Side Effects of Sodium Valproate among Children with Epilepsy under 2 Years of Age

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Abstract

Introduction: Sodium valproate is proposed for addition to the Model List of Essential Medicines, for use in the management of epilepsy in children. This is an effective in treating many seizure types, like generalized tonic clonic seizure, myoclonic seizure, absence seizure, in other epilepsy syndrome like infantile spasm, Landau-Kleffner syndrome (LKS) etc. Aim of the study: The aim of this study was to observe the side effects caused by sodium valproate in children below 2 years of age. Methodology: This observational cross sectional study was conducted in the Paediatric Neurology patient, department of National Institute of Neurosciences and Hospital (NINS), Sher-e-Bangla Nagar, Dhaka, Bangladesh, during September 2015 to February 2016. Fifty children under 2 years of age with epilepsy were enrolled in this study. Enrollment was done as per inclusion criteria and after informed verbal consent from the mother or the attendant. Detail history was taken about demographic factors which include children’s age, age of onset of seizure, height, weight. Data were collected in a pre-designed questionnaire. The data was processed and analyzed by the application of SPSS version 17. Results: Out of total studied respondents the male patients were 54% and female were 46%. Maximum 46% patients were diagnosed with epilepsy between 6-12 months, Out of total studied patients the maximum 44% started sodium valproate ages between 7-12 months. Among the total studied patients 40% toke 26-30mg/kg/day sodium valproate as their treatment regime. Total 16% had anaemia among the studied patients, whereas for the rest 84% patients no other symptoms were found during their general examination. Among the total studied patients, the most dominating side effect of the patients was vomiting which resulted 1/5th (20%) of the all side effects. The side effects of both hair loss and loss of appetite shows the same result of 10% for each whereas, only 4% and 2% had abdominal pain and weight gain respectively. Conclusion: In this study ‘vomiting’ was found as the most significant side effect which similar with other different studies also. This findings may be helpful for the future researchers in further research. In fact, it was a single centered study with a small sized sample. Keywords: Epilepsy, Anti-epileptic drug, Sodium valproate.

INTRODUCTION

Sodium valproate is an antiepileptic drug. Sodium valproate is effective in controlling tonic-clonic seizures particularly in primary generalized epilepsy. It is the drug of choice for primary generalized seizures, generalized absences and myoclonic seizures. It is used to control seizures (fits) in most types of epilepsy. Sodium valproate may be used alone or in combination with other anticonvulsant for the treatment of epilepsy. Sodium valproate may takes several days to show an initial effect and in some cases may takes two to six weeks for the maximum effect. Treatment is started with low doses and may be increased over a couple of weeks according to response. This is effective in treating many seizure types, like generalized tonic clonic seizure, other types of generalized epilepsy like myoclonic seizure, absence seizure, in other epilepsy syndrome like infantile spasm, severe myoclonic epilepsy (SME), Landau –Kleffner syndrome (LKS), myoclonic astatic epilepsy (MAE) etc. Sodium Valproate has rare but severe side effects on liver, bone marrow and pancreas [1]. Most of Sodium Valproate hepatotoxicity occurred in children younger than 2 years who had preexisting neurological or other physical defects [2]. Special precaution should be needed for its use in children below 2 years of age and

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children treated with multiple anti-epileptic drugs (AEDs). Sodium valproate is an anticonvulsant. The mechanisms by which valproate exerts its therapeutic effects have not been established. It has been suggested that activin is related to increased brain concentrations of gamma-amino butyric acid (GABA) [1]. Sodium valproate can be administered in the following way [3]; 1. Oral forms with food 2. Intravenous. Side effects [4]; Common (affect in 1 in 10 and 1 in 100 people); Diarrhea, Weight gain, Temporary hair loss, Drowsiness, Headache. Confusion Problems with memory or attention, Aggression, Tremor, Decreased level of sodium in the blood, Thrombocytopenia, Reduced erythrocyte count. Uncommon (affect between 1 in 100 and 1 in 1000 people): Leucopenia, Pancreatitis, Vacuities, Unsteady gait, Rash, Angioedema, Peripheral edema, Osteoporosis, Ecchymosis, Encephalopathy, Abdominal pain, Jaundice. Rare (Affect between 1 in 1000 and 1 in 10,000 people); Hyperactivity, Increased alertness, Abnormal behavior, Learning difficulties, Hyperammonaemia, Toxic epidermal necrolysis, Stevens-Johnson syndrome and Erythema multiform.

