OPEN ACCESS

ISSN: 2835-9496

Daly PO, et al. (2025): 862
Ameri J Clin Med Re, 2025; 5(3): 100206
DOI: 10.71010/AJCMR.2025-e206

Case Report

American Journal of Clinical and Medical Research

Oliguric Acute Kidney Injury Triggered by Supplemental Vitamin B12-Methylfolate: A Case Report

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Citation: Daly PO, Ward KC, Irvine N, Brodsky B, Setambar N, et al. (2025) Oliguric Acute Kidney Injury Triggered by Supplemental Vitamin B12-Methylfolate: A Case Report. Ameri J Clin Med Re: AJCMR-206.

Received Date: 04 March, 2025; **Accepted Date:** 10 March, 2025; **Published Date:** 14 March, 2025

Abstract

This case report presents a 53-year-old female who developed oliguric acute kidney injury (AKI) following the use of a vitamin B12-methylfolate liquid syrup supplement purchased through social media. The patient presented with severe gastrointestinal symptoms, leading to hypovolemia and AKI. Renal biopsy revealed acute tubular necrosis (ATN) and mild acute interstitial nephritis (AIN). The regional poison center was notified to investigate the potential contamination, but due to financial constraints, no evaluation was conducted. This case highlights the risks of unregulated supplements and the need for a thorough evaluation in cases of unexplained acute kidney injury.

Categories: Public Health, Internal Medicine, Nephrology

Keywords: poison center, acute renal failure, methylfolate, vitamin b12, acute interstitial nephritis, acute tubular necrosis, acute kidney injury

Introduction

The prevalence of dietary supplement use in the United States has been steadily increasing. Data from the Health and Retirement Study (HRS), which included a national sample of community-dwelling middle-aged and older adults, revealed that 84.6% of participants aged 50 years and older were regular dietary supplement users [1]. Another study focusing on postmenopausal women from the Iowa Women's Health Study cohort reported that the proportion of women using dietary supplements increased from 66% in 1986 to 85% in 2004 [2]. Furthermore, data from the National Health and Nutrition Examination Survey (NHANES) 2003-2006 indicated that 53% of women in the U.S. reported using dietary supplements, with multivitamin-multimineral supplements being the most frequently used [3].

While over-the-counter supplements are often perceived as safe, there is growing concern over unregulated products. Unlike prescription drugs, dietary supplements do not require U.S. Food and Drug Administration (FDA) approval. The FDA's role is limited to post-market surveillance, including monitoring adverse event reports [4]. This regulatory gap has led to significant variability in supplement quality, with issues including adulteration and misbranding [5,6].

Vitamin B12 and folate supplements are commonly used for various health purposes, including treating anemia and supporting cardiovascular health. However, high doses of these supplements have been associated with potential adverse effects, including kidney dysfunction in some cases, but is still not proven to have a causal relationship [7-11].

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The variability in supplement quality can lead to adverse health effects and drug-drug interactions. Potential mechanisms of supplement-induced kidney injury include direct toxic effects, oxidative stress, and hypersensitivity reactions. This case report presents a severe acute kidney injury (AKI) associated with the use of a vitamin B12-methylfolate supplement purchased from social media. It underscores the need for caution when recommending or using unregulated supplements and emphasizes the importance of thorough medication history in clinical practice.

Case Presentation

A 53-year-old female with a past medical history of hypertension, hepatitis C, which was cleared spontaneously (positive HCV antibody, negative HCV RNA PCR), bipolar 1 disorder, insomnia, allergic rhinitis, and multiple drug allergies presented to the emergency department with a 4-day history of intractable nausea, vomiting, diarrhea, abdominal pain, and decreased urine output with dark urine. Her home medications included amlodipine 5 mg, quetiapine 50 mg, trazodone 150 mg, cetirizine 10 mg and a new supplement that she had purchased from social media, vitamin B12-methylfolate drops. The liquid drop supplement had no other known active nor inactive ingredients in the supplement. She purchased this supplement because it was "trendy" on social media and wanted to improve her anxiety, mood regulation, and reduce fatigue.

