Valproic acid for children below 2 years of age with epilepsy

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ABSTRACT

Objectives: To evaluate the efficacy of valproic acid (VPA) in a cohort of children below 2 years of age. We also aim to review the characteristics of such patients and the role and safety of VPA for this age group.

Methods: A retrospective chart review conducted at King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia, for children below 2 years of age diagnosed with epilepsy and treated with valproic acid from January 2016 to January 2020.

Results: The cohort for this study includes 50 children below the age of 2 years (25 males, 25 females). Aged 3 months to 23 months at commencing valproic acid. The mean age of seizure onset was 9 months and the mean age of starting valproic acid was 16 months. Thirty-two patients (64%) had more than 50% seizure improvement after valproic acid. Eleven patients (22%) were seizure-free. No statistical significance abnormalities in blood count indices and ammonia were seen during the treatment period. Two patients had dose-related lethargy that improved after decreasing their dosage. Asymptomatic mild elevation in glutamate dehydrogenase was noticed in 18% of patients.

Conclusion: Using valproic acid in infants and children below the age of 2 years can be considered as a safe and effective treatment option for epilepsy in this age group.

Epilepsy is a major neurological disorder that occurs across different age groups. Children below the age of 2 years are an important subcategory. They are more prone to have seizures compared to older children. Moreover, uncontrolled seizures in early life can result in poor outcomes on cognition, motor and language development. Seizure-freedom in children below 2 years ranges between 49–57% compared to >60% in older children. A myriad group of etiologies can result in seizures in this vulnerable age group including: electrolytes disturbances, asphyxia, inborn errors of metabolism, structural brain etiologies, infection and genetic etiologies. Brain ion channels, neurotransmitters and cellular maturation is unique in this age group.
making them at higher risk for seizures. Response to antiseizure medications (ASMs) also is different in this category of patients. Safety and options of ASMs is also another challenge. Multiple electroclinical epilepsy syndromes occur in this category like West syndrome, Dravet syndrome and myoclonic epilepsy which can be challenging to treat. Most available ASMs has not been studied in this age group. Valproic acid (VPA) has been available as a treatment for more than 50 years. It is classified as broad spectrum ASM. It is one of old generation ASM with few side effects reported. Its use below the age of 2 years is limited by its potential hepatotoxicity especially when used as polytherapy or in high dosage. Other factors like POLG mutation and mitochondrial disease could increase the chance for hepatic insult.

The incidence of hepatotoxicity in children in general is higher than adults, 1:5000 compared to 1:40000, respectively. Multiple proposed mechanisms have been implicated like reduction of intracellular CoA, defects of oxidative phosphorylation and inhibition of gluconeogenesis.

The aim of this study is to evaluate the efficacy and safety of valproic acid (VPA) in this age group and to review the clinical characteristics of this cohort. Few studies in literature evaluated VPA usage below the age of 2 years.

Methods. Study setting. This is a retrospective chart review study. The data were collected from the paper records and electronic medical records at King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia. Files of patients from January 2016 to January 2020 were reviewed. The study protocol was approved by the institutional review board of King Abdulaziz University (311-20). The inclusion criteria of the study were children treated with VPA below the age of two years, diagnosed with epilepsy, children without liver disease or metabolic conditions affecting the liver and on VPA for a duration ≥ 3 months. Children above 2 years old, with liver disease or used VPA less than 3 months were excluded. The primary outcome measures were to describe different clinical manifestations of those children and evaluate efficacy and safety of VPA.

Demographic data, VPA dose and duration, etiologies, the number of current and previous antiseizure medications, seizure improvement, side effects and blood counts were reviewed and recorded. Patient consents were waived as the data were collected anonymously from medical records.

Statistical analysis. The mean and standard deviation were used to describe variables like age and number of medications. Percentages were also used to describe qualitative data like sex and seizure improvement. Association test statistics were calculated to examine the seizure improvement on study groups of pediatric patients. Data compilation and analyses were conducted using IBM statistical package for the social sciences version for Windows, version 21 (IBM Corp., Armonk, N.Y., USA). We evaluated associations as likelihood ratio Tests (LR), p-value (Sig), confidence interval (95%), and chi-square tests. A p-value less than 0.05 was considered to be statistically significant.

