1 Insert an IV cannula and send blood samples for bone profile, vitamin D (serum 25 OHD), PTH and U&Es. (The results will not be required before administration of Pamidronate.)

1.2.2.2 Obtain urine and send in plain bottle for calcium/creatinine ratio.
1.2.2.3 Pregnancy test should be performed before infusion in all female patients with childbearing potential. If positive, withhold treatment.

1.2.2.4 The first infusion of pamidronate will require overnight hospital admission to monitor for “acute phase reaction” (nausea, fever, pains in limbs & back). Treat these symptoms with oral ondansetron, paracetamol and ibuprofen; all to be routinely prescribed on PRN basis on the drug chart. Monitoring for heart rate, respiratory rate, blood pressure and temperature will be undertaken at time 0, 2 and 4 hours during each infusion.
For the first infusion, and where the child requires overnight stay, monitoring for heart rate, respiratory rate, blood pressure and temperature after the infusion will be undertaken every 4 hours i.e. routine observations as per nursing guidelines.

1.2.3 Pamidronate dosage

All children <2 years of age receiving pamidronate infusion should be under the care of a consultant from bone and calcium disorder team (see under contacts below).

<table>
<thead>
<tr>
<th>Weight &lt; 10kg</th>
<th>Weight ≥ 10kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard</strong></td>
<td></td>
</tr>
<tr>
<td>0.5mg/kg/day over 4 hours on 3 consecutive days (1 cycle), repeated every 2 months</td>
<td>1mg/kg/day (max 60mg) over 4 hours on 3 consecutive days (1 cycle), repeated every 3 months</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td></td>
</tr>
<tr>
<td>0.5mg/kg/day over 4 hours on a single day (1 cycle), repeated every 2 months</td>
<td>1mg/kg/day (max 60mg) over 4 hours on a single day (1 cycle), repeated every 3 months</td>
</tr>
</tbody>
</table>

* Consultant endocrinologist will make a decision for maintenance therapy which, will be based on results of bone mineral density scans and status of vertebral and long bone fractures.

1.2.4 Pamidronate intravenous infusion administration

<table>
<thead>
<tr>
<th>Dose of pamidronate to be infused, based on patient weight</th>
<th>Add to the following volumes of 0.9% Sodium Chloride</th>
<th>Duration of Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20mg</td>
<td>100mls of 0.9% Sodium Chloride</td>
<td>4 hours</td>
</tr>
<tr>
<td>20-30mg</td>
<td>150mls of 0.9% Sodium Chloride</td>
<td>4 hours</td>
</tr>
<tr>
<td>&gt;30-40mg</td>
<td>200mls of 0.9% Sodium Chloride</td>
<td>4 hours</td>
</tr>
<tr>
<td>40-60 mg</td>
<td>250mls of 0.9% Sodium Chloride</td>
<td>4 hours</td>
</tr>
</tbody>
</table>
*Maximum concentration of 60mg/250ml.

1.3 Zoledronic Acid infusion

1.3.1 Preparations for treatment with Zoledronic acid

1.3.1.1 Check serum Calcium, Phosphate, Urea, Creatinine, Alkaline Phosphatase, 25OH Vitamin D and Parathyroid hormone before commencing treatment. Zoledronic acid can only be infused if the results of these biochemical parameters are within the normal limit within three months of planned infusion. These measurements will be routinely undertaken during clinic appointments (3 monthly).

1.3.1.2 Maintain serum 25OH Vitamin D >50nmol/l before commencing infusion. If 25OH Vitamin D is <50 nmol/l, ensure that loading dose/maintenance therapy with colecalciferol have been administered/commenced, within three months of infusion.

1.3.1.3 Children will require a prescription for calcium supplements orally 48 hours before & after infusion. This could be any of the following:

- Calcium Sandoz 2.7mmol (5mls) four times a day
- Cacit 500mg effervescent tablets. Dissolve one tablet in 10ml of water and to take 2.5ml (≈3.1mmol) four times a day of prepared solution.

1.3.1.4 Children should be encouraged to drink their daily maintenance requirement of oral fluids before and for 24 hours after Zoledronic acid infusion.

Suggested oral maintenance fluid intake for child’s weight:

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Fluid Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 10kg</td>
<td>100ml/kg/day</td>
</tr>
<tr>
<td>10-15kg</td>
<td>1250ml/day</td>
</tr>
<tr>
<td>15-20kg</td>
<td>1500ml</td>
</tr>
<tr>
<td>&gt;20kg</td>
<td>2000ml</td>
</tr>
</tbody>
</table>

1.3.1.5 Zoledronic acid can be infused after a fracture but treatment needs to be deferred for 6 weeks after osteotomy for intramedullary rodding procedures, please discuss with paediatric bone team before recommencing treatment.

