


Syndrome of inappropriate secretion of antidiuretic hormone associated with angiotensin-converting enzyme inhibitor therapy in the perioperative period

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Abstract

Introduction: Angiotensin-converting enzyme (ACE) inhibitors are one of the most commonly used medications for hypertension. Rarely, ACE inhibitors have the potential to cause a syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

Case presentation: A 70-year-old woman with > 10 years ACE inhibitor therapy with normonatremia suddenly developed severe SIADH when she took a liquid diet in the uneventful perioperative period, with hemodynamic stability and no surgical complications. She promptly recovered from SIADH subsequent to discontinuing the ACE inhibitor therapy and changing her diet. Therefore, it was assumed that excess antidiuretic hormone secretion due to an ACE inhibitor and free water load from the liquid diet contributed to hyponatremia in our patient.

Conclusion: Patients treated with an ACE inhibitor can latently experience inappropriate secretion of antidiuretic hormone, and rapidly develop severe hyponatremia together with additional factors affecting water or salt homeostasis regardless of the length of the administration duration. Clinicians should monitor serum sodium levels in such patients not only just after the initiation of ACE inhibitors but also upon the appearance of those factors.

Keywords

Syndrome of inappropriate secretion of antidiuretic hormone, hyponatremia, angiotensin-converting enzyme inhibitor, lisinopril, perioperative

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Introduction

Many hypertension guidelines mention angiotensin-converting enzyme (ACE) inhibitors as key medications for treating hypertension.¹ However, there are scant reports on ACE inhibitor use and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), in which patients develop SIADH mostly within 1 year after the start of treatment with ACE inhibitors. Because severe hyponatremia can cause irreversible brain damage and even death, early detection and appropriate treatment are crucial.² Here, we report the case of a woman who had been taking lisinopril for > 10 years and developed severe hyponatremia during the perioperative period. Early treatment produced a favorable outcome.

Case presentation

A 70-year-old woman with a history of hypertension who had taken lisinopril for > 10 years was admitted to our hospital for a pancreatoduodenectomy due to intraductal papillary mucinous carcinoma. Her blood pressure decreased to approximately 110 mm Hg (systolic) on post-operative day 1, and lisinopril was discontinued. She

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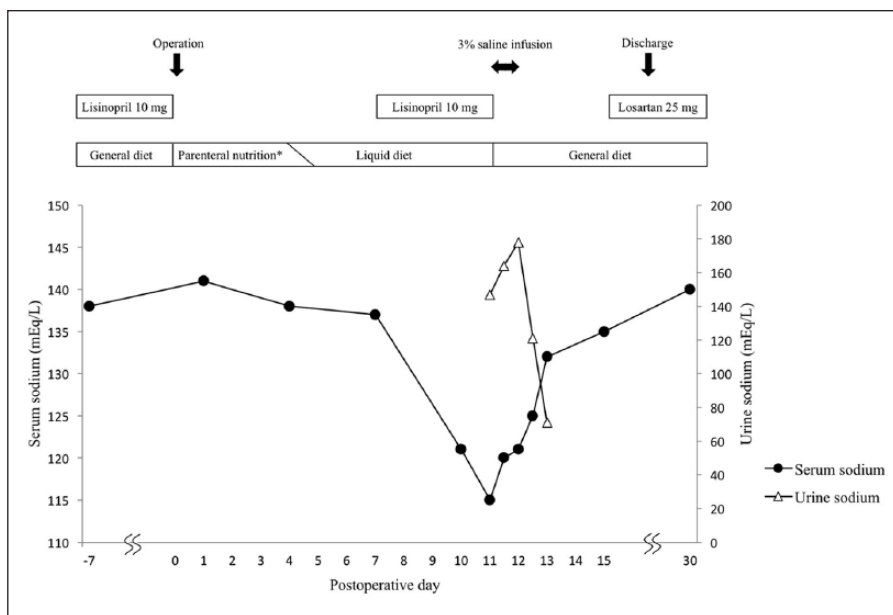


Figure 1. Clinical course.

