Recurrent Hyponatremia: Levetiracetam - An Uncommon Cause

Dear Editor,

Hyponatremia can be an adverse drug reaction with the use of some of the anti-seizure medications (ASM). Carbamazepine and oxcarbazepine are the most common ASMs which induce hyponatremia. Rarely sodium valproate, eslicarbazepine, lamotrigine, levetiracetam, and gabapentin have also been reported to cause hyponatremia.[1] We report a case of Levetiracetam induced hyponatremia and review the English literature of similar cases.

A 50-year-old male had traumatic brain injury in November 2015 and neuroimaging was normal. He was started on prophylactic levetiracetam at another facility. Since then, he had three admissions for hyponatremia: First admission was for acute symptomatic seizures due to hyponatremia, serum sodium of 118 mmol/L; second admission in February 2016 for dizziness, serum sodium 131 mmol/L; and third admission during April 2016 for drowsiness, serum sodium 108 mmol/L [Table 1]. During the latter two admissions, the work-up for hyponatremia was suggestive of syndrome of inappropriate antidiuretic hormone secretion (SIADH). During the first admission, patient was on levetiracetam 500 mg q12h and the dose was escalated to 1000 mg q12h at discharge. Patient was started on tolvaptan 15 mg q24h at discharge in the first admission (25.12.2015). During his subsequent admissions, workup for other causes of hyponatremia was negative. He was continued with tolvaptan intermittently. Review of the case records and drug chart suggested possible relation between hyponatremia and levetiracetam, a diagnosis of levetiracetam induced hyponatremia was considered and levetiracetam was discontinued. Since then, he had no further episode of hyponatremia. Patient was not started on any ASM as it is not

Table 1: Admission profile of the patient

Admission Date	Presenting complaints	Volume status of the patient	Serum sodium	Serum osmolality	Urine osmolality	Urine spot sodium	Tolvaptan dose
25/12/2015	Seizures	Euvolemia	118 mmol/L	Not done	Not done	Not done	15 mg once a day
1/2/2016	Dizziness	Euvolemia	131 mmol/L	264.7 mosm/kg	401 mosm/kg	152 mmol/L	15 mg once a day
1/4/2016	Drowsiness	Euvolemia	108 mmol/L	223.5 mosm/Kg	196.4 mosm/Kg	70 mmol/L	15 mg once a day

Table 2: Characteristics of the patients

S. No. of patient	Age*/ Sex**	Clinical History	Other medications	Mechanism	Outcome	Year of publication	Author
1	65/F	Patient was started on levetiracetam in view of focal seizures with impaired awareness	Pantoprazole	SIADH#	Hyponatremia was corrected after stopping levetiracetam, Topiramate was initiated	2005	Narsallah *et al*.[3]
2	76/M	Patient was started on levetiracetam in view of focal seizures with impaired awareness	Amlodipine	NA	Hyponatremia was corrected after stopping levetiracetam, Valproate was initiated	2008	Belcastro *et al*.[4]
3	74/M	Case of Congestive heart failure and epilepsy with resistant hyponatremia	Carvedilol, Furosemide, Trandolapril, Spironolactone, Hydrocholorothiazide, Warfarin	SIADH#	Hyponatremia did not improve despite starting tolvaptan, hyponatremia was corrected after stopping levetiracetam, Valproate was initiated.	2015	Arı H *et al*.[5]
4	73/M	Case of old traumatic intracerebral hemorrhage, had 2 episodes of generalized seizures, levetiracetam was started after patient developed hyponatremia due to valproate	Nil	SIADH#	Hyponatremia was corrected after stopping levetiracetam, Topiramate was initiated.	2017	Rosca *et al*.[6]
5 (Present case)	50/M	Patient of traumatic brain injury with normal imaging was started on levetiracetam prophylactically	Nil	SIADH#	Hyponatremia was corrected after stopping levetiracetam		

*Age in years, **sex (M- Male, F- Female), #Syndrome of inappropriate antidiuretic hormone

our practice to use ASMs for primary prophylaxis in traumatic brain injury.

In this patient, diagnostic workup suggested that SIADH was the possible mechanism for hyponatremia. He had a mild closed traumatic brain injury and normal brain imaging. This clinical scenario is very unlikely to cause SIADH. Workup for other causes of hyponatremia was negative. When levetiracetam was discontinued patient had no further episodes of hyponatremia. On Naranjo Adverse Drug Reaction Probability Scale[2] this patient had a score of 7 suggesting levetiracetam being the "probable" culprit responsible for hyponatremia.

Review of English literature revealed report of four patients with levetiracetam induced hyponatremia [Table 2]. In four patients, including the present case SIADH was the mechanism of hyponatremia. There are no specific clinical characteristics which are common among these 5 cases. In all the patients, hyponatremia was corrected after withdrawing levetiracetam. In patient "3" in addition to levetiracetam, hydrochlorothiazide would have added to the misery of hyponatremia.

In conclusion this case illustrates that chronic hyponatremia in a patient with epilepsy on ASMs, one should check the ASM list to exclude the possible drug that can be associated with hyponatremia.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Abhinay K. Gattu, Jagarlapudi M. K. Murthy

Department of Neurology, CARE Institute of Neurosciences, CARE Hospitals, Hyderabad, Telangana, India

Address for correspondence: Dr. Abhinay K. Gattu, Department of Neurology, CARE Institute of Neurosciences, CARE Hospitals, Banjara Hills, Hyderabad, Telangana, India.
E-mail: abhinay.gattu@gmail.com

References

1. Lu X, Wang X. Hyponatremia induced by antiepileptic drugs in patients with epilepsy. Expert Opin Drug Saf 2017;16:77-87.
2. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al*. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239-45. doi: 10.1038/clpt.1981.154. PMID: 7249508.
3. Nasrallah K, Silver B. Hyponatremia associated with repeated use of levetiracetam. Epilepsia 2005;46:972-3.
4. Belcastro V, Costa C, Striano P. Levetiracetam-associated hyponatremia. Seizure 2008;17:389-90.
5. Arı H, Kahraman F, Acaban MB. The first case of levetiracetam-induced and tolvaptan-resistant hyponatremia. Turk Kardiyol Dern Ars 2015;43:284-7.
6. Rosca EC, Simu M. Levetiracetam-induced hyponatremia. Acta Neurol Belg 2018;118:123-4.

Submitted: 15-Dec-2022 **Revised:** 13-Feb-2023 **Accepted:** 15-Feb-2023
Published: 11-Apr-2023

DOI: 10.4103/aian.aian_996_22