CKJ

Teaching Point
(Section Editor: W. Herrington)

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

Mihran Naljayan[1], Suresh Kumar[2], Theodore Steinman[3] and Efrain Reisin[2]

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

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

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.

In the 23 years since her chemotherapy, multiple physicians had treated this patient. Starting at the age of 9, she 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 with in 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

Renin	2.3 ng/mL/h (0.5–4.0 ng/mL/h)
Aldosterone	7.5 ng/dL (<31.0 ng/dL)
24-h urine aldosterone	338.4 pmol/L (55–250 pmol/L)
24-h urine potassium	50.6 mmol/day
24-h urine magnesium	6.4 mmol/day
24-h urine creatinine	10.59 mmol/day
Potassium (serum)	3.2 mmol/dL (3.5–5.0 mmol/L)
Magnesium (serum)	0.32 mmol/L (0.7–1.05 mmol/L)
Cortisol	394.5 nmol/mL (140–690 nmol/mL)
ACTH	2.86 pmol/mL (1.32–12.1 pmol/mL)
TTKG	4.97
Uric acid	481.8 μmol/L (178–487 μmol/L)
24-h urine uric acid	4.16 mmol/day (1.48–4.44 mmol/day)
Phosphorus	1.4 mmol/L (0.81–1.45 mmol/L)
Calcium (serum)	2.5 mmol/L (2.12–2.57 mmol/L)
Parathyroid hormone	1.3 pmol/L (1.2–5.9 pmol/L)
Creatinine	50.4 μmol/L (<106 μmol/L)

ACTH, adrenocorticotropic hormone; TTKG, transtubular potassium gradient.

Table 2. Timeline of events

Visit date	Regimen	K (mmol/L)	Mg (mmol/L)
9 April 2009	IV potassium and magnesium; start oral Mg oxide and oral KCl	3.1	0.45
13 May 2009	Benazepril 2.5 mg/day and high K diet		
17 June 2009	Benazepril 5 mg/day		
8 July 2009	Amiloride 5 mg/day	3.8	0.53
30 September 2009	No IV replacement in 2 months; asked to start MgCl 18 mEq/day	3.7	0.53
6 January 2010	No IV in 6 months	3.6	0.45
5 May 2010	No changes to regimen	3.8	0.49
8 September 2010	Increase MgCl to three tablets a day; KCl 10 mEq twice daily		
8 December 2010	Increase KCl to 20 mEq twice daily	3.7	0.45
18 July 2011	Had cervical biopsy, started taking PO Mg oxide due to cost	3.7	
14 January 2012	EGD showed slight villous atrophy; starts low-gluten diet		0.45
13 August 2012	No IV replacement needed for 38 months		

EGD, endoscopy.

high cost of the magnesium chloride, but this seemed to worsen her diarrhea, and her magnesium levels were low again at 0.45 mmol/L. Following our recommendation, she restarted the magnesium chloride, with subsequent improvement in her diarrhea and an increase in her magnesium level to 0.55 mmol/L.

More than 2 years after presenting to us, she had a repeat endoscopy due to her ongoing diarrhea, which, although improved, was still present to a mild effect. The biopsy showed very slight villous atrophy in the small intestine, consistent with mild gluten enteropathy. After the patient was placed on a gluten-free diet, her diarrhea resolved. At this point, she had been on an oral replacement regimen for >36 months and no longer required IV replacement therapy.

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 magnesium 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 diarrhea, but magnesium chloride is typically the best tolerated, likely due to the lower dose necessary to achieve therapeutic magnesium concentrations.

Amiloride is also useful for the treatment of hypomagnesemia because of the increases in magnesium reabsorption 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 cisplatin [6].

Conclusions

We carefully explored the possibility of secondary causes for K and Mg losses and used a stepwise approach that included a potassium-rich diet, ACE-I, amiloride and over-the-counter magnesium chloride and potassium supplements to treat the patient's electrolyte abnormalities. By utilizing this approach, we were able to successfully stop the IV replacement therapy that the patient had required for 16 years prior to seeing us and transition her to a well-tolerated oral regimen that maintained appropriate serum electrolyte levels.

This case demonstrates the need for the individualization of therapy and a step-by-step approach for chronic hypokalemia and hypomagnesemia.

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 disturbances; otherwise, outpatient therapy should focus on oral replacement if possible.

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

References

1. Zull DN. Disorders of potassium metabolism. *Emerg Med Clin North Am* 1989; 7: 771–794
2. Besunder JB, Smith PG. Toxic effects of electrolyte and trace mineral administration in the intensive care unit. *Crit Care Clin* 1991; 7: 659–693
3. Schwartz WB, Relman AS. Effects of electrolyte disorders on renal structure and function. *N Engl J Med* 1967; 276: 452–458
4. Riemenschneider T, Bohle A. Morphologic aspects of low-potassium and low-sodium nephropathy. *Clin Nephrol* 1983; 19: 271–279
5. Blachley JD, Hill JB. Renal and electrolyte disturbances associated with cisplatin. *Ann Intern Med* 1981; 95: 628–632
6. Martin KJ, Gonzalez EA, Slatopolsky E. Clinical consequences and management of hypomagnesemia. *J Am Soc Nephrol* 2009; 20: 2291–2295
7. van Rongen E, van der Kogel J, Durham SK. The influence of cisplatin and unilateral nephrectomy on the response of the rat kidney to irradiation. *Int J Radiat Biol* 1989; 55: 661–677
8. Kim GH, Han JS. Therapeutic approach to hypokalemia. *Nephron* 2002; 92(Suppl 1): 28–32
9. Cohn JN, Kowey PR, Whelton PK *et al.* New guidelines for potassium replacement in clinical practice: a contemporary review by the national council on potassium in clinical practice. *Arch Intern Med* 2000; 160: 2429–2436
10. Jahnen-Dechent W, Ketteler M. Magnesium basics. *Clin Kidney J* 2012; 5(Suppl 1): i3–i14
11. Agus ZS. Hypomagnesemia. *J Am Soc Nephrol* 1999; 10: 1616–1622
12. Quamme GA. Renal magnesium handling: new insights in understanding old problems. *Kidney Int* 1997; 52: 1180–1195
13. Wagner CA. Disorders of renal magnesium handling explain renal magnesium transport. *J Nephrol* 2007; 20: 507–510
14. Knoers NV. Inherited forms of renal hypomagnesemia: an update. *Pediatr Nephrol* 2009; 24: 697–705
15. Firoz M, Graber M. Bioavailability of US commercial magnesium preparations. *Magnes Res* 2001; 14: 257–262