*The sodium concentration was 75 mEq/L on postoperative day 1 and 50 mEq/L thereafter. The infusion volume was 40 ml/kg/day by postoperative day 3 and was subsequently tapered as the total volume was 40 ml/kg/day together with oral water administration.

received approximately 40 ml/kg/day infusion volume a day, and her urinary volume had been > 1 ml/kg/h. On postoperative day 4, she was started on a liquid diet and the infusion was tapered. On postoperative day 5, the intraperitoneal drain tube was removed and no surgical complications, such as anastomotic leakage, bleeding or ileus, were noted. She resumed lisinopril (10 mg) on postoperative day 7 after her blood pressure rose to approximately 150 mm Hg (systolic). However, she suddenly developed hiccups and fatigue 4 days later. She did not complain of abdominal pain. Her blood pressure was 142/79 mm Hg, her heart rate was 74 beats/min and her temperature was 36.2°C. The lung fields were clear to auscultation and neurological examination was symmetrical. She had no obvious symptoms of dehydration or overhydration. After taking lisinopril for 4 days, her serum sodium level decreased from 137 to 115 mEq/L (Figure 1). Other laboratory values included serum potassium 4.8 mmol/L, blood urea nitrogen 8.3 mg/dL, serum creatinine 0.42 mg/dL, uric acid 0.8 mg/dL, glucose 164 mg/dL, urine sodium 147 mmol/L, urine potassium 28.6 mmol/L, serum osmolality 245 mOsm/kg and urine osmolality 478 mOsm/kg. Thyroid, adrenal and liver function tests were normal. Chest X-ray revealed a cardiothoracic ratio of 49% and sharp costophrenic angles. Echocardiography revealed an ejection fraction of 60%, inferior vena cava diameter during quiet expiration 10 mm and during quiet inspiration 4 mm, and no valvular heart disease. At this point, she was suspected of having SIADH associated with lisinopril. After discontinuing lisinopril for 2 days and changing from a postoperative to a general diet with hypertonic saline administration, her serum sodium level increased

from 115 to 132 mmol/L and her urine sodium level decreased from 147 to 71 mmol/L. Moreover, her hiccups and fatigue, suspected to be due to hyponatremia, improved. Although she was started on losartan (25 mg), an angiotensin II receptor blocker (ARB), as a substitute for lisinopril on postoperative day 15, her serum sodium level was 141 mEq/L on postoperative day 30. Written informed consent for patient information to be published was provided by the patient.

Discussion

Our patient had been taking lisinopril (10 mg) for > 10 years without any side effects. After the operation, her urinary balance had been appropriate with hemodynamic stability, no surgical complications were noted and the wound pain also disappeared on postoperative day 6. These findings indicated that the postoperative process was uneventful. Although she received a postoperative diet with normonatremia for several days, her serum sodium level decreased rapidly 4 days after restarting lisinopril (10 mg) and normalized 2 days after discontinuing it. Therefore, it is possible that the latent inappropriate secretion of anti-diuretic hormone (ADH) due to lisinopril became evident with the increased water load from the postoperative diet.

Rarely, ACE inhibitors can cause SIADH, but the mechanism is unclear. We searched PubMed for the key words "ACE inhibitor, SIADH" and "ACE inhibitor, hyponatremia," and extracted 14 case reports in reference to the Saeed et al. diagnostic criteria for SIADH (Table 1).³⁻¹⁷ Although those criteria include no recent use of diuretic agents, we believe that hyponatremia, which is often

Table 1. Previous cases reporting relevance of angiotensin-converting enzyme inhibitors and syndrome of inappropriate secretion of antidiuretic hormone.

Reference (number)	Age (years)/sex	Past history	Serum sodium ^a (mEq/L)	ACE inhibitor		Onset of hyponatremia		Outcome
				Generic name	Administration period (month)	Hyponatremia-causing concomitant drugs	New factors affecting water or sodium homeostasis	
4	68/F	HT	Normal	Enalapril	4	Bendroflumethiazide Atenolol	Start of diuretics	Recovery
5	47/M	DCM	Not listed	Captopril	24	Furosemide	Exacerbation of heart failure	Recovery
6	63/F	HT	137	Lisinopril	< 1	None	None	Recovery
7	67/F	HT	141	Enalapril	< 1	None	None	Recovery
8	69/F	HT, DM	Not listed	Enalapril	4	None	None	Recovery
9	66/M	HT, IHD	132	Enalapril	< 1	Atenolol Amiloride Thiazide	Start of diuretics Cerebral hemorrhage	Recovery
10	76/F	HT	138	Lisinopril	66	Metoprolol Diclofenac	Increase of lisinopril	Recovery
11	85/F	HT, IHD	Not listed	Cilazapril	< 1	None	None	Recovery
12	60/M	DCM	140	Enalapril	< 1	Omeprazole	Myocarditis	Recovery
13	74/F	HT	Not listed	Lisinopril	< 18 (no follow-up)	None	None	Recovery
14	76/F	HT, AF, DM	Normal	Ramipril	< 1	Amiloride Hydrochlorothiazide	None	Recovery
15	5/M	HT ^b	140	Enalapril	< 1	None	None	Recovery
16	6/M	RCM	121	Cilazapril	< 1	Azosemide Trichlormethiazide	Exacerbation of heart failure	Recovery
17	78/F	HT	Normal	Enalapril	< 12	Chlorthalidone	Start of diuretics	Recovery
Our case	71/F	HT	137	Lisinopril	144	Lansoprazole	Free water load in perioperative period	Recovery

