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Journal of Movement Disorders 2011;4:46-48
pISSN 2005-940X / eISSN 2093-4939

CASE REPORT

Syndrome of Inappropriate Antidiuretic Hormone Secretion Associated with Pramipexole in a Patient with Parkinson's Disease

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The syndrome of inappropriate antidiuretic hormone secretion (SIADH) can be caused by a variety of drugs. Dopaminergic drugs might enhance the secretion of the antidiuretic hormone arginine vasopressin by reducing γ-amino butyric acid release through the dopaminergic receptor in supraoptic nucleus. A 75-year-old woman with Parkinson's disease developed asthenia, delirium, aggravated parkinsonian symptoms, and hypotonic hyponatremia along with the diagnostic criteria for SIADH during dose escalation of pramipexole. After pramipexole withdrawal, these symptoms disappeared, and sodium levels returned to normal values. The serum sodium levels of patients receiving pramipexole should be monitored, especially during dose escalation. **Journal of Movement Disorders 2011;4:46-48**

Key Words: Pramipexole, SIADH, Hyponatremia.

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is considered to be the most frequent cause of hyponatremia.[1] It is characterized by the following essential diagnostic criteria: 1) hypotonic hyponatremia, 2) a urine concentration inappropriate for the plasma osmolarity (> 100 mOsm/kg), 3) increased renal sodium excretion (> 30 mEg/L), 4) clinical euvolemia, and 5) normal renal, adrenal, and thyroid function.[2]

SIADH can be induced by malignant diseases, pulmonary disease, and disorders of the central nervous system.[3] In addition, the SIADH can be caused by a variety of drugs, mainly antipsychotic drugs, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, carbamazepine, and cytotoxic drugs.[3] Amantadine also has been reported to be associated with the SIADH.[4,5]

Hyponatremia can cause headache, nausea, vomiting, muscular weakness, bulbar palsy, confusion, and convulsions.[4] The clinical symptoms associated with hyponatremia may mimic some progression of parkinsonism in a patient with Parkinson's disease. We report a patient with Parkinson's disease who developed transient worsening of parkinsonian symptoms and SIADH related to treatment with pramipexole.

Case

A 75-year-old woman visited our neurology outpatient clinic because of feeling of leg weakness. She had chronic obstructive pulmonary disease and diabetes mellitus that was well controlled with 2 mg glimepiride. Upon neurological examination, she had a masked face, bradykinesia, a stooped posture, and limb rigidity that was more severe on the right side; she was diagnosed with Parkinson's disease. The medication taken by this patient was summarized in Figure 1. Her treatment started with 100 mg amantadine and 0.375 mg pramipexole per day, and her clinical symptoms slightly improved. After two weeks, the dosage of pramipexole was increased to 0.75 mg per day, and 0.375 mg alprazolam and 100 mg aspirin per day were added because of anxiety and mild white matter changes on T2-weighted magnetic resonance

Received September 29, 2010
Accepted October 14, 2010

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· The authors have no financial conflicts of interest.

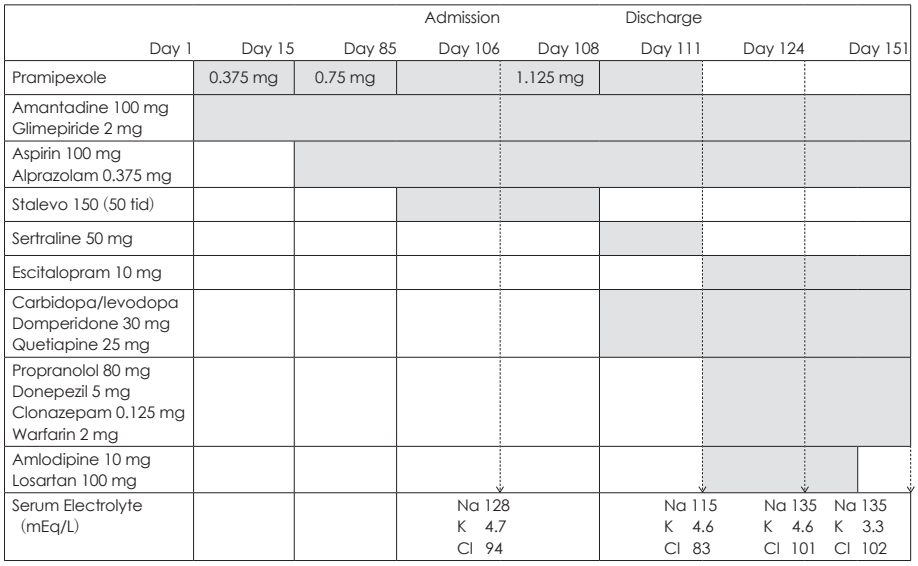

Figure 1. Overview of medication taken by this patient. The dosages are the amount taken daily. The gray-colored columns mean the durations of taking drugs.