She started taking the new supplement around the onset of symptoms but was unsure of her daily dosage, though the recommended dosage was 1-2 drops per day. Her symptoms led to non-adherence of her antihypertensive medications (amlodipine 5 mg P.O. daily). Pain and the non-adherence to amlodipine cumulatively led to an increase in a blood pressure of 138/93 mmHg upon arrival to the ED (baseline 119/77 mmHg from three months ago). Patient denied any recent travel or sick contacts. Other vitals upon arrival to the ED included 98.3°F, 112 heart rate, 22 respiratory rate, and 100% SpO2 on room air. She also had stopped taking the supplement once symptoms presented.

Upon physical examination, the patient was fully alert and oriented to person, place, time, and event. She also appeared fatigued and had dry mucous membranes. She was tachycardic with a normal rhythm. She had normal pulmonary effort with no wheezing, rales, or rhonchi. In addition, she had left lower quadrant abdominal tenderness without rebound tenderness or guarding. Her skin was non-icteric and there were no rashes.

The CBC results were stable, with a WBC count of 10.2k/mcL, RBC count of 5.2 mil/mcL, hemoglobin of 13.7 gm/dL, and platelet count of 343 k/mcL. Her CMP revealed that sodium (136 mmol/L), potassium (4.0 mmol/L), and chloride (98 mmol/L) were within normal limits. The patient was found to have high anion gap metabolic acidosis with an anion gap of 21 mmol/L and a CO2 of 17 mmol/L. Her BUN was elevated to 59 mg/dL (Ref range: 7-24 mg/dL), and creatinine was grossly abnormal at 11.76 mg/dL (baseline: 0.8-0.9 mg/dL; Ref range: 0.44-1.03 mg/dL), indicating severe renal impairment with an eGFR of 3 mL/min/1.73 m2. Additionally, hyperphosphatemia (phosphate 6.9 mg/dL; Ref range: 2.4-4.9 mg/dL), and hypermagnesemia (magnesium 2.5 mg/dL; Ref range: 1.8-2.4 mg/dL) were noted, likely due to renal impairment. Her calcium 10.2 mg/dL, Random Blood glucose 96 mg/dL. LFTs were stable, with an ALP of 91 U/L, AST of 14 U/L, ALT of 7 U/L, total protein of 8.4 g/dL, and albumin of 4.8 g/dL. C-Reactive Protein was elevated at 21.1 mg/L (Ref range: 0.0-9.9 mg/L). Lipase was negative. The UA showed trace ketones, negative nitrites and leukocyte esterase, 5-10 hyaline casts, 40-50 WBCs, 5-10 RBCs, and many squamous cells.

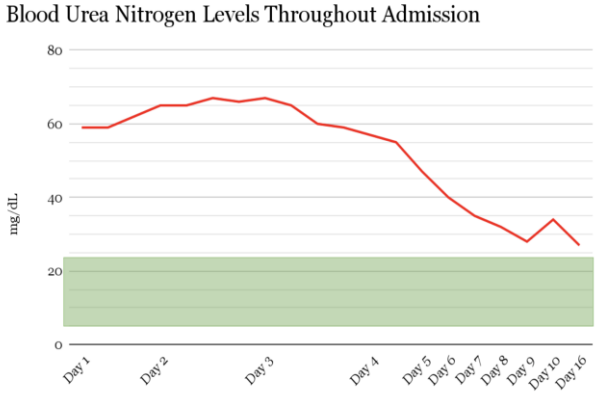
A chest x-ray and an abdominal x-ray showed the heart was not enlarged, lungs were clear, and a nonspecific abdominal bowel gas pattern. A computed tomography (CT) abdomen and pelvis without contrast showed no acute findings, no urinary tract abnormalities, and a previous cholecystectomy and previous partial colectomy. The ED gave the patient Toradol 15 mg IV for abdominal pain, Rocephin 1 g IV to cover for possible Bacterial Gastroenteritis, Famotidine 20 mg and Ondansetron 4 mg were administered intravenously in view of her gastrointestinal symptoms, and lactated ringer 1 L bolus and 0.9% normal saline (NS) 1 L bolus for volume resuscitation. Patient's tachycardia improved post-bolus, but was still complaining of abdominal pain and nausea. Patient was admitted for oliguric acute kidney injury and started on aggressive intravenous fluid maintenance therapy (0.9 NS @ 125 mL/hr) to maintain a urine output of 0.5 cc/kg/hr.