ACE: angiotensin-converting enzyme; AF: atrial fibrillation; DCM: dilated cardiomyopathy; DM: diabetes mellitus; F: female; HT: hypertension; IHD: ischemic heart disease; M: male; RCM: restrictive cardiomyopathy.

^aSerum sodium level before ACE inhibitor was added.

^bThe patient suffered from unilateral renal hypertension.

multifaceted, can result from both the use of diuretic agents and inappropriate ADH secretion. Consequently, we also extracted reports on patients undergoing diuretic therapy for hyponatremia to collect as much research as possible regarding the association between ACE inhibitors and ADH hypersecretion. However, only 7 patients did not receive diuretic agents, including our patient, whose hyponatremia was probably mostly due to the ACE inhibitor. We believe that ACE inhibitors are less frequently the primary cause of hyponatremia due to inappropriate ADH secretion than previously thought.¹²

The duration of ACE inhibitor administration varied widely, from 2 days to 5 years. Notably, almost all patients developed hyponatremia within 1 month of starting an ACE inhibitor, or based on the appearance of other factors affecting water or salt homeostasis, including exacerbation of respiratory or heart disease, adjustment of drugs affecting their homeostasis and a load of free water. This suggests that the additive factors first actualize inappropriate secretion of ADH by the ACE inhibitor. In fact, although

our patient had been taking the ACE inhibitor for > 10 years with normonatremia, she suddenly developed SIADH with a liquid diet, leading to a load of free water. Regardless of the duration of ACE inhibitor administration, ADH hypersecretion associated with ACE inhibitor therapy could be accompanied by the said factors affecting water or salt homeostasis.

The prognosis of ACE inhibitor-associated SIADH appears to be very good. All patients recovered from SIADH within 1 week of discontinuing ACE inhibitors and without any sequelae. In this context, the future management of hypertension remains controversial. Because two of four patients who relapsed when ACE inhibitors were reintroduced after cessation had improved their hyponatremia, we cannot recommend this approach.^{4,8-10} The mechanisms of action of calcium antagonists, alpha-1 antagonists and ACE inhibitors differ. To the best of our knowledge, an ARB has not induced SIADH, and a renin-angiotensin system inhibitor has the same effect as an ACE inhibitor. Consequently, we selected an ARB as an

alternative to an ACE inhibitor in the case of suspected SIADH associated with ACE inhibitor therapy, and our patient was normonatremic through postoperative day 30. Although it was necessary for our patient to consume a liquid diet with ARB therapy to adequately test this approach, she did not want to do so.

We still do not understand how ACE inhibitors induce SIADH. One possibility is that the ACE inhibitor blocks the conversion of angiotensin I to angiotensin II in the peripheral circulation, but not in the brain. Therefore, excess angiotensin I in the peripheral circulation enters the brain and is converted to angiotensin II, enhancing ADH secretion from the hypothalamus.^{18,19} Meanwhile, only five types of ACE inhibitor were reported to cause SIADH, and we have not found their pharmacokinetic properties to be different from other types of ACE inhibitors.^{20,21} In addition, we do not know why only a few patients are affected via this mechanism. Our search did not clearly reveal which patients are susceptible to ACE inhibitor-associated SIADH, but it appears to be more prevalent in women than in men (6 men and 10 women), and the majority of patients had a serum sodium level of < 140 mEq/L before starting the ACE inhibitor therapy. This might be related to the onset of ACE inhibitor-associated SIADH. It will be necessary to evaluate more cases that report an association between an ACE inhibitor and SIADH to better understand its underlying mechanisms and risk factors.

An ACE inhibitor can contribute to hyponatremia regardless of the length of the administration period. However, inappropriate secretion of ADH associated with ACE inhibitors may be overlooked in daily medical practice because, by themselves, ACE inhibitors induce symptomatic hyponatremia only very rarely. Clinicians should monitor serum sodium levels not only when an ACE inhibitor is introduced, but also on the appearance of factors affecting water or salt homeostasis.

Declaration of Conflicting Interest

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