



Short communication

Hyponatremia following esclicarbazepine therapy



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ABSTRACT

Purpose: To evaluate the safety of esclicarbazepine acetate (ESL) in new onset elderly poststroke seizure patients, especially with respect to hyponatremia.

Method: In a two year, single center open labeled observational study of ESL in patients with imaging proven stroke with new onset post stroke seizure were included. ESL was titrated between 400 mg and 1200 mg once daily during 1 month observation period. The titrated dose of ESL was continued during 96-week maintenance period. The patients were followed up for seizure control and side effects, including serum sodium on first examination, at the end of 1 month and then at three monthly intervals for 24 months (total eight visits).

Result: Hyponatremia developed in four out of 32 (12.5%) patients; it was symptomatic in three and asymptomatic in one patient. No statistically significant difference between mean sodium levels at different time period, compared to baseline was found.

Conclusion: High incidence of hyponatremia in ESL treated post stroke patients, was found, hyponatremia symptoms since can be subtle and delayed, so monitoring of serum sodium in the patients on ESL treatment is recommended especially in elderly.

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1. Introduction

Esclicarbazepine acetate (ESL) is a third generation antiepileptic drug (AED) with sodium channel blocking property with the advantage of once daily dosing. In three phase III randomized controlled trials, ESL has been found to be effective and safe in partial and secondary generalized epilepsy [1]. ESL belongs to the dibenzazepine family; the other members of this group are Carbamazepine (CBZ), and Oxcarbazepine (OXC). In neurologic patients, hyponatremia is not only the most common electrolyte imbalance. It is more common in neurologic patients than the patient with other diseases [2,3]. For both CBZ and OXC hyponatremia is one of the most common causes of treatment withdrawal limiting their use in neurological patients [4]. Since hyponatremia has been observed rarely (0.6–1.3%) in patients treated with ESL during the pre-marketing clinical trials [5], in this prospective study; we examine the safety of ESL in poststroke seizure patients especially with respect to hyponatremia.

2. Subject and methods

2.1. Study design

In a two year, single center open labeled observational study of ESL in patients with CT or MRI proven stroke with new onset post stroke seizure were included. The criteria of the Commission on Classification and Terminology of the International League against epilepsy were followed to differentiate between focal and focal with generalized epilepsy [6]. The type of stroke was divided into hemorrhagic or ischemic, and the etiologic subtypes of ischemic stroke were classified according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria [7].

ESL dose was titrated between 400 mg and 1200 mg once daily during 1 month observation period. The titrated dose of ESL was continued during the subsequent 96-weeks maintenance period. The patients were followed up for seizure control and side effects, including serum sodium on first examination, at the end of the observation period (1 month) and then at three monthly intervals for 24 months (Total eight visits). Patients having seizures on a daily ESL dose of 1200 mg were considered nonresponders and were switched to another AED, concomitant AEDs were not allowed. The clinician was free to decrease the dose of ESL or withdraw it if the patient had side effects.

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Written informed consent was obtained from all the patients. The study was approved by the Institutional Ethics Committee (PGI/BE/359/2014). Data were expressed in mean \pm standard deviation (SD). The continuous variables were analyzed by Students 't' test and categorical data by chi square test. The difference between the two means was considered statistically significant if two tailed *p* value was < 0.05 . The statistical analysis was done using SPSS version 16 software.

2.2. Inclusion criteria

1. Imaging (CT/MRI) proven stroke with the occurrence of seizures within 7 days (early) or after 7 days (late) post stroke seizure
2. Age ≥ 18 years
3. Having sodium level (Na^+) evaluated at baseline, 1 month, and then at 3 months. Normal serum sodium was defined as $\text{Na}^+ 135\text{--}145$ mEq/L, hyponatremia as $\text{Na}^+ \leq 134$ mEq/L, and severe hyponatremia as $\text{Na}^+ \leq 128$ mEq/L.