1.3.1.6 Ensure dental assessment and management of dental hygiene through the local community dentist or paediatric dentist at Royal Manchester Children’s Hospital has been arranged. Ongoing preventative dental care is advisable for all patients receiving these infusions.

1.3.1.7 Patients on Zoledronic acid will require bone profile, renal function and electrolytes, vitamin D and PTH measured 2 weeks before infusion in the day care unit. **Any derangement of bone profile and renal function will be a contraindication for infusion of Zoledronic acid.** If Vitamin D is low, Zoledronic acid can be infused following administration of loading dose of vitamin D according to trust guidelines.

1.3.2 On the day of infusion (prior to infusion)

1.3.2.1 Insert an IV cannula.
1.3.2.2 Pregnancy test should be performed before infusion in all female patients with childbearing potential. If positive, withhold treatment.

1.3.2.3 Obtain urine and send in plain bottle for calcium/creatinine ratio

1.3.2.4 First infusion of zoledronic acid will require overnight hospital admission to monitor for “acute phase reaction” (nausea, fever, pains in limps & back). Treat these symptoms with oral ondansetron, paracetamol and ibuprofen to be routinely prescribed on PRN basis on the drug chart.

1.3.3 Zoledronic acid dosage [9]

Zoledronic acid 4mg/5ml vials are stocked in pharmacy at MDGH

Zoledronic acid 0.025- 0.05 mg/kg/IV, 30-45min infusion every 6-month (Maximum Dose 2.0mg for <3 years and 4 mg for 3-17 years per infusion)

All children <2 years receiving Zoledronic acid infusion should be under the care of a consultant from bone and calcium disorder team (see under contacts below).

Dosage table

<table>
<thead>
<tr>
<th>Age</th>
<th>Dosage</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 years</td>
<td>0.025mg/kg/dose</td>
<td>3 months</td>
</tr>
<tr>
<td>2-5 years</td>
<td>0.035mg/kg/dose</td>
<td>4 months</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>0.05mg/kg/dose</td>
<td>6 months</td>
</tr>
</tbody>
</table>

This schedule corresponds to an annual dose of 0.1 mg per kg body weight.

Preparation of intravenous Zoledronic Acid 4mg/5ml injections[8]

<table>
<thead>
<tr>
<th>Dose of zoledronic acid to be infused, based on patient weight and age</th>
<th>Add to Normal Saline in a volume of</th>
<th>Duration of Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.025mg/kg/dose</td>
<td>50mls 0.9% Sodium Chloride</td>
<td>45 minutes</td>
</tr>
<tr>
<td>0.035mg/kg/dose</td>
<td>100mls 0.9% Sodium Chloride</td>
<td>45 minutes</td>
</tr>
<tr>
<td>0.05mg/kg/dose</td>
<td>100mls 0.9% Sodium Chloride</td>
<td>30 minutes</td>
</tr>
</tbody>
</table>

1.4 Potential side effects of bisphosphonates

1.4.1 There is a risk of an acute phase reaction after the first treatment course. This consists of fever, flu-like symptoms, nausea, and in some patients, pain in the back or limbs. It usually occurs 24-48 hours after the first infusion and should be treated symptomatically with paracetamol, ibuprofen and ondansetron.

1.4.2 Hypocalcaemia may occur following treatment, but it is rarely symptomatic. It is more common after Zoledronic acid treatment. Children will therefore be prescribed calcium supplements 48 hours before and after infusion of Zoledronic acid.
1.4.3 In neonates (Pamidronate infusion), the acute phase reaction may include respiratory distress if there is pre-existing respiratory difficulty. Management is with appropriate supportive care.

1.4.4 There is an increased risk of delayed healing, post operative pain and infection and possible osteonecrosis following dental extractions. This is more likely to occur in patients who have received IV infusions rather than oral bisphosphonates.

1.5 Contacts

At Macclesfield District General Hospital:
Dr Ignatius Losa, Consultant paediatrician – via switchboard

At Royal Manchester Children’s Hospital:
Endocrine registrar on bleep 1630
Consultants managing children with bone and calcium disorders through switchboard - Dr Zulf Mughal, Dr Raja Padidela, Dr Sarah Ehtisham, Dr Mars Skae and Dr Shaila Sukthankar.

2. References and Bibliography


8. Zoledronate (ACLASTA) Treatment, Protocol from Shrines Hospital, Montreal, Canada.
9. Protocol for the use of Intravenous Zoledronic acid (Zoledronate) in Children, Protocol from Birmingham Children’s Hospital, Birmingham, UK.


