CLINICAL VIGNETTE

Cyclophosphamide and Acute Hyponatremia

Susan D. Leonard, MD

Case Report

An 81-year-old female was hospitalized for weakness and altered mental status. History includes atrial fibrillation, sick sinus syndrome status-post pacemaker placement, hypothyroidism, metastatic ovarian cancer complicated by malignant ascites. History also includes left sided breast intraductal carcinoma. She also has baseline chronic mild hyponatremia in the low 130's. The breast cancer s/p mastectomy and chemotherapy. She was later diagnosed with ovarian cancer and started on carboplatin and taxol. She underwent total abdominal hysterectomy and bilateral salpingo-oopherectomy (TAHBSO) with omentectomy and recently was put on a phase 2 study with bevacizumab and oral cyclophosphamide. Her sodium one week prior to hospitalization was at baseline in the low 130's. However, upon hospital admission, her serum sodium had decreased to 119. She was altered, lethargic, and complained of worsening headaches and nausea. Extensive evaluation for hyponatremia, was suggestive of syndrome of inappropriate aldosterone hormone (SIADH) secretion. Imaging including chest x-ray, and CT head were negative and laboratory data for thyroid or hormonal derangements were unrevealing. On further questioning, the patient reported drinking up to 7-8 glasses of water a day in attempt to stay hydrated due to chemotherapy treatments. The culprit was likely cyclophosphamide for her ovarian and breast cancer. Furthermore, the excessive free water intake exacerbated her sodium drop and contributed to her acute clinical decline. Her sodium eventually normalized after one dose of tolvaptan, a vasopressin receptor antagonist, and she was advised to drink ad lib only when thirsty to avoid extra free water intake. Cyclophosphamide was discontinued and her sodium normalized back to 135, which was better than her prior baseline.

Discussion

This case illustrates acute hyponatremia related to cyclophosphamide use. Cyclophosphamide is an alkylating agent widely used to treat neoplasms and many rheumatologic diseases with anti-neoplastic and immunosuppressive properties. It is one of the cornerstone agents for neo-adjuvant, adjuvant and metastatic breast cancer treatment.[1] Common side effects may include myelosuppression, nausea, diarrhea, and alopecia, but a rare and severe side effect can be hyponatremia. Symptomatic hyponatremia can be life threatening and can have dire consequences, especially if levels drop below 120 mmol/l.

Hyponatremia can manifest with mild symptoms of headache, nausea and weakness, but severe hyponatremia can cause CNS derangements including hallucinations, seizures, coma, and respiratory arrest leading to death. Those who have developed acute severe hyponatremia, need immediate treatment to avoid fatal outcomes. The mechanism by which cyclophosphamide causes hyponatremia is not fully understood. Proposed mechanisms include the syndrome of inappropriate antidiuretic hormone secretion.[2] This was supported by the postmortem examination of a patient that showed loss of Herring's bodies and degranulation of hypothalamic neurosecretory organelle. Cyclophosphamide metabolites can also cause increased ADH release which was first reported in 1974.[3] This agent affects water secretion, leading to decreased serum osmolarity and decrease in serum sodium. The drug could also have a direct toxic effect on the renal tubules causing increased anti-diuretic hormone activity.[4]

As cyclophosphamide is a common chemotherapy agent for breast cancer, several cases reported significant hyponatremia as a consequence of this drug. Clifton et al described cases.[5] The first was a 56-year-old female who received doxorubicin and cyclophosphamide for early breast cancer. She was also on opioids and anti-anxiety medication. After treatment with cyclophosphamide, she had a seizure and sodium was extremely low at 116, with serum and urine studies consistent with SIADH. The second case was a 70-year-old woman on cyclophosphamide for neoadjuvant breast cancer treatment. She was also on an anti-depressant and was drinking large quantities of water to prevent dehydration as advised by her oncologist. Her hyponatremia was 109 and required hypertonic saline treatment.

Bruining et al discussed reported a third case of a 64-year-old female with breast cancer who received three cycles of cyclophosphamide, and was also was on higher doses of citalopram for her depression.[6] The first cycle of treatment was adequately tolerated. Prior to the second cycle, her citalopram dose was increased due to worsening depression. She was also drinking excessive fluids to avoid side effects and hypovolemia from chemotherapy. She later presented with generalized seizures with convulsions, altered mental status with impaired speech which later progressed to complete unresponsiveness with sodium nadir of 107. With urgent correction with hypertonic saline and ICU monitoring, her symptoms gradually improved. Citalopram dose was later reduced and her sodium levels

eventually normalized. She was able to receive her final chemotherapy cycle without cyclophosphamide and her electrolytes remained stable.

These examples showed the potential adverse effects of the chemotherapy agent, with hyponatremia exacerbated by other contributors such as opioids and antidepressants that can potentiate SIADH. In addition, consumption of excessive free water lowered the sodium further to extremely low levels. Many are advised to drink high quantities of water to reduce the risk of hemorrhagic cystitis, further increasing the risk for hyponatremia. Other contributing factors include underlying renal dysfunction, hypoalbuminemia, drug-drug interactions, or co-administration of platinum compounds. Additional drugs such as diuretics or SSRIs can cumulatively contribute to the increased risk for hyponatremia. Evaluation, should rule out other potential causes for hyponatremia and SIADH including CNS disturbances, lung disease and other malignancies or endocrine disorders.

Conclusion

Cyclophosphamide is a popular agent used in treating malignant neoplasms such as breast cancer as well as certain autoimmune conditions. Although the true biochemical and molecular cause is unclear, various mechanisms have been proposed that can potentiate the risk of hyponatremia. It is important to be aware of the potentially life-threatening drug complication of severe hyponatremia.

Whether cyclophosphamide can be safely continued after an episode of acute hyponatremia, is still to be determined. It should be deferred to the discretion of the oncologist and patient, weighing the risks and benefits of treatment, the need for active clinical and laboratory monitoring, while considering overall goals of care. In addition to health provider education and awareness, patients should be counseled on the possible side effects and remain advocates for their own health. Informed decision-making should be an active part of the management regime and patients should notify their providers of any unusual symptoms. In conclusion, judicious consideration of treatment options, balanced with the review of patient's medical history and overall goals are paramount in determining the advised management strategy and reducing the risk of negative sequelae from cyclophosphamide and other drugs.

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