2.3. Exclusion criteria

Patients, who had poststroke seizures only in specific circumstances, such as electrolyte imbalance and other metabolic conditions, were not included in this study. The patients with heart, liver or kidney failure were also excluded as these can affect serum sodium level. Other exclusion criteria were: pregnancy, history of status epilepticus, neoplastic disease, known allergy or contraindications to the use of ESL and life expectancy ≤ 1 year. Before ascribing hyponatremia to ESL, other causes of hyponatremia such as diuretic or poor salt intake were excluded, if hyponatremia persisted after withdrawing any other alleged drug and corrected after withdrawing ESL, it was attributed to ESL.

2.4. Management

The patients with hyponatremia were treated by withdrawing the offending drugs if any and sodium supplementation orally or intravenously/fluid restriction depending on the clinical and biochemical findings. Other treatments for stroke and co morbidities were prescribed as per the treating physician's decision.

3. Result

Thirty-three patients were enrolled in the study between July and October 2012. Thirty-two of them were followed for a period of 2 years (96 weeks); one patient was lost from follow up. Eighteen patients (58.3%) received ESL 800 mg, 13 (40.6%) 600 mg and 1 (3.1%) 1200 mg daily. Their baseline clinical characteristics were given in Table 1.

The side effects of ESL were fatigue in four (12.5%) patients, somnolence in two (6.3%), rash in one (3.1%), flu like symptoms in one (3.1%), ataxia in one (3.1%), and hyponatremia in four (12.5%) patients. Although hyponatremia developed in 4 (12.5%) patients, no statistically significant difference between mean sodium levels at different time period compared to baseline was found (Fig. 1) and all four patients who developed hyponatremia were in ESL 800 mg group. Fig. 2 shows the levels of serum sodium during 2 years followup amongst patients with or without hyponatremia, although there were fluctuation but usually serum sodium remains 1–2 mEq/L below the baseline levels. In three patients hyponatremia was severe requiring drug withdrawal. Our fourth patient presented with asymptomatic hyponatremia detected on followup visit, he was advised to increase salt intake with monitoring of fluid intake and output, he responded to it and was eunatremic on next

Table 1

Baseline clinical characteristics of post stroke seizure patients.

Clinical characteristics	Stroke <i>n</i> (%) / (M \pm SD)
Age (yrs), mean (SD)	51.88 \pm 15.17
NIHSS mean (range, SD)	8.90 \pm 3.94
Gender type, <i>n</i> (%)	
Male	24 (75.0%)
Female	8 (25.0%)
Addiction, <i>n</i> (%)	
Smoking	2 (6.3%)
Alcoholic	2 (6.3%)
Tobacco chewer	4 (12.5%)
Tobacco and alcohol both	3 (9.4%)
Comorbidities, <i>n</i> (%)	
Hypertension	17 (53.1%)
Diabetes mellitus	9 (28.1%)
Heart disease	5 (15.6%)
Baseline dementia	2 (6.3%)
Stroke type, <i>n</i> (%)	
Infarct	23 (71.9%)
Hemorrhage	9 (28.1%)
Etiology of ischemic stroke-TOAST criteria, ^a <i>n</i> (%)	
Large vessel atherosclerosis	12 (35.5%)
Cardioembolism	5 (16.1%)
Small vessel occlusion	1 (3.2%)
Stroke of other determined etiology	4 (12.9%)
Seizure semiology, <i>n</i> (%)	
Focal	3 (9.4%)
Focal with generalization	22 (68.8%)
GTCS	7 (21.9%)
Seizure temporal profile, <i>n</i> (%)	
Early	14 (43.8%)
Late	18 (56.2%)

^a Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria for etiologic subtypes of ischemic stroke [5].

visit while maintaining the same dose of ESL, he is asymptomatic and his serum sodium is normal since then. The case report of patient no 1 is described, clinical details of other patients with hyponatremia are presented in Table 2.

