

Avoiding The Severe Gastrointestinal Side Effects Associated with High Dose Potassium and Magnesium Supplementation with Gitelman's Syndrome Through Utilization of Canagliflozin, Aliskiren and Spironolactone

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ABSTRACT

Gitelman's Syndrome is an inherited renal tubulopathy that is characterized by renal potassium and magnesium wasting leading to hypokalemia and hypomagnesemia. Previously the only available therapies for the hypokalemia and hypomagnesemia associated with Gitelman's Syndrome were high dose oral potassium and magnesium supplements. With the availability of the SGLT-2 receptor blocker canagliflozin the need for magnesium replacement therapy can be minimized. Similarly, utilizing blockade of the renin and mineralocorticoid receptors with aliskiren and spironolactone respectively the need for oral potassium replacement can be avoided. By eliminating or reducing the need for oral potassium and magnesium replacement therapy, gastrointestinal problems, particularly diarrhea, can be avoided and the quality of life improved while achieving normal serum potassium and magnesium levels. In addition, by normalizing serum potassium and particularly by correcting serum magnesium levels, the risk of a cardiac arrhythmia is also reduced.

Keywords: *Gitelman's Syndrome, Hypomagnesemia, Hypokalemia, Canagliflozin, Aliskiren, Spironolactone*

Introduction

The Gitelman's variant of Bartter's Syndrome is the most commonly inherited renal tubulopathy. Gitelman's Syndrome is inherited as an autosomal recessive disease that is characterized by diverse abnormalities in electrolyte homeostasis. These abnormalities include hypokalemia, metabolic alkalosis, hypomagnesemia and hypocalciuria caused by mutations in the thiazide sensitive renal sodium-chloride cotransporter (Simon *et al.*, 1996a; Simon *et al.*, 1996b).

The thiazide sensitive sodium-chloride cotransporter is located in the thick ascending limb of the loop of Henle in the distal convoluted renal tubule and when affected by the Gitelman's gene reductions in chloride, magnesium, potassium and sodium absorption occur, while calcium is absorbed in excess. The end result is a hypokalemic and a metabolic alkalosis with the hypocalcemia (Blanchard *et al.*, 2017).

Clinically, Gitelman's Syndrome results in salt craving, fatigue, muscle weakness, limited endurance, carpo-pedal spasm, growth retardation, delay in the onset of puberty, short stature, polyuria, polydipsia, nocturia, enuresis, dizziness, vertigo, joint pains and visual problems (Pachulski *et al.*, 2005; Mrad *et al.*, 2021). Gitelman's is often mistaken for Bartter's Syndrome where the defect in electrolyte reabsorption is more proximal and the outcomes more severe. Clinically, Gitelman's can be distinguished from Bartter's by the presence of hypocalciuria⁵ and if needed may also be confirmed through genetic testing (Vargas-Poussou *et al.*, 2011).

The recommended therapies for Gitelman's Syndrome are a diet high in salt in addition to potassium and magnesium supplementation (Konrad *et al.*, 2021). However, other therapies such as prostaglandin inhibition and disruption of the renin-angiotensin-aldosterone axis that have been proposed in Bartter's Syndrome have not been reported to be utilized in Gitelman's Syndrome (Fulchiero and Seo-Mayer, 2021; Fichman *et al.*, 1976; Bell, 2009).

In this report I describe the need for oral potassium replacement being negated with a simultaneous blockade of both the renin and mineralocorticoid receptor as well as the need for oral magnesium being minimized through the utilization of the SGLT-2 receptor blocker canagliflozin.

Case Report

A 54-year-old female had, at age 32, been found to a serum potassium of 2.4 mmol/L. As a child she had a history of enuresis up to age 13 and as an adult she had continued to have polydipsia, polyuria and nocturia (3-4 times nightly). She was at first diagnosed as having Bartter's Syndrome and this diagnosis persisted until age 55 when a low urine calcium was documented and her diagnoses was changed to Gitelman's Syndrome. After this test her sister's diagnosis was also changed from Bartter's to Gitelman's as she was also found to have hypocalciuria.

On initial laboratory assessment she had a metabolic alkalosis, hypokalemia and hypomagnesemia in addition to an elevated serum renin activity and hyperaldosteronemia. Prior to utilization of blockade of the renin and mineralocorticoid receptors she was utilizing up to 25 potassium chloride 750 mEq (MicroK) tablets daily which caused severe gastrointestinal side effects particularly diarrhea.

