Case Report

A case of losartan-induced severe hyponatremia

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ABSTRACT

This case report outlines a very rare case of losartan-induced severe hyponatremia in a 73-year-old type 2 diabetic patient. The patient was initiated with 50 mg daily oral losartan monotherapy for newly diagnosed moderate hypertension. After 3.5 months of taking the drug, he presented to the emergency department in a drowsy state with severe generalized weakness and occasional palpitations. He was a known diabetic for the last 3 years and well controlled by oral metformin alone. On examination, his serum sodium level was found to be 123 meq/L. There were no evidences of any other possible metabolic, infective, organic or other pathologic causes giving rise to that condition, except losartan itself. De-challenge was done and he was treated vigorously resulting in reversal of the diseased state. Naranjo adverse drug reaction probability scale suggested that it was "probable" that oral losartan was responsible for the development of severe hyponatremia in this patient.

Key words: AV block, hypertension, hyponatremia, losartan, sodium

INTRODUCTION

Angiotensin (AT_1) receptor antagonist losartan potently and selectively inhibits most of the biological effects of angiotensin II like pressor responses, vasopressin release, release of aldosterone and adrenal catecholamines, enhancement of noradrenergic neurotransmission, increases in sympathetic tone, changes in renal function, etc., It is an approved and preferred first-line drug in hypertension with a favorable safety profile. It is also widely used in diabetic nephropathy as it is supposed to be reno-protective in type 2 diabetes mellitus, by some blood pressure-independent mechanisms.[1]

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All of the physiological effects of angiotensin II, including release of aldosterone, are antagonized in the presence of losartan. Reduction in blood pressure occurs independently of the status of the renin-angiotensin system. As a result of losartan dosing, plasma renin activity increases due to removal of the angiotensin II feedback. Losartan is well absorbed following oral administration and undergoes significant first-pass metabolism to produce 5-carboxylic acid metabolite. Metabolism is primarily by cytochrome P450 isoenzymes CYP2C9 and CYP3A4.

Losartan is excreted in the urine, and in the feces via bile, as unchanged drug and metabolites.[1]

Although teratogenic, losartan is otherwise a very safe drug. Few cases of cough and angioedema have been reported. In patients with advanced renal disease, it may cause hyperkalemia. Other rare adverse events include abnormal urticaria, hepatic dysfunction, hepatitis, agranulocytosis, neutropenia, leukopenia, Henoch-Schönleinpurpura, pruritus, hyponatremia, alopecia, and vasculitis.[1]

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CASE REPORT

A 73-year-old retired man, known diabetic and well controlled on oral metformin alone for last 3 years presented in the emergency in a drowsy state with severe generalized weakness. He reported to have nausea and occasional palpitations for the last week with occasional headache, confusion and severe lethargy in work.

Except being diabetic, he was absolutely well 3.5 months before, when he was diagnosed with asymptomatic moderate hypertension. Some routine blood tests done at that point of time are shown in Table 1. He was started with oral losartan, 50 mg daily and his blood pressure was adequately controlled within 2 weeks after taking the drug. He had no other relevant medical or surgical history. He was taking no other concomitant medications except metformin (500 mg twice daily). His bowel and bladder habits were also normal.

Table 1: Relevant blood investigation reports before initiating losartan therapy

Parameters detected	Values	Normal range
Hemoglobin	14.3 g/dL	13.3-16.2 g/dL
Total WBC count	8700/mL	4000-11000/mL
ESR	9.0 mm/h	0-15 mm/h
Fasting blood glucose	109 mg/dL	75-110 mg/dL
2 h postprandial blood glucose	132 mg/dL	70-120 mg/dL
Serum urea	82 mg/dL	70-120 mg/dL
Serum creatinine	0.9 ng/mL	0.6-1.2 ng/mL
Serum sodium	141 meq/L	136-146 meq/L
Serum potassium	4.2 meq/L	3.5-5.0 meq/L

WBC=White blood cells, ESR=Erythrocyte sedimentation rate

Table 2: Relevant blood and urine investigation reports after taking losartan (at the time of admission)

