




# Hyponatremia Induced by Amlodipine

**Lissa S, Sidharta S**
Mitra Keluarga Kemayoran Hospital, Jakarta, Indonesia

ABSTRACT

**Introduction:** Hyponatremia (<135 mmol/L) is one of the most common electrolyte disturbances in clinical practice. Correct treatment can prevent worse outcomes. A case of hyponatremia supposedly induced by amlodipine besylate was presented. **Case:** A 74 year-old male with lethargy and occasional nausea and admitted to having chronic hyponatremia in the past years. He's been taking clopidogrel, simvastatin, and amlodipine besylate regularly since 7 years ago and had a history of coronary angioplasty 7 years ago. His lowest serum sodium level was 128 mmol/L even though he already took a 500 mg of sodium chlorine once daily. His serum sodium level never reached the normal range despite increasing salt intake and fluid restriction. Discontinuation of amlodipine besylate and change to nebivolol result in increased serum sodium level to 131 mmol/L. **Conclusion:** This case of hyponatremia may be induced by amlodipine.

**Keywords:** Amlodipine, electrolyte disturbance, hyponatremia

ABSTRAK

**Pendahuluan**: Hiponatremia (<135 mmol/L) adalah salah satu gangguan elektrolit yang paling umum dalam praktik klinis sehari-hari. Tata laksana yang tepat dapat mencegah prognosis lebih buruk. Laporan ini memaparkan kasus hiponatremia diduga disebabkan oleh *amlodipine besylate*. **Kasus:** Laki-laki berusia 74 tahun datang dengan lesu dan mual sesekali dan mengaku menderita hiponatremia kronis dalam beberapa tahun terakhir. Dia telah mengonsumsi *clopidogrel, simvastatin,* dan *amlodipine besylate* secara teratur sejak 7 tahun yang lalu dan memiliki riwayat angioplasti koroner 7 tahun yang lalu. Kadar natrium serum terendahnya adalah 128 mmol/L, meskipun sudah mengonsumsi kapsul natrium klorida 500 mg sekali sehari. Kadar natrium serumnya tidak pernah mencapai kisaran normal, meskipun asupan garam dan pembatasan cairan sudah ditingkatkan. *Amlodipine besylate* dihentikan dan diganti dengan *nebivolol*; setelah itu kadar natrium serum menjadi 131 mmol/L. **Simpulan:** Kasus hiponatremia ini mungkin diinduksi oleh *amlodipine*. **Lissa S, Sidharta S. Hiponatremia Diinduksi *Amlodipine*.**

**Kata Kunci:** *Amlodipine*, gangguan elektrolit, hiponatremia



## INTRODUCTION

Hyponatremia is defined by serum natrium concentration <135 mmol/L; mild hyponatremia is when the concentration is between 130-135 mmol/L, moderate hyponatremia when it is 120-129 mmol/L, and severe hyponatremia when it is <120 mmol/L.[1]

Based on serum osmolality, hyponatremia can be divided into three main categories, which are hypotonic, isotonic, and hypertonic.[1] Hypertonic hyponatremia is a consequence of water shift into extracellular fluid from cell cytoplasm, as in a hyperglycemia state. Every increase of 100 mg/dL serum glucose level above 100 mg/dL may reduce serum natrium concentration by about 1,7 mEq/L.[1] Isotonic hyponatremia is due to the retention of large volumes of isotonic, sodium-free fluids in the extracellular space; usually after invasive procedures using flushing solutions such as irrigants, glycine, sorbitol, or mannitol.[1] The most frequent cause of hypotonic hyponatremia is water retention, resulting in dilutional hyponatremia; hypotonic hyponatremia seems to be a disorder of water homeostasis instead. The causes of dilutional hyponatremia are impaired production of dilute urine and/or excessive water intake exceeding the kidney's excretory capacity for water.[2] In clinical situations, what we usually encounter is hypotonic hyponatremia.

