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Hypomagnesemia and hypokalemia: a successful oral therapeutic approach after 16 years of potassium and magnesium intravenous replacement therapy

Mihran Naljayan1, Suresh Kumar2, Theodore Steinman3 and Efrain Reisin2

1Division of Nephrology and Hypertension, Department of Medicine, Louisiana State University Health Sciences Center, New Orleans, LA, USA, 2Division of Nephrology and Hypertension, Louisiana State University Health Sciences Center, New Orleans, LA, USA and 3Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA, USA

Correspondence and offprint requests to: Mihran Naljayan; E-mail: mnalj1@lsuhsc.edu

Keywords: electrolyte disturbance; hypokalemia; hypomagnesemia

Introduction

Electrolyte abnormalities are very common problems in clinical practice, and if chronic, their management can be difficult. Hypokalemia, defined as a serum potassium level <3.5 mmol/L, is an exceptionally common electrolyte abnormality encountered in clinical practice; >20% of hospitalized patients have been reported to have some degree of hypokalemia [1]. Hypomagnesemia is also common and has been observed in as many as 50% of critically ill and Intensive Care Unit patients [2].

Patients with severe electrolyte deficiencies may be treated with intravenous (IV) or oral replacement regimens. We discuss a case in which a patient was treated for 16 years with an IV electrolyte replacement regimen. Using a stepwise approach, we were able to stop the IV replacement therapy and transition the patient to an oral electrolyte replacement.

Case report

A 25-year-old woman with a history of chronic hypokalemic metabolic alkalosis and hypomagnesemia following chemotherapy and radiation at the age of 2 for a yolk sac tumor was referred to our clinic. She had recently moved to our area and had a peripherally inserted central catheter line in place for the IV infusion therapy of potassium and magnesium that had been prescribed by her previous physicians. She wanted to establish care with us to continue these IV infusions.

The patient had episodes of muscle weakness and fatigue secondary to her electrolyte abnormalities and was started on IV replacement therapy. Her serum potassium (K) and magnesium (Mg) levels ranged between 2.2–3.1 and 0.35–0.60 mmol/L, respectively, throughout her management with IV potassium chloride (60 mEq) and magnesium sulfate (3 g) replacement administered three times a week. Initially, gastrointestinal causes for her diarrhea were excluded; ongoing diarrhea was attributed to the use of oral magnesium oxide prescribed to supplement the IV magnesium.

During her first visit with us, she was noted to have a normal blood pressure of 124/80 mmHg and a heart rate of 72 beats per minute. She was 167 cm in height and 50 kg in weight. Her exam was otherwise within normal limits.

After our first encounter with the patient, she underwent an extensive workup that included serum and urine studies. Her results suggested renal losses of K and Mg as the cause of her electrolyte abnormalities (see Table 1). Urinalysis was normal without any evidence of hematuria or proteinuria. A renal ultrasound performed at that time revealed a kidney size of 9.1 by 4.5 by 3.3 cm on the right and 10.2 by 5.2 by 6.2 cm on the left; otherwise, the results were normal and no other normal abnormalities were noted.

In order to decrease the urine electrolyte wasting, and with the objective of keeping the patient only on an oral K–Mg replacement regimen, we recommended a high-potassium diet and started the following pharmacological approaches that were introduced one at a time in intermittent visits: oral benazepril up to 5 mg daily, amiloride 5 mg daily, magnesium chloride 192 mg daily and, eventually, potassium chloride 60 mEq daily. The sitting blood pressure remained at normal levels (122/80 mmHg), and the orthostatic measurement was 140/98 mmHg supine and 138/96 mmHg standing. The diarrhea improved on this regimen, and the levels of K and Mg were maintained at 3.1 and 0.6 mmol/L, respectively, for >1 year without the need for IV replacement (Table 2).

