

## Prospective Observational Study of Sodium Valproate in Seizure Control and Associated Adverse Drug Reactions in Pediatric Population

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**Abstract:** Sodium valproate is a commonly used antiepileptic drug for control of broad range of seizures. Adverse drug reactions (ADR) due to valproate widely range from severe to less severe effects like nausea, vomiting, weight gain, sedation, hepatotoxicity etc. The objective of this study was to evaluate the efficacy of valproate in seizure control, associated ADRs and to explore the extent of these effects in pediatrics. The prospective observational study was carried out for six months at pediatric department of Mahatma Gandhi Memorial Hospital, Warangal and the study population include 70 patients of age  $\leq 12$  yrs. ADRs are confirmed using Naranjo's causality assessment scale. Clinical data obtained was entered in Excel (windows 7); data was analyzed using Prism 5<sup>th</sup> version. A total of 70 patients were enrolled in the study. Majority (51.42%) are in age group of 8-12 yrs. Out of 70, 52 (74.28%) were exposed to ADRs; of them 32.68% presented with seizure relapse and 26.92% required dose adjustment. The most commonly found ADR was aggressiveness (59.61%). Others include GI upset (6), weight gain (2), transient alopecia (6), cognitive impairment (5), nocturnal enuresis (11), sedation (12), rash (2), thrombocytopenia (1) and minute deviation in hepatic enzyme levels. Study demonstrates that majority of patients with epilepsy will achieve long lasting remission on valproate treatment, but with wide range of ADRs. An early monitoring, management and counseling of health care team, parents and care takers regarding drug effects will aid in enhancing patient quality of life.

**Keywords:** Sodium valproate, Adverse drug reactions, Seizures, Pediatrics.

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### I. Introduction

Epilepsy is relatively a common condition characterized by the periodic and unpredictable occurrence of seizures, which is due to transient alteration in the spread of electrical discharge of cortical neurons<sup>[1]</sup>. WHO states that approximately eight people per 1000 worldwide have epilepsy disorders, the annual incidence of epilepsy in India alone is around 40-50 per 1,00,000 per year<sup>[2]</sup>. Up to 80% of people with epilepsy are able to manage their condition with AEDs. Valproate is a commonly prescribed AED for control of seizure attack. Sodium valproate or valproate sodium is the sodium salt of valproic acid, a broad spectrum anticonvulsant, was approved in 1967 and is used in the treatment of epilepsy, bipolar disorder, panic attack, anxiety disorder, posttraumatic stress disorder, and migraine as well as other psychiatric conditions requiring management with mood stabilizers<sup>[3]</sup>. Sodium valproate is first line therapy for primary generalized seizures such as tonic-clonic, myoclonic, atonic and absence seizures. It can be used as both mono and adjunctive therapy for partial seizures and can be very useful in patients with mixed type of seizure disorders<sup>[4]</sup>. Its structure is quite different from that of other anticonvulsant drugs; initially it was believed that sodium valproate act by increasing GABA levels by inhibiting its degradation or by activating its synthesis. Later it has been proposed that valproic acid may potentiate postsynaptic GABA responses, may have a direct membrane stabilizing effect, and may also affect potassium channels. Adverse drug reactions (ADR) due to valproate range from mild to life threatening effects like gastrointestinal (GI) disturbance, nausea, vomiting, weight gain, sedation, acute liver disease, hepatotoxicity, pancreatitis, effects on coagulation, thrombocytopenia, hyperglycemia and insulin resistance, hyperammonaemia, sedation, alopecia, and tremor<sup>[4,5,6]</sup>. Not only the ADRs which are well known, there are some under reported ADRs being addressed in the form of case reports in recent years like nocturnal enuresis etc. These drug related effects are most commonly seen in high risk groups like children, mentally retarded patients and those on multiple AEDs. Frequent monitoring of all drug related parameters, creating awareness among parents and physicians must be made in order to minimize these effects, which may badly effect the patient compliance and quality of life.

The current study aims to analyze the efficacy of sodium valproate in seizure treatment and seizure control, ADRs associated with it and to explore the extent of these drug effects in high risk group (i.e., pediatric population).

The main objective of this study is to create awareness among researchers, society, physicians and patients, care takers regarding the need for early and frequent monitoring, management and prevention of these undesired effects of valproate.