Equality Analysis (Impact assessment)

1. What is being assessed?

Paediatric Bisphophonate policy

Details of person responsible for completing the assessment:
- Name: Sally Chartres
- Position: Pharmacist
- Team/service: Paediatrics

State main purpose or aim of the policy, procedure, proposal, strategy or service:
(usually the first paragraph of what you are writing. Also include details of legislation, guidance, regulations etc which have shaped or informed the document)

Bisphosphonates such as pamidronate and zoledronic acid are occasionally recommended for children by the endocrinologists at Royal Manchester Children’s hospital (RMCH). This policy is their guidance on the treatment of children with bisphosphonates.

2. Assessment of Impact

RACE:
From the evidence available does the policy, procedure, proposal, strategy or service affect, or have the potential to affect, racial groups differently? Yes ☐ No X

Explain your response: Where the first language of the patient/parent/guardian/carer is not English, the Trust interpretation and translation policy will be followed to ensure that information can be given and understood.

GENDER (INCLUDING TRANSGENDER):
From the evidence available does the policy, procedure, proposal, strategy or service affect, or have the potential to affect, different gender groups differently? Yes ☐ No X

Explain your response: Pregnancy test should be performed before infusion in all female patients with childbearing potential. If positive, withhold treatment.

DISABILITY
From the evidence available does the policy, procedure, proposal, strategy or service affect, or have the potential to affect, disabled people differently? Yes ☐ No X

Explain your response: Where there are communication difficulties of the patient/parent/guardian/carer the trust interpretation and translation policy will be followed. There are communication aids including picture communication books for people with learning disabilities etc in the ward communications box.
AGE:
From the evidence available does the policy, procedure, proposal, strategy or service, affect, or have the potential to affect, age groups differently?    Yes  X  No □
Explain your response: This is a policy for paediatric patients and the doses contained within it are only applicable to the relevant age groups. Pregnancy test should be performed before infusion in all female patients with childbearing potential. If positive, withhold treatment.

LESBIAN, GAY, BISEXUAL:
From the evidence available does the policy, procedure, proposal, strategy or service affect, or have the potential to affect, lesbian, gay or bisexual groups differently?    Yes □  No X
Explain your response: No impacts identified.

RELIGION/BELIEF:
From the evidence available does the policy, procedure, proposal, strategy or service affect, or have the potential to affect, religious belief groups differently?    Yes □  No X
Explain your response: Where there are patient/parent /guardian/carer of a religious belief where certain substances cannot be consumed, then staff will always check with pharmacy the content of those drugs.

CARERS:
From the evidence available does the policy, procedure, proposal, strategy or service affect, or have the potential to affect, carers differently?    Yes X  No □
Explain your response: The use of zoledronic acid instead of pamidronate will mean that parents/carers will spend less time in hospital with the patient as the drug is given more quickly and less often. See also sections on age and disability.

OTHER: EG Pregnant women, people in civil partnerships, human rights issues.
From the evidence available does the policy, procedure, proposal, strategy or service affect, or have the potential to affect any other groups differently?    Yes x  No □
Explain your response: Pregnancy test should be performed before infusion in all female patients with childbearing potential. If positive, withhold treatment.

3. Safeguarding Assessment - CHILDREN

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Is there a direct or indirect impact upon children?</td>
<td>Yes X  No □</td>
<td></td>
</tr>
<tr>
<td>b. If yes please describe the nature and level of the impact (consideration to be given to all children; children in a specific group or area, or individual children. As well as consideration of impact now or in the future; competing / conflicting impact between different groups of children and young people:</td>
<td>The use of zoledronic acid instead of pamidronate will mean that children will spend less time in hospital as the drug is given more quickly and less often.</td>
<td></td>
</tr>
<tr>
<td>c. If no please describe why there is considered to be no impact / significant impact on children</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. Relevant consultation
Having identified key groups, how have you consulted with them to find out their views and that the made sure that the policy, procedure, proposal, strategy or service will affect them in the way that you intend? Have you spoken to staff groups, charities, national organisations etc?
5. Date completed:  11/02/2014   Review Date:

6. Any actions identified:  Have you identified any work which you will need to do in the future to ensure that the document has no adverse impact?

<table>
<thead>
<tr>
<th>Action</th>
<th>Lead</th>
<th>Date to be Achieved</th>
</tr>
</thead>
</table>

7. Approval – At this point, you should forward the template to the Trust Equality and Diversity Lead lynbailey@nhs.net

Approved by Trust Equality and Diversity Lead:

[Signature]

Date:  12.2.14