

Severe Hyponatremia Associated with the Use of Angiotensin II Receptor Blocker/thiazide Combinations

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There are several widely used combinations of angiotensin II receptor blocker (ARB)/ thiazide. The complimentary mechanism of action for such anti-hypertensive therapies is that, while ARB inhibits the vasoconstricting and aldosterone-secreting effects of angiotensin II, hydrochlorothiazide affects the renal tubular mechanisms of electrolyte reabsorption and increases excretion of sodium and chloride in the distal tubule, consequently promoting water excretion. In addition, hypokalemia, which may be triggered by a hydrochlorothiazide-induced increase in urinary potassium loss, is resisted by the use of ARB. Hence, the ARB/thiazide combination is safe in terms of potassium imbalance. For these reasons, fixed-dose ARB/thiazide combination anti-hypertensive drugs have been widely used for the treatment of hypertension. However, there have not been many studies done regarding cases where patients under such regimens showed severe hyponatremia, even when the amount of thiazide included was low. Here we report two cases in which severe hyponatremia occurred following treatment with the ARB/thiazide combinations. Upon discontinuation of the regimen, both patients showed recovery from hyponatremia.

Key Words: Angiotensin II type 1 receptor blockers, Hydrochlorothiazide, Hyponatremia

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Introduction

Hypertension is one of the most important risk factors for cardiovascular diseases such as left heart failure, myocardial infarction, and renal disease. Accordingly, effective management of hypertension can lead to the prevention of damage to major organs. It is also an effective means of slowing the progress of diabetes mellitus and diabetic nephropathies.

ARB/thiazide combination regimen, an antihypertensive agent with improved hypotensive effects, have been accepted as safe in terms of electrolyte imbalance, thanks to its effects in alleviating hydrochlorothiazide-induced

hypokalemia. We present two cases of patients in whom improvement of hyponatremia was observed after discontinuation of the ARB/thiazide combination regimen.

Case Report

Case 1

A 73-year-old Asian woman presented with progressive general weakness after switching to a different antihypertensive regimen at a local hospital 1 month before. She had been diagnosed with hypertension 20 years previously and diabetes mellitus 10 years later, for which she was taking oral medications consisting of olmesartan me-

doxomil 40 mg qd, aspirin 100 mg qd, vildagliptin 50 mg qd and atorvastatin 10 mg qd; the antihypertensive agent was changed to olmesartan/hydrochlorothiazide 20/12.5 mg qd 1 month before presentation.

On arrival, the patient's vital signs were stable, and physical, neurological and radiological examinations were within normal limits with the exception of a decrease in skin turgor. Initial laboratory results were as follows: WBC 6,160/mm³, Hb 12.3 g/dL, Hct 35.6%, and Platelet 302,000/mm³; Na 115 mmol/L, K 3.9 mmol/L, Cl 83 mmol/L, uric acid 10.0 mg/dL, BUN 15 mg/dL, creatinine 0.5 mg/dL, and serum osmolality 247 mOsm/kg H₂O; and urine creatinine 65 mg/dL, urine urea nitrogen 620 mg/dL, urine Na 74 mmol/L, and urine osmolality 596 mOsm/kg H₂O. The patient's blood sugar was 118 mg/dL, and the HbA_{1c} level was 7.6%. Thyroid function test and rapid ACTH stimulation test results were within normal range.

Initial blood tests revealed the presence of hyponatremia with a Na level of 115 mmol/L; blood sugar was 118 mg/dL with serum and urine osmolality at 247 mOsm/kg H₂O and 596 mOsm/kg H₂O, respectively, upon which the possibility of hyperglycemia-induced pseudohyponatremia and hyponatremia caused by polydipsia was ruled out. The hypovolemic state and a high urine sodium concentration of 74 mmol/L implied the presence of sodium loss through the kidneys. Endocrine test results revealed no evidence of hypoaldosteronism. The absence of recent vomiting led to the diagnosis of drug-induced hyponatremia.

We initiated treatment for hyponatremia with alteration of the current antihypertensive regimen to olmesartan medoxomil 40 mg qd, in addition to a continuous intravenous infusion of 0.9% NaCl. On the following day, the patient's laboratory test results improved to Na 125 mmol/L, serum osmolality 270 mOsm/kg H₂O, urine osmolality 352 mOsm/kg H₂O, and urine Na 39 mmol/L. On the second day of admission, 0.9% NaCl infusion was discontinued as we continued observation of the patient. By simply adjusting the antihypertensive regimen, the serum Na level improved substantially to 135 mmol/L, while the patient's blood pressure continued to be under control at 120/80 mmHg. The patient's symptoms improved remar-

kably, and she was discharged.