Contraindication: It is contraindicated in some conditions like;
- Hypersensitivity to drug
- Hepatic impairment
- Urea cycle disorders
- Pregnancy

Epilepsy is a common neurological disorder which demands immediate medical attention and often long term therapy. Sodium valproate is one of the most potent drug with a broad spectrum anticonvulsant effect for management of many seizure types, including generalized tonic-clonic seizure [5], Landau-Kleffner syndrome (LKS), Juvenile myoclonic epilepsy (JME), myoclonic astatic epilepsy (MAE), absence seizure and severe myoclonic epilepsy (SME) [1]. There are situation where sodium valproate is absolutely indicated where other potential anticonvulsants are not available or costly that includes west syndrome, severe myoclonic epilepsy, myoclonic astatic epilepsy (MAE). There is no need of monitoring drug level of the average patients continuously except for the high risk group (e.g. infants under 3 years age receiving poly therapy) which exhibited the highest between-subject as well as within-patient variability [6]. But in this study drug level of sodium valproate is not monitored, because children received this drug at maximum dose 40 mg/kg/day which is usually tolerable. However, in our country sodium valproate has been used for long time due to its wide range of effectiveness, availability and cost effectiveness. Sodium valproate achieved a high degree of seizure control with 75% of patients having at least 12 months of freedom free seizures [7]. This current study attempts to analyze the pattern of side effects after using the sodium valproate in children under 2 years of age with epilepsy and their impact on the continuation of sodium valproate therapy.

OBJECTIVES

General Objective
- To observe the side effects caused by sodium valproate in children below 2 years of age.

Specific Objective
- To find out proportion of side effects.
- To find out the pattern of side effects.

MATERIALS AND METHODS

This study was an observational cross-sectional study conducted in Pediatric Neurology outpatient and inpatient department of National Institute of Neurosciences and Hospital (NINS), Sher-E-Bangla Nagar, Dhaka, Bangladesh from September 2015 to February 2016. Children under 2 years of age attending in Paediatric Neurology outpatient and inpatient department of National Institute of Neurosciences and Hospital (NINS) were the study people. The total duration of the study was 6 months and at the first time the population size was roughly estimated 50. As per
sample estimation formula if N would less than 10,000 the required sample size would be smaller. In that case final sample estimated \((n)\) by using the following formula and according to the formula the estimated final sample size was 50. Sampling method was consecutive.

**Inclusion Criteria**

Children with epilepsy of both sexes under 2 years of age group, who prescribed sodium valproate as immunotherapy by pediatric neurology department of NINS.

**Exclusion Criteria**

Children with status epileptics and seizures associated with acute conditions like stroke are excluded. Patients with pre-existing hepatic impairment, bone marrow abnormalities and neuro-metabolic diseases were also excluded.

