Chlorpromazine-Induced Severe Hyponatremia in 66 Years Old Patient

Sri Soenarti[*], *Muchammad Kamal Hadi*

Division of Geriatric and Medical Gerontology, Department of Internal Medicine, Faculty of Medicine Universitas Brawijaya - Dr. Saiful Anwar Hospital, Malang, Indonesia.

**** Corresponding Author:***
Sri Soenarti, MD., PhD. Division of Geriatric and Medical Gerontology, Department of Internal Medicine, Faculty of Medicine Universitas Brawijaya - Dr. Saiful Anwar Hospital. Jl. Veteran, Malang 65145, Indonesia. Email: sri_sunarti.fk@ub.ac.id.

ABSTRACT

Hyponatremia is a common clinical problem in older people. The aging process is usually accompanied by various maladaptations to stress in different organs and physiologic functions. Medications are often the cause of hyponatremia such as thiazide diuretics, antidepressants, antiepileptic and antipsychotics. Antipsychotics can lead to severe hyponatremia by the mechanism of the development of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). We report a patient who presented with severe hyponatremia due to Chlorpromazine and improved after receiving corrective hyponatremia.

Keywords*: Hyponatremia, aged, chlorpromazine, syndroma of inappropriate antidiuretic hormone.*

INTRODUCTION

Hyponatremia in older adults is a common clinical problem.[1] There are many causes of hyponatremia, including various medications. Medications that are often the cause of hyponatremia include thiazide diuretics, antidepressants, antiepileptic and antipsychotics.[2,3] Chlorpromazine, an antipsychotic approved by the Food and Drug Administration (FDA) for use in the treatment of hiccups (singultus), has a side effect of hyponatremia, by the syndrome of inappropriate antidiuretic hormone secretion (SIADH) mechanism.[3,4] Severe hyponatremia that occurs rapidly can be fatal as a result of cerebral edema.[1] Hyponatremia is independently associated with a 55% increase in the risk of mortality, substantial hospital resource utilization, and costs. Treatment of hyponatremia due to SIADH involves managing the underlying cause, cessation of the suspected drug, restriction of water intake and correcting serum sodium level.[5] Although it is easy to detect sodium levels from serum electrolyte tests and easy to provide sodium correction with fluid restriction or correction with saline, the treatment of hyponatremia is a challenge for doctors because the symptoms that appear are very varied and various underlying diseases, so a careful examination needs to be done to prevent the mortality.

We describe a patient who developed severe hyponatremia due to chlorpromazine administration, and who improved after receiving correction of hyponatremia in this case report.

CASE ILLUSTRATION

A 66-year-old male patient was brought by his family to the ER, Dr. Saiful Anwar with altered mental status, accompanied by weakness, difficulty communicating, confused and a history of repeatedly falling at home since 2 days prior

to admission. History of taking chlorpromazine 3 days before hospital admission, complaining of nausea, flatulence and hiccups, 25 mg b.i.d. for two days.

The patient has a history of diabetes mellitus since 30 years ago, with regular monitoring and routine administration of metformin 500 mg p.o. t.i.d., gliquidone 30 mg p.o. b.i.d., and acarbose 50 mg p.o. b.i.d. He also has history of hypertension since 10 years ago, treated with candesartan 16 mg p.o. o.d. No history of allergies. No patient's family who suffers from the same complaint.

The physical examination when he came to the Emergency Department Dr. Saiful Anwar Hospital showed; decreased consciousness (GCS 345), the patient opened his eyes with verbal stimulation, he was still disorientated and was able to localize painful stimulation. The patient's blood pressure was 179/110 mmHg, pulse is 106 beats per minute, and the others found no abnormalities.

The laboratory finding, was found severe hyponatremia 107 mmol/L with serum osmolality 231 mOsm/kg (hypoosmolar), hypokalemia 2.8 mmol/L and hyperglycemia with a random blood sugar 237 mg/dL.

From the chest x-ray examination, it was concluded an aortic sclerosis, and CT scan of the head, was shown there were subacute infarction of the left corona radiata, chronic infarction of the left lentiform nucleus, pons, senile brain atrophy, and right maxillary sinusitis.

