



# Effect of Sodium Valproate Monotherapy on the Thyroid and Liver Function Tests of Pediatric Epileptic Patients

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**ABSTRACT**

**OBJECTIVE:** To determine the changes in thyroid function tests and liver function tests in children who underwent valproate therapy. To determine if there is a relationship between dose of sodium valproate used and its affection of thyroid and liver function tests and to determine the effect of sodium valproate on the body mass index and to know if there is a relationship between the dose and changes in body mass index.

**MATERIALS AND METHODS:** The blood from children confirmed clinically as epilepsy was used for the baseline liver function tests and thyroid function tests and the tests were repeated after 6 months of sodium valproate therapy.

**RESULTS:** TSH, SGPT and Body Mass Index was elevated in 34, 26 and 11 children respectively after 6 months of therapy with sodium valproate which were all statistically significant.

**CONCLUSION:** Treatment with sodium valproate is associated with altering the functions of thyroid and liver. It also caused an increase in the body mass index in children.

**KEYWORDS**

Sodium Valproate, epilepsy, TSH, SGPT, Body Mass Index

**INTRODUCTION:**

Epilepsy is defined as a chronic condition characterized by recurrent seizures with an interval of more than 24 hours unprovoked by any immediate identifiable cause. It can be controlled but not cured by various drugs depending on the type and severity of seizures. Epilepsy is one of the most common neurological disorders of childhood affecting more than 6% of all children and has a major impact on the development of children.

Treatment with antiepileptic agents is associated with a lot of complications such as affecting the function of endocrine glands, functions of the liver and bone marrow.

Many antiepileptic drugs can change the plasma levels of triiodothyronine and thyroxine as well as the enzymes of the liver. Most of these drugs are powerful inducers of liver microsomal enzymes which can result in changes in the metabolism of thyroid hormones and liver enzymes.

Sodium valproate is the sodium salt of valproic acid. It belongs to the Branched Chain Aliphatic Carboxylic Acid group of anticonvulsants and is used in the treatment of epilepsy, panic attack, anorexia nervosa, migraine, anxiety disorder, posttraumatic stress disorder, and bipolar disorder.

Sodium valproate is usually used orally and uncommonly used intravenously. Oral absorption is good. It is more than 90 percent bound to plasma proteins and completely metabolised in the liver by glucuronide conjugation and oxidation pathway and excreted by kidneys. The plasma half life is 10 to 15 hours but the anticonvulsant action lasts longer. Sodium valproate is usually started at a dose of 10mg/kg/day and can be increased gradually upto 60mg/kg/day.

The toxicity of valproate is low. Drowsiness, ataxia and tremors are dose related side effects. Asymptomatic rise in serum transaminase is common and hence monitoring of liver function has been advised. A rare but serious side effect is fulminant hepatitis occurring only in children especially below 2 years. Those with hepatic disease or hepatotoxic drugs are at greater risk.

The following side effects are more commonly reported in children using sodium valproate -gastrointestinal problems such as nausea or diarrhoea, alopecia, lethargy, hallucinations, excessive somnolence, behavioural problems or worsening of behavioural problems including aggression, hyperactivity and weight gain.

Considering its wide spread usage for so many conditions monitoring of its side effects becomes all the more important.

**AIMS AND OBJECTIVES**

1. To determine the changes in thyroid function tests in children who underwent valproate therapy.
2. To determine the changes in liver function tests in children who underwent valproate therapy.
3. To determine if there is a relationship between dose of sodium valproate used and its affection of thyroid and liver function tests.
4. To determine the effect of sodium valproate on the body mass index and to know if there is a relationship between the dose and changes in body mass index

**MATERIALS AND METHODS**

This study is carried out in a prospective fashion without an external control group on children with new onset epilepsy who had not been previously treated with any of the antiepileptic medications. All children who satisfy the inclusion criteria are included in the study and the patients and guardians were well informed regarding the potential complications. They were included only after their guardians consented for participation in the study.

