Teaching Point
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Disturbed calcium metabolism in a patient with bipolar disorder and impaired renal function

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Introduction

In recent years, the identification of a calcium-sensing receptor (CaR) has provided new insight into disorders of calcium metabolism [1]. As well as being located in numerous extra-renal tissues such as the parathyroid glands, gastrointestinal tract and bone [1], these CaRs are found on the basolateral aspect of the epithelial cells of the thick ascending limb of the loop of Henle [2]. Here they respond to a rise in serum calcium by reducing the diffusion of potassium back into the tubular lumen (Figure 1). This results in a reduced electrical gradient between the lumen and the blood which reduces the passive paracellular flow of calcium (magnesium and sodium) back into the bloodstream and consequently calcium excretion in the urine is increased.

The CaR is, therefore, pivotal in maintaining blood calcium levels within the pre-determined range. In certain conditions, however, the pre-determined target range for calcium is set higher than normal, such that higher calcium levels are required in the peritubular space to downregulate the reabsorption of calcium in the renal tubule and in the parathyroid gland to suppress parathyroid hormone (PTH) secretion. In adults, the clinical picture in these conditions is usually one of asymptomatic mild hypercalcaemia and hyperparathyroidism, with patients being identified when blood is taken for other purposes.

We present a case where a basic understanding of calcium handling in the kidney as well as an awareness of function of the CaR helped simplify a case which was otherwise becoming increasingly complex.

Case

A 61-year-old male was referred for investigation of renal impairment (serum creatinine 300 μmol/l) by a neighbouring psychiatric hospital. He had been on lithium therapy for 30 years for bipolar disorder and his serum creatinine was known to have been 257 μmol/l 3 years previously. Besides a history of moderate alcohol consumption, he had no other medical complaints and his only medication at the time of review was sodium valproate which had been instituted in place of the lithium at the time of the referral. Clinical examination revealed only hypertension, with a blood pressure of 160/86 mmHg, and urinalysis showed blood 1+, protein 1+ and glucose 2+.

Investigations showed his serum creatinine to be 270 μmol/l, adjusted calcium 2.85 mmol/l (normal 2.13–2.63), phosphate normal, random blood glucose 8.6 mmol/l and intact PTH (iPTH) 32.2 pmol/l (normal 0.9–5.4). Immunoglobulins and autoimmune profile were normal. Both kidneys were normal sized but echogenic on ultrasound.

The renal impairment was considered likely to be secondary to the long-term lithium therapy, but the inappropriately high serum calcium level for the degree of renal impairment raised the possibility of primary hyperparathyroidism (PHP). Hand X-rays showed no evidence of hyperparathyroidism, but a parathyroid subtraction scan demonstrated increased activity in the region of the left upper parathyroid gland (Figure 2) and the patient was referred to a parathyroid surgeon. The surgeons arranged a 24 h urine collection for calcium and found the urine calcium to be low at <2.4 mmol/24 h (urine volume 4879 ml) (the report quoted a normal range of 2.5–7.5 mmol/24 h as normal). The patient was referred back to the nephrologists for investigation of his hypercalcaemia with hypocalciuria.
Interpretation and discussion

Hypercalcaemia and hypocalciuria occur together in three situations: the milk-alkali syndrome, patients taking a thiazide diuretic and conditions associated with downregulation of the CaR. The first two diagnoses could be excluded from the history and other laboratory data. However, before concluding that this patient has a condition associated with reduced CaR sensitivity, we must return several steps to the urinary calcium and consider how calcium is excreted by the kidneys.

Although formulae are available to adjust urinary calcium for renal function, it is helpful to first work through the basics in a more transparent way. If we know a patient’s glomerular filtration rate (GFR) and serum calcium level, and remember that 40% of circulating calcium is protein bound and therefore not filtered by the kidneys, we can estimate the total amount of calcium filtered by the kidneys per day (Box 1). In health, 97–99% of this filtered calcium is then reabsorbed in the tubule, so that only 1–3% of filtered calcium is excreted in the urine. When serum calcium levels increase, as occurs in PHP, this is recognized by the CaR which sends signals to reduce the amount of calcium reabsorbed from the tubule into the blood stream, and therefore increase calciuresis. As a result, patients with PHP tend to reabsorb less of their filtered calcium load; 40% of patients with PHP reabsorb <97% of filtered calcium per day and the rest will reabsorb <99% [3]. In conditions associated with impaired CaR sensitivity, the same levels of hypercalcaemia do not stimulate the CaR (indeed the CaR still interprets calcium levels as being at the low end of normal). Consequently, maximal calcium reabsorption into the blood stream continues, with >99% of filtered calcium reabsorbed [3]. Because it has been well studied, the autosomal dominant familial hypocalciuric hypercalcaemia (FHH) is taken to represent conditions associated with impaired CaR sensitivity in the worked examples (Boxes 1 and 2).

When we then adjust for the level of renal function and consider the patterns of calcium reabsorption in the diagnoses being considered, we can see that the 24 h urinary calcium result of < 2.4 is unhelpful in distinguishing between PHP and reduced CaR sensitivity (Box 2).