3.1. Case report #1

A 40-year male with hypertensive caudate hemorrhage developed two episodes of focal seizure with generalization on 1st and 2nd day of stroke; the seizure lasted 3–5 min. He was prescribed ESL 800 mg, Amlodipine 5 mg, Atenolol 25 mg and Hydrochlorothiazide 12.5 mg daily. On seventh month followup he was found to be lethargic, complained of weakness and nausea. On examination he was confused, afebrile with normal skin turgor, his serum sodium was 113 mEq/L, potassium 3.1 mEq/L, albumin was 3.3 g/dl, uric acid 3.0 mg/dl, thyroid stimulating hormone 1.27 mIU/L, his serum osmolality was 272 mOsm/kg, urine osmolality 253 mOsm/kg, and urinary sodium 43 mEq/L, suggestive of syndrome of inappropriate secretion of antidiuretic hormone (SIADH), since his seizure were well controlled with ESL till 7 months, hydrochlorothiazide induced hyponatremia was considered and the diuretic was withdrawn. The patient was prescribed salt supplementation along with fluid restriction, on 3rd day of illness, his serum sodium was still found to be low (116 mEq/L), ESL was then substituted with Levetiracetam (LEV). Within 2 days his sodium improved to 128 mEq/L, he became eunatremic on the 10th day of admission, discharged on LEV and since then he is asymptomatic.

4. Discussion

Our study reveals that four out of 32 (12.5%) patients with post stroke seizures on ESL developed hyponatremia (symptomatic in 3 and asymptomatic in 1), which occurred after a mean duration of

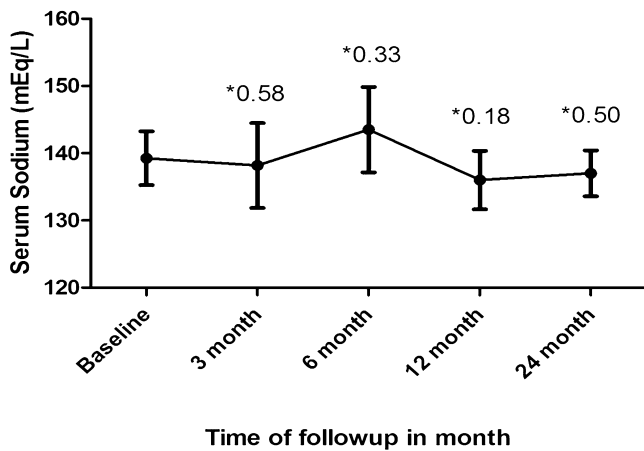


Fig. 1. Comparison of serum sodium at different time periods to baseline values are in mean \pm SD, *p value with respect to baseline, patient number ($n = 32$).

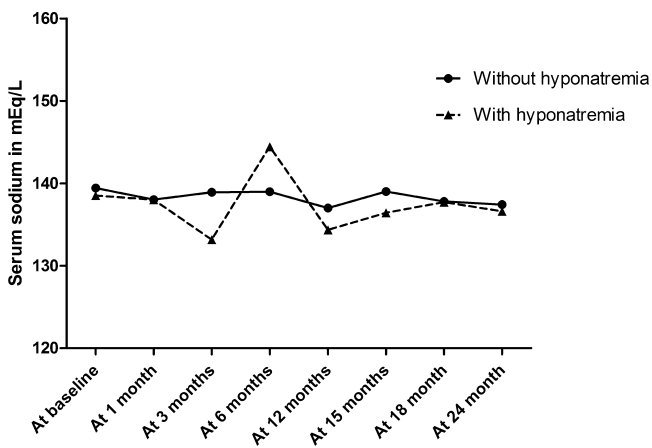


Fig. 2. Fluctuation of mean serum sodium at different time periods to baseline among patient with and without hyponatremia. Patient number ($n = 4/32$). Serum sodium level gradually declines during the first month of treatment and remain approximately 1–2 mEq/L below baseline levels.

7.25 months of ESL therapy. The hyponatremia in our patients was due to ESL because it had a temporal relationship to introduction of ESL; there was no other offending cause of hyponatremia such as

heart failure, or endocrine abnormality. Only one patient received thiazide diuretic. In this patient, hyponatremia persisted even after withdrawing the diuretic and responded to ESL withdrawal as in other patients.

