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ESTIMATION OF SERUM TOTAL BILIRUBIN LEVEL AND HYPONATREMIC EFFECT ASSOCIATED WITH THE USE OF LEVETIRACETAM THERAPY IN EPILEPTIC PATIENTS

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ABSTRACT

Epilepsy is a group of neurological diseases characterized by epileptic seizures. Levetiracetam is increasingly used as adjunctive anticonvulsant therapy. Levetiracetam is second generation anti -epileptic drug. The present review is aimed on the estimation of serum total bilirubin level and hyponatremic effect associated with the use of levetiracetam therapy in epileptic patients. The clinical monitoring of the serum sodium levels is done to identify the development of hyponatremia associated with the use of levetiracetam. Asymptomatic elevation in serum total bilirubin is found in patients taking levetiracetam. Patients treated with levetiracetam should be monitored and checked for hyponatremia when they develop symptoms suggestive of low sodium.The review also helps to understand the importance of monitoring of serum total bilirubin level while taking levetiracetam. Effective clinical management can be handled through awareness of the adverse effect of levetiracetam on serum sodium levels. The review provides clinical information about the incidence of hyponatremia and serum total bilirubin level associated with levetiracetam therapy.

KEYWORDS: Epileptic patients, levetiracetam, serum total bilirubin level, hyponatremia, Clinical monitoring.

INTRODUCTION

A seizure is the manifestation of an abnormal, hypersynchronous discharge of a population of cortical neurons**.** Epilepsy is a group of disorder characterized by two or more unprovoked seizures.[1] Epilepsy is classified based on the source of seizure into partial and generalized seizures. Epilepsy is a group of neurological diseases characterized by epileptic seizures. Epileptic seizures are episodes that can vary from brief and nearly undetectable to long periods of vigorous shaking.[8] Levetiracetam is second generation anti epileptic drug. Levetiracetam is available as tablets of 250, 500, 750 and 1000 mg generically and under the brand name Keppra. Liquid oral and injectable forms are also available**.** The recommended initial dose in adults is 500 mg twice daily with dose escalation based upon tolerance and effect to a maximum of 1500 mg twice daily.[2] Dosing in children is based upon body weight. Common side effects include dizziness, somnolence and fatigue. The treatment of epilepsy depends on appropriate classification of seizure type and the epileptic syndrome. The older or first generation antiepileptic drugs like phenytoin, carbamazepine and sodium valproate. Hyponatremia is defined as a decrease in the serum sodium concentration to a level below 136 mmol per liter.[3]

Levetiracetam is approved for adjunctive therapy for adults with partial, myoclonic, and generalized tonic clonic seizures. Patients taking levetiracetam found to have hyponatremia and their serum total bilirubin level is also elevated. So patients taking levetiracetam should monitor sodium and serum total bilirubin level.[6] Hyponatremia is an important and common electrolyte abnormality that can be seen in isolation or, as most often is the case, as a complication of other medical illnesses. Symptoms range from nausea and malaise, with mild reduction in the serum sodium, to lethargy, decreased level of consciousness, headache, and (if severe) seizures and coma. Overt neurologic symptoms most often are due to very low serum sodium levels (usually <115 mEq/L), resulting in intracerebral osmotic fluid shifts and brain edema.[4]

Hypoosmolality (serum osmolality <280 mOsm/kg) always indicates excess total body water relative to body solutes or excess water relative to solute in the extracellular fluid (ECF), as water moves freely between

the intracellular and the extracellular compartments. This imbalance can be due to solute depletion, solute dilution, or a combination of both.[7] Thus, hyponatremia can occur only when some condition impairs normal free water excretion. Therefore, correction of hyponatremia must take into account the chronicity of the condition. Acute hyponatremia (duration < 48 h) can be safely corrected more quickly than chronic hyponatremia.[9,10] Correction of serum sodium that is too rapid can precipitate severe neurologic complications. Most individuals who present for diagnosis, versus individuals who develop it while in an inpatient setting, have had hyponatremia for some time, so the condition is chronic, and correction should proceed accordingly.[5]

MATERIALS AND METHODS

Study design
Prospective experimental study.

Study population
Patients diagnosed with epilepsy.

Study site
Department of Neurology at Pushpagiri Medical College Hospital, Thiruvalla, Kerala.
Pushpagiri College of Pharmacy, Medicity, Thiruvalla.

Study period
6 months.

Sample size of the study
80 patients diagnosed with epilepsy.
$(Z^2_{1-\alpha/2})\ (1-p)p$

where p: Expected proportion
ζ^2 p ζ: Relative precision
1-α/2: Desired confidence level

Study criteria
Inclusion criteria
1. Both male and female epileptic patients taking 500 mg tablet of levetiracetam .
2. Patients of all age groups.
3. Both OP and IP patients.
4. Patients who are willing to sign the informed consent.

Exclusion criteria
1. Patients having liver diseases.
2. Alcoholic patients.
3. Those who are unable to give informed consent.
4. Avoid patients taking medications (statins, anti-rheumatic drugs or any
5. Other anti-hyperlipidaemic drugs) that affects liver.