**TYPE OF STUDY-PROSPECTIVE COHORT STUDY INCLUSION CRITERIA**

- New onset therapy with sodium valproate
- Monotherapy with sodium valproate
- 1 year to 11.5 years
- BMI percentile between 5 and 85

**EXCLUSION CRITERIA**

- Already on therapy with sodium valproate
- Started on other anticonvulsants along with sodium valproate
- Patients whose baseline thyroid or liver function tests are abnormal
- Less than 6 months
- Family history of hypothyroidism
- BMI less than 5<sup>th</sup> percentile
- BMI greater than 85<sup>th</sup> percentile
- Children with any of the congenital malformations

**PROCEDURE OF THE STUDY:**

Once they satisfied the inclusion criteria the study was explained to them and their guardians and they were included in the study after they consented to the study by signing the consent form which was signed by the guardians. Before the start of therapy morning fasting sample of blood was obtained. This blood was used for the baseline liver function tests and thyroid function tests. The children were excluded from the study if either the thyroid function test or liver function tests were abnormal.

The height and weight of the children were also measured at the time of taking blood samples. From the height and the weight their body mass index is calculated using the formula

$$\text{Body Mass Index} = \frac{\text{Weight (kg)}}{\text{Height}^2 \text{ (m)}}$$

From this body mass index is obtained and expressed as kg/m<sup>2</sup>. From the Centers for Disease Control and Prevention charts the body mass index was converted to percentiles.

The date was recorded as the starting date of therapy.

They were advised to start the sodium valproate in the recommended dosage after their blood samples had been taken. At each visit they were examined for any of the apparent side effects of sodium valproate and hypothyroidism and also their compliance to therapy.

Then at the end of 6 months of study period, 3 ml of blood was again obtained under sterile conditions for the repeat thyroid function tests and liver function tests along with the measurements of height and weight and again body mass index of the children were calculated using the same formula and converted to percentile using the Centre for Disease Control Chart. The patients were asked to continue the drugs at the same dosage and review whenever necessary and absolutely every two weeks for drugs.

**STATISTICAL ANALYSIS**

The results were then tabulated and then analysed using SSPE software version 17. Statistically a lower limit of 0.05 was considered as significant. The results were analysed as before starting therapy with sodium valproate and 6 months after starting therapy with sodium valproate using the paired t test, Chi square test and Pearson Correlation. Comparison were made between levels of free triiodothyronine, free thyroxine, Thyroid Stimulating Hormone, SGOT, SGPT and SAP at baseline and 6 months after start of therapy with sodium valproate.

**RESULTS:**

- The maximum number of children included in the study were in the age group of 5-10 years and most of them were boys. The maximum number of children included in the study were in the dose range of 10-15 mg/kg/day with the mean dose being 12.82mg/kg/day.
- TSH was elevated in 34 children (29.56%) and it was statistically significant.
- The rise in TSH was more in the dosage range of 15-20 mg/kg/day.
- The decrease in free Triiodothyronine was significant and was more common in the dosage range of 15-20 mg/kg/day.

- The levels of free thyroxine was not affected by sodium valproate in the 6 months of the study period.
- The rise in SGOT was not statistically significant
- The rise in SGPT was statistically significant and the children in the dose range of 15-20 mg/kg/day had a greater chance of elevation of SGPT.
- The rise in SAP was statistically significant and the rise was more common in children in the dosage range of 15-20 mg/kg/day.
- The Body Mass Index was increased to the overweight and obese category in 11 children and it was statistically significant and there was a greater chance of change of BMI to the above normal range in the dosage group of >20 mg/kg/day.
- The changes in bilirubin were not significant after start of therapy.
- The changes in protein were not significant after the start of therapy.
- The total number of children with abnormal liver function test were equal to the total number of children with abnormal thyroid function test.
- The number of children with both thyroid and liver function test abnormality were equally distributed between 10-15mg/kg/day group and 15-20mg/kg/day group with no patient in the >20mg/kg/day group.
- There were two boys and no girls at all with simultaneous abnormalities of thyroid function tests, liver function tests and body mass index with one boy in each of the 10-15mg/kg/day group and 15-20mg/kg/day group.

**RESULTS**

**TABLE -SEX DISTRIBUTION**

BOYS	66
GIRLS	49
TOTAL	115

- A total of 115 children were actually enrolled in the study. Boys accounted for 57.39% and girls 42.60%.
- The number of dropouts in the study were 5 of which 1 was a boy and 4 were girls.
- A total of 3 patients were excluded from the study of whom 1 was a boy and 2 were girls. All three were excluded because of abnormal thyroid function tests.