**Results**

Sodium Valproate is rarely used in case of epilepsy below 2 years of age. That is why the number of target group was small in size and only 50 children having epilepsy was seen and investigated in the data gathering period. In this study, the proportion and pattern of side effects were observed in 50 cases of children of epilepsy, who were prescribed sodium valproate by the attending physician of the study center. Study results have showed below in tabulated and graphic form. Table-1. Among the total study patients, the minimum and maximum age of them were 6 months and 36 months respectively, the mean±SD age was 15.88±6.81 months. In relation to the onset of seizure, the minimum and maximum age of the patients were 2 and 20 months respectively and their mean±SD age was 8.3±4.99 months. It also revealed that, the minimum and maximum weight were 7 kg and 14 kg respectively, the mean±SD weight was 10.26±1.66 kg. The study also revealed that the minimum and maximum height of the patients was 65 cm and 93 cm respectively and the mean±SD height was 76.82±7.02 cm. Sex composition of the study patients were presented in the Figure-1. Results revealed that the sex ratio of male to female was 1:1.17. Table-2 showed the age at diagnosis of the patients, which point out that the maximum 46% patients were diagnosed between 6-12 months, 28% patients below 6 months and rest 26% patients were range between 12-24 months. Table-3 showed the dose of sodium valproate among studied patients. Among the total studied patients 40% took 26-30mg/kg/day of sodium valproate, 32% patients took 20-25 mg/kg/day, 20% took 31-35 mg/kg/day of sodium valproate and only 8% took 36-40 mg/kg/day of sodium valproate. Table-4 illustrated that, out of total 50 patients 74% had GTCS, 12% and 14% had Myoclonic epilepsy and infantile spasm respectively. Table-5 illustrated the type of investigations done for the patients. Out of total studied patients, the minimum and maximum percentage for HB were 9% and 12.2% respectively, whereas their mean percentage for HB was 11.18±0.70. In regard to the ESR the minimum and maximum investigations were 6 mm in 1st hour and 25 mm in 1st hour respectively, whereas their mean investigation for ESR was 12.5±4.26. The investigation for TC of WBC showed that, the minimum and maximum count were 5.5X109/L and 13X109/L respectively, whereas the mean count for TC of WBC was 12.5±4.26. In relation to the percentage for Neutrophil illustrated that, the minimum and maximum percentage were 22% and 59% respectively, whereas their mean percentage for Neutrophil was 46.4±6.45. The investigation for Lymphocyte showed that, the minimum and maximum percentage among the total respondents were 2% and 7% respectively, whereas their mean percentage for Eosinophil was 3.13±1.81. In regard to the Platelet the minimum and maximum count among the 49 studied patients out of 50 were 210X109 /L and 410 X109 /L respectively, whereas the mean number for Platelet was 287.14±35.92. This table also revealed that, the investigation for Serum ammonia among the total patients which results that the minimum and maximum level were 21 micromole/L and 63micromole/L respectively, whereas the mean level for Serum ammonia was 43.1±9.68. The level for Serum SGPT showed that, the minimum and maximum level were 15 U/L and 35 U/L respectively, whereas their mean level for Serum SGPT was 25.08±5.29. Table-6 showed the side effect of the sodium valproate of studied patients. Among the total studied patients, the most common side effect was vomiting which resulted 1/5th (20%) of all side effects. The side effects of both hair loss and loss of appetite showed the same result of 10% for each whereas, only 4% and 2% had abdominal pain and weight gain respectively. No patient had clinical, serological or sonological evidence of pancreatitis and hepatic impairment. Table-7 showed the association between side effects of sodium valproate with type of epilepsy. Among the total studied patients 20% had vomiting which is a common side effect in all types of epilepsy. The trend of this result is almost same for both hair loss and loss of appetite of 10% for each side effect which hold all types of epilepsy. In addition, this table also revealed that the side effects of both weight gain and abdominal pain was contained by only one type of epilepsy out of three i.e., infantile spasm for weight gain, whereas GTCS for abdominal pain. The 2 cases of abdominal pain were further evaluated by USG of HBS.
Table-1: Descriptive statistics of some demographic characteristics of the patients (N=50)

| Demographic characteristics | Minimum | Maximum | Mean  | SD   |
|-----------------------------|---------|---------|-------|------|
| Age of patient (months)     | 6       | 36      | 15.88 | 6.81 |
| Age at onset of seizure (month) | 2   | 20      | 8.3   | 4.99 |
| Weight (Kg)                 | 7       | 14      | 10.26 | 1.66 |
| Height (cm)                 | 65      | 93      | 76.82 | 7.02 |

Table-2: Distribution according to age at diagnosis (n=50)

| Age at diagnosis | Frequency | Percentage (%) |
|------------------|-----------|----------------|
| < 6 months       | 14        | 28.0           |
| 6-12 months      | 23        | 46.0           |
| 12-24 months     | 13        | 26.0           |
| Total            | 50        | 100.0          |