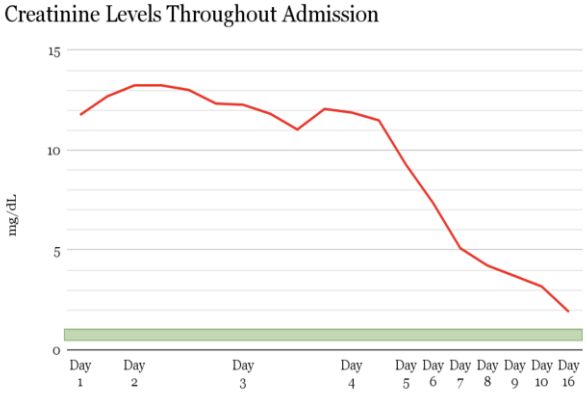
Nephrology was consulted and renal ultrasound with Doppler revealed no urinary tract abnormalities. On day two of admission, the patient had a downtrending hemoglobin to 11.4 gm/dL. This change in hemoglobin is likely due to volume resuscitation, reflecting a more accurate value as the fluid status normalized. Patient's BUN worsened from 59 mg/dL to 67 mg/dL and creatinine up trended from 11.76 mg/dL to 13.24 mg/dL and patient was noted to be anuric and remained symptomatic with nausea and abdominal tenderness.

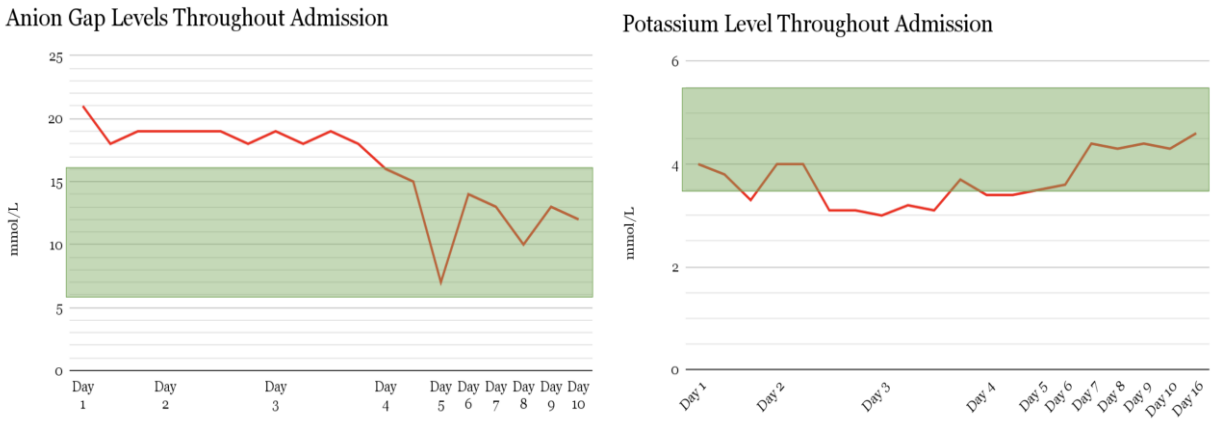
Day three of admission, the patient's potassium decreased to 3.0 mmol/L and was repleted. Anion gap had continued to fluctuate ranging from 18-19 mmol/L over the last 24 hours. BUN remained high at 66 mg/dL and creatinine remained high at 12.33 mg/dL. Through proper management of fluid resuscitation (intake 3155.34 ml), the patient produced 3850 ml of urine, making the transition from an oliguric state to a nonoliguric state.