Blood investigation reports		
Parameters detected	**Values**	**Normal range**
Hemoglobin	14.2 g/dL	13.3-16.2 g/dL
Total WBC count	8800/mL	4000-11000/mL
ESR	9.3 mm/h	0-15 mm/h
Fasting blood glucose	104 mg/dL	75-110 mg/dL
2 h postprandial blood glucose	121 mg/dL	70-120 mg/dL
Serum urea	84 mg/dL	70-120 mg/dL
Serum creatinine	0.9 ng/mL	0.6-1.2 ng/mL
Serum sodium	123 meq/L	136-146 meq/L
Serum potassium	3.9 meq/L	3.5-5.0 meq/L
Plasma osmolality	281 mOsmol/kg serum water	275-295 mOsmol/kg serum water
Serum lipid profile		
Total cholesterol	180.0 mg/dL	200 mg/dL
LDL cholesterol	87.0 mg/dL	100 mg/dL
HDL cholesterol	53.0 mg/dL	40-60 mg/dL
VLDL cholesterol	40.0 mg/dL	6-40 mg/dL
Triglyceride	129.7 mg/dL	30-200 mg/dL
Liver function tests		
Total bilirubin	0.9 mg/dL	0.3-1.3 mg/dL
Direct bilirubin	0.2 mg/dL	0.1-0.4 mg/dL
Indirect bilirubin	0.7 mg/dL	0.2-0.9 mg/dL
Serum glutamic oxaloacetictransaminase	30.1 U/L	12-38 U/L
Serum glutamic pyruvic transaminase	23.2 U/L	7-41 U/L
Alkaline phosphatase	88.9 IU/L	20-140 IU/L
Albumin	4.3 g/dL	4.0-5.0 g/dL
Globulin	3.1 g/dL	2.3-3.5 g/dL
Urine investigation reports		
Urine osmolality	625 mOsmol/kg water	500-800 mOsmol/kg water
Urine sodium	112 mmol/24 h	100-260 mmol/24 h
Urine potassium	59 mmol/24 h	25-100 mmol/24 h

WBC=White blood cells, ESR=Erythrocyte sedimentation rate, LDL=Low density lipoprotein, HDL=High density lipoprotein, VLDL=Very low density lipoprotein

On examination, the patient was in a drowsy delirious state. The pulse rate was 90/min and blood pressure was 134/88 mmHg. Except peripheral edema, no other significant findings were noted. Relevant blood and urine investigations done immediately after admission are listed in Table 2. Twelve-lead ECG showed a picture of increased PR interval. CT scan of brain revealed cerebral edema.

The patient was managed with sodium repletion, in the form of isotonic saline, coupled with dietary water restriction and promotion of water loss in excess of sodium using 40 mg i.v. twice daily frusemide for 5 days. He was discharged after 1 week in a stable condition with normalization of blood reports. He was prescribed oral hydrochlorothiazide 25 mg daily for controlling blood pressure along with 500 mg twice daily metformin as before.

DISCUSSION

There was no history and evidence of excessive integumentary, gastrointestinal or renal primary loss sodium (and water) in this patient. Adrenal insufficiency (glucocorticoid deficiency), hypothyroidism, and psychogenic polydipsia were also excluded. There was no evidence of hepatic cirrhosis, heart failure or nephrotic syndrome. Chronic renal insufficiency was also ruled out from blood reports.[2] Blood and urine osmolality, serum albumin level, liver function test and serum lipid profile were within normal limits. These features suggest that there were no other etiologies of hyponatremia in the patient except losartan. Hypoalbuminemia was also eliminated. Brain edema and increased PR interval was probably due to hyponatremia.[2,3]

Hyponatremia with losartan is a chance occurrence; it may be explained by the hypothesis that AT_1 receptor inhibition causes an angiotensin II-mediated decrease in renal tubular sodium reabsorption and reduced aldosterone release, resulting in hyperkalemia and hyponatremia.Additionally, in elderly patient with comorbid condition such as diabetes mellitus, losartan alone or in combination with a thiazide diuretic may cause such hyponatremia.[4]

A case series of patients on AT II inhibitors and thiazide diuretics presenting with hyponatremia were reported by Kim *et al.*, Kinoshita *et al.* and Sharabi *et al.*[4-6] Although similar adverse effects were not reported earlier conclusively with losartan monotherapy, particularly in the Indian population, hyponatremia is not quite unlike with this drug.[5-9]

Naranjo adverse drug reaction probability scale[10] suggested that there was a "probable" relationship between administration of losartan and severe hyponatremia in this patient. Although a very rare finding, physicians should have high index of suspicion and rule out hyponatremia in patients taking losartan, who present with the symptoms of generalized weakness, lethargy and dizziness.

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