During one of her clinic visits in the second year of follow-up, the patient reported that she had switched back to magnesium oxide on her own accord due to the...
Table 1. Initial laboratory results when patient first presented to our clinic for evaluation

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renin</td>
<td>2.3 ng/mL/h (0.5–4.0 ng/mL/h)</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>7.5 ng/dL (&lt;31.0 ng/dL)</td>
</tr>
<tr>
<td>24-h urine aldosterone</td>
<td>338.4 pmol/L (55–250 pmol/L)</td>
</tr>
<tr>
<td>24-h urine potassium</td>
<td>50.6 mmol/day</td>
</tr>
<tr>
<td>24-h urine magnesium</td>
<td>6.4 mmol/day</td>
</tr>
<tr>
<td>24-h urine creatinine</td>
<td>10.59 mmol/day</td>
</tr>
<tr>
<td>Potassium (serum)</td>
<td>3.2 mmol/dL (3.5–5.0 mmol/L)</td>
</tr>
<tr>
<td>Magnesium (serum)</td>
<td>0.32 mmol/L (0.7–1.05 mmol/L)</td>
</tr>
<tr>
<td>Cortisol</td>
<td>39±5.5 mmol/L (340–690 mmol/mL)</td>
</tr>
<tr>
<td>ACTH</td>
<td>2.86 pmol/mL (1.32–12.1 pmol/mL)</td>
</tr>
<tr>
<td>TTG</td>
<td>4.97</td>
</tr>
<tr>
<td>Uric acid</td>
<td>481.8 μmol/L (178–487 μmol/L)</td>
</tr>
<tr>
<td>24-h urine uric acid</td>
<td>4.16 mmol/day (1.48–4.44 mmol/day)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>1.4 mmol/L (0.81–1.45 mmol/L)</td>
</tr>
<tr>
<td>Calcium (serum)</td>
<td>2.5 mmol/L (2.12–2.57 mmol/mL)</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>1.3 pmol/L (1.2–5.9 pmol/L)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>50.44 μmol/L (&lt;106 μmol/L)</td>
</tr>
</tbody>
</table>

ACTH, adrenocorticotropic hormone; TTG, transtubular potassium gradient.

Table 2. Timeline of events

<table>
<thead>
<tr>
<th>Visit date</th>
<th>Regimen</th>
<th>K (mmol/L)</th>
<th>Mg (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 April 2009</td>
<td>IV potassium and magnesium; start oral Mg oxide and oral KCl</td>
<td>3.1</td>
<td>0.45</td>
</tr>
<tr>
<td>13 May 2009</td>
<td>Benazepril 2.5 mg/day and high K diet</td>
<td>3.8</td>
<td>0.53</td>
</tr>
<tr>
<td>17 June 2009</td>
<td>Benazepril 5 mg/day</td>
<td>3.8</td>
<td>0.53</td>
</tr>
<tr>
<td>8 July 2009</td>
<td>No IV replacement in 2 months; asked to start MgCl</td>
<td>3.7</td>
<td>0.53</td>
</tr>
<tr>
<td>30 September 2009</td>
<td>No changes to regimen with high K diet</td>
<td>3.8</td>
<td>0.49</td>
</tr>
<tr>
<td>6 January 2010</td>
<td>Increase MgCl to three tablets a day; KCl 10 mEq twice daily</td>
<td>3.8</td>
<td>0.49</td>
</tr>
<tr>
<td>8 September 2010</td>
<td>Increase KCl to 20 mEq twice daily</td>
<td>3.7</td>
<td>0.45</td>
</tr>
<tr>
<td>8 December 2010</td>
<td>Had cervical biopsy; started taking PO Mg oxide due to cost</td>
<td>3.7</td>
<td>0.45</td>
</tr>
<tr>
<td>18 July 2011</td>
<td>EGD showed slight villous atrophy; starts low-gluten diet</td>
<td>3.7</td>
<td>0.45</td>
</tr>
<tr>
<td>14 January 2012</td>
<td>No IV replacement needed for 38 months; restart MgCl</td>
<td>3.7</td>
<td>0.45</td>
</tr>
</tbody>
</table>

EGD, endoscopy.

Discussion

Physicians must be thorough when evaluating electrolyte disorders in order to determine the underlying etiology for such a disturbance.

Hypokalemia can be caused by insufficient potassium intake, transcellular shift of potassium from the extracellular to intracellular compartments or excessive potassium loss. The renal and gastrointestinal systems are the primary sites of excess potassium loss from the body. Potassium losses via the gastrointestinal tract are likely the second most common cause of hypokalemia in developed countries, and increased stool volumes will increase the amount of potassium lost and can result in hypokalemia [1].

Hypokalemia is a very common electrolyte abnormality and, when chronic, can cause a variety of renal problems, including impairments of tubular transport, chronic tubulointerstitial disease and cyst formation [3, 4].

