

CASE REPORT

An old friend turned foe: Metformin-induced diarrhea with resultant symptomatic hypokalemia, hypomagnesemia, hypocalcemia, and hypophosphatemia

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Abstract

Metformin is known for gastrointestinal side effects, but has rarely been associated with diarrhea severe enough to cause symptomatic electrolyte abnormalities and hospitalization. This case illustrates such that occurred despite multiple outpatient encounters for diarrhea. Additionally, this case highlights the importance of a comprehensive medical reconciliation as part of a thorough medical evaluation.

KEY WORDS

diarrhea, drug adverse event, hypokalemia, hypomagnesemia, medication reconciliation, metformin

1 | INTRODUCTION

Metformin is the first-line medication for type 2 diabetes mellitus given its efficacy.¹ However, it is known for gastrointestinal side effects.¹ The following describes a patient who presented with severe and symptomatic hypokalemia, hypomagnesemia, hypocalcemia, and hypophosphatemia secondary to metformin-induced diarrhea requiring hospitalization for intravenous repletion of electrolytes and close cardiac monitoring.

Metformin is one of most common medications used in the treatment of type 2 diabetes mellitus, often used as the first-line therapy to lower glycated hemoglobin (HbA1c) levels.² As a monotherapy, it can lower HbA1c by 1.5% and has been shown to have a 36% decrease in relative risk for all-cause mortality.² One of the most common side effects of metformin is gastrointestinal (GI) side effects, particularly diarrhea, with up to 20% of metformin users having medication-related diarrhea.³ A previous case report showed chronic diarrhea associated with metformin use leading to symptomatic hypomagnesemia, hypocalcemia with mild hypokalemia.⁴ Further descriptions in the literature are lacking.

The following report describes a case with chronic metformin use leading to symptomatic and severe hypomagnesemia, hypokalemia, hypocalcemia, hypophosphatemia, potential heart-rate corrected QT interval (QTc) prolongation, profound fatigue, and hospitalization.

2 | CASE HISTORY/EXAMINATION

The patient was a 54-year-old African American female with a past medical history of diabetes mellitus on metformin for 12 years, hypertension, breast cancer in remission, and gastroesophageal reflux disorder (GERD) who presented with lower extremity weakness, numbness, and multiple electrolyte abnormalities in the setting of undifferentiated chronic diarrhea. She was diagnosed with type 2 diabetes mellitus in 2008, where she was started on metformin, for which she reported episodes of diarrhea that began when she began taking the medication. The patient works as a nurse and reported days where she could not participate in patient care due to the diarrhea. She met with her primary care physician with these concerns. Changes

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were not made at that time citing the efficacy of the metformin in treating her diabetes. Over the last year, she self-reduced her metformin 1000 mg from twice a day to once daily, which she stated significantly reduced her diarrhea. However, the patient reported to her primary care physician 5 days before coming to the emergency department (ED) for routine follow-up and was encouraged to resume metformin 1000 mg twice a day.

She presented to the emergency department with a 1-day history of new-onset tingling in her arms and fingers bilaterally and muscle cramping in both of her thighs. She also described six episodes of diarrhea that occurred the day before her arrival to the ED. On interview, patient stated she has a history of diarrhea correlated with her metformin use, and recently increased her metformin dose based on her primary care physician's recommendations. Her home medications at the time of hospitalization included amlodipine, losartan, eplerenone, nadolol, albuterol, and gabapentin.

On examination, her blood pressure was 159/90 mmHg. Pertinent physical exam findings were significant for muscle tenderness of upper and lower extremities on palpation. Cardiovascular exam revealed a regular rhythm and normal rate. Lung exam was unremarkable. Neurologic exam revealed decreased sensation to light touch in the distal upper extremities and lower extremities, along with globally reduced strength in all four extremities.