After taking approval from Institutional ethics committee, a hospital based prospective experimental study was carried out. The study was carried out to estimate serum total bilirubin level and hyponatremic effect associated with the use of levetiracetam therapy in epileptic patients. The study was conducted in Department of Neurology at Pushpagiri Medical College Hospital. 80 patients were selected for the follow up study. The selection of patients were based upon the inclusion and exclusion criteria. All the patients were aware of brief introduction of the study. A written informed consent form was collected from the patient/care giver. Information regarding demographic details of the patient, aetiology, past medical history, past medication history, current medications, drug administration, type of seizure, co-morbidities, adverse drug reactions should be noted. About 3 ml of residual blood was obtained from the laboratory. Serum was separated by centrifugation and used for the estimation of serum levels of total bilirubin and sodium. The concentration was determined by using analytical kits in semi-auto analyser. Follow up study was conducted. The results obtained from the experiment was compared with the normal range of total bilirubin and sodium in blood. Morisky Medication Adherence Scale-4 was used to determine medication adherence.

Determination of sodium
Preparation of blank
- Pipette out 1000 µl of colour reagent into a test tube.

Preparation of standard
- Pipette out 1000 µl of colour reagent into another test tube.
- Add 10µl of standard.

Preparation of test
- Add 1000 µl of colour reagent into a test tube.
- Add 10 µl of serum to it

Mix and incubate for 5 min. at RT (15-30 ^{0} C). Measure absorbance of sample(AT) and standard (AS) against Reagent Blank at 630 nm.

Determination of total bilirubin
Preparation of blank
Pipette out 1000 µl total bilirubin reagent.
Add 20 µl activator total into a test tube.
Mix well and incubate for 5 min.

Preparation of test
Pipette out 1000 µl total bilirubin reagent into a test tube.
Add 20 µl activator total.
Add 50 µl serum.

Reagents
Total bilirubin reagent: sulfanilic acid 28.9 mmol/L
Total bilirubin activator: TAB 9 mmol/L.

RESULTS AND DISCUSSION

Gender
In this study, majority of epilepsy patients taking were males (75 %) followed by females (25%).

Age
In this study, most of the study population falls under the age group 61-75. The mean age of the patient was found to be 57.01.

Neuropsychiatric comorbidities
In this study, 13 (16.3%) patients had comorbidities, out of which 6.3 % patients had anxiety.

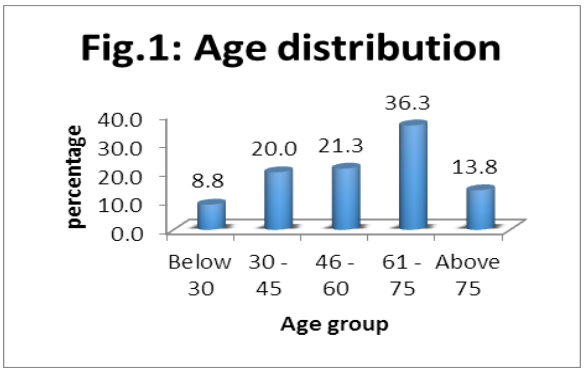
Etiology
In this study, most common etiology of epilepsy was found to be cryptogenic (68.8 %) followed by idiopathic (12.5 %).

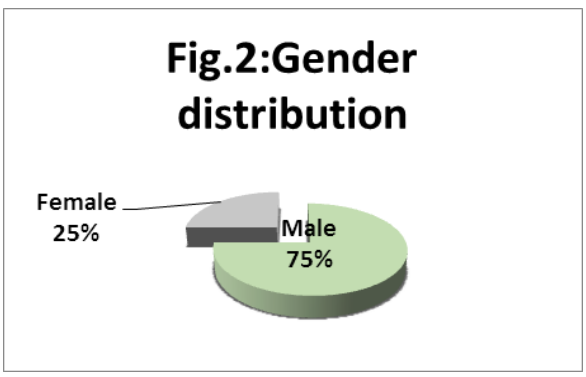
Side effects
Out of 80 patients, 30 (37.6 %) patients experienced side effects. Head ache was seen in 11 (13.8 %) followed by weakness in 9 (11.3 %) patients.

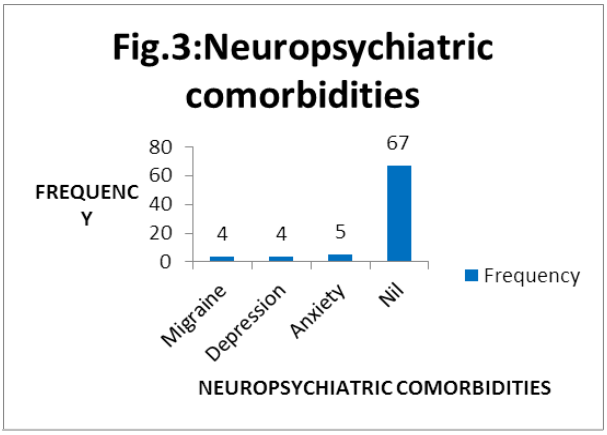
Effect of levetiracetam on sodium level
The mean value of sodium after drug use was 127.30 mmol/L and the p value was < 0.001 which is significant. Since P<0.001, the sodium level was significantly decreased.