**TABLE -AGE DISTRIBUTION**

AGE	BOYS	GIRLS
1-5Yrs	20	18
5-10Yrs	36	20
10-12Yrs	10	11
TOTAL	66	49

The maximum children included in this study were in the age group of 5-10 years accounting for 48.69 % of the total children and least being in the 10-12 year age group accounting for 18.26% of the total children and this trend was followed in the sex wise classification also.

The mean age of the children included in the study was 7.1 years.

**TABLE -DOSAGE**

DOSAGE	NO. OF PATIENTS
10-15mg/kg/day	86
15-20mg/kg/day	25
>20mg/kg/day	4

86 children were started in the dose ranging from 10-15 mg/kg/day which accounted for 74.78% of children followed by 25 patients in the 15-20 mg/kg/day which accounted for 21.73% of children. Children in the >20mg/kg/day group accounted for 0.03%/

**The mean starting dose of children was 12.82mg/kg/day. TABLE -TSH CHANGES**

TSH VALUES	NO. OF PATIENTS
NORMAL	81
ELEVATED	34

As described in the table above TSH values measured 6 months after start of therapy were elevated in 34 patients which accounted for 29.56%.The mean TSH value before start of therapy was 3.36mIU/ml and after start of therapy was 6.28mIU/ml.

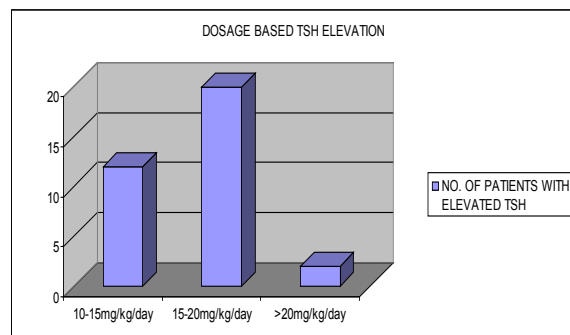
The changes in TSH 6 months after start of therapy were significant with ap value of <0.001 and hence there is a significant statistical difference between TSH values before and 6 months after start of valproate.

**TABLE -DOSAGE BASED TSH INCREASE**

DOSAGE	NO. OF PATIENTS WITH ELEVATED TSH	TOTAL NO. OF PATIENTS
10-15mg/kg/day	12	86
15-20mg/kg/day	20	25
>20mg/kg/day	2	4

The total number of patients with elevated TSH 6 months after start of sodium valproate therapy was 34 accounting for 29.56% of patients. Of these maximum children were in the dose range of 15-20mg/kg/day (58.82% of children with elevated TSH).This was also the dose range in which the maximum percentage of children had elevated TSH(80%) as compared to 13.95% in the 10-15mg/kg/day group and 50% in the >20 mg/kg/day group. There was a positive correlation between the dose of sodium valproate and TSH levels after start of therapy.

**DIAGRAM -DOSAGE BASED TSH INCREASE**



**TABLE -FT3 CHANGES**

FT3	NO. OF PATIENTS
NORMAL	113
DECREASED	2

Free Triiodothyronine was decreased in 2 patients and normal in 113 patients 6 months after start of valproate therapy. The mean value of Free triiodothyronine before start of therapy was 3.474 pg/ml whereas after the start of therapy it was 3.126 pg/ml. This change in Free Triiodothyronine 6 months after start of valproate therapy was not statistically significant. Both the children were in the 10-15 mg/kg/day group.

**TABLE -SGOT CHANGES**

SGOT	NO. OF PATIENTS
NORMAL	109
ELEVATED	6

SGOT was elevated in 6 children 6 months after start of sodium valproate therapy accounting for 5.21% of children started on therapy.The mean SGOT value before start of therapy was 41.43U/l whereas it was 46.07U/l 6 months after start of sodium valproate therapy.