Table-3: Distribution of the patients by dose of sodium valproate (n=50)

| Dose (mg/kg) | Frequency | Percentage (%) |
|--------------|-----------|----------------|
| 20-25 mg     | 16        | 32.0           |
| 26-30 mg     | 20        | 40.0           |
| 31-35 mg     | 10        | 20.0           |
| 36-40 mg     | 4         | 8.0            |
| Total        | 50        | 100.0          |

Table-4: Distribution of the patients by types of epilepsy (n=50)

| Types of epilepsy | Frequency | Percentage (%) |
|-------------------|-----------|----------------|
| GTCS              | 37        | 74.0           |
| Infantile spasm   | 7         | 14.0           |
| Myoclonic epilepsy| 6         | 12.0           |
| Total             | 50        | 100.0          |

Table-5: Descriptive statistics of different types of Investigations sought by the patients (n=50)

| Investigations       | N  | Minimum | Maximum | Mean  | Std. Deviation |
|----------------------|----|---------|---------|-------|----------------|
| Hb (%)               | 50 | 9.00    | 12.20   | 11.18 | 0.70           |
| ESR (mm in 1st hour)| 50 | 6.00    | 25.00   | 12.54 | 4.26           |
| TC of WBC (10^9/L)   | 50 | 5.50    | 13.00   | 7.77  | 1.58           |
| Neutrophil (%)       | 50 | 22.00   | 59.00   | 46.40 | 6.45           |
| Lymphocyte (%)       | 50 | 40.00   | 60.00   | 49.82 | 4.90           |
| Monocyte (%)         | 50 | 0.00    | 10.00   | 2.54  | 1.86           |
| Eosinophil (%)       | 8  | 2.00    | 7.00    | 3.13  | 1.81           |
| Platelet (10^9/L)    | 49 | 210.00  | 410.00  | 287.14| 35.92          |
| Serum ammonia (micromole/L) | 50 | 21.00   | 63.00   | 43.10 | 9.68           |
| Serum SGPT (U/L)     | 50 | 15.00   | 35.00   | 25.08 | 5.29           |
Thrombocytopenia is one of the side effects in valproate therapy. Along with some rare side effects, there are some common side effects in valproate therapy. In this study, among 50 patients, there were some milder side effects found such as vomiting (n=10), weight gain (n=5), hair loss (n=5), and loss of appetite (n=5). Similarly, another study conducted a retrospective analysis of 100 children with epilepsy treated with sodium valproate and found some milder but troublesome side effects which were increased weight gain (n=44), gastrointestinal disturbances (n=20), transient hair loss (n=6) [11]. In addition, 211 epileptic patients in a study were given sodium valproate as a single drug treatment. During the course of therapy, six cases of hair loss were found between sodium valproate users [7]. Though the studies had different sample size but the findings were quite similar especially the gastrointestinal disturbances and hair loss. Hepatotoxicity is a rare but very serious side effect in valproate therapy. High incidence of valproate hepatotoxicity in infants may relate to familial metabolic defects and the incidence of fatal hepatic failure associated with valproic acid (VPA) therapy is highest in children under the age of three years, particularly in those with developmental delay. Moreover, most cases of VPA hepatotoxicity occurred in children younger than 2 years who had preexisting neurologic or other physical defects. Many were developmentally delayed. A precipitating illness, possibly viral, occurred in many children [20]. However, our study did not find any valproate

Table-6: Distribution according to side effects of the patients (n=50)

| Side effects  | Frequency | Percentage (%) |
|--------------|-----------|----------------|
| Vomiting     | 10        | 20.0           |
| Hair loss    | 5         | 10.0           |
| Weight gain  | 1         | 2.0            |
| Abdominal pain | 2       | 4.0            |
| Loss of appetite | 5     | 10.0           |

Table-7: Association of side effects of sodium valproate with types of epilepsy (n=50)

| Side effects  | Types of epilepsy | Total       |
|--------------|-------------------|-------------|
|              | GTCS              | Infantile spasms | Myoclonic epilepsy |
| Vomiting     | 5(10.0%)          | 1(2.0%)      | 4(8.0%)            | 10(20%)           |
| Hair loss    | 3(6.0%)           | 1(2.0%)      | 1(2.0%)            | 5(10.0%)          |
| Weight gain  | 0                  | 1(2.0%)      | 0                   | 1(2.0%)           |
| Abdominal pain | 2(4.0%)     | 0            | 1(2.0%)            | 2(4.0%)           |
| Loss of appetite | 3(6.0%) | 1(2.0%) | 1(2.0%) | 5(10.0%) |

