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Short communication

Hyponatremia following esclicarbazepine therapy

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ABSTRACT

Purpose: To evaluate the safety of eslicarbazepine 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.

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 ± 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 $\geq$18 years
3. Having sodium level (Na^+) evaluated at baseline, 1 month, and then at 3 months. Normal serum sodium was defined as Na^+ 135–145 mEq/L, hyponatremia as $Na^+ \leq 134$ mEq/L, and severe hyponatremia as $Na^+ \leq 128$ 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 $\leq$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. There 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 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.

Table 1
Baseline clinical characteristics of post stroke seizure patients.

Clinical characteristics	Stroke *n* (%)/(M ± SD)
Age (yrs), mean (SD)	51.88 ± 15.17
NIHSS mean (range, SD)	8.90 ± 3.94
Gender type, *n* (%)	
Male	24 (75.0%)
Female	8 (25.0%)
Addiction, *n* (%)	
Smoking	2 (6.3%)
Alcoholic	2 (6.3%)
Tobacco chewer	4 (12.5%)
Tobacco and alcohol both	3 (9.4%)
Comorbidities, *n* (%)	
Hypertension	17 (53.1%)
Diabetes mellitus	9 (28.1%)
Heart disease	5 (15.6%)
Baseline dementia	2 (6.3%)
Stroke type, *n* (%)	
Infarct	23 (71.9%)
Hemorrhage	9 (28.1%)
Etiology of ischemic stroke-TOAST criteria,[a] *n* (%)	
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 seminology, *n* (%)	
Focal	3 (9.4%)
Focal with generalization	22 (68.8%)
GTCS	7 (21.9%)
Seizure temporal profile, *n* (%)	
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].

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 Hydrochlothiazide 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, hydrochlorthiazide 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