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COMPARATIVE EFFECT OF CONVENTIONAL AND NEW ANTIEPILEPTIC DRUG THERAPY ON SERUM THYROID PROFILE IN ADULT EPILEPTIC PATIENTS – A CROSS SECTIONAL STUDY

Medical Science

Swathi B Department of Clinical Pharmacology & Therapeutics, Nizam's Institute of Medical Sciences, Panjagutta, Hyderabad, India.

Aruna D* Department of Clinical Pharmacology & Therapeutics, Nizam's Institute of Medical Sciences, Panjagutta, Hyderabad, India. *Corresponding Author

Surya Prabha T Department of Neurology, Nizam's Institute of Medical Sciences, Panjagutta, Hyderabad, India.

Padmaja M Department of Clinical Pharmacology & Therapeutics, Nizam's Institute of Medical Sciences, Panjagutta, Hyderabad, India.

ABSTRACT

Background & Objective: Alteration in thyroid profile is associated with change in basal metabolic rate of every organ. Thus, we aimed to assess and compare the effect of conventional antiepileptic drug, valproate and newer antiepileptic drugs, levetiracetam and oxcarbazepine mono therapy on serum thyroid profile in adult epileptic patients.

Methods: Patients on stable dose of valproate (n=14), levetiracetam (n=14), or oxcarbazepine (n=14) mono therapy for at least six months, and age and gender matched healthy controls (n=14) were included and analyzed for T_3, T_4, TSH.

Results: With oxcarbazepine, significantly low T_3 (P=0.0138), T_4 levels (P=0.0021) and no significant difference in TSH (P=0.8566) was observed compared to control. No significant difference in thyroid profile was observed compared to control in other groups and when newer AEDs were compared to valproate.

Conclusion: Thus, patients on oxcarbazepine may require monitoring of thyroid profile. Advanced long term studies are warranted to confirm these results.

KEYWORDS

Valproate; Levetiracetam; Oxcarbazepine; Thyroid profile

INTRODUCTION:

Epilepsy is a second most common neurological disorder, which imposes heavy burden on health care systems. Among the 70 million persons with epilepsy worldwide, nearly 12 million are residing in India, with more prevalence in rural areas compared to urban population.[1] According to International League against Epilepsy (ILAE), epilepsy is defined as, "At least two unprovoked (or reflex) seizures occurring >24 h apart; one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; and diagnosis of an epilepsy syndrome".[2] The first antiepileptic drug was bromide discovered in 19th century.[3] From the 19th century to till now there has been a rapid expansion in the number and types of antiepileptic drugs. Most commonly used conventional antiepileptic drugs are phenytoin, phenobarbital, valproate and carbamazepine. Newer antiepileptic drugs commonly used are levetiracetam, oxcarbazepine (OXC), lamotrigine, topiramate. The treatment of epilepsy includes mainly mono therapy or combination therapy with anti epileptic drugs. Treatment with antiepileptic drugs (AEDs) is associated with many short and long term side effects.[4] Adverse effects associated with AEDs are psychiatric and behavioural problems, cognitive impairment, weight changes, and increased risk of teratogenicity, hypersensitivity reactions and endocrine effects such as effects on reproductive function, thyroid function and on bone health.[4] Changes in thyroid hormone levels alter basal metabolic rate of almost every organ and every system in the body.[5] Effect of antiepileptic drugs on thyroid hormone concentrations has been demonstrated in several studies.[6-9]

Alteration of thyroid hormone levels caused by antiepileptic drugs might be through several mechanisms. One of the mechanisms involved in change of thyroid hormone levels is stimulation of drug metabolizing enzymes by AEDs causing acceleration of metabolism and increase in turnover of free and bound thyroid hormone levels. Another mechanism proposed is alterations in the hypothalamic–pituitary–thyroid axis.[10]

The effect of valproate on serum thyroid concentrations has been controversial. Moreover limited data exist for the effect of oxcarbazepine and levetiracetam on thyroid function in adult epileptic patients. Therefore, we aimed to investigate the effect of conventional antiepileptic drug, valproate and newer antiepileptic drugs, levetiracetam and oxcarbazepine monotherapy on serum thyroid profile in adult epileptic patients.

