Solving intractable hypocalcaemic seizures with IV alfacalcidol, a lesson learnt in calcium metabolism?

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Purpose
This complex case highlights the multi-factorial causes of hypocalcaemia and the approach to its investigation and treatment. It also highlights the need for better communication when a complex multi-morbid patient is managed in both a tertiary centre and the local district general hospital.

Case report
• 67 years old, normally fit free, presented to Grantham District Hospital with the fourth episode of hypocalcaemia-induced seizures in 2013.
• Past medical history:
  - Renal transplant 3 years ago (for chronic kidney disease of unknown aetiology)
  - Living related donor transplant from daughter
  - Mastectomy for breast cancer
  - Colectomy for Ulcerative colitis 30 years ago with ileostomy
  - Malabsorption secondary to a high stoma output
  - Partial parathyroidectomy for secondary hyperparathyroidism 10 years ago (single gland retained)
• On admission, her medications included:
  - Tazorotrex 4mg bd.
  - Folic acid 5mg od
  - Oral Alfacalcidol 1mg od in divided doses
  - VI D2 3IM monthly injection 300,000 IU
  - Prednisolone 5mg od
  - Aspirin 75mg od
  - Propanolol 40mg bd
  - Hydrocortisone 1mg IM 3 monthly
  - SandoCal 1000 5 tabs QDS
  - Atorvastatin 10mg ON
  - Loperamide 4mg PRN
• Observation stable. Examination - unremarkable. Chvostek’s sign and Trousseau’s sign - negative. Scars consistent with previous surgery noted. Hickman line and ileostomy in situ.

Investigations
ECG – Normal sinus rhythm. No prolongation of QT interval.
CXR – No abnormality detected.

Table 1: Summary of admission blood results

<table>
<thead>
<tr>
<th>Blood test</th>
<th>Blood results</th>
<th>Normal ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted calcium</td>
<td>1.75mmol/L</td>
<td>2.2-2.6mmol/L</td>
</tr>
<tr>
<td>25-hydroxyvitamin D</td>
<td>35nmol/L</td>
<td>50-140nmol/L</td>
</tr>
<tr>
<td>Phosphate</td>
<td>1.88mmol/L</td>
<td>1.2-2.6mmol/L</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.65mmol/L</td>
<td>0.7-1.3mmol/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>137mmol/L</td>
<td>133-146mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.8mmol/L</td>
<td>3.5-5.5mmol/L</td>
</tr>
<tr>
<td>Urea</td>
<td>5.5mmol/L</td>
<td>2.5-7.1mmol/L</td>
</tr>
<tr>
<td>Creatinine</td>
<td>282umol/L</td>
<td>54-110umol/L</td>
</tr>
</tbody>
</table>

Figure 1: Adjusted serum calcium levels for MS in 2013-14. Attendances to A&E with seizures noted by arrows.

Figure 2: Algorithm for requesting investigations to elucidate the cause of Hypocalcaemia
(Below) Synthesis of Vitamin D²

Timeline showing the Calcium and Vitamin D treatments that the patient received in 2013:

<table>
<thead>
<tr>
<th>First fit</th>
<th>Second fit</th>
<th>Sandostatin 1000 5 tabs QDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO Alfacalcidol 12mcg daily</td>
<td>PO Alfacalcidol 5mcg daily</td>
<td>PO Alfacalcidol 10mcg daily</td>
</tr>
<tr>
<td>April</td>
<td>May</td>
<td>June</td>
</tr>
<tr>
<td>Pre-2013</td>
<td>March</td>
<td>January</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Third fit</th>
<th>Fourth fit</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO Alfacalcidol 16 mcg daily</td>
<td>PO Cholecalciferol 20,000 IU weekly</td>
</tr>
<tr>
<td>Sept</td>
<td>Oct</td>
</tr>
<tr>
<td>PO Alfacalcidol 2mcg 3 times weekly</td>
<td>PO Cholecalciferol 20,000 IU weekly</td>
</tr>
<tr>
<td>Nov</td>
<td>Dec</td>
</tr>
</tbody>
</table>

Management
• Previous stable dose of Alfacalcidol 12mcg daily had been reduced by tertiary renal team to 5mcg daily in Feb 2013 and not recognised by the local DGH.
• Patient treated with intravenous calcium gluconate and magnesium when Calcium levels dropped but levels dropped following discharge.
• Alfacalcidol 1000 was injection to 20 tablets daily to counter hypocalcaemia but made little difference.
• Intravenous infusion of magnesium sulphate was also unsuccessful.
• Intramuscular vitamin D3(cholecalciferol 300,000IU) tried, but was ineffective.
• Intravenous calcium gluconate and magnesium was unsuccessful at preventing fits and hypocalcaemia.
• Oral Alfacalcidol 2.5mg daily per week was prescribed and the dose was increased to 2mcg 3 times per week.
• Her Calcium levels rose and are now maintained within normal limits.
• Husband now administers Alfacalcidol through her Hickman line.

Discussion
Several factors contributed to patient’s profound hypocalcaemia:
1. Previous parathyroidectomy - low PTH levels
2. Colectomy with high stoma output - malabsorption of many medications and nutrients
3. Reduction of her stable dose of Alfacalcidol by the tertiary centre but patient presented with fits to her local hospital who did not have these records. Better information sharing is required between tertiary centres and local hospitals when dealing with complex patients (or alternatively patients should carry complex records)²
4. Suboptimal renal function – reduced capacity to activate Vitamin D
5. Vitamin D deficiency - due to a lack of sun exposure and malabsorption.

Intravenous Alfacalcidol, an analogue of vitamin D, is an elegant solution. Because vitamin D needs hydroxylation by kidney to its active form, hydroxylated derivative alfacalcidol is therefore used for people with chronic kidney diseases.

Teriparatide, a recombinant form of parathyroid hormone, was another option to consider but was avoided initially due to the patient’s history of low Vitamin D, the cost of treatment and its relative contraindication in patients with renal impairment.

References
3. Cooper MS, Gittos NIL. Diagnosis and management of hypocalcaemia. BMJ 2008;336:1298