Results. Demographic characteristics of the participants. The study included 50 children below the age of 2 years on VPA treatment. Of the 50 patients, 25 (50%) males and 25 (50%) females (Table 1). The mean age of infants and children from 3 months to 24 months started on VPA was 16 months. Valproic acid average dose was 31.4 mg/kg/day among this cohort. The average duration of VPA usage was 14 months.

Clinical diagnosis, neuroimaging and EEG features. Symptomatic etiologies were identified in 88% of patients like structural etiologies, genetic causes and asphyxia. Generalized epileptic discharges on EEG were documented in 21 patients (42%). Focal epileptic discharges represented in 8 patients (16%). Infantile spams and hypsarrhythmia on EEG were seen in 7 patients (14%). Non-specific slow EEG background and encephalopathy were in 14 children (28%). Most of the included children has developmental delay (82%). Clinical and diagnostic investigations are summarized in Table 2.

VPA effect and side effects. In all the included infants and children, VPA was used as a second line ASM. The initial total number of ASMs prescribed for all

| Parameter          | Mean   | SD    |
|--------------------|--------|-------|
| Age                | 3.43 (years) | 1.71 |
| Age of seizure onset | 9.57 (m)  | 5.83 |
| Age of VPA start  | 16.29 (m) | 4.87 |
| Duration of VPA    | 14.86 (m) | 15.50 |
| VPA Dose           | 31.4 (mg/kg/day) | 7.4 |

SD - Standard deviation, M - months
Table 2 - Clinical characteristics.

| Patient / Clinical diagnosis | EEG | Brain imaging | Development |
|------------------------------|-----|---------------|-------------|
| Microcephaly                | Focal discharges | Normal | Cognitive delay |
| Focal epilepsy               | Focal discharges | Lissencephaly | GDD* |
| Meningitis (HSV meningitis)  | Generalized epileptic discharges | Atrophy | GDD |
| Focal epilepsy               | Focal discharges | Normal | Normal |
| Focal epilepsy               | Focal discharges | Sturge weber syndrome | Mild hemiparesis |
| Infantile spasms, congenital Muscular dystrophy | Hypsarrhythmia | Hydrocephalus, Muscle eye brain disease | GDD |
| Hydrocephalus                | Hypsarrhythmia | Hydrocephalus and brain tumor (astrocytoma) | GDD |
| Noonan syndrome and infantile spasms | Hypsarrhythmia | Normal | GDD |
| Epilepsy (genetic), infantile spasms, panhypopituitarism | Hypsarrhythmia | brain atrophy & corpus callosum agenesis also panhypopituitarism | GDD |
| Meningoencephalitis         | Generalized epileptic discharges | Atrophy and cystic encephalomalacia | Normal |
| VP shunt hydrocephalus       | Generalized epileptic discharges | Hydrocephalus & Chiari malformation type 2 | GDD |
| VP shunt Hydrocephalus       | Generalized epileptic discharges | Hydrocephalus | GDD |
| Metabolic, aminoacidopathy   | Encephalopathy | Normal | Normal |
| Down syndrome & congenital heart disease | Focal epileptic discharges | Enlarged ventricles | Cognitive delay |
| Focal seizures               | Slow background | Normal | Normal |
| GM1 gangliosidosis           | Slow background | Brain atrophy | GDD |
| Meningoencephalitis         | Generalized epileptic discharges | Normal | Normal |
| Mitochondrial disease       | Encephalopathy | Mitochondrial disease (leigh disease) | GDD |
| Idiopathic epilepsy         | Slow background | Normal | Normal |
| Infantile spasms            | Hypsarrhythmia | Hypoxic ischemic encephalopathy | GDD |
| Birth asphyxia               | Generalized epileptic discharges | Periventricular leukomalacia | GDD |
| NCL* type 14                 | Generalized epileptic discharges | Brain atrophy | GDD |
| Down syndrome               | Encephalopathy | Hypoxic ischemic encephalopathy | GDD |
| Birth asphyxia, Lennox-Gastaut syndrome | Generalized epileptic discharges | Hypoxic ischemic encephalopathy & brain atrophy | GDD |
| Idiopathic epilepsy         | Encephalopathy | Normal | Normal |
| Down syndrome and generalized epilepsy | Slow background | Normal | GDD |
| Wolf-Hirschhorn syndrome (chromosome 4p deletion), hypotonia, meningitis, myoclonic epilepsy | Generalized epileptic discharges | Meningitis and agenesis of corpus callosum | GDD |
| Birth asphyxia, Lennox-Gastaut syndrome | Generalized epileptic discharges | Occipital encephalomalacia | GDD |
| Brain tumor                  | Focal discharges | Brain tumor (Dyssembryoplastic neuroepithelial) | Normal |