Initial therapy for hypokalemia was with the combination of the renin receptor blocker aliskiren and the aldosterone receptor blocker spironolactone. This resulted in normokalemia and negated the need for potassium supplements. The success of correcting the hypokalemia was tempered by the inability to increase her serum magnesium level. Her serum magnesium levels in spite of a daily dose of

eleven 71.5 mg tabs of magnesium chloride remained in the 1.4 to 1.8 mg/dl (normal 1.9-2.7 mg/dl) range. When she tried to increase her magnesium intake above 11 tablets per day intolerable diarrhea that interfered with her lifestyle occurred. Based on reports that SGLT-2 inhibitors increased serum magnesium levels through increased renal absorption and since she had prediabetes she was started on ertugliflozin at 15 mg daily which was later increased to 30 mg daily due to a lack of efficacy. Ertugliflozin, 30 mg daily, had no effect on either her serum magnesium levels or her need for oral magnesium supplementation. However, when ertugliflozin was discontinued and canagliflozin therapy was initiated at 100 mg daily and later at 300 mg daily her serum magnesium level rose to 2.0 mg/dl and this level was maintained as she reduced her magnesium chloride intake to 3x 71.5 mg tabs daily. Later when her magnesium supplements were discontinued her serum magnesium level dropped back to 1.4 mg/dl but was maintained at levels between 1.8 and 2.0 mg/dl with 3 x 71.5 mg tabs daily. The three daily tablet regimen was not associated with gastrointestinal or other symptoms. HbA1c prior to SGLT-2 therapy was 6.1% and 3 months after initiation of canagliflozin dropped to 5.9%. Over the six month period after discontinuing both potassium supplements and reducing magnesium supplements there was no recurrence of gastrointestinal symptoms.

Discussion

Gitelman's Syndrome is a more benign variant of Bartter's Syndrome. Both syndromes are associated with hypokalemia and hypomagnesemia and can be differentiated clinically by the presence of hypercalciuria with Bartter's Syndrome and hypocalciuria with Gitelman's Syndrome (Mrad *et al.*, 2021). In addition, genetic testing may or may not be needed to establish the diagnosis (Vargas-Poussou *et al.*, 2011).

Traditionally, the only recommended therapies for both Bartter's and Gitelman's Syndromes are a high oral intake of potassium and magnesium.⁷ However, these supplements at maximally tolerated doses are usually not enough to correct either the serum potassium or the serum magnesium levels. Since in both Bartter's and Gitelman's Syndromes renin activity is elevated, direct inhibition of the renin receptor with aliskiren combined with inhibition of the steroidal mineralocorticoid receptor blocker spironolactone, has been shown to normalize serum potassium without the use of potassium supplements (Konrad *et al.*, 2021).

Hypomagnesemia is a particular concern because hypomagnesemia can prolong the QT interval which can be associated with increased rates of cardiac arrhythmias which are of particular significance in those patients who are older and more likely to have underlying cardiovascular disease (Whang *et al.*, 1994; Kieboom *et al.*, 2016; Del Gobbo *et al.*, 2012). In fact, a meta-analysis of controlled trials showed

that for every 0.2 mmol/L increase in serum magnesium there was a 30% decrease in fatal and non-fatal ischemic heart disease (Burch and Giles, 1977; Iseri *et al.*, 1975). Since cardiac complications are unlikely to occur if the magnesium level is above 1.6 treating the magnesium level into the normal range is imperative (Kieboom *et al.*, 2016).

Data from four placebo-controlled studies of canagliflozin in patients with a magnesium of less than 0.74 mmol/L showed that canagliflozin 100 mg raised serum magnesium by 13% and the 300 mg canagliflozin by 15.1% (Gilbert *et al.*, 2017). In addition, a meta-analysis of 18 randomized placebo controlled trials showed that 100 mg canagliflozin raised serum magnesium by 0.06 mmol/L and the 300 mg dose by 0.09 mmol/L. On the other hand, with empagliflozin serum magnesium rose by 0.04 mmol/L with the 10 mg dose and 0.07 mmol/L with the 25 mg dose while with dapagliflozin serum magnesium only rose by 0.01 mmol/L (Tang *et al.*, 2016; Weir *et al.*, 2014). From this data and my own experience we can conclude that for elevating serum magnesium and therefore decreasing the risk of a cardiac arrhythmia the SGLT-2 inhibitor of choice is canagliflozin at the maximally approved dose.

In conclusion, in patients with Gitelman's Syndrome, blockade of the renin and mineralocorticoid receptors may negate the need for potassium supplementation. Furthermore, the need for magnesium supplementation may be negated or reduced utilizing an SGLT-2 inhibitor. In this case ertugliflozin was ineffective and based on the literature both empagliflozin and dapagliflozin are less effective than canagliflozin. Therefore, canagliflozin seems to be the most preferred and effective SGLT-2 inhibitor for increasing the absorption of magnesium and elevating serum magnesium levels. Reducing or eliminating the need for potassium and/or magnesium supplementation will result in a reduction or elimination in the gastrointestinal symptoms associated with the excess intake of potassium and magnesium supplements in addition to an improvement of the quality of life which is decreased with both high dose potassium and/or magnesium supplementation.

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