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PATIENT SAFETY NETWORK

Diuretics and Electrolyte Abnormalities

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Case Objectives

- Recognize that thiazide diuretics can lead to serious adverse events.
- State how commonly used thiazide diuretics can contribute to hyponatremia.
- Discuss risk factors that predispose to the development of thiazide-induced hyponatremia.
- List other common adverse effects of thiazide diuretics.
- Describe precautionary measures that may reduce the risks associated with thiazide diuretics.

The Case

A 62-year-old woman with morbid obesity and a past medical history of chronic obstructive pulmonary disease, hypertension, heart failure with preserved ejection fraction, diabetes mellitus, and a previous hospitalization for hyponatremia was seen by her primary care provider for a routine visit. At the visit, the patient complained of worsening lower extremity edema over the prior few weeks. She had no shortness of breath nor other new symptoms.

On examination, her blood pressure was well controlled (128/55 mm Hg) on an angiotensin-converting enzyme inhibitor, and her other vital signs were normal. She did have 1–2+ pitting edema of the bilateral lower extremities, slightly worse than her usual. Her primary care provider decided to prescribe chlorthalidone 50 mg daily for the edema, thinking it might also help with the patient's blood pressure. Her baseline creatinine was normal.

Ten days later, the patient presented to the emergency department (ED) with 3 days of worsening somnolence and confusion. Laboratory results revealed a serum sodium of 105 g/dL and a potassium of 2.3 g/dL. She had a seizure in the ED, which was treated with lorazepam, and she was admitted to the intensive care unit. The critical care provider consulted a nephrologist, and both agreed the severe symptomatic hyponatremia and hypokalemia had been caused by the chlorthalidone.

The patient was treated with hypertonic (3%) normal saline, potassium repletion, and supportive care. She had gradual improvement in her serum sodium and mental status over the next few days, and she was

discharged home on hospital day 5.

The Commentary

by Tobias Dreischulte, MPharm, MSc, PhD

This case illustrates how a commonly used medicine can lead to severe adverse events when not used judiciously and cautiously, especially in vulnerable patients. Specifically, the case highlights some of the risks associated with diuretics.

Chlorthalidone is a member of the class of thiazide diuretics, which are among the most widely used, effective, and least costly medications available. Thiazides are first-line antihypertensives (1), with all-cause mortality benefits equivalent to angiotensin-converting enzyme inhibitors or calcium channel antagonists.(2) Despite their benefits, many adverse effects are associated with thiazide diuretics, with hyponatremia one of the most potentially dangerous. Other adverse effects include hypokalemia, hypomagnesemia, and hypercalcemia.

Thiazide diuretics are one of the most common causes of hyponatremia. In one study, 14% of 951 thiazide-treated outpatients developed hyponatremia (serum sodium concentration 3) Hyponatremia may be asymptomatic but can also be associated with nausea, vomiting, altered mental status, and seizures, as in this case.

Thiazide diuretics act by reducing reabsorption of sodium (and chloride) in the distal renal tubules, which causes excretion of sodium in excess of water (hypertonic urine).(4) In contrast, loop diuretics act at the loop of Henle and lead to excretion of water in excess of sodium (hypotonic urine). Loop diuretics therefore do not cause hyponatremia, and in fact may cause hypernatremia when water losses are not sufficiently replaced. The hyponatremia that is occasionally observed under treatment with loop diuretics is usually due to the conditions they are commonly used to treat, namely heart failure and ascites.(5)

Thiazides can help reduce water retention in patients with mild congestive heart failure (loop diuretics are indicated in case of more severe symptoms), and worsening heart failure was a possible cause of the pitting edema of the bilateral lower extremities observed in this 62-year-old woman.(6) However, the patient did not report any other new symptoms suggesting heart failure exacerbation, such as increasing dyspnea, orthopnea, or rapid weight gain. Her edema also worsened over the course of weeks, whereas symptoms generally appear more suddenly when edema is caused by heart failure exacerbation or deep vein thrombosis.(7) In addition, her renal function was normal and she had no known history of liver disease. Therefore, it appears likely that her increasing pitting edema was due to a more benign cause such as worsening venous insufficiency.

The effectiveness of thiazide diuretics, or any diuretics for that matter, in treating edema of causes other than heart failure, liver disease, or renal disease is poor, and their adverse effects usually outweigh any benefits.(7) Occasionally, a short course of diuretics may be attempted when swelling due to venous insufficiency of the legs is particularly severe. However, the patient should be monitored closely, and diuretic treatment should be stopped if weight loss or a clear reduction in the swelling does not occur over the course of several days.

Nevertheless, thiazide diuretics remain a valuable therapeutic option in treating hypertension, and most patients do not develop hyponatremia. In fact, patients treated with thiazides generally don't experience meaningfully altered serum sodium concentrations. However, certain individuals may be particularly susceptible (2), and a growing body of research has identified risk factors.(2,4,5,8) The most common nonmodifiable risk factors include advanced age (due to declining ability of the kidneys to reabsorb sodium), female gender (possibly due to lower muscle mass), specific medical conditions (heart failure, liver disease, and malignancy, which themselves may cause hyponatremia), diabetes, and more than five comorbidities. In addition, a genetic predisposition is likely, given a high degree of reproducibility of hyponatremia on single-dose thiazide rechallenge.(2,9) Modifiable risk factors include unmeasured or low sodium at baseline (possibly due to low salt or high fluid intake), use of other medicines that may cause or exacerbate hyponatremia (selective serotonin reuptake inhibitors, nonsteroidal anti-inflammatory drugs, benzodiazepines, potassium-sparing diuretics), use of high doses, and use of chlorthalidone (which has a long duration of action) rather than shorter acting thiazides.(5,8)

Given that this patient had several nonmodifiable risk factors (female gender, heart failure, diabetes, and prior history of hyponatremia), starting treatment with a dose of 50 mg chlorthalidone was not a wise choice. For the treatment of hypertension, 12.5 mg to 25 mg doses are recommended. Either of these doses would also have been more appropriate if the chlorthalidone had been prescribed for her edema. In susceptible individuals, hyponatremia can develop rapidly after the initiation, and measuring sodium levels on the day of initiation and soon thereafter may have prevented the severe course of hyponatremia experienced by this woman.

Evidence-based guidelines to prevent thiazide-induced hyponatremia are lacking, so it is natural to be influenced by hindsight bias after hearing about a case like this one. However, several reasonable preventive steps have been recommended (although based on limited evidence) (5): (i) avoid thiazides in patients with a history of thiazide-induced hyponatremia; (ii) start with a low dose; (iii) counsel patients on the risk of excessive fluid intake; (iv) consider monitoring urea and electrolytes within 1–2 weeks after initiation in high-risk patients; and (iv) monitor electrolytes periodically thereafter. In addition, electronic health records (EHRs) could be harnessed to improve safe prescribing. The EHR could highlight risk factors for hyponatremia at the point of thiazide prescription, remind providers that thiazides cause hyponatremia, and notify providers when routine monitoring has been missed.

Take-Home Points

- Despite being widely used and recommended by guidelines, thiazide diuretics are a class of medicines that may cause severe harm if used inappropriately.
- The main adverse effects of thiazides include hyponatremia, hypokalemia, hypomagnesemia, and hypercalcemia.
- Thiazide-induced hyponatremia is an often underestimated risk that requires proactive management by clinicians and patients.
- A number of readily identifiable risk factors may predispose patients to thiazide-induced hyponatremia, and these should trigger precautionary measures.

- These measures include using low starting doses and intensified monitoring around the time of treatment initiation.

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