The manifestations are mainly based on the rapidity of the hyponatremia onset, which is defined as acute (in the last 48 hours) or chronic (more than 48 hours). Chronic hyponatremia is usually less symptomatic; it usually occurs when the serum sodium level falls below 125 mmol/L. Severe symptoms may appear when serum sodium levels reach <120 mmol/L or even <110 mmol/L.[3]

Hypotonic hyponatremia with impaired urinary dilution is classified based on volume status: hypovolemia, hypervolemia, and euvolemia.[1] Hypovolemic hypotonic hyponatremia occurs when there's an intravascular volume depletion of any cause, for instance in hemorrhage, fluid loss from gastrointestinal disease, use of diuretics, or

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***Alamat Korespondensi*** *email: lissasab@gmail.com*

salt wasting in Addison crisis.[1] Hypervolemic hypotonic hyponatremia usually occurred in decompensated heart failure or advanced cirrhosis. The hypoperfusion with reduced effective circulating volume leads to vasopressin release resulting in water retention.[1] The main cause of euvolemic hypotonic hyponatremia is a syndrome of inappropriate antidiuretic hormone secretion (SIADH). Diagnosis of SIADH can be made when unsuppressed levels of arginine vasopressin (AVP) are detected.[4] SIADH is sometimes called a syndrome of inappropriate antidiuresis (SIAD). Some patients with this syndrome are identified with gain-of-function mutations of the vasopressin type 2 (V2) receptor genes which is constitutively activated and causes water reabsorption via the activation of aquaporin-2 in the collecting duct cells. It will cause plasma to be hypotonic, and it will inhibit ADH secretion.[1]

Recognition of the underlying disease is an important factor in treating hyponatremia. First, serum osmolality was measured for hypotonicity. Hyponatremia can be classified as vasopressin-mediated or vasopressin-independent by assessing urine osmolality. Urine sodium concentration should be measured to confirm SIADH.[4]

Fluid restriction intake is a basic management for hyponatremia, but a weak measure to restore water balance. The patient should also increase their oral salt consumption, whether from food or capsules, and protein intake should also be encouraged. If it is mild hyponatremia with no symptoms, the discontinuation and restriction of fluid should be sufficient to restore the serum sodium level to the normal range.[5]

The most serious clinical manifestations of acute severe hyponatremia are cerebral edema with brain herniation. Other nonspecific symptoms like headache, vomiting, and nausea can lead to seizures and respiratory arrest. The important key factors to prevent these complications are early detection and rapid management. Acute hyponatremia (moderate or severe) with symptoms should be treated with hypertonic saline such as 3% of sodium chlorine. Both United State and European guidelines recommend 100 -150 ml hypertonic saline boluses over 10–20 min that can be repeated 2–3 times until the symptoms are improved. This correction will increase serum sodium level by 4–6 mEq/L, resulting in the immediate reversal of cerebral edema.[4]

Hyponatremia correction with hypertonic solution such as sodium chloride 3% could lead to hypotonic environment in the brain, causing its cells to be depleted of its organic osmolytes, and the brain may get dehydrated and shrink if the tonicity in the surrounding brain increases faster than reaccumulation of effective osmoles in the brain. And if the correction of hyponatremia is too fast or overcorrected, osmotic demyelination syndromes (ODS) can occur.[4] Frequent monitoring of serum sodium levels is required to prevent overcorrection. Sequelae of ODS are often irreversible and include dysphagia, dysarthria, spasticity, behavioral disturbance, cognitive impairment, delirium, seizures, quadriparesis, coma, or locked-in syndrome.[4] Several notable risk factors for developing ODS are chronic hypotonic hyponatremia, an initial serum sodium level <105 mEq/L, alcoholism, advanced liver disease, and malnutrition state.[4] Severe hyponatremia should be corrected slowly.[4]

