Magnesium and Drugs Commonly Used in Chronic Kidney Disease

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As with other electrolytes, magnesium homeostasis depends on the balance between gastrointestinal absorption and kidney excretion. Certain drugs used commonly in patients with CKD can decrease gastrointestinal ingestion and kidney reclamation, and potentially cause hypomagnesemia. Other magnesium-containing drugs such as laxatives and cathartics can induce hypermagnesemia, particularly in those with impaired glomerular filtration and magnesium excretion. In this review, we will discuss the potential magnesium complications associated with a range of commonly encountered drugs in the care of CKD patients, discuss the potential mechanisms, and provide basic clinical recommendations.

Key Words: Drugs, Hypomagnesemia, Hypermagnesemia, Proton pump inhibitor, CKD

INTRODUCTION

As with most electrolytes, the balance of gastrointestinal absorption and kidney excretion, and the flux between the circulating and storage compartments, determines serum magnesium concentrations. The average intake of dietary magnesium is approximately 300-400 mg/d, but varies considerably. Approximately 30% of ingested magnesium is absorbed across the intestine, utilizing both paracellular and active transport mechanisms. While 35% of absorbed magnesium complexes to either albumin or other anions, the remaining circulates unbound, fluxing between the serum and the much larger intracellular depot. About 2.5 g of magnesium are filtered daily, and while the great majority is reclaimed in the thick ascending limb (TAL) by the paracellular route, active magnesium transport via transient receptor potential melastatin (TRPM) 6/7 channels in the distal convoluted tubule (DCT) fine tunes magnesium homeostasis.

In contrast to other predominantly intracellular cations such as potassium and calcium, and despite its crucial roles in cell proliferation and intracellular enzymatic activity, there is no described hormonal axis dedicated to magnesium homeostasis. Alterations in circulating serum magnesium concentrations are offset by intracellular stores, so that a negative daily magnesium balance may not manifest with lower magnesium concentrations. Intracellular magnesium depletion and normal serum magnesium concentrations may coexist, and total magnesium deficiency might not manifest until cellular stores are exhausted. Therefore, using serum magnesium levels to diagnose magnesium deficiency is inherently complex.

With this as a background, understanding the effect of drug exposure on magnesium homeostasis can be challenging. Some drugs interfere with gastrointestinal magnesium absorption and kidney reclamation and are associated with hypomagnesemia, an effect that is often independent of kidney function. Other drugs have a high magnesium content, particularly those used as part of a gastrointestinal cleansing regimen. In patients with kidney dysfunction and consequent impaired magnesium excretion, this magnesium load can be associated with frank hypermagnesemia. As will be discussed below, understanding which drugs commonly used in patients with CKD are associated with hypomagnesemia and hypermagnesemia is essential to the care of these patients.

DRUGS ASSOCIATED WITH HYPOMAGNESEMIA

Hypomagnesemia via Gastrointestinal Magnesium Losses

Proton Pump Inhibitors. Proton pump inhibitors (PPIs) have received attention for their potential role in hypomagnesemia, with observational data in a wide array of settings.[1,2] The mechanism is generally thought to be a block of intestinal magnesium absorption rather than an effect on kidney magnesium handling. In PPI-associated hypomagnesemia, urinary magnesium concentrations are low, reflecting appropriate urinary magnesium conservation rather than magnesium wasting, and PPI-associated hypomagnesemia can typically only be corrected by intravenous, not oral magnesium.[3] Several recent studies have suggested that dialysis patients, who obviously lack kidney handling of magnesium, have a similar PPI association with hypomagnesemia, supporting an intestinal absorption defect.[4,5] A balance study similarly suggests a decrease in overall magnesium absorption despite similarities in dietary magnesium ingestion,[6] although no well-designed clinical study has yet been done.

The exact mechanism as to how PPIs might affect intestinal magnesium absorption is not known. However, emerging data suggest that PPI use might decrease the function of TRPM 6/7 channels, the site of active intestinal magnesium transport.[7] This channel is particularly important in times of low magnesium intake and might explain why malnutrition is a specific risk factor for PPI-associated hypomagnesemia. Other risk factors include chronic diuretics use and alcoholism, suggesting that a "double hit" phenomenon is needed to induce frank

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hypomagnesemia.[8] Whether chronic PPI use might be associated with a negative magnesium balance in the general population, and potential intracellular magnesium depletion, despite normal serum concentrations, remains conjecture. Studies examining whether PPI use is associated with an increased risk of arrhythmias, a potential clinical consequence of intracellular magnesium depletion, have had disparate conclusions.[9,10]