Based on these principles, the calcium to creatinine clearance ratio (Ca:Cr clearance ratio) has long been proposed to improve discrimination between PHP and conditions of reduced CaR sensitivity [4].

\[
\text{Ca : Cr clearance ratio} = \frac{\text{U[Ca]} \times \text{P[Cr]}}{\text{P[Ca]} \times \text{U[Cr]}}
\]

where \( \text{U} \) = urinary, \( \text{P} \) = plasma, [Ca] = calcium concentration and [Cr] = creatinine concentration.

With this formula, most patients with PHP have a Ca:Cr clearance ratio of >0.02, whereas patients with impaired CaR sensitivity will tend to have Ca:Cr clearance ratios <0.01 [4]. The Ca:Cr clearance ratio in our patient was <0.01.
Calcium excretion in our patient with renal impairment

Box 2. Calcium excretion in our patient with renal impairment

<table>
<thead>
<tr>
<th>Serum calcium</th>
<th>2.8 mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6 × 2.8 = 1.68 mmol of calcium filtered per litre</td>
<td></td>
</tr>
<tr>
<td>If the GFR = 40 ml/min, the total volume filtered by the kidneys per day is:</td>
<td></td>
</tr>
<tr>
<td>40 × 60 min × 24 h = 60 l</td>
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<tr>
<td>The total amount of calcium filtered by the kidneys per day is therefore</td>
<td></td>
</tr>
<tr>
<td>60 × 1.68 = 100 mmol</td>
<td></td>
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<tr>
<td>Normal: (97–99%) urinary calcium excretion = 1.0–3.0 mmol/24 h</td>
<td></td>
</tr>
<tr>
<td>FHH: (&gt;99%) urinary calcium excretion &lt;1.0 mmol/24 h</td>
<td></td>
</tr>
<tr>
<td>PHP: (&lt;99%) urinary calcium excretion &gt;1.0 mmol/24 h</td>
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The patient’s lithium therapy is, of course, also relevant to the discussion. As well as being associated with renal impairment, lithium enhances PTH secretion and reduces urinary calcium excretion such that 10–20% of patients on long-term lithium are hypercalcaemic [5]. Furthermore, 6% of patients on long-term lithium develop hyperparathyroidism [6] and a smaller percentage of patients have hyperplasia or nodules in the parathyroid glands [5, 7]. How much this represents the unmasking of a predisposition to PHP remains unclear.

Before considering how lithium might interfere with calcium and PTH homeostasis, we must briefly review the sequence of intracellular signals that controls PTH secretion. PTH secretion by parathyroid cells is reduced in response to raised intracellular calcium concentration released from cytoplasmic calciosomes. This release of intracellular calcium has been triggered by inositol monophosphate (IP1) and inositol 1,4,5-triphosphate (IP3)–phosphoinositol (PI) signalling, which are produced by the hydrolysis of phosphatidylinositol bisphosphate (PIP2). It is the rate of this step, the hydrolysis of PIP2, which is controlled by the CaR in the cell membrane [8].

The effects of lithium on intracellular enzymes have been thoroughly studied by those seeking to explain its mechanism of action in bipolar disorder (for a recent review, see [9]). Among the list of intracellular enzymes inhibited by lithium are inositol phosphate phosphatase (IPPase) and inositol monophosphatase (IMPase)—enzymes which appear critical in the recycling of IP3 to inositol and therefore the continuation of the PI signalling. One possible explanation for the mechanism of action of lithium is the ‘inositol depletion hypothesis’, which suggests that lithium exerts some of its therapeutic and side effect actions by depleting free inositol—the substrate required for PI signalling (reviewed in Quiroz et al. [9]). Two studies, however, are against this explanation. Firstly, McHenry et al. [8] has shown no difference in IP1 and IP3 levels between lithium-treated and control bovine parathyroid cells, and argues that this suggests that lithium is acting lower down the signalling pathway. More recently, Berry et al. found that reducing the substrate for PI signalling, intracellular inositol, in the brains of sodium-myo-inositol knockout mice has no effect on PI levels [10]. The mechanism of action of lithium on calcium sensing therefore remains undetermined, but appears unlikely to be mediated at the level of the CaR or even its second messenger system—PI signalling. Nonetheless, the result of the reduced sensitivity to calcium observed in some patients on chronic lithium therapy is a shift in the Ca–PTH response curve to the right, causing a picture very similar to FHH [11].

Despite having discontinued lithium for 6 months, this patient’s calcium and iPTH levels remained elevated. In light of the area of increased activity in his left upper parathyroid gland on the subtraction scan, he was referred for surgery. Histology confirmed a 1.54 g parathyroid adenoma with no evidence of malignancy. His serum calcium is now, 81 months later, within the normal range (2.57 mmol/l, normal range 2.13–2.63), his phosphate remains normal, but his iPTH remains elevated at 36.8 pmol/l, suggesting that he still has parathyroid gland hyperplasia. Whether this is related to a persisting effect of lithium on the Ca–PTH response curve is unknown.

Teaching points

1. Urinary calcium excretion must be adjusted for GFR before hypocalciuria can be established.
2. Lithium therapy is associated with hypercalcaemia, hypocalciuria and hyperparathyroidism in a proportion of patients by shifting the Ca–PTH response curve to the right. Although this pattern is similar to that seen in FHH, the site of action of lithium appears to be beyond the CaR at the intracellular level.

Conflict of interest statement. None declared.

References


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