METHODS:

The present study was a comparative cross-sectional study carried out by department of Clinical Pharmacology in collaboration with department of Neurology, Nizam's Institute of Medical Sciences, Hyderabad. After obtaining permission from the institutional ethics committee (EC/NIMS/1885/2017;21st ESGS No. 455/2017), study was initiated. The study was registered with CTRI (CTRI/2017/12/010809). Written informed consent was taken from all the eligible subjects prior to study. Patients aged between 18-60 years of age of either gender with epilepsy who are on stable dose of single antiepileptic drug for at least 6 months, age and gender matched healthy subjects were included. Patients on combination therapy with antiepileptic drugs, those who were noncompliant to the drug, having progressive or psychiatric neurological disorder, those with refractory seizures, who were on anti thyroid drugs or on thyroid hormone replacement therapy and with other co morbid conditions like ischemic heart disease, stroke, chronic kidney disease, liver disease, diabetes mellitus, and hypertension and other metabolic diseases, pregnant and lactating mothers were excluded from the study. Patients who had received the drugs, which could affect the level of thyroid hormones, in the past 6 months, were excluded from the study. Total 56 subjects were enrolled, in which 14 subjects were age and gender matched healthy controls and 42 were epileptic patients. The forty two epileptic patients were classified into three groups, valproate group, oxcarbazepine group and levetiracetam group. Each group consisted of 14 patients. Detailed information including demographic characteristics, age at onset of seizures, seizure type, seizure frequency, antiepileptic drug details, duration of AED therapy, details of concomitant medications and electroencephalographic findings were collected. Fasting venous blood sample of 5 ml was collected from the patients and control subjects for assessment of T_3, T_4, and TSH levels by Chemiluminescence Immuno Assay method. The normal range of serum T_3 is 1.3–3.1 nmol/l, serum T_4 is 5–14 µg/dl, and serum TSH is 0.2–4 µIU/ml.

Statistical analysis:

Sample size was calculated based on proportion of patients with epilepsy attending outpatient department as 3% and with precision of 5% and type 1 error of 5%. Values were expressed as mean ± standard

deviation. Mean ± standard deviation was calculated for entire sample and individual groups. One-way analysis of variance followed by *post hoc* Dunnett's test was performed for between group comparisons using GraphPad Prism 7. P-value < 0.05 was considered to be statistically significant.

RESULTS:

A total of 56 patients were enrolled into the study, 42 were epileptic patients and 14 were healthy controls. Among 42 subjects with epilepsy 23 (55%) were males and 19 (45%) were females. In control subjects 8 (57%) were females and 6 (43%) were males. The demographic characteristics and duration of anti epileptic therapy were shown in Table 1. There was no significant difference among age (*P*=0.0946), weight (*P*=0.8983), body mass index (BMI) (*P*=0.3622), duration of anti epileptic therapy (*P*=0.5411) between the groups. In valproate group males were predominant, but in other groups females were predominant.

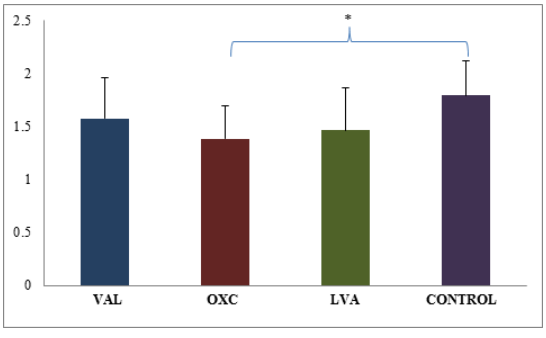
Table 1: Demographic characteristics of study population

