https://doi.org/10.5664/jcsm.8970

JCSM | Journal of Clinical Sleep Medicine

CASE REPORTS

Syndrome of inappropriate antidiuretic hormone secretion induced by suvorexant: a case report

Manabu Takano, MD; Tsuyoshi Okada, MD; Toshiyuki Kobayashi, MD, PhD; Shiro Suda, MD, PhD

Department of Psychiatry, Jichi Medical University, Tochigi, Japan

Syndrome of inappropriate antidiuretic hormone release (SIADH) can sometimes be caused by an adverse effect of certain psychotropic drugs. However, suvorexant has never been reported to cause SIADH. A 77-year-old man with type 2 diabetes was admitted to the Jichi Medical University Hospital for the treatment of major depression. During the treatment, he was prescribed suvorexant for insomnia. Twelve days after the initiation of suvorexant, he developed hyponatremia, which met the diagnostic criteria of SIADH. We suspected the hyponatremia to be an adverse drug effect of suvorexant because no other cause for SIADH was detected. Accordingly, suvorexant was discontinued 15 days after the onset of SIADH, and hyponatremia improved in 6 days. Although suvorexant has fewer adverse drug reactions and is considered relatively safe, clinicians should be aware of the possibility of SIADH induced by suvorexant.

Keywords: suvorexant, syndrome of inappropriate antidiuretic hormone secretion, adverse drug reactions

Citation: Takano M, Okada T, Kobayashi T, Suda S. Syndrome of inappropriate antidiuretic hormone secretion induced by suvorexant: a case report. *J Clin Sleep Med*. 2021;17(3):593–594.

INTRODUCTION

Suvorexant, a novel hypnotic drug, shows selective and dual orexin receptor antagonism (orexin receptor 1/2).[1] Although it has some adverse effects, such as somnolence, fatigue, and unusual dreams,[1] it has been generally considered to be safe and well tolerated, with a lower risk of dependence and cognitive impairment than benzodiazepines. Herein, we report the first case of suvorexant-induced syndrome of inappropriate antidiuretic hormone release (SIADH).

REPORT OF CASE

A 77-year-old man with major depression was referred to the psychiatric ward of Jichi Medical University Hospital. He had a 20-year-history of type 2 diabetes mellitus and had been taking repaglinide and teneligliptin. One year ago, he developed lassitude and numbness of the lower limbs; however, complete physical examination including blood tests, systemic computed tomography, abdominal ultrasound examination, and upper and lower gastrointestinal endoscopy revealed no apparent abnormality. Subsequently, the patient developed depressed mood and anxiety; he was suspected of major depression and referred to the psychiatric ward. On admission, the patient presented with depressed mood, diminished interest, weight loss (from 50 kg to 41 kg in 3 months), loss of appetite, loss of energy, feeling of worthlessness, anxiety, and insomnia. He was diagnosed as a case of major depressive disorder according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), and prescribed mirtazapine up to 45 mg/day. After 1 month of hospitalization, the patient's symptoms of depression gradually improved. However, he reported poor quality of sleep. Therefore, on the 31st day of hospitalization, suvorexant was added at a dose of 15 mg/day. On the 43rd day, the patient suddenly developed general malaise. His blood tests revealed low levels of serum sodium (127 mEq/L) with no other electrolyte abnormalities, and normal renal function. Since the plasma osmotic pressure (275 mOsm with hyperglycemia: 281 mg/dL) and arginine vasopressin (AVP; 1.4 pg/mL) were normal, he did not meet the diagnostic criteria for SIADH.[2–4] However, SIADH was still suspected due to hyponatremia of unknown cause. Contrast-enhanced systemic computed tomography and brain magnetic resonance imaging were performed to determine the possible cause of SIADH; however, no abnormalities were found. We suspected that mirtazapine, which reportedly causes SIADH,[5] had induced SIADH. Hence, mirtazapine was withdrawn on the 55th day. However, on the 58th day, his hyponatremia worsened; investigations showed serum sodium levels of 123 mEq/L, serum osmolality levels of 256 mOsm/kg, blood glucose levels of 115 mg/dL, urine sodium levels of 167 mEq/L, and urine osmolality of 590 mOsm/kg, which met the criteria for SIADH. Among the other clinical investigations, the cortisol level was 17.66 μg/dL, the adrenocorticotropic hormone level was 53.7 pg/mL, and the AVP level was 1.1 pg/mL.

Since hyponatremia was prolonged and there were no other apparent causes, we considered that the SIADH could have been induced by suvorexant and it was discontinued on the 65th day. On the 71st day, the serum sodium level increased to 132 mEq/L, and on the 79th day, the serum sodium level and serum osmolality recovered to 135 mEq/L and 280.2 mOsm/kg, respectively. Thereafter, the patient had a relapse of depression. Since we believed that his SIADH was not associated with mirtazapine administration, we resumed mirtazapine at a

dose of 7.5 mg/day on the 83rd day. The dose was titrated to 45 mg/day until the 93rd day. We maintained the dose of mirtazapine, and the patient's serum sodium level and serum osmolality on the 111th day stayed within normal limits (ie, 136 mEq/L and 286 mOsm/kg, respectively). Although we resumed mirtazapine, there was no significant improvement in his depression. We administered modified electroconvulsive therapy, after which the patient's depression improved, and he was discharged on the 197th day of hospitalization. The patient's biochemical data were within normal limits after 6 months.

