

Hypokalemia and ST Elevation Induced by Angiotensin II Type 1 Receptor Blocker and Thiazide Diuretic Combination

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ABSTRACT

The combination of an angiotensin II type 1 receptor blocker (valsartan) and a thiazide diuretic (hydrochlorothiazide) has been evaluated in the treatment of patients with hypertension in several clinical trials. The valsartan/hydrochlorothiazide (VAL-HCT) combination was found to be generally more effective than either drug given alone.

The incidence of adverse events in VAL-HCT recipients was not significantly different than in placebo recipients. Valsartan attenuated the hydrochlorothiazide-associated decrease in serum potassium concentrations.

In this report, a 73-year old female patient, who after using VAL-HCT com-

bination for 1 month, was evaluated with lethargy, restlessness, atypical chest pain, and presyncope at our emergency room. She had ST elevation in D2, D3, aVF, and severe hypokalemia.

INTRODUCTION

Numerous studies have evaluated the antihypertensive efficacy of angiotensin II receptor antagonists in patients with mild to moderate or severe hypertension.¹⁻⁵ The antihypertensive effectiveness of angiotensin II receptor antagonists is potentiated by the addition of a small dose of a thiazide diuretic.⁶ The valsartan/hydrochlorothiazide (VAL-HCT) combination was generally more effective than either drug given alone.⁷

The incidence of adverse events in valsartan plus hydrochlorothiazide recipients was not significantly different than that in placebo recipients.



Figure 1. ST elevation on D 2,3, AVF at 9 AM.

Headache, dizziness, and fatigue were the most common adverse events occurring in clinical trials. Valsartan attenuated the hydrochlorothiazide-associated decrease in serum potassium concentrations; hypokalemia occurred in 4.5% of valsartan plus hydrochlorothiazide recipients.⁷

CASE

A seventy three year old female patient was evaluated at our emergency room in Duzce Medical faculty with symptoms of lethargy, restlessness, atypical chest pain, and presyncope. The patient had hypertension for 10 years and she was taking VAL-HCT 160/12.5 mg for 1 month after the discontinuation of ACE inhibitor due to dry cough. Other cardiovascular risk factors were not present.

Physical examination revealed systolic blood pressure of 90/60 mmHg, regular heart rate of 96 bpm, 37°C fever, and 3/5 muscular strength. Other findings were normal, as was chest x-ray. The ECG showed sinus rhythm, 1 to 2 mm ST elevation on D2, D3, aVF, and a negative T wave on AVL (Figure 1). Blood count, CK-MB, CPK, D-dimer, were all

normal, Troponin T was negative and other laboratory values were as follows: sodium, 128 mEq/L; potassium, 1.7 Eq/L; pH, 7.50; bicarbonate, 32 mEq/L.

The patient was triaged to the coronary care unit with a prediagnosis of acute inferior myocardial infarction. Thrombolytic therapy, 1.5 million units of streptokinase in 1 hour IV, was given. In addition, potassium (K⁺) replacement at 40 meq/hour was started because of hypopotasemia.

One hour later, ST elevations resolved and chest pain subsided (Figure 2). Serum potassium rose to 2.7 meq/ L. During the 1-week follow up at the cardiology clinic, cardiac enzymes did not rise. At the transthoracic echocardiography, a left ventricular wall motion abnormality was not seen and ejection fraction was 63%. Coronary arteries, visualized at the coronary arteriography, were normal. Ergonovine provocation was performed to exclude Prinzmetal's angina, but the result was normal. In addition, the myocardial perfusion imaging did not show any perfusion defects.

DISCUSSION

The results of the antihypertensive treat-

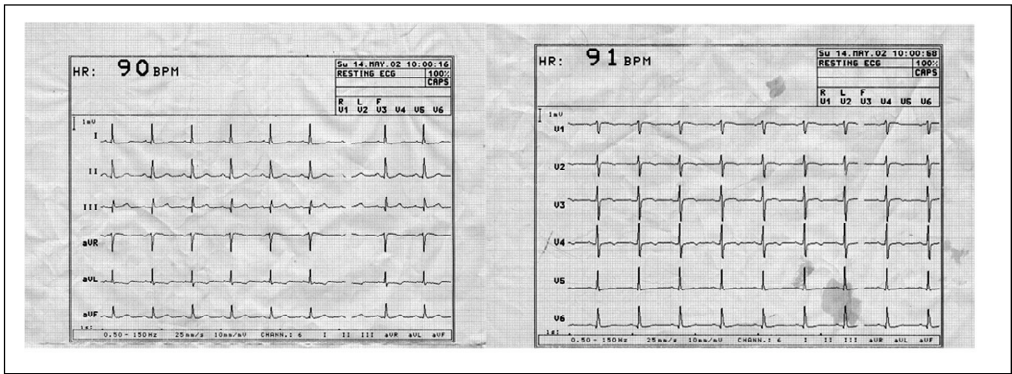


Figure 2. At 10 AM, 1 hour later, ST elevations resolved.