Characteristic	Total (n=56)	Valproate (n=14)	Oxcarbazepine (n=14)	Levetiracetam (n=14)	Control (n=14)
Age (years)	33.05±12.06	39.29±11.89	32.86±13.47	28±8.62	32.07±12.16
Gender (M/F)	29/27	12/2	6/8	5/9	6/8
Weight (kg)	60.52±11.27	61.07±12.02	62±12.76	58.79±11.65	60.21±9.42
BMI (kg/m2)	23.63±4.18	22.8±3.7	25.25±5.39	22.76±3.89	23.7±3.44
Duration of therapy (years)	2.27±1.64	2.4±1.9	1.87±1.56	2.54±1.47	-

The duration of anti epileptic therapy ranged from six months to seven years among persons with epilepsy. Generalized tonic clonic seizures were observed in 32 (76.2%) subjects, followed by absence seizures in 4 (9.52%) subjects, complex partial seizures in 4 (9.52%) subjects, and myoclonic seizures in 2 (4.76%) subjects.

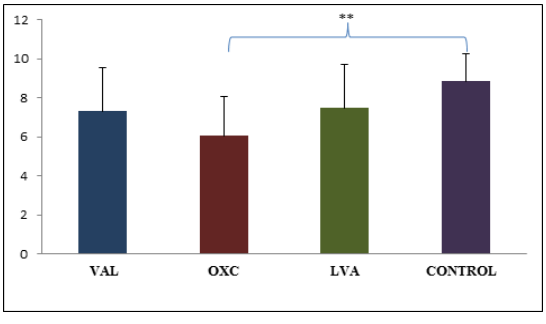
In valproate, oxcarbazepine, levetiracetam and control groups serum T_3 (nmol/l) levels were 1.57±0.39, 1.38±0.31, 1.46±0.4, 1.79±0.33; serum T_4 (µg/dl) levels were 7.31±2.26, 6.04±2.01, 7.49±2.21, 8.85±1.42; and serum TSH (µIU/ml) levels were 3.16±1.05, 3.45±1.41, 3.08±2.2, and 3.03±1.74 respectively (Figure 1, 2, & 3).

Figure 1: Serum triiodothyronine (T_3) levels in study population



VAL – Valproate; OXC – Oxcarbazepine; LVA - Levetiracetam
p < 0.05: OXC vs Control
NS: VAL vs Control; LVA vs Control; LVA vs VAL; OXC vs VAL

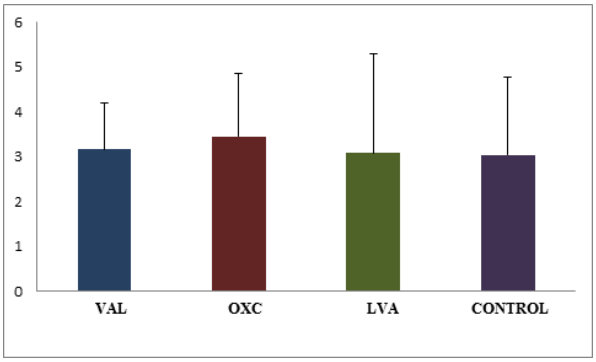
Figure 2: Serum thyroxine (T_4) levels in study population



VAL – Valproate; OXC – Oxcarbazepine; LVA - Levetiracetam
p < 0.01: OXC vs Control

NS: VAL vs Control; LVA vs Control; LVA vs VAL; OXC vs VAL

Figure 3: Serum thyroid stimulating hormone (TSH) levels in study population



VAL – Valproate; OXC – Oxcarbazepine; LVA – Levetiracetam
NS: VAL vs Control; OXC vs Control; LVA vs Control; LVA vs VAL; OXC vs VAL

There was statistically significant low levels of serum T_3 (*P*=0.0138), T_4 (*P*=0.0021) and no significant difference in TSH (*P*=0.8566) observed in patients treated with oxcarbazepine compared to control group.

And no statistically significant difference in serum T_3 (*P*=0.281), T_4 levels (*P*=0.1345) and TSH (*P*=0.9952) was seen in patients on valproate compared to control group.

Similarly, there was no statistically significant difference observed in serum T_3 (*P*=0.0598), T_4 (*P*=0.2094) and TSH levels (*P*=0.9996) in patients on levetiracetam compared to control group.