2.1 | Investigation and treatment

Laboratory data were notable for serum levels of sodium 143 mEq/L (132–146), potassium 2.5 mEq/L (3.5–5.5), chloride 101 mEq/L (99–109), bicarbonate 30 mEq/L (20–31), blood urea nitrogen 5 mg/dl (9–23), creatinine 0.48 mg/dl (0.6–1.6), glucose 170 mg/dl (74–106), HbA1c 8.4% (4–6), calcium 8.2 mg/dl (8.7–10.4), phosphorous 1.5 mg/dl (2.4–5.1), magnesium 1.2 (1.3–2.7) mg/dl, 25 Hydroxyvitamin D2 17.59 ng/ml (25–80), parathyroid hormone (PTH) 298.6 pg/ml (11.1–79.5); calcium urine 21.2 mg/dl, potassium urine 29 mEq/L, and creatinine urine 36.2 mg/dl. Electrocardiogram (EKG) demonstrated normal sinus rhythm with prolonged QTc of 534, elevated from previous baseline of 439. Analysis of serum and urine electrolytes showed a normal fractional excretion of potassium. Gastrointestinal viral and *Clostridium difficile* panels were performed to evaluate infectious etiologies of diarrhea, which both returned with negative results. A thorough medication reviewed was undertaken and revealed a possible association with metformin use. This medication was held. The electrolytes were repleted appropriately, with patient describing resolution of symptoms after her ions returned to reference range levels. The patient was discharged, with metformin discontinued and dapagliflozin 5 mg used as a replacement to prevent GI symptoms.

2.2 | Outcomes and follow-up

The patient was ultimately switched to monotherapy with the sodium/glucose cotransporter 2 inhibitor (SGLT2) dapagliflozin with resolution of her diarrhea and electrolyte abnormalities. At follow-up, 3 weeks later patient reported immediate resolution of her symptoms, with no diarrhea since her hospitalization, and the ability to return to her normal activities.

3 | DISCUSSION

Given the onset of diarrhea with the patient beginning metformin, the increase in diarrhea when the drug dose was increased, and the cessation when the metformin was replaced with dapagliflozin, the case described above is most likely suggestive of metformin directly causing severe diarrhea, hypomagnesemia, hypokalemia, hypophosphatemia, hypocalcemia, and the associated symptoms. To support this conclusion, the Naranjo algorithm⁵ was used to determine the likelihood of whether the adverse drug reaction was the most likely reason for these symptoms rather than another possible cause. Using the algorithm, the patient scored +1 on whether there are previous reports of severe diarrhea from metformin, +2 on diarrhea occurring after metformin was given, +1 on the stopping after metformin was discontinued, +2 on hospital work-up determining no other causes for the chronic diarrhea, +1 diarrhea being more severe when metformin was increased, +1 on the patient having diarrhea from metformin on previous exposure for over a decade, +1 for objective evidence of ion deficiencies and QTc prolongation on EKG, for a total of 9 on the Naranjo algorithm. Based on this algorithm, a score of 9 or greater defines a definite adverse drug reaction.⁵

Despite gastrointestinal side effects being common, severe diarrhea is a rare but reported side effect seen in literature. Svare et al.⁴ in 2009 reported a similar case of symptomatic hypomagnesemia. Our case additionally describes severe hypokalemia and possible prolonged QTc interval⁶ not seen in the case cited above. The reason for why metformin causes gastrointestinal adverse effects is a topic of ongoing research.

Adverse drug events account for over 1 million ER visits and 350,000 hospitalizations per year.⁷ Medication reconciliation, defined as the process where the list of prescribed medications are documented and compliance is verified, is known to contribute to medication errors with up to 40% of errors being the result of medication reconciliation errors.⁸ Studies have been performed to assess the efficacy of electronic medication reconciliation, with one study showing that electronic medication reconciliation reduced medication discrepancy, but had no effect on adverse drug events (ADE).⁹ Additionally, pharmacy lead medication reconciliation teams have been

shown to decrease medication discrepancies on admission and decrease adverse drug events, suggesting the benefits of an inter-disciplinary approach to prevent adverse drug events and improve health care.^{10,11} However, many places may be resource limited and unable to provide this level of support. Reasons for adverse drug reactions vary, are often multifactorial, and can include patient factors such as co-morbidities and older age, as well as provider factors such as incorrect drug selection and regularly monitoring symptoms.¹² Therefore, a thorough medical reconciliation performed on a regular basis is important to help minimize adverse drug reactions and prevent unnecessary hospitalizations. Non-pharmacy lead randomized control trials are needed to investigate interventions that could potentially improve ADE rates.

This case serves as a reminder of the importance to continually investigate and follow-up ongoing symptoms and review medications for adherence and side effects on a periodic basis.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

AS: Helped in providing care to the patient during hospital stay. Responsible for drafting and formatting the manuscript. DW: Physician responsible for providing care to the patient during hospital stay. Responsible for drafting and formatting the manuscript. All authors participated in the research and preparation of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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