Case 2

An 86-year-old Asian woman presented with general weakness which began on the day of presentation. She had been suffering from nausea while working in the fields in hot weather for 1 week prior to admission. The patient had been on losartan potassium/hydrochlorothiazide 50/12.5 mg qd, amlodipine 5 mg qd, and aspirin 100 mg for hypertension which had been diagnosed 4 years before.

On arrival, the patient's vital signs were stable, and physical, neurological and radiological examinations were within normal limits. Initial laboratory results were as follows: WBC 8,240/mm³, Hb 12.4 g/dL, Hct 33.5%, and Platelet 488,000/mm³; Na 102 mmol/L, K 3.5 mmol/L, Cl 67 mmol/L, BUN 10 mg/dL, creatinine 0.4 mg/dL, and serum osmolality 223 mOsm/kg H₂O; and urine creatinine 79 mg/dL, urine urea nitrogen 309 mg/dL, urine Na 79 mmol/L, and urine osmolality 398 mOsm/kg H₂O. The patient's blood sugar was 142 mg/dL, and the HbA_{1c} level was 5.6%. Thyroid function test and rapid ACTH stimulation test results were within normal range.

Initial blood tests revealed the presence of hyponatremia with a Na level of 102 mmol/L, and serum osmolality was also low at 223 mOsm/kg H₂O. Urine osmolality was 398 mOsm/kg H₂O, upon which primary polydipsia was ruled out; the patient was hypovolemic, in combination with endocrine test results, implied that the possibility of hypothyroidism, adrenal cortex dysfunction, or SIADH was low. An increased urine Na level of 79 mmol/L and normal aldosterone levels, with no history of vomiting, led to the diagnosis of diuretic-induced hyponatremia.

We changed the patient's antihypertensive medication to a single-drug regimen of amlodipine 5 mg qd. Hyponatremia was corrected with continuous intravenous infusion of 0.9% NaCl. On the following day, the serum Na level improved to 110 mmol/L; on the second day, it further improved to Na 121 mmol/L, at which point 0.9% NaCl infusion was discontinued.

On the fourth day of admission, the serum Na level and osmolality were substantially recovered to 130 mmol/L and 271 mOsm/kg H₂O respectively, with urine osmolality of 207 mOsm/kg H₂O and urine Na of 14 mmol/L. Blood pressure was stable at 120/80 mmHg. The patients' symptoms showed recovery and she was discharged.

Discussion

Angiotensin II which attaches to AT1 receptors affects vasoconstriction and intravascular volume expansion³. Olmesartan medoxomil has antagonistic effects specific to AT1 receptors located in vascular tissue^{4,5}. Losartan potassium, another ARB, is used interchangeably with olmesartan medoxomil as a part of antihypertensive therapy⁶.

Thiazide diuretics such as hydrochlorothiazide reduce plasma volume by increasing sodium excretion⁷. In addition, Kjeldsen et al. suggested that hydrochlorothiazide could activate the RAAS in relation to blood pressure, and thus hydrochlorothiazide in combination with ARB is more effective in lowering blood pressure than existing single-drug regimens⁸⁻¹⁰.

According to a study by Neutel et al., dizziness was the single complication with significance that occurred in patients more frequently under olmesartan medoxomil monotherapy than in the control group¹¹. In addition, Norwood et al. reported that adverse events related to treatment with olmesartan medoxomil were nearly equivalent to those of the placebo group, including headache and influenza-like symptoms, while dizziness was found in a higher number of cases¹².

In our cases, neither patient complained of dizziness, but did complain of constant general weakness. Metabolic disturbances and electrolyte imbalances including hypokalemia and hyponatremia were reported to be possible side effects of hydrochlorothiazide administration¹³.

Initial therapy for elderly patients with hypertension begins with diuretics, which effectively reduces the prevalence and mortality of cardiovascular diseases¹⁴. Hyponatremia which was observed in these case reports with initiation of the combination antihypertensive therapy in both patients, seems to have been induced by the use of

hydrochlorothiazide. Hyponatremia is an adverse effect of hydrochlorothiazide which is easily overlooked, while greater attention is paid to the prevention of hydrochlorothiazide-induced hypokalemia, as it can lead to sudden cardiac death^{15,16}. Hyponatremia is often found in the early stages of diuretic therapy^{17,18}. Kinoshita H et al. reported that hyponatremia was observed as a primary adverse effect in all ARB/thiazide combinations¹⁹. According to a report by Sharabi et al., hyponatremia was observed in 45% of patients 6 months after the initiation of diuretic¹³. Thus, continuous monitoring of blood electrolytes is necessary when administering diuretics as an antihypertensive therapy; symptoms such as general weakness or nausea could also be a sign of hyponatremia. Furthermore, usage of low-dose diuretics and constant monitoring of blood sodium level is strongly recommended in elderly female patients, as they are more susceptible to hyponatremia¹³. Additionally, in elderly patient with comorbid condition such as diabetes mellitus, telmisartan/hydrochlorothiazide may cause significant hyperkalemia and hyponatremia²⁰.