Subclinical hypothyroidism (TSH > 4 µIU/ml) was observed in 15 subjects out of 56, among them 6 were in oxcarbazepine group, 3 were in levetiracetam group, 3 were in valproate group and 3 were in control group. More number of subjects with subclinical hypothyroidism was present in oxcarbazepine group.

Additionally, there was no significant difference in serum T_3 (*P*=0.3211, *P*=0.6738) and T_4 levels (*P*=0.2426, *P*=0.9674) and TSH (*P*=0.8564, *P*=0.9907) among oxcarbazepine and levetiracetam treated patients when compared to conventional antiepileptic drug valproate. Adverse drug reactions observed with levetiracetam were hair loss in one subject and withdrawal seizures in one subject. With OXC weight gain was seen among 8 subjects. And in valproate group, weight loss was observed in 2 subjects.

DISCUSSION:

In the present study, there were significantly low levels of T_3, T_4 but no significant difference in TSH was observed with oxcarbazepine compared to control group. This is in accordance with a study [9] conducted in 55 newly diagnosed epileptic children who had normal thyroid function before initiating treatment. Among 55 epileptic children, 25 were treated with OXC and 30 were treated with valproate. In the OXC treated children, serum T_3 and T_4 levels were found to be significantly decreased at the third and six months and no significant change in TSH was observed compared to baseline. Vainionpaa et al,[7] evaluated thyroid function in girls with epilepsy taking carbamazepine (CBZ), oxcarbazepine or valproate monotherapy, among them 18 were taking OXC. When compared to control girls there was significant decrease in T_4 and fT_4, but TSH levels were normal in girls taking CBZ or OXC. However, in another study[6] 223 children with epilepsy were evaluated for thyroid function at baseline, first, sixth and twelfth month of anti epileptic therapy. Among them 14 were treated with OXC showed significantly decreased fT4 levels at first month and insignificant decrease at sixth and twelfth months.

In our study there was no significant alteration in T3, T4 and TSH in patients treated with valproate compared to control group. Isojarvi et al

[11] showed that in ninety men with epilepsy taking CBZ, OXC or Valproate, the concentrations of thyroid hormones, thyrotropin, and antithyroid antibody were normal in men treated with valproate. In another study[8] done in India there was no significant difference in T3, T4 and TSH levels compared to baseline in valproate group consisting of 30 patients. In girls with epilepsy receiving valproate, had normal serum T_4 and fT_4 concentrations, and slightly increased TSH levels.[7] But in contrast to these studies, 129 children with new onset and controlled epilepsy treated with valproate had decreased fT4 and increased TSH levels at months 1, 6, and 12.[6] Similarly, in another study done by sahu et al,[12] there were significantly elevated median titres of TSH in valproate group compared with the control group and out of 57 children 15 had subclinical hypothyroidism in valproate group.

The present study showed no significant difference in T3, T4 and TSH levels in 14 subjects treated with levetiracetam compared to control group. Only limited data exists for levetiracetam effect on thyroid hormone levels. A study done by aygun et al[13] demonstrated that in 5% out of 106 children treated with levetiracetam, no significant difference observed in fT_4 values and TSH levels at the third, sixth and ninth month of therapy. In another study [6] 11 children treated with levetiracetam monotherapy showed no significant change in fT_4 and TSH levels at first, sixth and twelfth months. In the present study all the patients were clinically euthyroid with no signs and symptoms of hypo or hyperthyroidism.

In conclusion, significantly low thyroid hormone levels (T_3, T_4) were observed in patients on oxcarbazepine compared to control group. No significant difference in thyroid profile was observed compared to control group in levetiracetam and valproate groups. Although in the present study antiepileptic drug therapy was not associated with clinical hypothyroidism, it is suggested that evaluation of thyroid hormone levels in patients on antiepileptic drug therapy is needed especially for oxcarbazepine. But to strengthen these results further advanced studies of randomized double blind nature with long term use of antiepileptic drugs are warranted.

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