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Selected Topics: Critical Care

SEVERE HYPONATREMIA ASSOCIATED WITH THIAZIDE DIURETIC USE

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☐ **Abstract—Background: Thiazide diuretics are commonly used as first-line antihypertensive agents. Hyponatremia is a reported, though uncommon, complication of thiazide use. Although the exact mechanism of thiazide-induced hyponatremia (TIH) is unclear, it can be a significant cause of morbidity and mortality. Case Report: We report a 69-year-old man with generalized weakness beginning 2 weeks after starting hydrochlorothiazide (HCTZ). Evaluation revealed a serum sodium level of 120 mmol/L. The patient was admitted and successfully treated with free water restriction and discontinuation of the HCTZ. Why should an emergency physician be aware of this?: Hyponatremia is an uncommon complication of thiazide diuretic use, which frequently presents with nonspecific symptoms. Identification of TIH is crucial to prevent its potentially life-threatening complications.** © **2015 Elsevier Inc.**

☐ **Keywords—hyponatremia; thiazides; diuretics; hyponatremia management; thiazide-induced hyponatremia**

INTRODUCTION

Hyponatremia associated with thiazide diuretics was first described in 1962, not long after their introduction as antihypertensive agents (1). The exact mechanism of thiazide-induced hyponatremia (TIH) is unclear, though it is a known cause of significant morbidity and mortality (2,3). Although several studies of TIH have been published, it is not a well-described entity in the emergency medicine literature. We report a case of TIH in a 69-year-old man with recent initiation of hydrochlorothiazide.

CASE REPORT

A 69-year-old man was brought by his family to the Emergency Department (ED) for one week of generalized weakness. He also reported poor appetite and recent nausea but no vomiting. He denied any dizziness, confusion, headaches, or recent gait abnormalities. His past medical history was significant for hypertension, non-insulin-dependent diabetes mellitus, hyperlipidemia, and asthma. He denied tobacco, alcohol, and illicit drug use.

A review of his recent clinic visits revealed he had started a once-daily combination of hydrochlorothiazide (HCTZ) 12.5 mg and lisinopril 10 mg approximately 3 weeks earlier for hypertension. He began a reduced salt diet at the same time. One week later he was switched to HCTZ 25 mg alone, as the HCTZ/lisinopril combination was believed to be responsible for an elevated serum potassium of 5.7 mmol/L. Other serum values at that time included sodium 136 mmol/L, chloride 104 mmol/L, blood urea nitrogen (BUN) 26 mg/dL, and creatinine 1.2 mg/dL.

Upon arrival to the ED the patient was alert and oriented and able to give a complete and coherent history. He denied experiencing any recent chest pain or shortness of breath. He had a longstanding history of constipation, for which he took bisacodyl (Dulcolax; Boehringer Ingelheim, Ridgefield, CT). His other medications included; glipizide, lovastatin, metformin, and an albuterol inhaler. On presentation his vital signs

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were: blood pressure 153/72 mm Hg, pulse 92 beats/min, respiratory rate 16 breaths/min, and an oral temperature of 36.7°C (98.1°F). Physical examination revealed a well-nourished elderly man with no significant abnormalities. Specifically, he had no physical signs of dehydration and no abnormal findings on neurologic examination. Laboratory test results were significant for hyponatremia with a serum sodium of 120 mmol/L and hypochloremia with a serum chloride of 82 mmol/L. His serum potassium was 4.4 mmol/L, CO_2 28 mmol/L, BUN 20 mg/dL, creatinine 1.3 mg/dL, and glucose 264 mg/dL. Additional testing ordered in the ED included serum osmolality, magnesium, phosphorus, cortisol, and thyroid-stimulating hormone, as well as urine osmolality, urine creatinine, urine electrolytes, and urine specific gravity. The only abnormalities found on this additional testing were a serum osmolality of 263 mOs/kg (reference range 279–300 mOs/kg), urine osmolality of 210 mOs/kg (reference range 300–900 mOs/kg), and a urine-specific gravity of 1.002 (reference range 1.003–1.035). His urine sodium concentration at the time of admission was 20 mmol/L. After receiving 1 L of intravenous normal saline, the patient was admitted to the medical floor for further evaluation and treatment of hyponatremia.