The frequent cause of hyponatremia is various medications such as diuretics, psychotropic drugs, and anticonvulsants. These drugs may cause hyponatremia through two mechanisms, either by affecting the homeostasis of sodium and water or by altering the water homeostasis as a consequence of the syndrome of inappropriate secretion of antidiuretic hormone. Rare causes of drug-inducing hyponatremia have also been reported, such as angiotensin-converting enzyme inhibitors, amlodipine, immune globulin (intravenous), ecstasy, antibiotics (trimethoprim-sulfamethoxazole, ciprofloxacin, cefoperazone/sulbactam, rifabutin), antiarrhythmic (amiodarone, lorcainide, propafenone, theophylline), proton pump inhibitors, bromocriptine, terlipressin, duloxetine, fluorescein angiography, and bupropion.[6]

Management of drug-induced hyponatremia is to discontinue all potential agents immediately. Previous and current medical history is important. Drug-induced hyponatremia patients are usually elderly people with polypharmacy. Any comorbidity, such as heart failure or cirrhosis, should be considered. The patient should also be advised to restrict their daily fluid intake.[5]

## CASE

A 74 year-old male with a history of hypertension and coronary artery disease came to our clinic with chronic lethargy, mild headache, and occasional nausea. Coronary angioplasty was done 7 years ago. He has been regularly taking clopidogrel 75 mg once daily, simvastatin 5 mg once daily, and amlodipine besylate 5 mg once daily. He's been having chronic hyponatremia with the lowest level of 128 mmol/L in the past year. He was advised to take sodium chloride capsules, but the natrium level never reached the normal range. The physical examination was unremarkable. Systolic blood pressure ranged between 130 to 160 mmHg with regular 70-80 heart beats per minute, no edema. Laboratory examination showed a prediabetic state with fasting blood glucose 108 mg/dL, hyponatremia 128 mmol/L and normal potassium level (3,9 mmol/L) and normal magnesium level (1,68 mg/dL); PSA level was below 1 ng/mL. Abdomen ultrasound showed that his prostate was mildly enlarged and protruded into the urinary bladder, indicating benign prostate enlargement. Post-voiding residual urine was 10:6 mL (the normal range for the elderly is 50-100 mL). We deduced that the hyponatremia might be due to polyuria because of prostatic hypertrophy; silodosin and nebivolol 2,5 mg once daily were added to his regular medication and sodium chloride capsules were stopped due to hypertension. After a year of treatment, he was still in hyponatremia with natrium level 126 mmol/L, so sodium chloride 500 mg once daily was given and fluid intake was restricted to 1-2 liters/day; and sodium level was elevated to 131 mmol/l. The sodium level remained 131 mmol/L despite increasing his intake of sodium chloride to 1 gram once daily. Hyponatremia is suspected to be induced by amlodipine besylate because several cases of amlodipine besylate induced hyponatremia have been reported8-10 and natriuretic is one of the mechanisms of amlodipine besylate. Amlodipine besylate and sodium chloride were stopped. After two months, his natrium level reached normal range. It was concluded that chronic hyponatremia may be induced by amlodipine besylate. Although simvastatin and clopidogrel can rarely cause hyponatremia[6] the continuation of both




medicines didn't result in hyponatremia.

## DISCUSSION

Pharmacologic agents have been implemented to induce hyponatremia, most commonly associated with diuretics, selective serotonin reuptake inhibitors and anticonvulsants.[5] The underlying pathogenetic mechanisms involve changes of sodium and water homeostasis (e.g., diuretics) or the water homeostasis due to syndrome of inappropriate secretion of antidiuretic hormone (SIADH). The mechanisms include: a) Increased antidiuretic hormone arginine vasopressin (AVP, also called ADH) secretion by the pituitary, b) Potentiating the effect of endogenous AVP on the renal medulla, and c) Resetting the osmostat to a lower threshold for AVP secretion.[5]