In our study incidence of hyponatremia is higher than that reported in the literature where it has been reported in only 0.6% to 1.3% in the premarketing clinical trials [1]. In three controlled epilepsy studies, 1/196 patients (0.5%) treated with 400 mg, 4/415 patients (1.0%) treated with 800 mg, and 6/410 patients (1.5%) treated with 1200 mg of ESL had one or more serum sodium values less than 125 mEq/L during treatment whereas none in placebo group [5]. In contrast hyponatremia is the most frequently reported adverse drug reactions in the post-marketing database for Aptiom [8] (ESL brand approved by the US FDA). In this database there were 140 cases of hyponatremia, in half of them hyponatremia occurred within the recommended range of 400–1200 mg of ESL and sodium level as low as 103 mEq/L had been reported [8]. In our study all four patients who developed hyponatremia were in ESL 800 mg group, and lowest sodium level recorded was 113 mEq/L. As hyponatremia develops across all dose ranges of ESL, thus it appears that ESL induced hyponatremia is probably not dose dependent.

Data regarding time interval between initiation of ESL to development of hyponatremia is scarce. In three controlled epilepsy trials and post marketing studies, hyponatremia generally appeared within the first 8 weeks of treatment (as early as after 3 days) and, in some cases lead to ESL withdrawal [1,5,8], in comparison followup studies on OXC shows that oxcarbazepine-associated hyponatremia develops slowly over several weeks and months [9]. Evidence indicate that small mean sodium value decreases usually occurs in all OXC treated patients with epilepsy. This small mean decrease occurs mostly within the first 2 months after treatment initiation and does not change over time, unless sodium depleting drugs, are added [10], since ESL matches OXC in many aspects [1] so it is also likely to cause delayed hyponatremia and majority of the patients are supposed to be asymptomatic. Absence of long term followup again may be the reason behind the low incidence of hyponatremia attributed to ESL in previous studies. In our study one patient was asymptomatic, in which hyponatremia was detected in 3rd month. Amongst the symptomatic patients with ESL related hyponatremia, one was having diuretic coadministration, presented to us in the 7th month. We could not find any precipitating factor in other two symptomatic patients with delayed presentation.

Table 2

Summarizing the clinical and laboratory findings in the patient's with ESL associated hyponatremia.

Parameter	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)/sex	40/male	55/male	76/female	60/male
Stroke type	Hypertensive caudate hemorrhage	Hypertension, diabetes mellitus and multi infarct state with poststroke seizure	Right middle cerebral artery territory and anterior cerebral territory (partial) infraction	Thalamic hemorrhage, hypertension
Time of Na ⁺ deficit	7th month	4th month	15th month	3rd month
Lowest Na ⁺ level	113 mEq/L	126 mEq/L	124 mEq/L	129 mEq/L
Symptoms of hyponatremia	Nausea, lethargy, weakness	Weakness and asthenia	Decrease oral intake and drowsiness	Asymptomatic
Volume status	Euvolemic	Euvolemic	Euvolemic	Euvolemic
Serum osmolality	272 mOsm/kg	268 mOsm/kg	266 mOsm/kg	268 mOsm/kg
Urine output	Normal to low	Normal to low	Normal to low	Normal
Urine osmolality	253 mOsm/kg	167 mOsm/kg	202 mOsm/kg	210 mOsm/kg
Reversal of hyponatremia	On 10th day with fluid restriction and salt supplementation, ESL withdrawn	On 3rd day with fluid restriction and salt supplementation, ESL withdrawn	On 5th day with fluid restriction and salt supplementation, ESL withdrawn	Was eunatremic at next visit with salt supplementation
Other offending factors	Diuretic ^a	None	None	None

^a Thinking of hydrochlorthiazide induced hyponatremia, first diuretic was withdrawn and he was kept on salt supplementation along with fluid restriction, but sodium was still low, then ESL was withdrawn and substituted with Leveteracetam. Within 2 days his sodium improved to 128 mEq/L.