On day four of admission, the patient continued to worsen with a net I/O of -910 ml (intake 2134.59 ml, output 4035 ml). A renal biopsy was discussed with the patient, including risks (e.g., retroperitoneal bleeding due to elevated blood pressure) and benefits. The patient agreed to proceed and was placed on NPO. The biopsy was ultrasound-guided and performed under local anesthesia on the left kidney, with blood pressure controlled prior to the procedure. Minimal post-op pain was reported with no complications. The renal biopsy revealed minimal tubular atrophy and interstitial fibrosis, with mild lymphocytic tubulitis and focal interstitial edema. These findings were consistent with predominantly acute tubular necrosis and mild acute interstitial nephritis.

Given the unusual presentation and temporal link to an unregulated over-the-counter drug, the local poison center was notified to monitor the case. The patient's condition and kidney function gradually improved with supportive care (IV Zofran, continued maintenance IV fluids), as seen in the creatinine, BUN, and GFR lab values (Figures *1-4*). The patient's creatinine had not completely returned to baseline (0.8-0.9) before discharge, but was trending in the right direction and was close to baseline value.







Figures 1-4: Line graphs of the patient's important labs upon admission until discharge show the patient's progression throughout admission. Red lines indicate the patient's lab values, while the green box indicates the reference ranges of the specific lab value.

She was discharged on hospital day ten, when she was able to tolerate a regular diet and maintain a normal net I/O balance. Upon discharge, the patient's blood pressure was 132/80, and her home medications for HTN, bipolar, insomnia, and allergic rhinitis were resumed. She was advised to maintain a high fluid intake and avoid nephrotoxic agents (NSAIDs, Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Blockers). In addition, this social-media purchased supplement was added to her allergy list. She was advised to follow up with her primary care provider (PCP) within a week and nephrology in 4-6 weeks.

Discussion

Pathophysiological Mechanisms

The renal biopsy findings of acute tubular necrosis (ATN) and mild acute interstitial nephritis (AIN) suggest a complex pathophysiology underlying this case of oliguric acute kidney injury. Several mechanisms may be at play including toxic and oxidative stress effects, hypersensitive reactions, and/or potential contamination of the supplement with an unknown nephrotoxic substance.

High doses of vitamin B12 and folate may have directly contributed to the patient's tubular injury. Studies have shown that while high doses of folic acid are associated with increased oxidative stress and kidney injury, low-dose supplementation with specific forms of folate (5-methyltetrahydrofolate) may have protective effects through activation of nuclear factor erythroid 2-related factor 2 (Nrf2) and antioxidant defense mechanisms [7-9]. This paradoxical finding underscores the complex relationship between folate metabolism and kidney function.

Research has also found that high preoperative serum B12 levels were associated with a 2.8-fold increase in postoperative AKIs in patients undergoing donor liver transplantation [10]. Another study observed that elevated vitamin B12 levels were associated with reduced kidney function in participants with high baseline homocysteine levels [11]. While these studies highlight a correlation between high doses of vitamin B12- methylfolate and kidney dysfunction, the exact mechanisms remain unclear, and a direct causal relationship cannot be confirmed.

The presence of mild AIN on the patient's biopsy suggests a possible allergic or hypersensitivity reaction to components of the supplement. Individuals with multiple drug allergies, as seen in this patient, are at higher risk for hypersensitivity reactions, including acute interstitial nephritis [12,13].