images of the brain. After ten weeks, the dosage of pramipexole was increased to 1.125 mg per day, and levodopa/carbidopa/entacapone at 150/37.5/600 mg (Stalevo 50 tid) per day was added to treat postural instability and increased rigidity. After three additional weeks, she was admitted to our hospital because of asthenia, frequent falling, more aggravated rigidity, and dysarthria. Biochemical studies showed a serum sodium level of 128 mEq/L, a serum potassium level of 4.7 mEq/L, a serum chloride level of 94 mEq/L, a serum urea level of 23.1 mg/dL, and a serum creatinine level of 0.84 mg/dL. On the third day in the hospital, 50 mg sertraline was added. On the fourth day in the hospital, Stalevo was switched to carbidopa/levodopa at 37.5 mg/375 mg per day, and domperidone 30 mg per day was added. On the fifth day in the hospital, 25 mg quetiapine was added because of delirium. On the sixth day, sertraline was switched to 10 mg escitalopram, and biochemical studies showed a serum sodium level of 115 mEq/L, a serum potassium level of 4.6 mEq/L, a serum chloride level of 83 mEq/L, a serum osmolarity of 247 mOsm/kg, a urine osmolarity of 311 mOsm/kg, a urine sodium level of 56 mEq/L, a urine potassium level of 21.7 mEq/L, and a urine chloride level of 51 mEq/L. A thyroid function test was normal. She did not have any clinical evidence of adrenal insufficiency. She also did not have any hypervolemic features, such as subcutaneous edema, or any hypovolemic features, such as orthostatic hypotension, increased pulse rate, or dry mucous membranes. She did not have weight loss or any clinical symptoms that were related to malignancy. The serum levels of alpha-fetoprotein, cancer antigen-125, carbohydrate antigen 19-9, and beta-human chorionic gonadotropin were in normal range. She was diagnosed with SIADH possibly induced by a drug. The clinical symptoms and the serum sodium levels improved after stopping pramipexole. On the 19th day in the hospital, which was also the day of discharge, her medication consisted of 100 mg amantadine, carbidopa/levodopa at 225 mg/1,125 mg, 30 mg domperidone, 80 mg propranolol, 25 mg quetiapine, 5 mg donepezil, 10 mg escitalopram, 2 mg glimepiride, 0.125 mg clonazepam, 0.375 mg alprazolam, 100 mg aspirin, 10 mg amlodipine, 100 mg losartan, and 2 mg warfarin per day because of deep vein thrombosis, and biochemical studies showed a serum sodium level of 135 mEq/L, a serum potassium level of 4.6 mEq/L, and a serum chloride level of 101 mEq/L. Two weeks after discharge, amlodipine and losartan were stopped because of low blood pressure. On the 27th days after discharge, biochemical studies showed a serum sodium level of 135 mEq/L, a serum potassium level of 3.3 mEq/L, and a serum chloride level of 102 mEq/L.

Discussion

Our patient developed SIADH 21 days after increasing the dosage of pramipexole, and SIADH disappeared after pramipexole withdrawal. The temporal relationship between the development/disappearance of SIADH and the pramipexole dosage suggests a possible cause-effect relationship between pramipexole and SIADH.

The development of SIADH associated with amantadine has been rarely reported.[4,5] Although our patient continued to take amantadine, SIADH disappeared after pramipexole withdrawal. Therefore, SIADH was associated with parmipexole in our patient. SSRIs can also induce SIADH.[3] Our patient took sertraline after the development of hyponatremia, and sertraline was switched to escitalopram without a washout period. Pramipexole withdrawal induced the disappearance of SIADH in spite of her taking an SSRI. Therefore, SIADH was not associated with SSRIs in our patient.

Arginine vasopressin (AVP) is induced by noradrenalin and serotonin through adrenergic α1 receptor and 5-HT2A/2C receptors in supraoptic nucleus.[6,7] AVP-secreting supraoptic neu-

rons are under the control of prominent γ-amino butyric acid (GABA) inhibition, and D4 receptors are located on GABA terminals in the rat supraoptic nucleus.[6] Dopaminergic activation via D4 receptors reduces GABA release in the supraoptic nucleus, and then AVP release is facilitated.[6] Pramipexole has a high affinity for the D2, D3 and D4 receptors.[7,8] Therefore, a possible explanation for SIADH in this patient is the pramipexole-enhanced AVP secretion resulting from reducing GABA release through D4 receptors in the supraoptic neurons. Pramipexole has a higher selectivity for D4 receptor than other dopamine agonists.[9] Thus, it may be more likely to increase AVP secretion compared with other dopamine agonists.

This case had some limitations. Although she did not have any clinical evidence of adrenal insufficiency or malignancy, we did not perform adrenal function test and thorough diagnostic work-up to exclude adrenal insufficiency and malignancy. We did not think that drug interactions between pramipexole and other drugs contributed to inducing SIADH in this case because 90% of pramipexole is excreted unchanged in the urine.[9] However, the synergistic effect of amantadine and pramipexole on inducing SIADH could not be excluded in this case.

In this case, the SIADH induced rapid aggravation of parkinsonian symptoms such as falling, rigidity, and dysarthria, but those symptoms were fully recovered as correcting hyponatremia. Clinicians should consider medical derangement when a rapid aggravation of parkinsonian symptoms is developed in a patient with Parkinson's disease. Recently, two cases with SIADH induced by pramipexole were reported.[7,10] In one case, SIADH developed during first two weeks of pramipexole therapy,[10] and in the other case, SIADH developed during dose escalation of pramipexole,[7] as with our patient.

Pramipexole might facilitate AVP secretion in some patients, which is a prerequisite for developing SIADH. The serum sodium levels of patients receiving pramipexole should be monitored, especially in the first few weeks after starting therapy and during dose escalation.

Acknowledgments

This study was supported by a grant of the Inha Univeristy School of Medicine, Incheon, Republic of Korea.

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