ment studies show that the angiotensin II antagonists are as effective as ACE inhibitors, calcium antagonists, Beta-blockers, and diuretics.²⁻⁴ The antihypertensive effectiveness of angiotensin II receptor antagonists are potentiated by the addition of a small dose of a thiazide diuretic.⁶

Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.⁶ ACE inhibitors and angiotensin receptor antagonists can cause hyperkalemia because of a decrease in aldosterone. This effect is usually not significant in patients with normal renal function.⁸

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in urinary potassium loss, plasma renin activity, and aldosterone secretion, and decreases in serum potassium.^{9,10}

Hypokalemia, defined as a plasma K^+ concentration less than 3.5 mmol/L, may result from one (or more) of the following: decreased net intake, shift into cells or increased net loss.^{11,12} The clinical manifestations of K^+ depletion vary greatly between individual patients, and the severity depends on the degree of hypokalemia. In patients without underlying heart disease, abnormalities in cardiac conduction are extremely unusual, even when the serum potassium concentration is below 3.0 mmol/L. In patients with cardiac ischemia, heart failure or left ventricular hypertrophy, however, even mild-to-moderate hypokalemia increases the likelihood of cardiac arrhythmias.¹³⁻¹⁵

The electrocardiographic changes of hypokalemia are due to delayed ventricular repolarization and do not correlate well with the plasma K^+ concentration. Early changes include flattening or inversion of the T wave, a prominent U wave, ST-segment depression. Severe K^+ depletion may result in a prolonged PR interval, decreased voltage, and widening of the QRS complex, and an increased risk of ventricular arrhythmias, especially in patients with myocardial ischemia or left ventricular hypertrophy. None of these changes are specific for hypokalemia.¹⁶

As noted above, ECG changes of

hypopotasemia are T wave flattening or inversion and ST segment depression. An increase in T wave amplitude is also reported, however, ST segment elevation is very unusual.¹⁷ In our case, an atherosclerotic lesion that might cause an ST elevation was not observed in the coronary angiography. In addition, the ergonovine test was negative. But, when the patient presented at our emergency room, she had severe hypokalemia and systemic alkalosis and the coronary arteriography was performed after they were corrected. Therefore, the ST elevation was thought to have been caused by a coronary artery spasm due to systemic alkalosis.

Diuretic therapy is the most common cause of hypokalemia. Hypokalemia during diuretic therapy is the result of excessive loss of potassium in the urine (kaliuresis). All diuretics (thiazides, loop diuretics, and carbonic anhydrase inhibitors) produce kaliuresis and hypokalemia of variable severity.¹⁸ Thiazide diuretics have frequently been recommended as combination therapy in patients with mild to moderate hypertension. However, their undesirable metabolic consequences have been suspected of contributing to increases in cardiovascular morbidity and mortality. Even at low doses, there is a definite decrease in potassium levels. The degree of decrease in potassium levels has been shown to be directly related to the hydrochlorothiazide dosage.¹⁹

In controlled trials comparing various doses of the combination of valsartan and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalemia (serum potassium < 3.5 mEq/L) was 4.5%, and the incidence of hyperkalemia (serum potassium > 5.7 mEq/L) was 0.3%.⁹ HCT-induced hypokalaemia is less common during combination therapy. Hypokalaemia, associated with the use of thiazide diuretics, was more common-

ly reported in the higher dose HCT 25 mg groups.²⁰ In controlled clinical trials of valsartan/hydrochlorothiazide, the average change in serum potassium was near zero in subjects who received valsartan/hydrochlorothiazide 160/12.5 mg, however, the average subject who received valsartan/hydrochlorothiazide 80/12.5 mg, 80/25 mg or 160/25 mg experienced a mild reduction in serum potassium.²⁰ Our patient, however, was on the 160/12.5 mg form of VAL-HCT combination for one month and other factors which could be responsible for severe hypopotasemia were not present.

As a result, although it is known that ACEI and angiotensin II receptor blockers are capable of causing hypopotasemia, it must also be kept in mind that diuretic combinations of these drugs can cause hypopotasemia, especially in older patients. Therefore, patients on thiazide should be carefully followed for electrolyte imbalance such as hypopotasemia, hypochloremic alkalosis, and hyponatremia periodically and when symptoms (ie, dry mouth, thirst, lethargy, restlessness, confusion, muscle pain, cramps, muscle weakness, oliguria, tachycardia, nausea, vomiting) occur, serum electrolytes should be urgently measured and necessary treatment instituted.

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