## **II. Materials And Methods**

The prospective observational study was carried out attending the paediatric in and out patient department of Mahatma Gandhi Memorial Hospital (MGMH), Warangal, Telangana, India. MGM Hospital is a 1200 bedded tertiary care hospital in urban area of the Warangal district. The duration of study was six months from May 2014 to October 2014. Ethical clearance was obtained from the human ethical committee. Data collection was performed according to hospital regulations after obtaining approval from the Hospital administration and ethical committee. The study population consisted of 70 epileptic cases reviewed between the considered study periods.

Children with seizures of all types who are being treated with Sodium valproate, of age less than or equal to ( $\leq$ ) 12 years were included in the study.

Patients of age above 12 years who are on AEDs other than valproate (e.g. Carbamazepine, Phenytoin etc), with abnormal base line reading for Renal, Hepatic, Haematological parameters and patients with other neurological illness were excluded from the study.

Both safety and efficacy parameters of valproate were assessed in patients for six months to one year after initiation of treatment. Efficacy parameters include observation for seizure relapse and need for dose adjustments. Safety parameters include assessment of ADRs which include mild effects like weight gain, skin rash, altered hair texture, cognitive impairment, nocturnal enuresis, sedation, aggressiveness, GI upset and serious effects like Hepatotoxicity and thrombocytopenia. Adverse effects of drug are confirmed using Naranjo's probability assessment scale. Clinical data obtained during study period was entered in MS excel of windows 7; data was analysed using Graph Pad Prism of 5<sup>th</sup> version.

## **III. Results**

According to the inclusion criteria and availability of paediatric epileptic patients in the selected hospital, the study population comprised 70 patients.

Out of 70 subjects, 35 are (50%) males and 35 are (50%) females. The age-gender categorisation reveals that more epileptic patients (M= 24.28%, F=27.14%) were found between age group of 8 to 12 years in both males and females. The age gender categorisation data was presented in table 1.

### **Effect on seizures**

A total of 70 subjects being treated with sodium valproate, of them 52 (74.28%) patients were found to be exposed to undesired effects of drug during the study period.

Out of 52 subjects, seizure relapse was seen in 17 patients (32.68%) from which 14 (26.92%) patients required dose increment, visit figure 1 and the other 2 required counselling on the importance of medication adherence with any dose changes, as relapse in these patients was found to be due to improper adherence to valproate.

### **Adverse drug effects**

#### **Gastro intestinal effects**

Sodium valproate due to its pharmacokinetic and dynamic properties is most commonly associated with gastro intestinal disturbances like nausea, vomiting, abdominal pain etc. Nausea, vomiting, and abdominal pain occurred in 6 (11.53%) patients. These disturbances were transient when treatment was started in a low dose and increased gradually. Nausea and vomiting was, however, severe in two patients and made them to suddenly stop taking medication which had lead to seizure relapse and hospital admission.

#### **Nocturnal enuresis**

Out Of 70 children, 11 (21.15%) cases reported with sudden onset of involuntary night time bed wetting (nocturnal enuresis) after initiation of treatment with valproate. Two patients were relieved from symptoms after being symptomatically treated with Imipramine for three months.

### **Hair changes**

Transient hair loss was seen in six (11.53%) patients who developed transient hair loss at the beginning of treatment, without any alteration in their hair colour or hair texture and was later subsided even with continuation of drug therapy.

### **Weight gain**

As the follow up of patients was done only for 6 months to 1 year after their initiation of treatment and weight gain is usually seen with long term therapy, we found only 2 (3.84%) out of 70 patients with a drastic increase in their weight. A few other cases showed a minute variation in their weight scale.

### **Sleep changes**

12 (23.07%) cases were found with altered sleep pattern. Parents complained about increased both day and night time duration of sleep and the child being drowsy all the day, in working hours at school etc.

### **Other side effects**

Our study found aggressive nature as the most common complaint seen in almost 31 (59.61%). Also found 5 cases with decreased cognitive functional status like decreased learning ability, memory disturbances and loss of interest in daily activities. Two patients presented with rash immediately within few days after initiation of treatment with valproate, but was not confirmed whether it was due to the drug or due to other external factors. The adverse drug effects seen are presented in figure 2.