Social Media's Impact on Supplemental Use

Social media plays a substantial role in the marketing of dietary supplements, often lacking specific policies regarding advertisements and user-generated content. This gap can lead to the widespread dissemination of unverified and potentially misleading information, amplifying the risks associated with supplement use as consumers may be misled by false claims [14,15]. In this context, the Federal Trade Commission (FTC) plays a crucial role in regulating the marketing of dietary supplements and other health-related products. The FTC's Health Products Compliance Guidance requires that advertising claims be truthful, not misleading, and backed by scientific evidence. This guidance extends to social media marketing, where the FTC holds advertisers responsible for claims made through consumer testimonials and expert endorsements. Proper enforcement of these regulations could help mitigate the spread of false or unsubstantiated claims about dietary supplements on social media platforms, reducing consumer risk and preventing misleading information from influencing purchasing decisions.

Supplemental Use Raising Public Health Concerns

This case is not isolated; other supplements have been reported to trigger acute tubular necrosis and acute interstitial nephritis. For instance, red yeast rice supplement which is used as a lipid-lowering supplement, has been found to trigger ATN and achyranthes japonica extract has been reported to be associated with AIN [16,17]. Chinese herbal remedies have also been linked to nephrotoxic compounds leading to renal failure [18].

The potential risks associated with unregulated supplements emphasize the need for improved oversight and quality control in the supplement industry. The global nature of the supplement market, with significant imports from countries like China, adds another layer of complexity and concern for public health [19].

Limitations and Future Directions

While this case report provides valuable insights, it has several limitations. The patient was initially in a pre- renal state due to nausea, vomiting, and diarrhea, which then progressed to ischemic acute tubular necrosis (ATN) and worsened by the use of Toradol. While drug-induced ATN from Vitamin B12-methyl folate is a possibility, given the temporal relationship, the most likely cause remains the prolonged pre-renal state resulting from ongoing nausea, vomiting, and diarrhea. Additional limitations

include the lack of knowledge about the other inactive ingredients in the supplement and other potential confounding factors such as the patient's history of hepatitis C and daily cannabis use. Finally, acute interstitial nephritis (AIN) could potentially be a renal response to one of her known drug allergies. Overall, there are multiple confounding factors into this patient's acute kidney injury and nothing could directly be proven.

Future research should focus on how high-dose vitamin B12 and folate supplements can directly affect kidney function, interactions between these supplements, and developing better methods for quality control and safety assessment of dietary supplements.

Conclusion

This case of oliguric acute kidney injury linked to the use of a vitamin B12-methylfolate supplement highlights the need for caution when using unregulated supplements, especially in patients with pre-existing medical conditions or multiple drug allergies. It emphasizes the importance of a thorough medication history, including over-the-counter drugs and supplements, and comprehensive workup in cases of unexplained AKI. The case also stresses the value of renal biopsies in determining the cause of AKI, especially when the clinical picture is unclear. The need to involve the poison center highlights the potential risks of unregulated supplements and the need for vigilance in monitoring and reporting adverse effects.

Healthcare providers should maintain a high index of suspicion for supplement-related adverse effects, conduct thorough medication histories, including over-the-counter products, and consider involving the poison center in cases where adulteration or contamination is suspected. Further research is needed to better understand the potential renal effects from high-dose vitamin B12 and folate supplements, as well as the need to improve regulatory oversight of the supplement industry.

Additional Information

Disclosures

Human subjects: Consent for treatment and open access publication was obtained or waived by all participants in this study. RHS Institutional Review Board issued approval NA. Dear Ms. Daly, this is to notify you that the project titled: Acute Kidney Injury Triggered by Vitamin B12-Methylfolate: A Cautionary Tale from Social Media Supplements was recently reviewed by the RHS IRB staff. Based on this administrative review the above mentioned project does not meet the definition of human subjects research as outlined in 45 CFR 46 and 21 CFR 56. Therefore, this project does not require RHS IRB oversight. Thank you for providing us with this information. Sincerely, Jennifer L. Brown Manager, RHS Institutional Review Board cc: Mike Dacey, Institutional Official Lauren Hurst, IRB Coordinator.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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