Amlodipine is an oral dihydropyridine calcium channel blocker used for hypertension therapy.[7] Amlodipine has the longest half-life at 30 to 50 hours compared to other medications in the dihydropyridine class. The benefit of such a long half-life is once-daily dosing.[7] Amlodipine also has natriuretic and diuretic characteristics. Low doses of calcium antagonists can cause a marked increase in urinary sodium by up to fourfold.[8] Another proposed mechanism of hyponatremia may be via direct action on the renal tubule with resultant increased sodium excretion and inhibition of renal sodium reabsorption. This natriuretic characteristic seems to be common to all dihydropyridine calcium channel blockers and may be the mechanism of causing hyponatremia.[8]

Several studies have reported hyponatremia induced by amlodipine. Tun, *et al*, reported a case of chronic hyponatremia (125 mmol/L) in patients that took amlodipine as an antihypertensive agent. Their euvolemic hypotonic hyponatremia resolved after discontinuation of amlodipine.[10] Han, *et al*, (2017)[8] also reported a geriatric patient with chronic hyponatremia taking amlodipine as her current antihypertensive drug; the lowest serum sodium level is 119 mmol/L. The hyponatremia was resolved with serum sodium level above 135 mmol/L after amlodipine was stopped. Malaterre, *et al*, also reported a geriatric case of hyponatremia induced by amlodipine despite taking 400 mg of chlorine per day. The patient's improved and serum sodium level raised within normal range with the discontinuation of amlodipine, increased salt intake, and fluid restriction.[9]

The exact mechanism isn't quite clear, but a hypothesis involved the natriuretic and diuretic effects of amlodipine. Hyponatremia is considered to be an adverse effect of the long-term use of amlodipine. The proposed mechanisms are: 1) Excess renal loss of potassium and sodium compared with water losses resulting from both diuretic-induced electrolyte losses and ADH-induced water retention; 2) Diuretic-induced volume depletion that will stimulate ADH secretion; 3) A coexistent hypokalemia leading to transcellular cation exchange: potassium leaves the cells to replenish the extracellular stores, and then sodium moves into cells to preserve electroneutrality; 4) Diminished sodium chloride reabsorption in the renal tubules will directly inhibit of urinary dilution; 5) Diuretic will stimulate thirst; 6) Magnesium depletion; and (7) Excessive ADH secretion.[11]

The continuation of clopidogrel and simvastatin didn't result in hyponatremia. And there are no reports of hyponatremia associated with clopidogrel and simvastatin.

Since amlodipine is one of the most common and frequently prescribed antihypertensive agents in clinical practice, this case that hyponatremia can rarely be associated with amlodipine use,[8-10] especially in the elderly with polypharmacy.

## REFERENCES


1. Peri A. Management of hyponatremia: Causes, clinical aspects, differential diagnosis and treatment. Expert Rev Endocrinol Metabolism 2019;14(1):13-21.
2. Burst V. Etiology and epidemiology of hyponatremia. Disord Fluid Electrolyte Metabolism 2019;52:24-35.
3. Peri A. Morbidity and mortality of hyponatremia. Disord Fluid Electrolyte Metabolism, 2019;52:36-48.
4. Kheetan M, Ogu I, Shapiro JI, Khitan ZJ. Acute and chronic hyponatremia. Front Med. 2021;8:693738.
5. Kim GH. Pathophysiology of drug-induced hyponatremia. J Clin Med. 2022;(11)19: 5810.
6. Liamis G, Megapanou E, Elisaf M, Milionis H. Hyponatremia-inducing drugs. Disord Fluid Electrolyte Metabolism 2019;52:167-77.
7. Godfraind T. Discovery and development of calcium channel blockers. Front Pharmacol. 2017;8:286.
8. Han J, Arasu A. A curious case of amlodipine induced hyponatremia. Proc UCLA Healthcare 2017;21:1-2.
9. Malaterre HR, Kallee K, Daver LMH. Hyponatremia and amlodipine therapy. Cardiovascular Drugs Ther. 1999;13(2):71.
10. Tun TZ, San NC, Fernando D. Amlodipine induced hyponatraemia. Clin Med. 2022;22(Suppl 4):41.
11. Liamis G, Milinois H, Elisaf M. A review of drug-induced hyponatremia. Am J Kidney Dis. 2008;52(1):144-53.