### **Thrombocytopenia**

Serum Valproate levels of >450micromole/L or a daily dose of > 40mg/kg usually leads thrombocytopenia. In our study, as all the subjects were treated with optimal doses (<40mg/kg), only one patient presented with a transient decrease in platelet count which was normalised even with continuation of drug therapy.

### **Hepatotoxicity effects**

Only minute deviation of liver enzyme levels without any possible symptomatic outcomes was observed. Alkaline phosphatase was found to be elevated abnormally in 15 cases without any deviation in other enzyme levels like SGOT, SGPT, bilirubin. Data was represented in figure 3, 4, 5.

Table (2) gives information on mean, standard deviation and p- value of different study parameters.

## **IV. Discussion**

Epilepsy is a chronic neurological condition characterized by the periodic and unpredictable occurrence of seizures. Sodium valproate is a first generation antiepileptic drug which is considered as drug of choice in all types of seizures. Many studies state that frequent follow up and monitoring must be done in order to trace out the undesired drug effects and to adopt different measures to manage and prevent them. Not only ADRs that are commonly known, there are some under reported ADRs of valproate (nocturnal enuresis) which have been specified in some case reports, suggesting the need for special attention and efficient monitoring of drug effects.

Weight gain is a well known ADR with valproate, occurring in 40% of children <sup>[7]</sup>. Various mechanisms had proposed to explain this effect: an increased consumption of food, energy rich beverages because of an increased appetite, an abnormal thirst <sup>[8, 9]</sup> and increased insulin concentrations and insulin/glucose ratio which may be involved in weight gain by stimulating appetite <sup>[10]</sup>. But exact factor contributing for weight gain during valproate treatment are not completely understood till today. Many studies reported weight gain as the most seen ADR of valproate in children <sup>[8, 11, 12]</sup>. But as the study was conducted for 6 months to 1 year after the initiation of treatment with valproate we found only 2 (3.84%) out of 70 patients with a drastic increase in their weight. A few other cases showed a minute variation in their weight scale.

Nocturnal enuresis is an under reported ADR of valproate. Several studies reported cases on nocturnal enuresis attributed to sodium valproate <sup>[8, 13, 14, 15]</sup>. The two most likely explanations for valproate induced enuresis include: Enuresis secondary to a central effect on the thirst centre and as a consequence of the increased depth of sleep with valproate therapy <sup>[8, 14]</sup>. Out of 70 children, 11 (21.15%) cases presented with sudden onset of involuntary night time bed wetting (nocturnal enuresis). Two patients were relieved from symptoms after being symptomatically treated with Imipramine for 3 months.

Review of literature had suggested that valproate was associated with increased depth and duration of sleep in children <sup>[16]</sup>. Our study found 12 (23.07%) cases with increased depth of night time sleep and the child was found to be drowsy all over the day.

Review of literature found many studies suggesting risk of thrombocytopenia in patients who are taking valproate but the effect was seen with valproate levels of >450 micromole/L or a daily dose of > 40mg/kg [17]. In this study, all subjects were treated with optimal doses (<40mg/kg) and so only one patient developed a transient decrease in platelet count which was normalized even with continuation of treatment.

Egger and Brett in their study found 4 out of 100 children developed aggressive behaviour [8]. Our study similarly found it as the most common symptom seen in almost 31 (59.61%) cases out of 70. Also found 5 cases with decreased cognitive functional status which included decreased learning ability, memory disturbances, loss of interest in daily activities etc.

Sodium valproate due to its pharmacokinetic and dynamic properties is most commonly associated with GI disturbances like nausea, vomiting, abdominal pain etc. Nausea, vomiting, and abdominal pain occurred in 6 (11.53%) patients. Such disturbances were transient when treatment was started in a low dose and increased gradually. Nausea and vomiting was, however, severe in two patients and made to suddenly stop taking their medication which had led to new seizure episodes and hospital readmission.

Transient hair loss and altered hair texture was seen in patients on valproate [18]. 6 (11.53%) patients developed transient hair loss without any alteration in hair colour and texture during the initiation of treatment which was later subsided even with continuation of valproate.

