Case Report

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Hyponatremia Due to Sodium Valproate: A Case Report

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Psychiatric patients often suffer from hyponatremia due to polydipsia secondary to anticholinergic side effects of psychotropic drugs and abnormalities in hypothalamic thirst centers. Therefore, they often drink a large amount of water in a short period of time and blood sodium levels become suddenly diluted, causing "hyponatremia". Syndrome of inappropriate antidiuretic hormone (SIADH) is a less common cause of hyponatremia in psychiatric patients but has been reported to be associated with several psychotropic drugs. Valproic acid (VPA), a commonly used mood stabilizer, was less frequently reported to be associated with SIADH. In this case report, we describe a schizophrenic patent suffering from hyponatremia secondary to VPA-induced SIADH. His hyponatremia was found on a regular blood test and he did not have any obvious symptoms of hyponatremia. His blood sodium level returned to normal after withdrawal of VPA treatment. This side effect did not occur during first 5 years of VPA treatment but occurred a year after withdrawal of lithium treatment. This case suggests that long-term monitoring of blood sodium level is important for patients treated with VPA and especially after any adjustment of therapeutic regimen.

Key words: valproic acid, hyponatremia, syndrome of inappropriate antidiuretic hormone (SIADH), psychiatry, antidiuretic hormone (ADH)

Introduction

Hyponatremia, a common electrolyte imbalance, is defined as the plasma sodium level lower than 135 mmol/L.[1] According to a patient's body fluid volume status, it can be divided into three categories: hypovolemic, isometric, and hypervolemic.[1] In addition to nutritional problems and certain medical conditions such as vomiting, diarrhea and blood loss, drugs may also cause hyponatremia.[1] Hyponatremia caused by drugs is usually isometric hypotonic or low-volume hypotonic hyponatremia.[2] It is usually caused by excessive secretion of antidiuretic hormone (ADH), resulting in retention of water in the body.[2] Diuretics, antipsychotic drugs, antidepressants, antiepileptics

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(AEDs), oral hypoglycemic drugs, non-steroidal anti-inflammatory drugs have all been reported to be associated hyponatremia.[2]

Psychiatric patients are more prone to hyponatremia because they often suffer from polydipsia due to anticholinergic side effects of psychotropic drugs and abnormalities in hypothalamic thirst center.[3] However, mechanism of drug-induced hyponatremia is different from that of polydipsia.[2,3] In polydipsia, an abnormal blood sodium level is caused by excessive intake of water,[3] but in drug-induced hyponatremia, patients suffer from hyponatremia due to inappropriate secretion of AHD, which is also called drug-induced syndrome of inappropriate antidiuretic hormone (SIADH).[2] However, drug-induced SIADH is frequently overlooked in psychiatric patients, and water restriction protocol, which is standard treatment for polydipsia,[3] may be used inappropriately for patients with drug-induced SIADH. In fact, serum osmolality is often decreased in patients with drug-induced SIADH but not in polydipsia.[3,4] It is therefore quite important for clinicians to check serum osmolality to also consider SIADH for psychiatric patients suffering from hyponatremia.

AEDs, which are also used as mood stabilizers, are found to be associated with drug-induced SIADH in psychiatric patients.[5] Carbamazepine and oxcarbazepine are the most commonly reported AEDs associated with SIADH.[5] However, only a few case reports found drug-induced SIADH in other AEDs, including Valproate acid (VPA).[5] In this case report, we present a case of hyponatremia caused by VPA-induced SIADH in a psychiatric patient in Taiwan.

Case Report

A 26-year-old male with diagnosis of paranoid schizophrenia had no other underlying medical diseases. He received treatment with several different antipsychotics and mood stabilizers including olanzapine, haloperidol, VPA and lithium for symptom controls more than six years. VPA was used regularly with daily dose range between 500 – 1,200 mg (VPA level: 47.6 – 148.1 μg/mL) for mood problems from 2015 to 2020. His blood sodium levels were checked on regular basis at least once a year, and hyponatremia was never found during first 5 years of VPA use (Table 1). Lithium was stopped due to poor effects and unstable blood Lithium level since February 2019. In February 2020, low blood sodium level was found on regular check-up and dose of VPA used was 750 mg/day (Table 1). He did not suffer from any obvious symptoms of hyponatremia. Other medications used at that time included olanzapine 25 mg/day and haloperidol 10 mg/day. Water restriction protocol was implemented and deity sodium supplements were given but his blood sodium level did not return to normal. Serum osmolality was 259.7 on 2020/03/27 and SIADH was suspected. VPA was therefore stopped on 2020/03/30, and his blood sodium level normalized (Table 1). Due to unstable mood and psychotic symptoms, VPA was used again on 2021/08/23, his blood sodium levels were normal prior to use of VPA (Table 2). Other medications used at that time included olanzapine 25 mg/day and haloperidol 10 mg/day. His blood sodium level dropped immediately after VPA use and returned to normal again after withdrawal of VPA (Table 2). Results of other biochemistry examination were all within normal range (Table 3) and he had no history of other medical problems such as heart, liver and renal diseases or endocrine problems. His physical examination showed no signs of dehydration such as sunken eyes, a dry skin, mouth, lips or eyes, and his heart rates were within normal range (60 – 80/minutes). We were unable to monitor urine output as patient was uncooperative due to poor mentality. His body weight remained relatively stable during this period of time (63 – 64 kg). VPA-induced SIADH was highly suspected, because hyponatremia was observed during VPA use

Table 1. Biochemistry examination from 2015 – 2020.

