Hypercalcaemia

Introduction

Hypercalcaemia is a raised level of corrected calcium\(^1\) 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 (LFTs) and calcium.

**eGFR Caution Note**

- The use of creatinine-based equations will lead to an overestimation of the Creatinine Clearance (CrCl) and eGFR in individuals with reduced body size or muscle mass, e.g. frail, elderly, critically ill or patients with cancer or muscle wasting diseases. The absolute GFR or CrCl calculated by the Cockcroft & Gault formula should be used to adjust drug dosages in patients at extremes of body weight (BMI <18.5kg/m\(^2\) or >30kg/m\(^2\)). If using C&G for these patients it may be necessary to base the calculation on ideal body weight or adjusted body weight, see below.

**Estimation of creatinine clearance (CrCl)**

- The following 'Cockcroft Gault' equation can be used to estimate creatinine clearance (CrCl).

\[
CrCl \text{ (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)} \times 1.23 \text{ (male)} \text{ OR } x 1.04 \text{ (female)}}{\text{serum creatinine (micromol/L)}}
\]

**Caution**

- Use actual body weight or maximum body weight whichever is lower. Refer to: [https://www.sapg.scot/media/4471/maximum-body-weight-table.pdf](https://www.sapg.scot/media/4471/maximum-body-weight-table.pdf)
- In patients with low creatinine (<60 micromol/L), use 60 micromol/L.

\(^1\)Corrected calcium = Measured calcium +0.022 x (40 - serum albumin g/l)
• Use of estimated glomerular filtration rate (eGFR) is not recommended.

**Points to consider prior to treatment**

• First episode or long interval since previous episode.
• Patient reports good quality of life prior to episode.
• Multidisciplinary 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>
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**Treatment**

• The aim of treatment is to improve symptoms and reduce corrected calcium\(^1\) level to within the normal range.
• Normal corrected calcium value\(^1\) 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 (for example non-steroidal anti-inflammatory drugs, diuretics, thiazide diuretics, angiotensin-converting enzyme inhibitors).

**Practice points**

• If the patient is asymptomatic with corrected calcium\(^1\) between 2.62 mmol/l and <2.8 mmol/l, rehydrate with fluids and review as per table above.
• 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.

### Corrected Calcium* (mmol/l)

<table>
<thead>
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<th>Diluent and maximum infusion rate</th>
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<td>500ml NaCl 0.9% over &gt; 90 minutes</td>
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<td>2.62 to 4.0</td>
<td>15mg to 30mg</td>
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**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
- Recheck Calcium after 5 days
- Calcium has decreased from pre-treatment but is still elevated

**Calcium normal**

- Maintain good hydration; recheck calcium after 2-3 days. Do not repeat bisphosphonate until 7 days after first dose to avoid causing hypocalcaemia

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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 4mg in 100ml sodium chloride 0.9% over ≥ 15 minutes. Dose alteration may not be needed in mild to moderate renal impairment in patients with TIH (ie eGFR >30ml/min).
- Avoid if eGFR <30ml/min, refer to Summary of Product Characteristics (SPCs) ([www.medicines.org.uk](http://www.medicines.org.uk)) for further details.

**Resources**

- SPC for Zometa 4mg/5ml Concentrate for Solution for Infusion: [www.medicines.org.uk/EMC/medicine/14062/SPC/Zometa+4mg+5ml+Concentrate+for+Solution+for+Infusion/](http://www.medicines.org.uk/EMC/medicine/14062/SPC/Zometa+4mg+5ml+Concentrate+for+Solution+for+Infusion/)
- SPC for Disodium Pamidronate: [https://www.medicines.org.uk/emc/search?q=disodium+pamidronate](https://www.medicines.org.uk/emc/search?q=disodium+pamidronate)
- UKMi (2016) What factors need to be considered when dosing patients with renal impairment?.