We make hypothesis as delirium, hypertension, type 2 diabetes mellitus, severe hypoosmolar hyponatremia due to chlorpromazine induced SIADH, moderate hypokalemia and geriatric problems (innanition, instability). The patient received initial therapy to correct hyponatremia with 3% saline 41 ml/hour over 24 hours (total sodium deficit 585 mEq ~ 1,140 ml 3% saline). Correction of hypokalemia with KCl 25 mEq in NS 500 ml for 4 hours repeated for 3 times, citicoline 250 mg i.v. b.i.d., metoclopramide 10 mg i.v. t.i.d., candesartan 16 mg p.o. o.d., metformin 500 mg p.o. t.i.d., gliquidone 30 mg p.o. b.i.d., and acarbose 50 mg p.o. b.i.d.

Outcome and Follow Up

The patient was transferred to the High Care Unit for further evaluation and management. On the second day of treatment, the patient still complained of weakness, consciousness had begun to improve but still fluctuated from GCS 345 to 456. Blood pressure was 146/81 mmHg, and other vital signs were within normal limits. From the results of serum electrolytes, serum sodium level increased to 110 mmol/L, potassium level became 3.6 mmol/L and blood sugar level was 182 mg/dL. The patient was treated for correction of hyponatremia with 33 ml/hour 3% saline for 15 hours (total sodium deficit 487 mEq ~ 950 ml 3% saline).

On the third day of treatment, the patient still complained of feeling weak, no longer nauseous, and was able to eat by spending 1 portion. Mental status started to improve but remained fluctuating. Vital signs were within normal range. From the results of serum electrolytes, it was found that blood sodium levels were 119 mmol/L and blood glucose levels were 144 mg/dL. The patient received therapy for correction of hyponatremia with 31 ml/hour 3% saline for 12 hours (total sodium deficit 195 mEq ~ 380 ml 3% saline) and received salt capsules 1000 mg 3 times daily.

On the fourth day of treatment, the patient was fully conscious, there was no disorientation, the limp body had improved. The sodium level has increased to 126 mmol/L. The patient received maintenance fluid 0.9% saline 1,500 ml/24 hours and was transferred to the chronic ward.

On the fifth day of treatment, the patient felt improvement in his weakness. Vital signs were within normal limits, and the patient was allowed to go home that day.

Barthel ADL index assessment result before he was discharged suggested 16 points as opposed to the previous score of only 7 points, the patient experienced an improvement from a condition of severe dependence to mild dependence in carrying out daily activities. The subsequent outpatient follow-up visit showed that the Barthel ADL index was 20 points suggestive of functional independence. From the nutritional status of malnutrition screening (MNA) a score of 11 points was obtained as opposed to the previous 7 points, patients with nutritional status are at risk of malnutrition but have improved.

DISCUSSION

Hyponatremia is the most common electrolyte disturbance affecting 15–30% of hospitalized patients. Symptoms range from mild, nonspecific symptoms such as lethargy, agitation and confusion to severe life-threatening symptoms such as seizures, coma and ultimately death due to brain oedema. Medications are often the cause of hyponatremia resulting in hospitalization. Thiazide diuretics, antidepressants and antiepileptic drugs are the most frequent culprits. In addition, antipsychotics can occasionally lead to severe hyponatremia. Since decreased sodium values can result in symptoms resembling those seen in psychiatric conditions, including dementia, hyponatremia may be difficult to recognize.[2]

First-generation (typical) antipsychotics (FGAs) have been available for over 6o years and produce a combination of strong D2-antagonism together with anticholinergic and antihistaminergic effects. Antipsychotic drugs have been associated with hyponatremia in schizophrenia and other severe mental illnesses.[2]

One of the first generation antipsychotics is chlorpromazine. Apart from being an antipsychotic, chlorpromazine is the Food and Drug Administration (FDA)-approved treatment for persistent singultus, a medical problem where hiccupping can last for more than 48 hours. Persistent singultus can be treated by giving 25 to 50 mg of chlorpromazine orally every 6 to 8 hours. If hiccups persist even after oral treatment of 2 to 3 days, chlorpromazine is given as an intramuscular or intravenous dose.[4]