The patients in this case report presented with general weakness after administration of an ARB/thiazide combination regimen. Both were diagnosed with hyponatremia induced by hydrochlorothiazide; upon alteration of their antihypertensive regimen, blood pressure, blood sodium and osmolality returned to normal levels. We strongly recommend that antihypertensive therapy involving diuretics should always be accompanied by adequate monitoring for hyponatremia, as well as patient education regarding its symptoms and management.

References

1. Chobanian AV, Bakris GL, Black HR, et al.: Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 42:1206-1252, 2003
2. Cifkova R, Erdine S, Fagard R, et al.: Practice guidelines for primary care physicians: 2003 ESH/ESC hypertension guidelines. *J Hypertens* 21:1779-1786, 2003
3. Burnier M. Angiotensin II type 1 receptor blockers. *Cir-*

- ulation. 103:904-912, 2001
4. Mizuno M, Sada T, Ikeda M, et al.: Pharmacology of CS-866, a novel nonpeptide angiotensin II receptor antagonist. *Eur J Pharmacol* 285:181-188, 1995
 5. Koike H, Sada T, Mizuno M. In vitro and in vivo pharmacology of olmesartan medoxomil, an angiotensin II type AT1 receptor antagonist. *J Hypertens* 19:S3-14, 2001.
 6. Giles TD, Oparil S, Silfani TN, Wang A, Walker JF.: Comparison of increasing doses of olmesartan medoxomil, losartan potassium, and valsartan in patients with essential hypertension. *J Clin Hypertens* 9:187-195, 2007
 7. Meredith PA. Angiotensin II receptor antagonists alone and combined with hydrochlorothiazide: potential benefits beyond the antihypertensive effect. *Am J Cardiovasc Drugs* 5:171-183, 2005
 8. Kjeldsen SE, Os I, Høieggen A, Beckey K, Gleim GW, Oparil S: Fixed-dose combinations in the management of hypertension: defining the place of angiotensin receptor antagonists and hydrochlorothiazide. *Am J Cardiovasc Drugs* 5:17-22, 2005
 9. Manolis AJ, Grossman E, Jelakovic B, et al.: Effects of losartan and candesartan monotherapy and losartan/hydrochlorothiazide combination therapy in patients with mild to moderate hypertension. *Losartan Trial Investigators. Clin Ther* 22:1186-203, 2000
 10. Chrysant SG, Weber MA, Wang AC, Hinman DJ: Evaluation of antihypertensive therapy with the combination of olmesartanmedoxomil and hydrochlorothiazide. *Am J Hypertens* 17:252-259, 2004
 11. Neutel JM: Clinical studies of CS-866, the newest angiotensin II receptor antagonist. *Am J Cardiol* 87:37C-43C, 2001
 12. Norwood D, Branch E, Smith B, Honeywell M. Olmesartanmedoxomil for hypertension: a clinical review. *Drug Forecast* 27:611-618, 2002
 13. Sharabi Y, Illan R, Kamari Y, et al.: Diuretic induced hyponatremia in elderly hypertensive women. *J Hum Hypertens* 16:631-635, 2002
 14. Messerli FH, Grossman E, Goldbourt U: Are beta blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. *JAMA* 279:1903-1907, 1998
 15. Kostis JB, et al.: The effect of chlorthalidone on ventricular ectopic activity in patients with isolated systolic hypertension. The SHEP Study Group. *Am J Cardiol* 74:464-467, 1994
 16. Siegel D, Hulley SB, Black DM, et al.: Diuretics, serum and intracellular electrolyte levels, and ventricular arrhythmias in hypertensive men. *JAMA* 267:1083-1089, 1992
 17. Friedman E, Shadel M, Halkin H, Farfel Z: Thiazide induced hyponatremia. reproducibility by single dose challenge and an analysis of pathogenesis. *Ann Intern Med* 110:24-30, 1989
 18. Fichman MP, Vorherr H, Kleeman CR, Telfer N: Diuretic-induced hyponatremia. *Ann Intern Med* 75:853-863, 1971
 19. Kinoshita H, Kobayashi K, Yaguramaki T, et al.: Yasuda M, Fujiki K, Tomiyama J, Koga N, Yakushiji F. Losartan potassium/hydrochlorothiazide (Preminent[®]) and hyponatremia: case series of 40 patients. *Hum Exp Toxicol* 30:1409-1414, 2011.
 20. Cakir M: Significant hyperkalemia and hyponatremia secondary to telmisartan/hydrochlorothiazide treatment. *Blood Press* 19:380-382, 2010