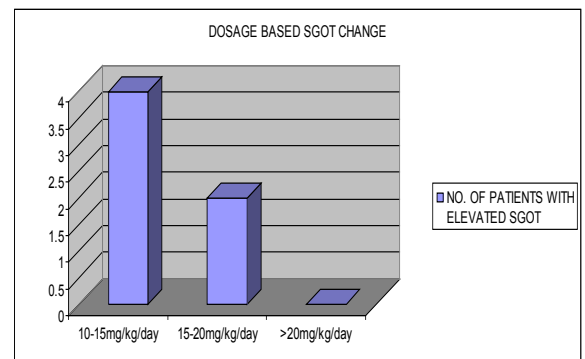
This difference was not significant statistically

**TABLE -DOSAGE BASED SGOT INCREASE**

DOSAGE	NO. OF PATIENTS WITH ELEVATED SGOT
10-15mg/kg/day	4
15-20mg/kg/day	2
>20mg/kg/day	0

The number of children with elevated SGOT 6 months after start of therapy was 6 accounting for 5.21% of children included in this study.Out of these 4 children that is 66.67% were in the 10-15mg/kg/day and the rest were in the 15-20mg/kg/day.Surprisingly SGOT wasn't elevated in none of the 4 children in the >20mg/kg/day group.

**DIAGRAM -DOSAGE BASED SGOT INCREASE**



**TABLE -SGPT CHANGES**

SGPT	NO. OF PATIENTS
NORMAL	89
ELEVATED	26

The number of children with elevated SGPT 6 months after start of valproate was 26 which constituted 22.6% of children include in the study. The mean value of SGPT before the start of therapy was 32.23U/l in comparison to 43.88U/l 6 months after the start of therapy.

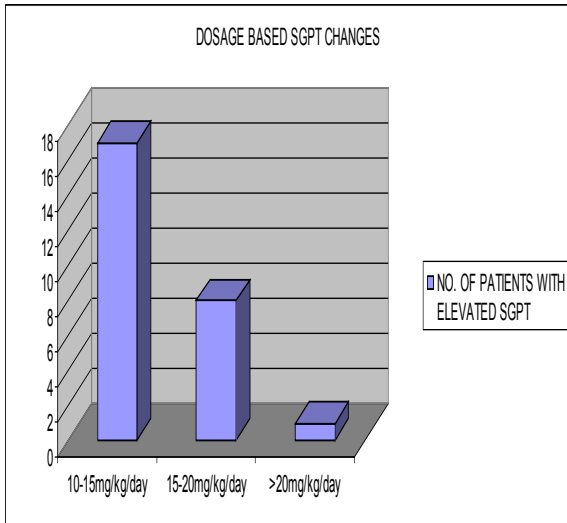
The change in SGPT was statistically significant with a p value of less than 0.001(p<0.001).

**TABLE -DOSAGE BASED SGPT CHANGES**

DOSAGE	NO. OF PATIENTS WITH ELEVATED SGPT	TOTAL NO. OF PATIENTS
10-15mg/kg/day	17	86
15-20mg/kg/day	8	25
>20mg/kg/day	1	4

The total number of children with elevated SGPT 6 months after start of therapy was 26 accounting for 22.6% of patients. Of these maximum number of children were in the 10-15mg/kg/day group which constituted 65.38% but the group with the maximum percentage of children when compared to total no. of patients was the 15-20mg/kg/day group in which there was a 32% change whereas it was 25% in the >20mg/kg/day group compared to 19.76% in the 10-15mg/kg/day group. There was also a positive correlation between the dose of sodium valproate and SGPT.

**DIAGRAM -DOSAGE BASED SGPT CHANGES**



**TABLE -SAP CHANGES**

SERUM ALKALINE PHOSPHATASE	NO. OF PATIENTS
NORMAL	100
ELEVATED	15

The number of children in whom serum alkaline phosphatase was elevated 6 months after start of therapy was 15 which constituted 13.04% of the children included in the study.

The mean value of serum alkaline phosphatase before start of therapy was 231.87 IU/L whereas 6 months after start of therapy with sodium valproate was 274.10IU/L.