DISCUSSION

SIADH is characterized by excessive unsuppressible release of antidiuretic hormone. The causes of SIADH are variable; certain psychotropic drugs such as carbamazepine, neuroleptics, tricyclic antidepressants, and selective serotonin reuptake inhibitors have been found to induce this condition.[5,6] However, cases of SIADH induced by hypnotic agents have rarely been reported; there is only 1 report of zolpidem-induced hyponatremia.[7] This is the first case report of SIADH induced by a novel hypnotic agent, suvorexant.

The patient developed hyponatremia 12 days after the initiation of suvorexant therapy. We suspected SIADH, although the diagnostic criteria were not met because of normal serum osmolality, which might have been due to hyperglycemia. Fifteen days later, the patient met the diagnostic criteria for SIADH: the plasma osmolality decreased to less than 275 mOsm/kg, the urine concentration was more than 100 mOsm/kg, the patient was euvolemic, with elevated urine sodium levels (> 20 mEq/L), euthyroid, eucortisolemic, and no diuretic was used. Additionally, AVP above the measurement threshold supported the diagnosis. Since hyponatremia improved 6 days after the withdrawal of suvorexant with the absence of other possible causes of SIADH, such as infection, respiratory disease, malignancy, or neurological disease,[6] we diagnosed that SIADH was caused by suvorexant. Using the Naranjo algorithm, the total score was 6, which indicates a "probable" relationship between the intake of suvorexant and SIADH.[8]

The pharmacological mechanism of suvorexant-induced SIADH is unclear, but it might be related to the interaction between orexin and AVP. Suvorexant induces sleep by inhibiting orexin 1/2 receptors, which act on sleep centers to promote arousal. Previous animal studies have shown that the orexin system is related to the regulation of AVP, in terms of cardiovascular regulation. In animal models, intracerebroventricular administration of orexin A increases the AVP mRNA in the parvocellular neurons of the hypothalamic paraventricular nucleus and plasma AVP levels.[9] The sustained antagonism of suvorexant on the orexin receptors might induce the expression of orexin peptide through negative feedback, which could increase AVP, thereby causing SIADH.

Suvorexant has fewer adverse drug reactions than benzodiazepines and is considered relatively safe.[1] However, if hyponatremia is suspected after the use of the suvorexant, clinicians should consider the possibility of SIADH induced by suvorexant. Although this is a single case report, further studies with a larger number of patients are necessary to validate our findings.

ABBREVIATIONS

AVP, arginine vasopressin
SIADH, syndrome of inappropriate antidiuretic hormone release

REFERENCES

1. Kuriyama A, Tabata H. Suvorexant for the treatment of primary insomnia: a systematic review and meta-analysis. *Sleep Med Rev.* 2017;35:1–7.
2. Bartter FC, Schwartz WB. The syndrome of inappropriate secretion of antidiuretic hormone. *Am J Med.* 1967;42(5):790–806.
3. Tee K, Dang J. The suspect—SIADH. *Aust Fam Physician.* 2017;46(9):677–680.
4. Yasir M, Mechanic OJ. *Syndrome of inappropriate antidiuretic hormone secretion (SIADH)*. Treasure Island, FL: StatPearls Publishing; 2020.
5. De Picker L, Van Den Eede F, Dumont G, Moorkens G, Sabbe BG. Antidepressants and the risk of hyponatremia: a class-by-class review of literature. *Psychosomatics.* 2014;55(6):536–547.
6. Shepshelovich D, Leibovitch C, Klein A, et al. The syndrome of inappropriate antidiuretic hormone secretion: distribution and characterization according to etiologies. *Eur J Intern Med.* 2015;26(10):819–824.
7. Shanmuga Priya S, Britto DI, Saravanan T. Zolpidem induced hyponatremia: a case report. *J Clin Diagn Res.* 2014;8(9):HD03–HD04.
8. Parida S. Clinical causality assessment for adverse drug reactions. *Indian J Anaesth.* 2013;57(3):325–326.
9. Huber MJ, Fan Y, Jiang E, et al. Increased activity of the orexin system in the paraventricular nucleus contributes to salt-sensitive hypertension. *Am J Physiol Heart Circ Physiol.* 2017;313(6):H1075–H1086.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication September 9, 2020
Submitted in final revised form October 27, 2020
Accepted for publication October 28, 2020

Address correspondence to: Tsuyoshi Okada, MD, Department of Psychiatry, Jichi Medical University, 3311-1 Yakushiji Shimotsuke-Shi, Tochigi-Ken 329-0498, Japan; Tel: +81-285-58-7364; Fax: +81-285-44-6198; Email: okada-tsuyoshi@clear.ocn.ne.jp

DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. The authors report no conflicts of interest.