Case in Point

Hyponatremia Secondary to Lisinopril in a Veteran Patient

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Hyponatremia should be considered a potentially serious adverse effect associated with angiotensin-converting enzyme inhibitor therapy.

Angiotensin-converting enzyme (ACE) inhibitors are commonly used medications in the treatment of hypertension in the ambulatory care setting. Serum sodium concentrations are not usually affected in the majority of patients treated with ACE inhibitors. Nonetheless, hyponatremia, defined as serum sodium level < 135 mEq/L, has been reported in patients taking ACE inhibitors.[1,2] The authors report a case of hyponatremia attributed to the use of lisinopril.

CASE PRESENTATION

In 2012, a 49-year-old man with a past medical history significant for polysubstance abuse, alcohol use, and hypertension was referred to the pharmacy clinic by his primary care physician (PCP) for management of hypertension. At the PCP visit, the patient's blood pressure (BP) was above the goal of < 140/90 mm Hg and hydrochlorothiazide (HCTZ) 12.5 mg by mouth daily monotherapy was initiated. At the follow-up pharmacy appointment 6 weeks later, his BP remained uncontrolled, and HCTZ was increased to 25 mg daily. Of note, at that time the patient reported drinking about 6 beers per week. His electrolytes—serum sodium, potassium, chloride, carbon dioxide (CO_2), blood urea nitrogen (BUN), and serum creatinine (SCr)—were all within normal limits and stable to previous baseline results after taking HCTZ for about 2 weeks.

The patient returned to the pharmacy clinic at week 11, and his BP was controlled (136/83 mm Hg) on HCTZ 25 mg daily. His electrolytes, BUN, and SCr continued to be stable. The patient requested another appointment 8 weeks later to continue to monitor his BP.

The patient did not return to the pharmacy clinic until week 31, when he reported that he was told his BP was very high when attempting to donate plasma. The patient reported drinking a "6 pack of beer per day" at that visit. Two BP readings were taken in the clinic. The first of systolic blood pressure (SBP) was 144 mm Hg and the second was below the patient's goal (< 140 mm Hg). His pulse (94 bpm) was also noted to be higher than baseline range (66-84 bpm). Atenolol 25 mg daily by mouth was added to the patient's regimen of HCTZ 25 mg daily.

The patient returned at week 38, and his BP of 149/101 mm Hg was elevated above goal range. Lisinopril was added to HCTZ 25 mg in a combination formulation of lisinopril/HCTZ 20 mg/25 mg by mouth daily. The patient reported drinking 4 beers on days he worked (5 days per week) and 6 beers on days he was off (2 days per week). A repeated electrolyte, BUN, and SCr panel 1 month later (week 42) revealed a drop in the patient's sodium level from 136 mEq/L (baseline) to 130 mEq/L (Table 1). Other measured electrolytes remained within normal limits with the exception of a slight decrease in serum chloride to 93 mEq/L (Table 2). No symptoms of hyponatremia were noted.

The patient was instructed to cut the lisinopril/HCTZ tablet in half and take it daily, then repeat blood work in 5 days. The patient's repeated laboratory work noted an increase in sodium level to 134 mEq/L. All other measured electrolytes, including serum chloride, were within normal limits. During his follow-up visit, the patient reported stopping lisinopril/HCTZ altogether and resuming HCTZ 25 mg daily for the 5 days prior, in lieu of taking the reduced lisinopril/HCTZ dose as

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Table 1. Patient Therapy and Laboratory Results

Timeline	BP, mm Hg	Pulse, bpm	Drug Regimen	Serum Sodium, mEq/L	Serum Potassium, mEq/L
Baseline	150/100	71	Started HCTZ 12.5 mg daily	135	4.5
Week 2	-	-	HCTZ 12.5 mg daily	139	4.2
Week 6	159/112	84	HCTZ increased to 25 mg daily	-	-
Week 11	136/83	80	HCTZ 25 mg daily	136	4.4
Week 31	138/76	94	Started atenolol 25 mg daily HCTZ 25 mg daily	-	-
Week 38	149/101	66	Atenolol 25 mg daily HCTZ 25 mg daily Added lisinopril 20 mg daily	-	-
Week 42	-	-	Atenolol 25 mg daily Stopped lisinopril 20 mg Self-resumed HCTZ 25 mg daily	130	4.6
Week 43	136/84	80	Atenolol increased to 50 mg daily HCTZ 25 mg daily	134	4.8
Week 46	-	-	Atenolol 50 mg daily HCTZ 25 mg daily	139	4.4
Week 49	129/71	75	Atenolol 50 mg daily HCTZ 25 mg daily	-	-

Abbreviations: BP, blood pressure; HCTZ, hydrochlorothiazide.

instructed. The patient continued to report drinking 6 beers daily.

Medication was changed to HCTZ 25 mg daily, with lisinopril discontinued, and atenolol increased to 50 mg daily. At week 46, the patient repeated electrolytes, BUN, and SCr laboratory work while on HCTZ 25 mg and atenolol 50 mg daily, and the serum sodium level increased to 139 mEq/L. After the laboratory work at week 49, he noted a reduction in alcohol to 4 beers daily at the pharmacy appointment. The patient's BP was controlled to below the < 140/90 mm Hg goal. Medications were not changed. He was instructed to follow up with his PCP and return to the pharmacy clinic as needed for BP control.

Of note, serum magnesium levels are not included in the standard electrolyte panel and must be ordered separately. Additionally, serum magnesium levels are not monitored routinely with thiazide and ACE inhibitor therapy. In this case, serum magnesium levels were not drawn at baseline or in subsequent laboratory monitoring.