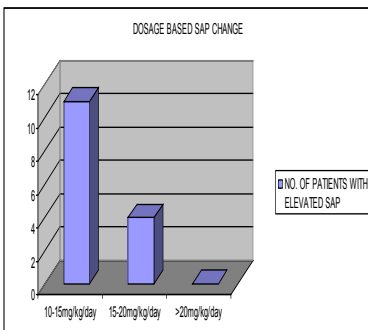
The change in serum alkaline phosphatase was significant statistically at p value less than 0.001(p<0.001)

**TABLE 13-DOSAGE BASED SAP CHANGES**

DOSAGE	NO. OF PATIENTS WITH ELEVATED SAP	TOTAL NO. OF PATIENTS
10-15mg/kg/day	11	86
15-20mg/kg/day	4	25
>20mg/kg/day	0	4

The total number of patients with elevated SAP 6 months after start of sodium valproate therapy was 15. Of these the maximum number of children was in the 10-15mg/kg/day group which constituted 73.33% with the rest belonging to the 15-20mg/kg/day group. When we compare this with the conversion rate its higher in the 15-20mg/kg/day group (16%) compared to 12.79% in the 10-15mg/kg/day.

**DIAGRAM -DOSAGE BASED SAP CHANGES**



**TABLE 14-SGOT, SGPT & SAP**

DOSAGE	NO. OF PATIENTS WITH SGOT,SGPT & SAP ABNORMAL
10-15mg/kg/day	2
15-20mg/kg/day	1
>20mg/kg/day	0

There were 3 children in whom all three SGPT,SGOT and SAP were abnormal 6 months after start of therapy with sodium valproate with two children being in the 10-15mg/kg/day group and one child in the 15-20mg/kg/day group.

**TABLE -CHANGES IN BMI**

BMI	NO OF PATIENTS
NORMAL	104
INCREASED	11

The Body Mass Index of 9 patients was changed from healthy weight to overweight and for 2 patients it was increased from normal range to obese range after the start of therapy with sodium valproate.

The mean Body Mass Index in absolute values before the start of therapy was 16.4817 kg/m<sup>2</sup> whereas 6 months after the start of valproate therapy it was 16.8099 kg/m<sup>2</sup>.

The change in Body Mass Index percentile was significant statistically with a p value less than 0.001(p<0.001)

**TABLE -DOSAGE BASED BMI CHANGE**

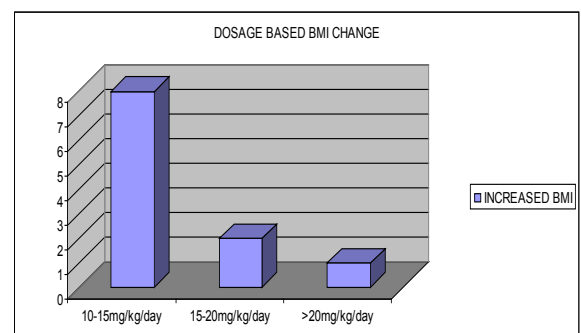
DOSAGE	NO. OF PATIENTS WITH INCREASED BMI	TOTAL NO. OF PATIENTS
10-15mg/kg/day	8	86
15-20mg/kg/day	2	25
>20mg/kg/day	1	4

A total of 11 patients had their body mass index above the normal range 6 months after the start of valproate accounting for 9.56% of patients. Of these the maximum number of children 8 (72.72%) were in the 10-15mg/kg/day group. But when individual groups were considered in the >20 mg/kg/day group there was a conversion of 25% compared to 9.3% in the 10-15 mg/kg/day group and 8% in the 15-20 mg/kg/day group.

The change in BMI was statistically significant with a p value of less than 0.001 (p<0.001)

Therefore a higher dose range had a higher chance of increase in BMI and thus there was a positive correlation between the dose of sodium valproate and changes in the body mass index.

**DIAGRAM : DOSAGE BASED BMI CHANGE**

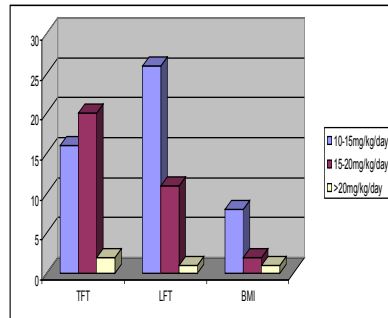


**TABLE -COMPARISON BETWEEN LFT, TFT AND BMI**

DOSAGE	NO. OF PATIENTS WITH ABNORMAL TFT	NO. OF PATIENTS WITH ABNORMAL LFT	NO. OF PATIENTS WITH ABNORMAL BMI
10-15mg/kg/day	14	26	8
15-20mg/kg/day	20	11	2
>20mg/kg/day	2	1	1
TOTAL	36	38	11

As shown in the above table changes in Liver Function Tests and Thyroid Function tests are comparable 6 months after start of therapy.