Several studies reported about the risk of developing hepatotoxicity while taking sodium valproate, with incidence being more in high risk groups like children less than 2 years [19, 20]. Our study found only minute deviations of liver enzyme levels without any possible symptomatic outcome. Alkaline phosphatase was found to be elevated abnormally in 15 cases. But review of reasons for solitary elevation of ALP has suggested that, this elevation could be due to some rapid metabolic changes seen in some fast growing children.

All the ADRs are confirmed using Naranjo's probability assessment scale and valproate was found to be the 'probable' cause for these observed ADRs with a score of 7. Dechallenge with valproate is not planned for now as the patient currently seizure free although dechallenge can confirm the causality relationship of this ADRs. But dechallenge or change in drug was not attempted as it could have resulted in worsening of epilepsy.

## V. Conclusion

Sodium valproate was found to be effective in achieving long lasting remission on treatment. Although found to be effective in good control of seizures, but at the same time was presented with wide range of mild to moderate adverse drug effects in the study paediatrics population. Counselling the health care team members, parents and patient care takers regarding different adverse drug outcomes, their early identification, management and measures that can be taken to prevent them may enhance treatment compliance. An early monitoring of these drug effects and managing them will aid in negotiating negative drug effects and obtaining positive outcomes and an overall increase in quality of life of the patient.

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1. Tables

Table 1: Age-gender categorization

Age (years)	Male	Female
0-4 years	5.71%	4.28%
4-8 years	20%	18.57%
8-12 years	24.28%	27.14%

Table 2: Mean Standard deviation and P- value of different parameters.

Parameter	Mean	Standard Deviation	p- value
Bilirubin total	0.6950	0.2107	<0.0001
Bilirubin direct	0.3470	0.1497	<0.0001
SGOT	26.75	27.00	<0.0001
SGPT	28.73	6.656	<0.0001
ALP	93.11	52.21	0.0035

Figures

Figure 1: Sodium valproate and seizure control

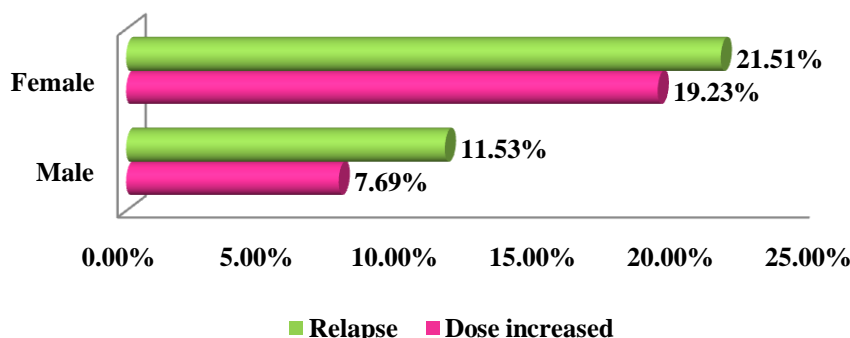


Figure 2: Sodium valproate and adverse drug effects.