2015 – 2020/M/D	Change in prescription	Valproic acid		Na (135 – 150) mmol/L	Serum/urine osmolality 275 – 295 (mosm/L)
		Dose (mg/day)	Concentration (ug/mL)		
2015/08/10	-	500	54.6	138	-
2016/11/21	-	900	105.2	139	-
2017/09/29	-	1,200	142.2	139	-
2018/03/30[discharged]	-	1,200	47.6	143	-
2018/09/14	-	800	82.5	144	-
2018/11/09	-	800	97.6	136	-
2019/02/27	Sopped lithium	750	90.4	142	-
2020/02/04	-	750	86.5	134	-
2020/03/02	-	750	-	124	-
2020/03/09	Sopped trihexyphenidyl	750	-	131	-
2020/03/16	-	750	-	133	-
2020/03/23	-	750	86.2	122	-
2020/03/26	-	750	-	130	-
2020/03/27	-	750	84	-	-
2020/03/30	Sopped valproic acid	0	-	127	259.7/267
2020/04/06	-	0	-	138	-
2020/04/13	-	0	-	140	-
2020/04/20	-	0	-	143	-
2020/04/29	-	0	-	138	-
2020/05/06	-	0	-	138	-
2020/05/13	-	0	-	138	-

Table 2. Biochemistry examination and therapeutic regimen in 2021.

2021/M/D	Change in prescription	Valproic acid		Na (135 – 150) mmol/L	Serum osmolality 275 – 295 (mosm/L)
		Dose (mg/day)	Concentration (ug/mL)		
2021/07/12	-	-	-	144	-
2021/09/01	-	750	127.4	133	-
2021/09/08	-	500	84.6	125	-
	Sopped valproic acid				
2021/09/14	-	-	-	135	-

Table 3. Results of other biochemistry examination.

Year/M/D	BUN/Cr (mg/dL)	TSH (uIU/mL)	T3 (ng/mL)	G.O.T/G.P.T (U/L)	Cortisol (ug/dL)	Alb (g/dL)	Chol/TG (mg/dL)	Glu AC (mg/dL)
2020/03/27					4.9			
2021/07/12		1.09	1.08	33/11		4.0	180/81	
2021/09/01	5/0.6							107

AC: Ante Cibum (before meals); Alb: albumin; Chol: cholesterol; BUN: blood urea nitrogen; Cr: creatinine; Glu: glucose; G.O.T: glutamate oxaloacetate transaminase; G.P.T: glutamate-pyruvate transaminase; TG: triglycerides; TSH: thyroid-stimulating hormone.

but resolved immediately after withdrawal of VPA on two occasions.

Discussion

Hyponatremia is a common electrolyte abnormality in hospitalized patients, and the annual incidence of hyponatremia in hospitalized patient with mental illnesses is about 0.01%.[6] The risk of hyponatremia was significantly higher in male psychiatric inpatients or in patients with a disease course of more than one year.[6] In addition, hyponatremia is also more prevalent in patients with schizophrenia than other primary mental illnesses ($p < 0.007$).[6] Hyponatremia usually occurs as a result of water intoxication in psychiatric patients, as they often drinks water that exceeds the maximum renal intake clearance capacity.[6] Less commonly, hyponatremia can also be caused by several psychotropic drugs including antipsychotics, mood stabilizers and antidepressants.[7] In drug-induced hyponatremia, the most common cause of abnormal blood sodium levels was due to inappropriate secretion of ADH, which is also commonly called SIADH.[5] In SIADH, kidneys retain too much water due to over-secretion of ADH.[5] Subsequently, serum osmotic pressure becomes abnormally low, and urine osmotic pressure becomes abnormally high.[5] There are several risk factors associated with drug-induced SIADH (increased age, female, medical comorbidities, and multiple medications) in psychiatric patients.[8] The overall prevalence of SIADH caused by antipsychotics is estimated to be between 0.004% and 26.1% in psychiatric patients.[6,7] However, there were relatively less case reports about SIADH induced by VPA,[5] which is one of most commonly used mood stabilizer in psychiatric patients.