Treatment of the patient's hyponatremia in the hospital consisted of a 1000 cc/day free water restriction, a general diet, and discontinuation of the HCTZ. On hospital day 2, the patient's serum sodium had increased to 128 mmol/L and his urine osmoles were 250 mOs/kg. His urine sodium concentration had increased to 29 mmol/L. His nausea and weakness had resolved and he was discharged home with instructions to discontinue the HCTZ and to adhere to a general diet. The patient had remained asymptomatic when seen by his primary care physician 3 days after hospital discharge. Serum laboratory values at that time were: sodium 132 mmol/L, chloride 97 mmol/L, potassium 5.2 mmol/L, BUN 20 mg/dL, creatinine 1.2 mg/dL, and glucose 281 mg/dL. The patient was instructed to no longer use HCTZ and was prescribed hydralazine for future blood pressure control.

DISCUSSION

Thiazide and thiazide-like diuretics are recommended as first-line antihypertensive medications by several authorities (4–6). These medications are often relatively inexpensive and are typically well tolerated by patients. Although much attention has been focused on hypokalemia caused by thiazides, their capacity to cause hyponatremia has also been well documented (2,3,7–10). Several authors have published case series attempting to identify which patient characteristics put them at increased risk for TIH (3,7,8,10). In general, patients with TIH are older than 65 years, female, and have a small body mass index. Chow et al. published the only case-control study of TIH and found advanced patient age, low body mass, residence in a long-term care facility, physical immobility, and a low serum potassium level to be risk factors for TIH (9).

TIH can develop acutely or gradually. The onset is within 2 weeks of starting the medication in 50–90% of cases, but can occur within a few days or even after a single dose (3,8,11,12). Hyponatremia can also occur years after taking a thiazide and is likely due to subsequent contributory factors such as a decline in renal function with aging, changes in water or sodium intake, or the ingestion of other drugs that affect free water clearance. Drugs known to increase the likelihood of developing TIH include nonsteroidal antiinflammatory drugs, carbamazepine, and selective serotonin reuptake inhibitors (13–15). Polydipsia caused by psychotropic medications may also predispose to TIH (16). Other drugs commonly associated with hyponatremia are listed in Table 1. In general, an increasing thiazide dose correlates positively with the development of hyponatremia (17). In one study of hypertensive patients who developed hyponatremia on diuretics, the average daily dose of those taking HCTZ was 35 mg. Forty-four percent of these patients were taking more than 50 mg daily, whereas only 10% were on a daily dose of < 25 mg (8).

Simply stated, TIH occurs when the intake of free water is greater than the amount the kidneys are able to excrete. Although the pathophysiology of TIH remains unclear, several mechanisms have been proposed. Sonnenblick

Table 1. Drugs Commonly Associated With Hyponatremia

Class	Drug
Loop diuretic	Furosemide
Anticonvulsant	Carbamazepine
Fibrate	Clofibrate
Methylxanthine	Theophylline
Antidysrhythmic	Amiodarone
Opiate	Morphine
ACE inhibitor	Enalapril
	Captopril
Hormone analogues	Desmopressin
	Oxytocin
Phenothiazine	Haloperidol
	Chlorpromazine
Oral hypoglycemic	Chlorpropamide
	Tolbutamide
Chemotherapeutic	Vinblastine
	Carboplatin
	Cisplatin
	Cyclophosphamide
Barbiturates	
Nonsteroidal antiinflammatory drugs	
Selective serotonin reuptake inhibitors	
Tricyclic antidepressants	

ACE = angiotensin-converting enzyme.