DISCUSSION

This case demonstrates a potential link between administration of lisinopril and the development of hyponatremia. Adverse effects (AEs) of ACE inhibitors frequently include elevation in SCr, hyperkalemia, and/or a dry cough. Hyponatremia, although not commonly associated with ACE inhibitors, has been reported in the literature.[1,2]

Although the mechanism is not completely understood, previous case reports hypothesized that ACE inhibitor therapy can lead to Syndrome of Inappropriate Antidiuretic Hormone (SIADH).[1,3] Angiotensin I is not converted to angiotensin II peripherally with ACE inhibitor therapy. This elevated circulating level of angiotensin I is available to cross the blood-brain barrier where it is converted to angiotensin II. Angiotensin can then stimulate vasopressin release, which, in turn, increases thirst and leads to decreased amounts of concentrated urine.[4] The combination of increased thirst and concentrated urine can lead to hyponatremia.

Table 2. Patient's Electrolyte and BUN/SCr Panel

Timeline	Serum Sodium, mEq/L	Serum Potassium, mEq/L	Serum Chloride, mEq/L	Serum CO_2, mEq/L	Serum BUN, mEq/L	SCr, mEq/L
Baseline	135	4.5	98	26	8	0.7
Week 2	139	4.2	98	26	7	0.7
Week 11	136	4.4	99	29	8	0.9
Week 42	130	4.6	93	27	10	0.8
Week 43	134	4.8	100	24	8	0.7
Week 46	139	4.4	102	30	8	0.8

Abbreviations: BUN, blood urine nitrogen; CO_2, carbon dioxide; HCTZ, hydrochlorothiazide.

The clinical manifestations of hyponatremia can vary. In patients with ACE inhibitor-induced hyponatremia, an early sign may be polydipsia. Once hyponatremia develops, patients may experience nausea, muscle spasms or weakness, and general malaise. Additionally, lethargy, a decreased level of consciousness, and headaches may occur. In the most severe cases, hyponatremia may lead to seizures, coma, and eventually death.

Several case reports involving various ACE inhibitors, such as captopril, enalapril, and lisinopril, have been reported over the past 30 years, citing the connection linking these medications to SIADH and symptomatic hyponatremia. A large number of cases involved patients with established congestive heart failure for whom ACE inhibitors were added because of their beneficial impact on improved survival and reduced left ventricular dysfunction.[5] Angiotensin converting enzyme inhibitor-induced hyponatremia may be confounded by heart failure, due to the complex disease pathophysiology.[1] Therefore, case reports of ACE inhibitors use in patients treated for indications other than heart failure, such as hypertension, provide a clearer picture of ACE inhibitor-induced hyponatremia.

One such striking case report involved a 63-year-old woman taking lisinopril 10 mg daily as monotherapy (no other medications) for mild hypertension with a baseline serum sodium level within normal limits.[6] One month later, the patient was admitted a with serum sodium level of 101 mEq/L and symptomatic with altered mental status and generalized tonic-clonic seizures. Once the serum sodium was corrected, the patient's mental status improved, and her 1-year follow-up examination was unremarkable. This case report is significant for its findings that there may be a cause-and-effect relationship between lisinopril monotherapy and symptomatic hyponatremia that occurred within a month.

There are cases of hyponatremia in patients receiving ACE inhibitor therapy in addition to established diuretic therapy. For example, a woman aged 71 years was admitted for elevated BP with an initial medication regimen that included HCTZ and other antihypertensive medications.[7] She was given captopril at increasing doses up to 150 mg daily. The patient's serum sodium levels dropped correspondingly with titrated doses of captopril. The patient reported feeling confusion, and her serum sodium levels dropped to 114 mEq/L. Once captopril was discontinued and serum sodium corrected with IV fluids, the patient's confusion subsided. The patient was discharged on a medication regimen that continued HCTZ but not the ACE inhibitor, with no clinical consequences and normal serum sodium levels over the following year. Similarly, the patient in this case study had established HCTZ therapy with normal serum sodium that declined upon addition of an ACE inhibitor.

Other factors that could contribute to hyponatremia, such as beer potomania, confound the current case of hyponatremia. This patient reported chronic beer ingestion, which can lead to hyponatremia and may have aggravated the hyponatremia upon initiation of lisinopril. Additionally, the patient was taking HCTZ, an agent known to cause hyponatremia, prior to initiation of the ACE inhibitor. Another limiting factor noted was that serum magnesium levels were not measured to assess for potential hypomagnesemia, which may affect other electrolytes.

Using the Naranjo Assessment scale, a score of 3 was calculated, in-

dicating a possible link to lisinopril as the cause of hyponatremia.[8] Although the patient had the aforementioned risk factors, the notable drop of serum sodium level correlated with the lisinopril administration, which was previously stable despite HCTZ treatment and alcohol consumption. The time line of events led the authors to believe that hyponatremia was strongly related to lisinopril. This patient was fortunate that he experienced no neurologic complications, which have been reported in other cases of ACE inhibitor-induced hyponatremia, manifested from the drop in serum sodium.

CONCLUSION

Though rarely occurring, hyponatremia should be considered a potentially serious AE associated with ACE inhibitor therapy. Timely monitoring of electrolytes, BUN, and SCr should continue to assess for more common AEs of elevated SCr and hyperkalemia, but clinicians should be aware of the potential for ACE inhibitor-induced hyponatremia.

Author disclosures

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