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hepatotoxicity among the studied children. Acute pancreatitis is another serious side effect in valproate therapy. In this study no cases of acute pancreatitis was observed. By the way, a study was conducted and found that there is a definitive association between valproate therapy and acute pancreatitis. They found only 2 cases of Valproate associated pancreatitis described below 2 years of age. Though the definite association between valproate and acute pancreatitis has reported but the underlying etiology is still unknown [21]. Considering the different study around the use of Sodium Valproate including the current one, has stated that there was no significant incidence of side effects with the exception of patients who developed vomiting, hair loss, loss of appetite and weight gain. No hepatic and pancreatic impairment was found due to the use of sodium valproate in treating epilepsy of children under 2 years of age. The average annual incidence of epilepsy in developed countries is 40-70 per 100,000 of the general population. In developing countries, this figure is much higher at around 100-190 per 100,000 of the general population per year [22]. Though high rates of acquired brain injury may contribute, the possibility that malnutrition may lower seizure threshold has rarely been examined. This review suggests potential biochemical mechanisms that could adversely affect seizure threshold, particularly the effect of malnutrition on inhibitory neurotransmitters and electrolyte imbalance [20]. This is effective in treating many seizure types, like generalized tonic clonic seizure, other types of generalized epilepsy like myoclonic seizure, absence seizures, in other epilepsy syndrome like infantile spasm, severe myoclonic epilepsy of infancy, Landau–Kleffner syndrome (LKS), severe myoclonic atatic epilepsy etc. Sodium Valproate has rare but severe side effects on liver, bone marrow and pancreas [1]. Most of Sodium Valproate hepatotoxicity occurred in children younger than 2 years who had preexisting neurological or other physical defect. Special precaution should be needed for its use in children below 2 years of age and children treated with multiple anti-epileptic drugs (AEDs) [20]. Various clinical studies over the last decades have demonstrated that VPA is effective in the treatment of many seizure types, including absence, tonic-clonic, and partial seizures. Both as add-on therapy and as mono therapy VPA is well-established as a first-line drug. In addition, it is also used to treat infantile spasms (West syndrome), Lennox-Gastaut syndrome, febrile seizures, and status epilepticus [1]. Amicro-dialysis study in humans demonstrated the pharmacokinetic rationale for acute treatment with VPA. It is based on the rapid distribution of VPA to the brain [2]. Recently, Marson et al. performed a meta-analysis that compares VPA with carbamazepine in the mono therapy of epilepsy. The investigators concluded that there was no reason for the preference of VPA for generalized-onset seizures, while the preference for carbamazepine was supported in the case of partial-onse seizures [22]. Gastrointestinal side effects, e.g., nausea, vomiting, and gastrointestinal distress have been reported to occur in up to 25% of the patients, probably less with enteric-coated formulation [1]. Weight gain is a frequent problem, and increase in body weight and body mass index following VPA treatment have recently been studied. These studies show that weight gain occurs within the first ten weeks of treatment and is in the order of six kilograms [23]. Weight gain during VPA therapy is associated with metabolic changes like a decrease in Beta-oxidation of fatty acids [24], increased insulin and insulin/glucose ratios, and increased leptin and insulin levels [18]. The problem appears to be more common in females, it is not necessarily eliminated by caloric restriction, and it may lead to discontinuation of VPA therapy [24].

CONCLUSION AND RECOMMENDATIONS

In this study ‘vomiting’ was found as the most significant side effect which similar with other different studies also. This findings may be helpful for the future researchers in further research. In fact, it was a single centered study with a small sized sample. So the findings of this study may not reflect the exact scenario of the whole country. For getting more specific findings we would like to recommend for conducting more studies with larger sized sample.

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