The mechanism of hyponatremia caused by VPA is unclear, but VPA may affect the secretion of ADH in the pituitary glands.[9] ADH is synthesized in the paraventricular nucleus and supraoptic nucleus of the hypothalamus and then transported to the posterior lobe of the pituitary gland for storage.[4] When the blood osmolality (serum osmolality) rises or the body fluid is insufficient, the pituitary gland secrets more ADH to restore fluid balance.[4] ADH acts on the V2 receptor (V2R) of the renal medulla to enhance the action of cyclic adenosine monophosphate in the urinary tubule cells and promotes the binding of aquaporin to the lumen of the urinary tubule to open the water channel.[4] ADH is one of the most important hormone for stabilizing blood osmotic pressure (or blood sodium concentration) and controls the blood osmotic pressure in a very narrow range (270 – 290 mOsm/kg) by recovering or excreting water from the body.[4] In SIADH, over-secretion of AHD leads to conservation of water in the body and dilution of blood sodium concentration.[4] There are several possible mechanism of VPA-induced SIADH, including abnormal stimulation of ADH released from pituitary glands or enhancing action of ADH on the kidney.[9] The exact cause of VPA-induced SIADH however remains unclear.[9]

In our case report, this male schizophrenic patient received treatment of VPA for several years. Hyponatremia secondary to VPA-induced SIADH was highly suspected, as his serum osmolality was abnormally low. Moreover, hyponatremia resolved after withdrawal of VPA but recurred again after introduction of VPA on two occasions. It is quite interesting that VPA-induced hyponatremia was not observed during initial use of VPA for several years. However, once this side effect occurred, he continued to suffer from VPA-induced hyponatremia immediately after use of VPA. It is unlikely that hyponatremia was not observed during initial use of VPA, because he had blood tests for sodium concentration many times during that period of time. Although previous case reports regarding VPA-induced SIADH suggested a dose-related adverse effects,[9] but we were unable to identified cases

similar to ours in which SIADH only occurred after several years of VPA use. However, hyponatremia occurred also after lithium was stopped for about a year and serum sodium level was not checked during that period of time. Therefore, we cannot rule out the possibility that VPA-induced hyponatremia was corrected by diuretic effects of lithium,[10] during first 5 years of VPA use. This finding of VPA-induced SIADH in our case suggests that clinicians should consider checking blood sodium level regularly, even if this side effect was not observed during initial use of VPA. Moreover, any change in therapeutic regimen may influence serum sodium balance; therefore, blood sodium level should also be checked after any adjustment of medications.

Conclusions

In summary, our case describes hyponatremia secondary to VPA-induced SIADH only after 5 years of VPA use, when lithium was stopped. Long-term use of VPA or changed of therapeutic regimen may both be responsible for this side effect. Clinicians should be aware of VPA-induced SIADH and check for serum sodium level regularly even if initial serum sodium levels were normal initially. Any adjustment of therapeutic regimen may also lead to blood sodium imbalance.

Author Contributions

Concept and Design, Shu-Fang Shou and Yu-Shian Cheng; Data Acquisition, Shu-Fang Shou; Drafting of the Manuscript, Shu-Fang Shou and Yu-Shian Cheng; Critical Revision of the Manuscript, Cheuk-Kwan Sun; Supervision, Cheuk-Kwan Sun. All authors read and approved the final manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

References

1. Verbalis JG, Goldsmith SR, Greenberg A, et al: Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med 2013;126:S1-42. doi: 10.1016/j.amjmed.2013.07.006.
2. Pillai BP, Unnikrishnan AG, Pavithran PV: Syndrome of inappropriate antidiuretic hormone secretion: revisiting a classical endocrine disorder. Indian J Endocrinol Metab 2011;15 Suppl 3:S208-15. doi: 10.4103/2230-8210.84870.
3. Goldman MB: The mechanism of life-threatening water imbalance in schizophrenia and its relationship to the underlying psychiatric illness. Brain Res Rev 2009;61:210-20. doi: 10.1016/j.brainresrev.2009.06.004.
4. Miller M: Hyponatremia and arginine vasopressin dysregulation: mechanisms, clinical consequences, and management. J Am Geriatr Soc 2006;54:345-53. doi: 10.1111/j.1532-5415.2005.00609.x.
5. Lu X, Wang X: Hyponatremia induced by antiepileptic drugs in patients with epilepsy. Expert Opin Drug Saf 2017;16:77-87. doi: 10.1080/14740338.2017.1248399.
6. Shafti SS, Memarie A, Rezaiel M, et al: Hyponatremia in psychiatric inpatients: a native pilot study. Online J Neurol Brain Disord 2019;3:225-8. doi: 10.32474/OJNBD.2019.03.000157.
7. Siddiqui JA, Qureshi SF, Zaharani AA: Psychotropic-induced hyponatremia: a review. Psychiatry and Behavioral Sciences 2018;8:213-21. doi: 10.5455/PBS.20180324094723.
8. Meulendijks D, Mannesse CK, Jansen PA, et

al: Antipsychotic-induced hyponatraemia: a systematic review of the published evidence. Drug Saf 2010;33:101-14. doi: 10.2165/11319070-000000000-00000.

9. Beers E, van Puijenbroek EP, Bartelink IH, et al: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) or hyponatraemia associated with valproic acid: four case reports from the Netherlands and a case/non-case analysis of vigibase. Drug Saf 2010;33:47-55. doi: 10.2165/11318950-000000000-00000.
10. Baker RS, Hurley RM, Feldman W: Treatment of recurrent syndrome of inappropriate secretion of antidiuretic hormone with lithium. J Pediatr 1977;90:480-1. doi: 10.1016/s0022-3476(77)80721-x.