Hypercalcaemia

Introduction
Hypercalcaemia is a raised level of corrected calcium in the blood. It is the commonest life-threatening metabolic disorder in cancer patients, most frequently occurring in myeloma, breast, renal, lung and thyroid cancers however, 20% of patients with hypercalcaemia do not have bone metastases.

Assessment

Signs and symptoms
- Common symptoms include malaise, weakness, anorexia, thirst, nausea, constipation and polyuria
- Severe symptoms include nausea, vomiting, ileus, delirium, seizures, drowsiness and coma
- Pain can be precipitated or exacerbated by hypercalcaemia
- Onset of symptoms raising clinical suspicion should be investigated. Bloods should be checked for urea and electrolytes (U&Es), estimated glomerular filtration rate (eGFR), liver function tests (LFT's) and calcium.

Points to consider prior to treatment
- First episode or long interval since previous episode
- Patient reports good quality of life prior to episode
- Multi-disciplinary team expectation is that treatment will have durable effect
- Patient is willing and able to have intravenous treatment and blood tests
- Treatment may not be appropriate in a dying patient at the end of life – seek advice.

Management

Bisphosphonates and duration of action

<table>
<thead>
<tr>
<th></th>
<th>zoledronic acid</th>
<th>disodium pamidronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous (IV) dose</td>
<td>4mg</td>
<td>30 to 90mg</td>
</tr>
<tr>
<td>Onset of effect</td>
<td>&lt;4 days</td>
<td>&lt;3 days</td>
</tr>
<tr>
<td>Maximum effect</td>
<td>4 to 7 days</td>
<td>5 to 7 days</td>
</tr>
<tr>
<td>Duration of effect</td>
<td>4 weeks</td>
<td>2.5 weeks</td>
</tr>
</tbody>
</table>

Corrected calcium = Measured calcium +0.022 x (40 - serum albumin g/l)

Treatment
- The aim of treatment is to improve symptoms and reduce corrected calcium level to within the normal range
- Normal corrected calcium value 2.12 to 2.62mmol/l (locally defined ranges will apply)
- IV fluid replacement and IV bisphosphonates are treatments of choice
- The choice of bisphosphonate may be determined by local policy (such as disodium pamidronate/zoledronic acid). Refer to local formulary
- To reduce risk of renal toxicity from bisphosphonate treatment, consider withholding medication that affects the renal function (eg non-steroidal anti-inflammatory drugs, diuretics, thiazide diuretics, angiotensin-converting enzyme inhibitors).

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1 Corrected calcium = Measured calcium +0.022 x (40 - serum albumin g/l)
Practice Points

- If the patient is asymptomatic with corrected calcium * between 2.62 mmol/l and <2.8 mmol/l, rehydrate with fluids and review as per Table 1
- Explain signs, symptoms and treatment options to the patient, family and carers
- Not all symptoms resolve after treatment. This may be due to other cause(s) or underlying disseminated disease
- Bisphosphonates may cause mild flu-like symptoms
- Bisphosphonates are implicated risk factors in osteonecrosis of the jaw, osteonecrosis of the auditory canal and atypical fractures
- Where possible, patients should have regular dental checks and avoid invasive dental procedures whilst on treatment
- The severity of symptoms is related to the rate of increase; not the level of corrected calcium
- The speed of recurrence may signify a poor prognosis
- Review current treatments for underlying disease
- Untreated severe hypercalcaemia can be fatal.

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* Indicates this use is off licence
\[\text{Corrected calcium} = \text{Measured calcium} + 0.022 \times (40 - \text{serum albumin g/l})\]
Check calcium, U&Es, eGFR and albumin

Corrected Calcium* >4.0mmol/l
Severe hypercalcaemia can cause seizures or arrhythmias - seek consultant advice

Corrected Calcium* 2.62 to 4.0mmol/l
Rehydrate with 1 to 3 litres of NaCl IV - check calcium, U&E next morning

Corrected Calcium* normal
Monitor risk if patient at risk for hypercalcaemia

Calcium remains raised - treat as per Table 1
Continue IV fluids until patient able to maintain hydration
Monitor renal function

Calcium has increased from pre-treatment level after rehydration and bisphosphonate
Seek advice; review diagnosis and treatment plan

Calcium has decreased from pre-treatment but is still elevated
Recheck Calcium after 5 days

Maintain good hydration; recheck calcium after 2- days. Do not repeat bisphosphonate until 7 days after first dose to avoid causing hypocalcaemia

<table>
<thead>
<tr>
<th>Corrected calcium* (mmol/l)</th>
<th>Drug &amp; Dose</th>
<th>Diluent and maximum infusion rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.62 to 3.0</td>
<td>disodium pamidronate</td>
<td>15mg to 30mg 500ml NaCl 0.9% over &gt; 60 minutes</td>
</tr>
<tr>
<td>3.0 to 3.5</td>
<td></td>
<td>60mg 500ml NaCl 0.9% over &gt; 60 minutes</td>
</tr>
<tr>
<td>3.5 to 4.0</td>
<td></td>
<td>90mg 500ml NaCl 0.9% over &gt; 90 minutes</td>
</tr>
<tr>
<td>&gt;4.0</td>
<td></td>
<td>90mg 500ml NaCl 0.9% over &gt; 90 minutes</td>
</tr>
<tr>
<td>&gt;3.00</td>
<td>zoledronic acid</td>
<td>4mg 100ml NaCl 0.9% over 15 minutes</td>
</tr>
</tbody>
</table>

Table 1 - Bisphosphonate treatment for Hypercalcaemia

If corrected calcium >3.0mmol/l, some units routinely give pamidronate 90mg as a higher dose.
Reduced doses in renal impairment

Disodium pamidronate in renal impairment, seek advice
- eGFR > 30ml/min: Minimum infusion period 90 minutes, maximum infusion rate 20mg/hour: consider dose reduction.
- eGFR < 30ml/min: avoid except in life threatening hypercalcaemia where specialist advice should be sought to determine if benefit outweighs risk.

Zoledronic acid in renal impairment
- Patients with tumour induced hypercalcaemia (TIH) and deteriorating renal function should be appropriately assessed to determine if the potential benefit of treatment with zoledronic acid outweighs the possible risk.
- After 24 - 48 hours of rehydration, consider a single IV dose of zoledronic acid 4 mg in 100 ml sodium chloride 0.9% over ≥ 15 minutes. N.B Dose alteration may not be needed in mild to moderate renal impairment in patients with TIH (i.e. eGFR >30ml/min)
- Avoid if eGFR <30ml/min, see Summary of Product Characteristics (www.medicines.org.uk) for further details.

Resources

Guidelines

Patient and professional website resources
- Palliativedrugs.com www.palliativedrugs.com
- Summary of product characteristics, Zometa 4mg/5ml Concentrate for Solution for Infusion www.medicines.org.uk/EMC/medicine/14062/SPC/Zometa+4mg+5ml+Concentrate+for+Solution+for+Infusion/
- SPC for disodium pamidronate: www.medicines.org.uk/emc/medicine/16939

Textbooks
- Palliative Care Formulary 4th edition (PCF4) 2011 Endocrine system and immunomodulation p469-479
- British National Formulary 65 (BNF) 2013 6.6.2 Bisphosphonates and other drugs affecting bone metabolism p491-495