GDD - Global developmental delay, HSV - herpes simplex virus, GM1 - gangliosidosis 1, NCL - neuronal ceroid lipofuscinosis

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patients was 141 (mean 2.8, median 3). The number of ASM after starting VPA and 3 months of follow up was 94 (mean 1.8, median 2) (antiseizure medications list in Table 3). Valproic acid dosage mean was 31.4 mg/kg/day. After starting VPA, 32 patients (64%) showed more than 50% seizure improvement (11 of them were seizure free). Eighteen patients (36%) had less than 50% seizure improvement (5 of them had no major improvement in their baseline seizures).

Two patients showed signs of encephalopathy: sleepiness and hypoactivity. Valproic acid dose decrement led to clinical improvement. Complete blood counts were carried out before and after VPA. No major changes were seen in white blood cells or platelets.
Comparing changes in white blood cells before and after VPA usage showed a statistically insignificant p-value ($p=0.747$). Similarly, for platelets p-value before and after treatment was not statistically significant ($p=0.585$) (Table 4). Valproic acid levels were taken after 3 months of treatment and repeated if needed to gauge drug dosage. Liver function tests (LFTs) including aspartate aminotransferase (AST), alanine aminotransferase (ALT), glutamate dehydrogenase (GGT), alkaline phosphatase (ALP) and total bilirubin were done before and 3 months or more after VPA (Table 5). A mild increase in ALT, GGT and ALP of less than 2 times the normal was seen in patients on polytherapy (3 or more ASM) and patients on another enzyme-inducing medication (carbamazepine). Abnormal LFTs were statistically significant when comparing before and after VPA usage (ALT $p=0.002$, GGT $p=0.013$ and ALP $p=0.002$). Ammonia level was also reviewed before and
Table 3 - Antiseizures medications.