Because of the over-the-counter nature use of PPIs and that magnesium testing is not always part of routine clinical care, documenting the prevalence of PPI-associated hypomagnesemia is difficult. Given the widespread use of PPIs, however, it is clear that the majority of PPI users do not develop hypomagnesemia. It is plausible that some individuals might have a genetic susceptibility, with autosomal recessive mutations in the TRPM6 gene associated with decreased intestinal magnesium absorption.[11] Moreover, a recent case-control study has suggested that single nucleotide polymorphisms in the TRPM6 channel might increase the risk for PPI-associated hypomagnesemia.[12] However, it is also plausible that conclusions from observational data linking PPI use and hypomagnesemia are flawed by residual confounding. Given the myriad indications for PPI use, the most likely type of confounding is due to indication. While many studies have used histamine receptor antagonists (H_2RAs) as a comparative control in statistical models, since PPIs are often prescribed in the setting of H_2RA failure and typically for more severe disease, this approach is likely flawed. A large epidemiologic study of 21,000 Dutch citizens aimed at characterizing the lifestyle differences between PPI users and nonusers found PPI users more likely to smoke, be overweight, eat unhealthily, and exercise less,[13] and more likely to gain weight.[14] Given that lifestyle factors are notoriously difficult to quantify in observational studies and magnesium-rich foods are generally those from a healthy diet (dark leafy greens, nuts, seeds, fish, beans, whole grains, avocados, dark chocolate, etc.), it is plausible that PPI-associated hypomagnesmia is simply due to poorer eating habits and that PPI use might simply mark a sicker population.

Residual confounding in PPI studies is also supported by the nonspecificity of PPI-associated outcomes. For example, in a recent epidemiologic study using a "falsification approach," PPI use was associated with a multitude of seemingly unrelated outcomes with no biologically plausible mechanisms, further suggesting that PPI use was simply a proxy for sicker patients.[15] A single prospective study did not find an effect of PPI use on magnesium concentrations, although hypocalcemia was interestingly noted.[16] Given the recent emergence of PPI use and incident CKD association,[17] fully understanding the role of residual confounding is critical in avoiding premature conclusions. As of this point, the American Gastroenterology Association does not support serum magnesium monitoring or routine magnesium supplementation in PPI users,[18] but in those patients with other risk factors for magnesium loss, such as malnutrition and diuretic use, periodic magnesium surveillance might be justified.

CLINICAL SUMMARY

- Drugs commonly used in the care of patients with CKD can be associated with alterations of magnesium balance.
- A potential decrease of intestinal magnesium absorption might explain why some drugs are associated with hypomagnesemia.
- In patients with impaired kidney function, magnesium-containing bowel regimens might induce hypermagnesemia.

Cation Exchange Polymers. Since lower gastrointestinal secretions contain magnesium and are essentially unregulated, medications that lead to excessive losses through diarrhea can predispose to hypomagnesemia.[19] These magnesium wasting medications include stool softeners (docusate), stimulants (senna), and osmotic laxatives. Sodium polystyrene sulfonate, a sodium cation exchange resin, has been used for over 60 years as a treatment for hyperkalemia, particularly in those with CKD. Hypomagnesemia does not typically occur with sodium polystyrene sulfonate exposure. Patiromer and sodium zirconium cyclosilicate (ZS-9), 2 new agents gaining widespread attention, are selective cation exchange polymers used to treat hyperkalemia. In a multicenter, randomized controlled trial of patiromer in patients with CKD, hypomagnesemia was the most commonly observed treatment-related adverse event, occurring in 7% of patients.[20] A recent meta-analysis and systematic review of patiromer and sodium ZS-9 confirm these findings for patiromer but not for ZS-9.[21] This difference may be related to the cation selectivity of the compounds themselves, although the mechanism has not been fully elucidated.

Hypomagnesemia via Kidney Losses

Diuretics. Loop and thiazide diuretics inhibit magnesium reabsorption in the Loop of Henle and distal convoluted tubules (DCTs), respectively. Loop diuretics compete with chloride on the Na-K-2Cl cotransporter in the TAL, which impairs the generation of the lumen-positive potential important for the paracellular egress of magnesium. In addition, the back leak of potassium into the tubular lumen similarly inhibits lumen positivity, further decreasing magnesium reclamation.[22] However, the effect of loop diuretics on magnesium concentrations is generally mild, as the associated volume loss results in compensatory proximal sodium reclamation, creating a favorable gradient for paracellular divalent cation (magnesium and calcium) reabsorption. Magnesium reabsorption in the DCT is primarily active and transcellular, through the TRPM6 luminal channel. The activity of TRPM6 is enhanced by the favorable electrochemical gradient created by the inhibition of sodium entry through the NaCl transporter by thiazide diuretics in the acute setting. However, in the context of chronic administration, there seems to be a paradoxical effect. Current explanations for the increased magnesium