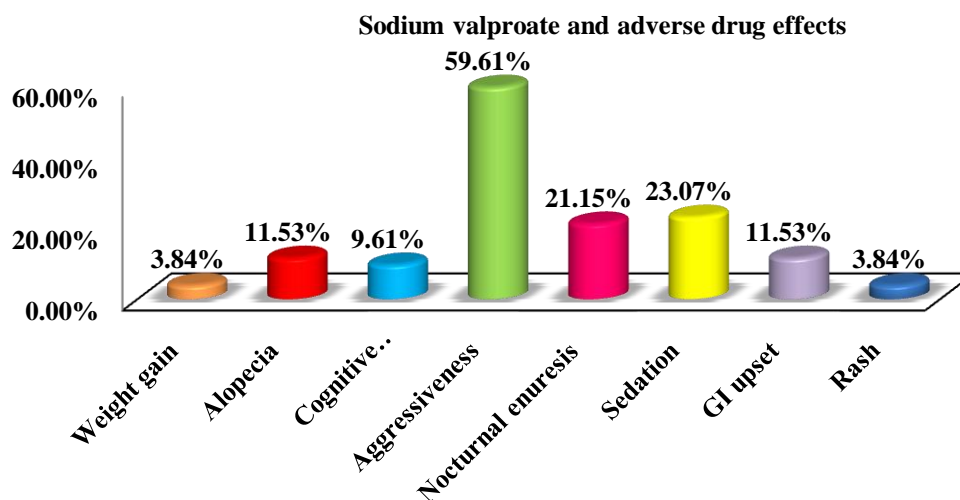
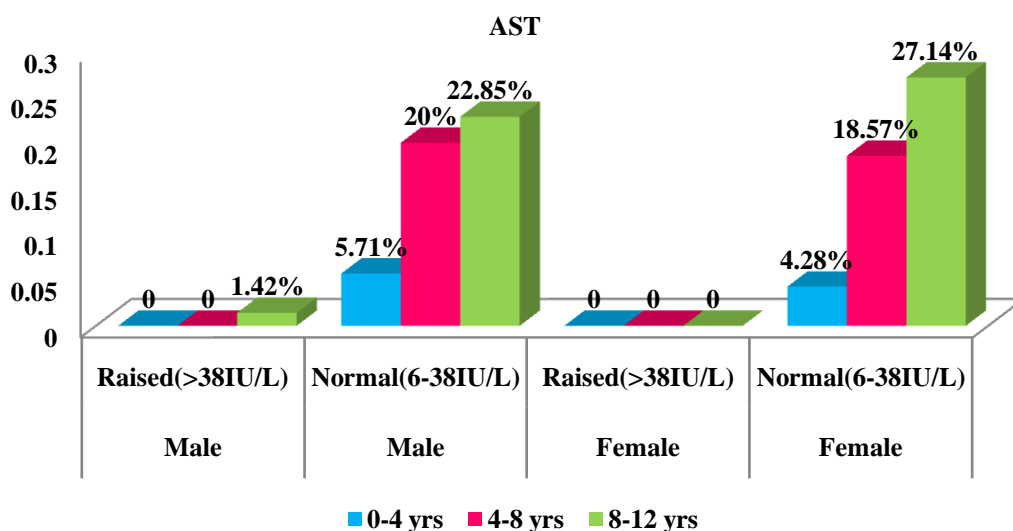
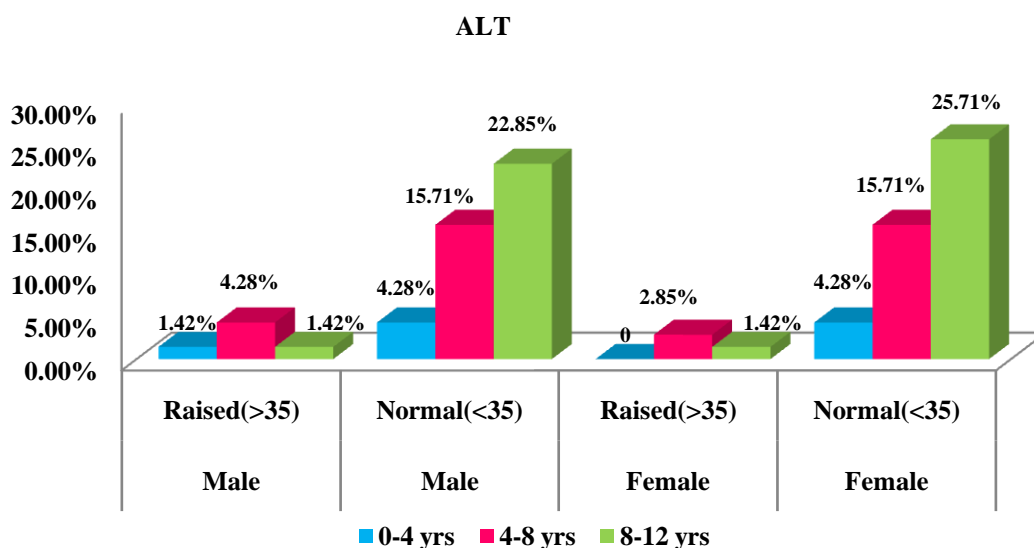


Figure 3: Liver enzyme: AST (enzyme level deviation from normal values with valproate treatment)



AST: Aspartate aminotransferase.

Figure 4: Liver enzyme: ALT (enzyme level deviation from normal values with valproate treatment)



ALT: Alanine aminotransferase

Figure 5: Liver enzyme: Alkaline phosphatase (enzyme level deviation from normal values with valproate treatment).