| Patient / ASMs before | ASMs after VPA |
|-----------------------|----------------|
| 1 (Levetiracetam)     | 1 (Valproic acid) |
| 1 (Levetiracetam)     | 2 (Valproic acid, Levetiracetam) |
| 6 (Topiramate, Carbamazepine, Levetiracetam, Lamotrigine, Prednisolone, IVIG) | 2 (Valproic acid, Lacosamide) |
| 5 (Prednisolone, Topiramate, Carbamazepine, Levetiracetam, Lamotrigine) | 2 (Valproic acid, Topiramate) |
| 4 (Carbamazepine, Levetiracetam, Lamotrigine, Topiramate) | 3 (Carbamazepine, Levetiracetam, Valproic acid) |
| 2 (Vigabatrin, Prednisolone) | 2 (Vigabatrin, Valproic acid) |
| 2 (Vigabatrin, Prednisolone) | 1 (Valproic acid) |
| 3 (Levetiracetam, Vigabatrin, Prednisolone) | 2 (Valproic acid, Lamotrigine) |
| 3 (Levetiracetam, Clonazepam, Topiramate) | 2 (Valproic acid, Levetiracetam) |
| 3 (Levetiracetam, Carbamazepine, Topiramate) | 1 (Valproic acid) |
| 1 (Levetiracetam) | 2 (Clonazepam, Valproic acid) |
| 5 (Clonazepam, Levetiracetam, Phenobarbital, Carbamazepine Topiramate) | 3 (Valproic acid, Levetiracetam, Lamotrigine) |
| 2 (Levetiracetam, Topiramate) | 1 (Valproic acid) |
| 1 (Levetiracetam) | 1 (Valproic acid) |
| 5 (Phenytoin, Levetiracetam, Phenobarbital, Topiramate, Carbamazepine) | 2 (Levetiracetam, Valproic acid) |
| 2 (Levetiracetam, Topiramate) | 1 (Valproic acid) |
| 3 (Levetiracetam, Phenobarbital, Topiramate) | 1 (Valproic acid) |
| 3 (Levetiracetam, Phenytoin, Topiramate) | 2 (Levetiracetam, Valproic acid) |
| 3 (Topiramate, Levetiracetam, Prednisolone) | 2 (Valproic acid, Valproic acid) |
| 2 (Levetiracetam, Clonazepam) | 3 (Clonazepam, Valproic acid, Lamotrigine) |
| 3 (Carbamazepine, Topiramate, Clonazepam) | 2 (Levetiracetam, Valproic acid) |
| 1 (Levetiracetam) | 3 (Topiramate, Levetiracetam, Valproic acid) |
| 6 (Prednisolone, Vigabatrin, Levetiracetam, Topiramate, Lamotrigine, Clonazepam) | 1 (Valproic acid) |
| 3 (Levetiracetam, Phenobarbital, Topiramate) | 1 (Valproic acid) |
| 1 (Levetiracetam) | 1 (Valproic acid) |
| 1 (Phenobarbital) | 1 (Valproic acid) |
| 1 (Levetiracetam) | 1 (Valproic acid) |
| 2 (Levetiracetam, Carbamazepine) | 2 (Levetiracetam, Valproic acid) |
| 2 (Vigabatrin, Topiramate, Levetiracetam, Prednisolone) | 3 (Levetiracetam, Lamotrigine, Valproic acid) |
| 3 (Vigabatrin, Topiramate, Levetiracetam, Prednisolone) | 2 (Vigabatrin, Valproic acid) |
| 6 (Levetiracetam, Lamotrigine, Topiramate, Prednisolone, Clonazepam, Phenytoin) | 3 (Levetiracetam, Lamotrigine, Valproic acid) |
| 3 (Levetiracetam, topiramate, phenobarbital) | 2 (Levetiracetam, Valproic acid) |
| 4 (Levetiracetam, Topiramate, Phenobarbital, Prednisolone) | 2 (Levetiracetam, valproic acid) |
| 4 (Levetiracetam, Topiramate, Carbamazepine, Pyridoxine) | 3 (Levetiracetam, Valproic acid, Topiramate) |
| 2 (Levetiracetam, Topiramate) | 1 (Valproic acid) |
| 2 (Levetiracetam, Carbamazepine) | 1 (Valproic acid) |

ASMs - antiseizure medications, VPA - valproic acid, IVIG - intravenous immunoglobulin

after treatment. No statistically significant changes were observed ($p=0.8$) (Table 6).

**Discussion.** This study evaluated the use of valproic acid in children below the age of 2 years. No previous similar studies were performed in the Middle East as far as we know. Valproic acid has been used safely in different age groups for decades. It acts on GABA ($\gamma$-aminobutyric acid) in the central nervous system and blocks voltage-gated ion channels “sodium, potassium, and calcium”. Reports of acute drug reaction and hepatotoxicity were more common below the age of two years. In our study, no reported death related to VPA. Multiple studies showed the safety of valproic acid as monotherapy in younger patients and less side effects were reported. We noticed less ASMs (94 medications) compared to (141) before starting VPA. This can be explained by the improvement in seizures burden noticed in 64% of the cohort that led to weaning-off other ASMs.
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Table 3 - Antiseizures medications.