**DIAGRAM -COMPARISON BETWEEN LFT,TFT & BMI**



**TABLE -COMPARISON BETWEEN SGPT, TSH & BMI**

DOSAGE	NO. OF PATIENTS WITH ELEVATED TSH	NO. OF PATIENTS WITH ELEVATED SGPT	NO. OF PATIENTS WITH ELEVATED BMI
10-15mg/kg/day	12	17	8
15-20mg/kg/day	20	8	2
>20mg/kg/day	2	1	1

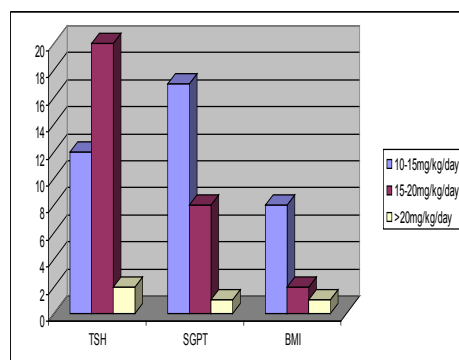
This table is summary of the number of patients with elevated Thyroid Stimulating Hormone, SGPT And Body Mass Index and has been described earlier.

The total number of patients with elevated TSH 6 months after start of sodium valproate therapy was 34 accounting for 29.56% of patients .

The total number of children with elevated SGPT 6 months after start of sodium valproate therapy was 26 accounting for 22.6% of patients.

A total of 11 patients had their body mass index above the normal range 6 months after the start of valproate accounting for 9.56% of patients.

**DIAGRAM -COMPARISON BETWEEN SGPT, TSH & BMI**



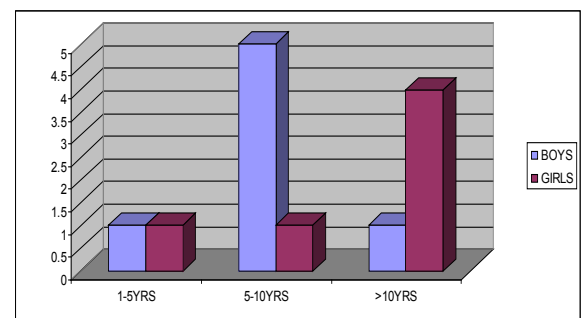
**TABLE -THYROID AND LIVER FUNCTION TESTS**

DOSAGE	NO. OF PATIENTS WITH BOTH LFT&TFT ABNORMAL
10-15mg/kg/day	7
15-20mg/kg/day	6
>20mg/kg/day	0

The number of children in whom both liver and thyroid function tests were abnormal 6 months after start of therapy were almost equally distributed in both the 10-15mg/kg/day as well as 15-20 mg/kg/day groups and with none of the patients in the >20mg/kg/day group.

The number of children in whom both thyroid and liver function tests were abnormal are almost equally distributed in both sexes but they are more common in the age group of 5-10 years in boys whereas in girls they are more common in the age group of >10 years.

**DIAGRAM 18: THYROID AND LIVER FUNCTION TESTS**



**TABLE 24-THYROID FUNCTION TESTS & BODY MASS INDEX**

DOSAGE	NO. OF PATIENTS WITH BOTH TFT & BMI ABNORMAL
10-15mg/kg/day	1
15-20mg/kg/day	1
>20mg/kg/day	0

The were 2 children in whom both Thyroid function tests and Body mass index were abnormal 6 months after start of therapy with one child in each 10-15mg/kg/day group and 15-20mg/kg/day group.

Both the children in whomTFT and BMI were abnormal 6 months after start of therapy were boys and were in the age group of 5-10 years.

**TABLE -LIVER FUNCTION TESTS & BODY MASS INDEX**

DOSAGE	NO. OF PATIENTS WITH BOTH LFT &BMI ABNORMAL
10-15mg/kg/day	2
15-20mg/kg/day	2
>20mg/kg/day	0

The number of children in whom both Liver Function Tests and Body Mass Index were abnormal 6 months after start of therapy with sodium valproate were equally distributed between the 10-15 mg/kg/day group and 15-20 mg/kg/day group with none of the patients in the >20mg/kg/day group.