Antipsychotics have been hypothesized to promote ADH release through inducing hypersensitivity of the D2 receptor, hypotension related baroreflex stimulation, and serotonin-mediated effects (involving the 5-HT1A and 5-HT2 receptors). Patients with SIADH from psychotropic medications will have normal volume status, low serum osmolality (<285 mOsm/kg), and urine osmolality >100 mOsm/kg.[5]

Table 1 lists established risk factors and potential causes of SIADH. Patients over age 60 are at a higher risk of developing hyponatremia. The increased risk in the elderly is multifactorial in etiology and is likely to be secondary to lower total body mass and lower volume of distribution, which amplifies the impact of ADH-dysregulation, decreased glomerular filtration rate as well as increased rates of polypharmacy and medical comorbidity. Females have a higher risk of psychotropic medication-induced SIADH

Table 1. Risk factors and potential causes of SIADH[5].

Risk factors and potential causes of SIADH.		
Age	≥60 years old	
Sex	Female gender	
Nutritional status	Low Body Weight (BMI <18.5 kg/m2)	
Baseline Na	History of hyponatremia ([Na+] <135 mEq/L)	
Medications	CNS Active Drugs	Antipsychotics, Antidepressants, Amphetamines, Carbamazepine, Oxcarbazepine, Valproate, Opiates, Barbiturates, Nicotine, Bromocriptine
	Other Drugs	Amiodarone, Ciprofloxacin, Vincristine, Vinorelbine, Vinblastine, Cisplatin, Cyclophosphamide, Ifosfamide, Sulfonylureas, Interferons-alpha/gamma, NSAIDs, Methotrexate
CNS disorders	CVA, infection, TBI, hemorrhagea, MS, lupus cerebritis, epilepsy, hydrocephalus, encephalitis, meningitis	
Malignancies	Lung (especially small cell carcinoma), gastrointestinal, head & neck, genitourinary, sarcomas, lymphomas and neuroblastomas	
Pulmonary Disorders	Bacterial/viral infection, bronchial asthma, atelectasis, acute respiratory failure, pneumothorax, positive pressure ventilation, tuberculosis, aspergillosis, COPD, pulmonary fibrosis, sarcoidosis	
Major surgery	Abdominal, thoracic, brain	
Hormone administration or deficiency	Vasopressin, desmopressin, oxytocin	
Other	AIDS, Malaria, Rocky Mountain Fever, Hereditary SIADH, smoking	

than males. Underweight patients as well as those with a history of hyponatremia are also at an increased risk. Many non-psychotropic medications and medical conditions are associated with SIADH and may add to the risk of psychotropic-induced hyponatremia. Smoking is considered a risk factor for hyponatremia in the context of psychiatric illness and nicotine was found to stimulate ADH in humans.[5]

In this case, the patient was a 66-year-old man, with a history of taking the antipsychotic drug chlorpromazine on the indication of persistent hiccups for 2 days. There was no baseline data on the patient's previous sodium levels, no other risk factors.

The most common classification system for hyponatremia is based on volume status: hypovolemic (decreased total body water with greater decrease in sodium level), euvolemic (increased total body water with normal sodium level), and hypervolemic (increased total body water compared with sodium).[6,7]

Symptoms of hyponatremia depend on its severity and on the rate of sodium decline. Gradual decreases in sodium usually result in minimal symptoms, whereas rapid decreases can result in severe symptoms. Polydipsia, muscle cramps, headaches, falls, confusion, altered mental status, obtundation, coma, and status epilepticus may indicate the need for acute intervention. Most patients with hyponatremia are asymptomatic, and hyponatremia is noted incidentally.[6]

Euvolemic hyponatremia is most commonly caused by SIADH, but can also be caused by hypothyroidism and glucocorticoid deficiency. Euvolemia is diagnosed by findings from the history and physical examination, low serum uric acid levels, a normal blood urea nitrogen–to-creatinine ratio, and spot urinary sodium greater than 20 mEq per L. Diuretic therapy can artificially elevate urinary sodium, whereas a low-salt diet can artificially lower urinary sodium, thus clouding the diagnosis of hypovolemia versus euvolemia. Treatment generally consists of fluid restriction and correcting the underlying cause. Fluid restriction should be limited to 500 mL less than the daily urinary volume. Salt and protein intake should not be restricted. Predictors of failure with Salt and protein intake should not be restricted. Predictors of failure with fluid restriction include