| Patients | ASMs before | ASMs after VPA |
|----------|-------------|----------------|
| 5 (Levetiracetam, Topiramate, Carbamazepine, Phenobarbital, Vigabatrin) | 2 (Topiramate, Valproic acid) |
| 1 (Levetiracetam) | 1 (Valproic acid) |
| 4 (Levetiracetam, Phenytoin, Phenobarbital, Topiramate) | 3 (Levetiracetam, Valproic acid) |
| 3 (Prednisolone, Vigabatrin, Lamotrigine) | 3 (Valproic acid, Levetiracetam, Clonazepam) |
| 2 (Levetiracetam, Carbamazepine) | 1 (Valproic acid) |
| 3 (Levetiracetam, Carbamazepine, Topiramate) | 2 (Levetiracetam, Valproic acid) |
| 4 (Vigabatrin, Prednisolone, Levetiracetam, Lamotrigine) | 3 (Valproic acid, Clonazepam, Topiramate) |
| 3 (Levetiracetam, Carbamazepine, Topiramate) | 2 (Valproic acid, Clonazepam) |
| 3 (Levetiracetam, Topiramate, Carbamazepine) | 2 (Valproic acid, Prednisolone) |
| 3 (Levetiracetam, Topiramate, Valproic acid) | 2 (Valproic acid, Topiramate) |
| 2 (Levetiracetam, Lamotrigine) | 1 (Valproic acid) |
| 4 (Phenobarbital, Lamotrigine, Levetiracetam, Topiramate) | 2 (Levetiracetam, valproic acid) |
| 1 (Topiramate) | 2 (Levetiracetam, Valproic acid) |
| Total ASMs | 141 | 94 |
| Mean | 2.8 | 1.8 |
| Median | 3 | 2 |

Table 5 - Liver function tests before and after VPA.

| Liver Function Test (Before VPA doses received) | AST | ALT | GGT | ALP | Bilir (Total) |
|-----------------------------------------------|-----|-----|-----|-----|--------------|
| Normal | 32 (64) | 45 (90) | 44 (88) | 40 (80) | 50 (100) |
| Low | 0 | 3 (6) | 2 (4) | 7 (14) | 0 |
| Abnormal (High) | 18 (36) | 2 (4) | 4 (8) | 3 (6) | 0 |
| M±SD | 37.8±18.98 | 33.28±29.7 | 36.7±42.6 | 236.5±76.9 | 3.12±1.12 |

| Liver Function Test (After VPA doses received) | AST | ALT | GGT | ALP | Bilir (Total) |
|-----------------------------------------------|-----|-----|-----|-----|--------------|
| Normal Range | 28 (56) | 44 (88) | 36 (72) | 39 (78) | 50 (100) |
| Low | 2 (4) | 4 (8) | 5 (10) | 9 (18) | 0 |
| Abnormal (High) | 20 (40) | 2 (4) | 9 (18) | 2 (4) | 0 |
| M±SD | 38±20.13 | 26.24±15.9 | 46.58±67.5 | 233±86.8 | 2.62±1.21 |

P-value Sig. (2-tailed) (comparison between each of subcategory of LFTs) F(1.076)=0.435 F(3.372)=0.002 F(2.897)=0.013 F(9.378)=0.002 F(1.011)=0.423

Liver function enzymes abnormalities were seen in patients on 3 or more ASMs or on enzyme-inducing medications. Compared to other studies, 0 to 50% of individuals on VPA can develop asymptomatic elevation in LFTs. Asymptomatic mild elevation in GGT was noticed in 18% of patients of the cohort. ALT and ALP changes are likely because some results were lower than normal were included. International Serious Adverse Events Consortium (iSAEC) defined drug-induced liver injury (DILI) criteria by Aithal et al. None of our cohort met the criteria of DILI. In our cohort, 72% had asymptomatic hyperammonemia which is statistically not significant (p=0.8) when comparing before and after treatment with VPA. Hyperammonemia is one of the common side effects of VPA. Some studies found 16 to 100% asymptomatic hyperammonemia in individuals taking VPA.

Valproic acid side effects can be related to its dosage. Bone marrow suppression, pancreatitis, hepatotoxicity and acute encephalopathy were related to high dose of VPA in some cases (more than 40 mg/
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The recommended maintenance dose of VPA starts from 10-15 mg/kg/day up to 60 mg/kg/day. Some studies recommended up to 100 mg/kg/day. Valproic acid average dose in this cohort was 31.4 mg/kg/day which can be one factor that can explain its tolerability in this study.