The children in whom both Liver Function Tests and Body Mass Index were abnormal 6 months after start of therapy were all boys with 75% of them being in the age group of 5-10 years.

**TABLE -THYROID FUNCTION TESTS, LIVER FUNCTION TESTS & BMI**

DOSAGE	NO. OF PATIENTS WITH TFT,LFT & BMI ABNORMAL
10-15mg/kg/day	1
15-20mg/kg/day	1
>20mg/kg/day	0

There were 2 children in whom all three parameters Thyroid function tests, Liver Function Tests and Body Mass Index were abnormal with one child in each 10-15mg/kg/day group and the 15-20mg/kg/day group.

Both the children in whom Thyroid Function Tests, Liver Function Tests and Body Mass Index were abnormal 6 months after start of therapy with sodium valproate were boys and were in the age group of 5-10 years.

### DISCUSSION

In the present study after 6 months of therapy with sodium valproate TSH was elevated in 34 patients which accounted for 29.56% of children. The rise in TSH was significant. Whereas there were no significant changes in Free Triiodothyronine and Free Thyroxine. This is similar to the other studies done in pediatric patients.

Vainionpaa et al in their study compared the plasma levels of thyroid hormone between 41 children who were treated with carbamazepine and 14 children who were treated with sodium valproate with 54 healthy volunteers who served as the control group in Finland. They showed that children on sodium valproate showed an increase in TSH level but the plasma levels of triiodothyronine & thyroxine were normal.

Cansu et al. in his study evaluated 55 children with epilepsy who were treated with sodium valproate and carbamazepine. In the group of children receiving sodium valproate, plasma levels of Free thyroxine, thyroxine, Free triiodothyronine and triiodothyronine were within normal range and the same as baseline but TSH plasma level increased significantly 6 months after treatment with a significant p value of <0.05.

Mishra Harsha, Mishra Asha et al in their study involving 40 patients had similar results. In their study TSH which was significantly raised without any changes in Free Triiodothyronine and Free Thyroxine.

In the study done by Attilakos A, Katsarou E et al involving 30 children very similar result was obtained for TSH after 6, 12 and 24 months of therapy whereas there were significant changes in Free Triiodothyronine and Free thyroxine.

Mohamed Gomaa, Yasser Wasel et in their study involving 42 children concluded that sodium valproate significantly increased the levels of TSH at 6 months and that of free triiodothyronine decreased significantly at 6 months whereas the change in thyroxine was not significant.

In the present study 6 months after start of therapy with sodium valproate Body Mass Index was increased to above normal that is to overweight category in 11 children which constituted 9.56% of total children. The change in body mass index is significant in our studies. Various studies gave very similar conclusions.

Salvatore Grosso, Rosa Mostardini et al in their study to monitor body mass index

in children on sodium valproate therapy concluded that body mass index increased significantly over a 16 month period and appeared to plateau off after 16 months of continuous therapy.

In the present study changes in liver function tests that is serum glutamic pyruvic transaminase and serum alkaline phos-

phatase were significant. The change in serum glutamic oxaloacetic transaminase was not significant. Some studies gave similar conclusions.

Raghdar S. Hussein, Rasha H. Soliman et al in their study obtained a very similar result with 6.25% changes in SGPT and 62.5% changes in SAP and change in SGOT was not significant. Accepted 29 October 2012 Available online 13 September 2013

### CONCLUSIONS

- Subclinical Hypothyroidism suggested by elevations of Thyroid Stimulating Hormone alone without changes in Free Triiodothyronine and Free Thyroxine is more common in children treated with sodium valproate for at least 6 months.
- Liver Function Tests especially serum glutamic pyruvic transaminase and serum alkaline phosphatase are affected after 6 months of therapy with sodium valproate.
- There exists a linear relationship between dose of sodium valproate and the abnormality of thyroid function tests and liver function tests.
- The Body Mass Index was increased significantly at the end of 6 months of therapy with sodium valproate and there was a linear relationship with dose the dose of sodium valproate.

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