Clinically relevant ESL induced hyponatremia requires dose reduction or discontinuation and alternative anti-epileptic medication should be considered [8,11], along with salt supplementation and fluid restriction depending upon intake-output charting, all three symptomatic patients in our study responded to ESL withdrawn along with these measures. Management of patients with asymptomatic hyponatremia detected during routine visit is not well established. They should be put on close followup, warned about possible symptoms of hyponatremia (e.g., nausea, malaise, headache, lethargy, confusion, obtundation, or increase in seizure frequency or severity), along with regular sodium level monitoring particularly if the patient has had a previous history of hyponatremia, has other comorbidities, or is receiving other medications concurrently known to decrease serum sodium level (e.g., diuretics, drugs associated with SIADH) [8,11].

The high incidence of hyponatremia in our study may be due to old age of the patients (51.88 ± 15.17 years) with co morbidities such as diabetes and hypertension. Age is an important risk factor for hyponatremia in ESL treated patients. In an uncontrolled study, in 72 elderly (aged ≥ 65 years) patients on ESL, the incidence of hyponatremia was 8.3% [12]. There is probably a subset of patients with epilepsy who are inherently susceptible to ESL induced hyponatremia [4]. Bucher et al. [13], in their study found a bimodal distribution of Na^+ in persons exposed to risk factors for SIADH, they suggested that SIADH may only affect a genetically distinct vulnerable subpopulation. Occurrence of ESL induced hyponatremia across all dose ranges also support this hypothesis. Our study group was a selected cohort of post stroke seizure patients, stroke in itself may cause hyponatremia due to cerebral salt wasting or SIADH, these abnormalities however would appear earlier rather than after several months.

ESL differs from OXC as it is metabolized almost exclusively to the (S) enantiomer (designated as S-licarbazepine) with less than 5% chiral conversion to the (R)-enantiomer [1]. Possible mechanism of ESL induced hyponatremia can be understood by the mechanism of hyponatremia in OXC. Sachdeo et al. found that OXC intake results in significant reductions in serum osmolality and serum sodium concentration after a water-load test. This hypotonic hyponatremia, which is not associated with a significant change in serum arginine vasopressin (AVP), is the result of both a relative inability to dilute the urine and a reduction in the percentage of water excreted after the water-load test [14]. He suggested that OXC induced hyponatremia is not attributable to the SIADH. Possible mechanisms include a direct effect of OXC on the renal collecting tubules or an enhancement of their responsiveness to circulating AVP [14]. Irrespective of the possible mechanism there occurs a euvoletic hyponatremia that responds to fluid restriction, salt supplementation with or without ESL withdrawal.

Ours is a select group of elderly stroke patients with comorbidities and is not representative of true population. We although excluded the patients with other potential causes of hyponatremia like heart failure, cirrhosis of liver and renal failure but there is possibility of missing the patients with subclinical abnormalities. With sodium level estimation at baseline, 1 month and then at 3 months interval and in symptomatic patient at onset of symptoms, there is a chance of missing the patient with short lasting asymptomatic hyponatremia developing in between these visits. Our study has a small sample size; a larger study is needed to estimate the exact incidence of hyponatremia in ESL. We have not measured the ESL serum concentration so we cannot definitely state that ESL induced hyponatremia is dose independent.

The difficulty of diagnosis of ESL related hyponatremia is due to asymptomatic hyponatremia as one of our patients had no symptoms. In CBZ/OXC related hyponatremia also usually the patients are asymptomatic [4]. Neurological abnormalities such as

stupor, convulsion and coma occurs when serum sodium falls below 110 mEq/L [15]. High frequency of hyponatremia in our study justifies the need of regular sodium monitoring in elderly patients on ESL therapy especially if they have comorbidities.

5. Conclusion

In conclusion we found a high incidence of hyponatremia in ESL treated post stroke patients, since symptoms of hyponatremia can be subtle and delayed, so we recommend close follow up and regular sodium level monitoring of patients on maintenance treatment of ESL, especially in elderly patients.

Conflict of interest statement

There is no conflict of interest to declare.

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Ethical approval

The study was approved by the Institutional Ethics Committee (PGI/BE/359/2014).

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