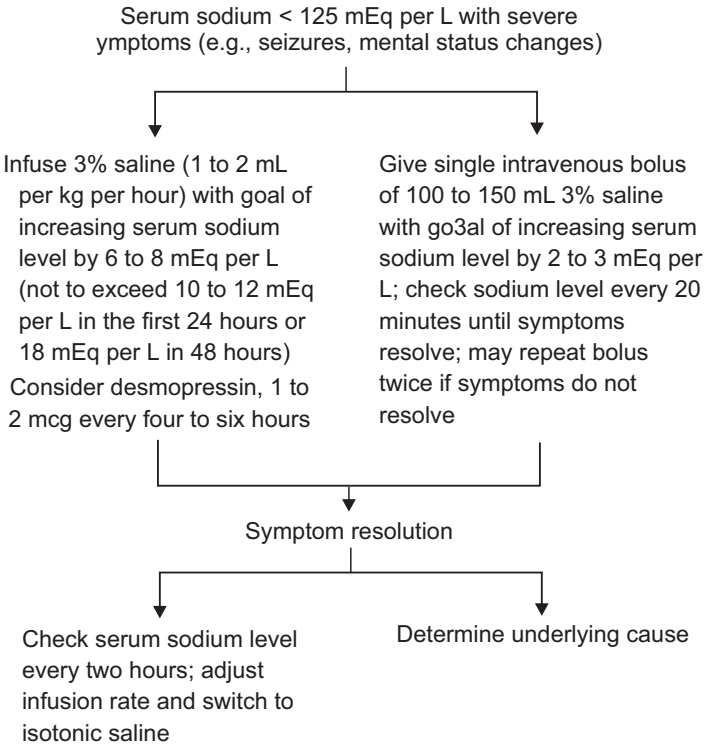

Figure 1. Algorithm for the treatment of severe symptomatic hyponatremia[6]

urinary osmolality greater than 500 mOsm per kg, 24-hour urinary volume less than 1.5 L, an increase in the serum sodium level of less than 2 mEq per L within 24 to 48 hours, and a serum sodium level less than the sum of the urinary sodium and potassium levels.[13] Volume status can be difficult to determine; therefore, a trial of intravenous fluids may be warranted.[6]

Severe symptomatic hyponatremia occurs when sodium levels decrease over less than 24 hours. Severe symptoms (e.g., coma, seizures) typically occur when the sodium level falls below 120 mEq per L, but can occur at less than 125 mEq per L. Severe symptomatic hyponatremia must be corrected promptly because it can lead to cerebral edema, irreversible neurologic damage, respiratory arrest, brainstem herniation, and death. Treatment includes the use of hypertonic 3% saline infused at a rate of 0.5 to 2 mL per kg per hour until symptoms resolve. The rate of sodium correction should be 6 to 12 mEq per L in the first 24 hours and 18 mEq per L or less in 48 hours. An increase of 4 to 6 mEq per L is usually sufficient to reduce symptoms of acute hyponatremia.[6] Oral salt tablets at 6–9 g per day in two to three divided doses is typically used to correct this level of hyponatremia. Correction calculations using salt tablets can be made knowing that a 1 g oral salt tablet is the equivalent to about 35 ml of a 3% saline solution.[5]

From this case, patient symptoms were decreased consciousness, lethargy, difficulty communicating, confused and a history of fall. From the laboratory examination, it was found that severe hyponatremia was 107 mmol/L with a serum osmolality of 231 mOsm/kg (hypoosmolar). The patient was treated for correction of hyponatremia with 3% saline 41 ml/hour for 24 hours. (total sodium deficit 585 mEq ~ 1,140 ml 3% saline).

CONCLUSION

Severe hyponatremia is associated with high morbidity and mortality. In order to implement correct treatment, an accurate clinical assessment must be made, focusing on potential etiology, chronicity and fluid status. It is crucial that a thorough investigation is made to secure the correct diagnosis.

A case has been reported, a 66-year-old man with a history of chlorpromazine treatment for the indication of singultus and a patient who fell into severe hyponatremia with complaints of loss of consciousness, weakness, difficulty communicating, confusion and a history of repeated falls. The patient received corrective therapy for hyponatremia with intravenous sodium and oral saline and the patient experienced improvement in both clinical and laboratory conditions.

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