CASE REPORT

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Mimicking Gitelman Syndrome with Proton Pump Inhibitors

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ABSTRACT Proton pump inhibitors (PPI) are widely used drugs for both prophylaxis and treatment of peptic ulcer and gastroesophageal reflux disease. Although electrolyte abnormalities are common, there is only a single report of Gitelman syndrome related to PPI in the literature. In this report, we described another case of a 58 years old woman with Gitelman-like electrolyte disturbances and metabolic alkalosis related to PPI usage. This case is important because of a new look of an old drug-related disorder mimicking a rare syndrome.

Keywords: Gitelman syndrome; proton pump inhibitors; electrolyte disturbances

Proton pump inhibitors (PPI) are widely used drugs for both prophylaxis and treatment of peptic ulcer and gastroesophageal reflux disease.[1-3] Although long considered as quite safe drugs, recent studies associated with PPIs reported potential severe side effects including increased risk of malignancy, pneumonia, fractures, acute kidney injury and chronic kidney disease.[4-7] Post-marketing data of long-term use of these drugs also revealed an association with electrolyte disturbances like hypomagnesemia, hypokalemia and rarely hyponatremia.[8]

Although electrolyte abnormalities are common, there is only a single report of Gitelman syndrome related to PPI in the literature.[9] In this report, we described another case of a 58 years old woman with Gitelman-like electrolyte disturbances and metabolic alkalosis related to PPI usage.

CASE REPORT

A 57-years-old woman was admitted to our hospital with weakness, fatigue, muscle cramps and spasms. One week before her admission, she was diagnosed with coronary artery disease and hypertension, and was prescribed a combination of drugs including atorvastatin sodium, low molecular weight heparin, acetylsalicylic acid, ramipril, carvedilol, clopidogrel and pantoprozol. Her medical history or family history was unrevealing except for active smoking. She had never used thiazide diuretics or laxatives, had no family history of kidney disease. Her physical examination had no positive findings with a blood pressure of 130/78 mmHg.

Her laboratory results were as follows on admission; creatinine: 0.6 mg/dL (normal range: 0.51-0.95 mg/dL), blood urea nitrogen: 11 mg/dL (normal

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range: 6-20 mg/dL) , sodium: 142 mEq/L (normal range:135-145 mEq/L), potassium: 3.1 mEq/L (normal range: 3,5-5,1 mEq/L), magnesium:0.5 mg/dL (normal range: 1,9-2,5 mg/dL), uric acid: 6.5 mg/dL (normal range: 2,6-6 mg/dL), calcium: 9.9 mg/dL (normal range: 8,8-10.6 mg/dL), phosphorus: 4.5 mg/dL (normal range: 2.5-4.5 mg/dL), albumin: 4.3 g/dL (normal range: 3,5-5,2 g/dL), glucose: 111 mg/dL (74-100 mg/dL). Complete blood count was normal. Urinary pH was 5.5 and there were no positive urinary sediment findings or proteinuria.

Her blood magnesium (on admission; 0.5 mg/dL despite one week before it was 1.9 mg/dL) and potassium levels (on admission 3.17 mg/dL despite it was 4.1 mg/dL one week before) were markedly decreased. In further evaluation her blood pH was 7.415, HCO_3 level was increased with 29.2 mmol/L, 24 hour urine potassium excretion [31.46 mmol/24 hour (normal range: 25-125 mmol/24 hour)] was normal but 24 hour urine calcium excretion was markedly decreased (3.99 mg/24 hour (normal range: 100-300 mg/24 hour)-spot urinary calcium to creatinine ratio: 0.006 mg/mg). Renal ultrasonography was normal.

With these findings, the patient was considered as Gitelman syndrome and treated with high sodium and potassium diet and oral magnesium and potassium replacement therapy.

Her symptoms were not improved under this treatment and control blood tests were performed two weeks later. Her laboratory blood tests were similar as following; creatinine: 0.64 mg/dL, blood urea nitrogen: 10 mg/dL, sodium: 140 mEq/L, potassium: 3.05 mEq/L, magnesium: 0.8 mg/dL. Aldactone was added to the patient's treatment and PPI was changed to a H2 receptor blocker. Her symptoms progressively resolved and two months later her symptoms completely resolved as creatinine: 0.6 mg/dL, blood urea nitrogen: 13 mg/dL, sodium: 140 mEq/L, potassium: 3.74 mEq/L, magnesium: 1.9 mg/dL. During the follow-up, oral replacement therapies for magnesium and potassium were stopped and gastric prophylaxis was continued with a H_2 receptor blocker. Meanwhile, the electrolytes were completely within normal values.

After a year with no symptoms and laboratory anomalies because of gastroesophageal reflux symptoms, a different PPI was prescribed in another hospital. Ten days after the initiation of this drug, the patient was admitted to our hospital with fatigue, muscle aches and cramps. Laboratory evaluation showed again a low plasma potassium and magnesium as follows; creatinine: 0.5 mg/dL, sodium: 138 mEq/L, potassium: 3.74 mEq/L, magnesium: 0.9 mg/dL. The new PPI was discontinued, and symptoms disappeared within one week together with normalization of laboratory values without an extra treatment.

There is no need for a consent form in this paper, since no personal information belonging to the patient was disclosed as all data and figures were anonymized.

DISCUSSION

Gitelman syndrome is one of the rare causes of hypokalemia. It is a familial tubulopathy characterized by metabolic alkalosis, hypomagnesemia and hypocalciuria beside hypokalemia.

In a patient with hypokalemia, presence of increased urinary potassium loss, metabolic alkalosis and normal blood pressure indicates vomiting, Gitelman syndrome or Bartter syndrome as the potential etiologies. After excluding vomiting from the history of patient, one should discriminate Gitelman syndrome and Barrter syndrome. Gitelman syndrome is usually seen in adults, and hypomagnesemia and hypocalciuria strongly favors the diagnosis.[10]

Acquired Gitelman syndrome can be a component of autoimmune disorders like systemic lupus erythematosus or Sjögren syndrome.[11] Thiazide diuretics had Gitelman-like effects on kidney but other drugs with similar effect have rarely been reported including kanamycin, bendamustin, prostaglandin and cisplatin.[12-14]

In our case, all the symptoms and tests were compatible with Gitelman syndrome but a careful history revealed that all these were began with the prescription of a PPI and improved with the withdrawal of the drug. An unplanned rechallange also

provoked another attack which was completely reversed with discontinuation of PPI.

Hypomagnesemia is a very well-known effect of PPI. Hypokalemia is a typical finding in patients with hypomagnesemia. However, hypocalciuria and metabolic alkalosis are not typically observed or not specifically looked for in patients with PPI-related hypomagnesemia. Gitelman syndrome related to PPI was only reported in a single patient previously.[9] In that report, Gitelman syndrome related to PPI was hypothesized to be a result of countercross inhibiton of renal ion pump Na-K ATPase with PPI. But still there is no clear evidence related to this hypothesis.

In conclusion, 24-hour calcium excretion and blood gas analyses should be evaluated in all patients with PPI-induced hypomagnesemia to detect a Gitelman-like syndrome.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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