Chemotherapy with cisplatin is known to cause hypokalemia and hypomagnesemia with metabolic alkalosis as a possible complication [5, 6]. Cisplatin is a coordinate metal complex with significant antineoplastic activity, and its side effects include acute and chronic renal insufficiency, renal magnesium wasting and electrolyte disturbances like hypomagnesemia, hypocalcemia, hypophosphatemia and hypokalemia [6]. In one rat model with unilateral nephrectomy, cisplatin combined with radiation led to alterations in urine osmolality and volume due to tubular damage, which was histopathologically evident [7]. Treatment approaches should be appropriate and specific to the underlying cause for the disturbance. In this case, we noted renal wasting of potassium and magnesium, likely due to a tubulopathy secondary to the patient’s previous exposure to chemotherapy and radiation for her yolk sac tumor.

When evaluating causes of hypokalemia, a physician must also address other underlying causes of the hypokalemia, such as volume depletion and hypomagnesemia. Asymptomatic and mild hypokalemia can be treated with a potassium-rich diet, whereas symptomatic or severe hypokalemia requires oral or IV potassium [8, 9].

As was evident with our patient, other agents may also be used to correct hypokalemia. These include angiotensin-converting enzyme (ACE) inhibitors, which decrease angiotensin II with a subsequent decrease in aldosterone secretion resulting in increased serum potassium levels [9]. Amiloride, a potassium-sparing diuretic, can also be used by the same principle; it blocks the epithelial sodium channel and therefore causes sodium wasting without concomitant potassium wasting as seen with loop or thiazide diuretics.

Hypomagnesemia is also a serious electrolyte disorder, particularly with severe cardiac effects. Magnesium homeostasis is tightly controlled by intestinal absorption from diet and by renal excretion or reabsorption mechanisms [10]. Approximately one-third of dietary magnesium is absorbed principally in the small bowel, and ~100 mg is excreted in the urine [11]. Magnesium ions are freely filtered in the glomerulus, and unlike other ions, only a small fraction (~10%) is reabsorbed in the proximal tubule. The majority of the filtered magnesium, 50–70%, is reabsorbed in the thick ascending limb (TAL) of Henle’s loop via paracellular pathways and in the distal tubule via transcellular pathways. The driving force for Mg reabsorption in the TAL of the nephron is the positive transluminal epithelial voltage generated by potassium.
recycling across the apical membrane [12]. There is also
distal active transcellular Mg reabsorption, which depends
on the epithelial Mg TRPM6 channel [13] and plays a
pivotal role in regulating the urinary electrolyte excretion
rate [14].

In the cases of severe (<0.5 mmol/L in the serum) and
symptomatic hypomagnesemia with neuromuscular or
neurologic manifestations or cardiac arrhythmias, Mg
repletion should be achieved by IV administration of mag-
nesium sulfate. Maintenance therapy may require the oral
administration of magnesium oxide (400 mg two or three
times daily) or magnesium gluconate (500 mg two or
three times daily). Magnesium oxide is the most readily
available form of magnesium supplementation, but it has
the least bioavailability. One study showed the fractional
absorption of magnesium oxide to be 4%, as opposed to
magnesium chloride’s significantly higher percentage
[15]. All magnesium supplements can cause some diar-
rhea, but mineral magnesium is typically the best toler-
ated, likely due to the lower dose necessary to achieve
therapeutic magnesium concentrations.

Amiloride is also useful for the treatment of hypomag-
sesemia because of the increases in magnesium reab-
sorption in the cortical collecting duct. It is particularly
useful in treating Gitelman’s or Bartter’s syndrome, as well
as in combating the renal Mg wasting associated with cis-
platin [6].

Conclusions

We carefully explored the possibility of secondary causes
for K and Mg losses and used a stepwise approach that in-
cluded a potassium-rich diet, ACE-I, amiloride and over-
the-counter magnesium chloride and potassium sup-
plements to treat the patient. Maintenance therapy may require the oral
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Teaching points

(i) When evaluating electrolyte abnormalities, physicians
must do a thorough history and physical exam, as well as serum and urine electrochemical testing,
in order to ascertain the etiology of the electrolyte
 disturbance.

(ii) Treatment of electrolyte disturbances can be done
either orally or intravenously. IV therapy should be
reserved for serious or life-threatening electrolyte dis-
turbances; otherwise, outpatient therapy should focus
on oral replacement if possible.

(iii) Other options besides electrolyte repletion are avail-
able to maintain homeostasis in the body. By under-
standing the physiologic pathways of electrolyte
alterations, one may determine other therapeutic
options to treat such abnormalities.

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