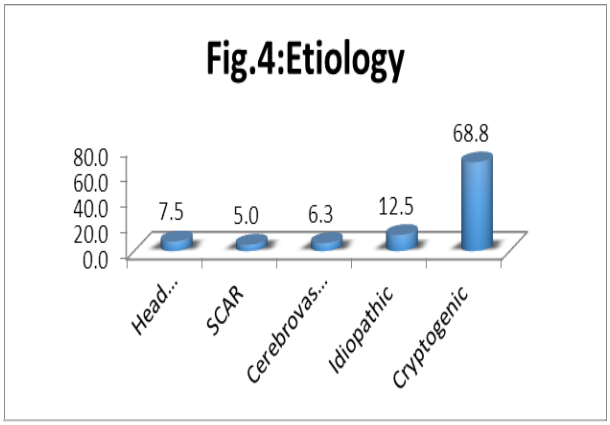
Effect of levetiracetam on total bilirubin
The mean value of total bilirubin was 2.71mg/dl and the p value is < 0.001 which is significant. Since P<0.001, the total bilirubin level was significantly increased.

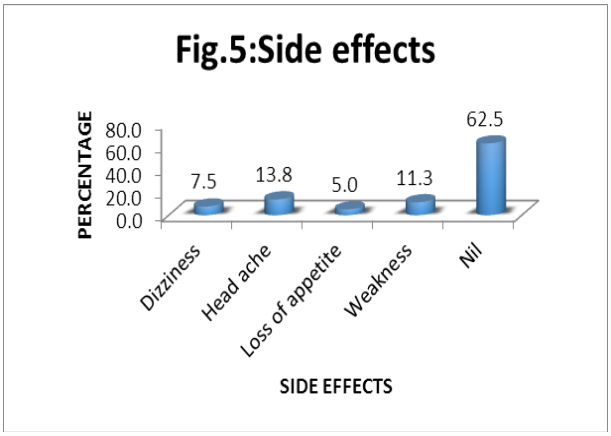
Medication adherence
In this study, medication adherence was found to significant increase after patient counselling with a p value <0.001. MMAS -4 was used for determining medication adherence.

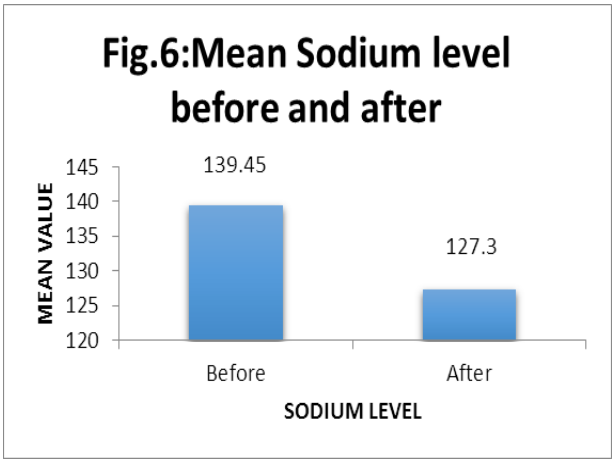


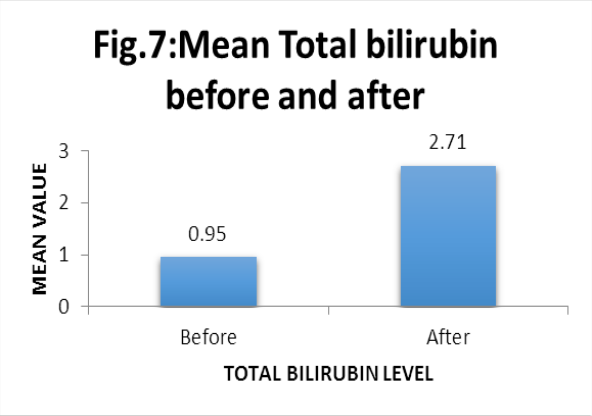












CONCLUSION

Levetiracetam is a second generation anti epileptics. It is used as adjunctive therapy for partial onset seizures, generalized tonic-clonic seizures and myoclonic seizures in both children and adults. The studies regarding the elevation of serum total bilirubin and hyponatremic condition associated with the treatment of levetiracetam are very rare. The importance of serum total bilirubin elevation and hyponatremic condition with levetiracetam can be magnified by carrying out further studies and assessments. Patients taking levetiracetam should monitor the serum total bilirubin level and serum sodium levels. Medication adherence was increased after patient counselling. Regular monitoring of sodium and total bilirubin of epileptic patients while taking levetiracetam is required for the betterment of therapy. Adequate dose adjustments should be done, if needed during the levetiracetam therapy.

The mean value of sodium after drug use was 127.30 mmol/L and the p value was < 0.001 which is significant. Since P<0.001, the sodium level was significantly decreased.

The mean value of total bilirubin was 2.71mg/dl and the p value is < 0.001 which is significant. Since P<0.001, the total bilirubin level was significantly increased.

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