Polytherapy is another reported factor contributing to valproic acid related major side effects. In our study, not all patients on polytherapy had side effects. However, reported side effects of encephalopathy and mild increase in LFT were seen in children receiving VPA and one or more ASMs. Most children with intractable epilepsy will need polytherapy. However, rational polytherapy is recommended. Medications like carbamazepine and phenytoin were reported to increase the level of VPA and hence its toxicity. Star et al showed that when VPA is used as monotherapy, less side effects were reported.

Some of commonly reported valproic acid side effects are: nausea, alopecia, diarrhea, vomiting, and increased appetite. Rare but possibly fatal side effects like pancreatitis and hepatotoxicity should be monitored especially in young children. However, fatalities due to VPA-induced encephalopathy and liver disease are not limited to children. It can occur across different age groups. Bryant et al reviewed US experience with VPA. Out of 7630 patients below the age of 2 years received valproic acid, 5 patients developed fatal hepatotoxicity (0.06%). There have been 268 individual case safety reports “ICSR” to the WHO Global ICSR database from 55 countries since 1977.

Seizure frequency in most of patients improved (64%) after introducing VPA. Despite a moderate dose of VPA (31 mg/kg/day), some of the children in this cohort were even seizure-free. Some studies reported cessation of infantile spasms in more than 70% of their cohort after introducing VPA. Valproic acid is one of the effective antiseizure medications in infantile epilepsies. It is one of the first line medications for Dravet syndrome, myoclonic epilepsy and generalized epilepsy across different age groups.

The limitations of the study are the retrospective design, and the relatively small sample size.

In conclusion, Valproic acid is an effective and tolerable ASM in this age group. It can be considered for the treatment of seizures in children below the age of 2 years. It is potentially safer when used in moderate doses with close follow up of LFT and valproic acid levels. Avoiding polytherapy and concomitant use of enzyme inducers is recommended. Screening for children with metabolic and hepatic diseases should be

Table 4 - Complete blood counts before and after VPA (White blood cells (WBCs) and platelets, PLT).

| Patient | WBCs | PLT |
|---------|------|-----|
|         | Before | After | Before | After |
| 15.56   | 13.91  | 405   | 309    |
| 12.05   | 7      | 177   | 201    |
| 10.59   | 319    | 616   |
| 18.25   | 9      | 444   | 267    |
| 6.6     | 11.4   | 222   | 418    |
| 4.3     | 12     | 367   | 190    |
| 6.12    | 8.18   | 154   | 507    |
| 8       | 8      | 500   | 350    |
| 9       | 12     | 167   | 269    |
| 13.90   | 10     | 389   | 336    |
| 20      | 9      | 412   | 230    |
| 7       | 9.5    | 228   | 394    |
| 13      | 12.5   | 241   | 290    |
| 8       | 8      | 405   | 430    |
| 9.5     | 11     | 306   | 351    |
| 12.6    | 10.2   | 260   | 387    |
| 4       | 11     | 335   | 274    |
| 4.3     | 14     | 269   | 256    |
| 10      | 15     | 269   | 323    |
| 7       | 7      | 476   | 318    |
| 10      | 8      | 413   | 460    |
| 9       | 6      | 449   | 283    |
| 17      | 15     | 303   | 254    |
| 15      | 6      | 275   | 475    |
| 6       | 8      | 324   | 334    |
| 5       | 8      | 117   | 136    |
| 7       | 6      | 250   | 270    |
| 6       | 8      | 177   | 306    |
| 9       | 9      | 268   | 374    |
| 8       | 14     | 398   | 450    |
| 6       | 7      | 460   | 400    |
| 7       | 7      | 416   | 380    |
| 7       | 9      | 299   | 424    |
| 12      | 7      | 455   | 800    |
| 15      | 7      | 408   | 490    |
| 8       | 5      | 600   | 560    |
| 8       | 10     | 425   | 376    |
| 4       | 3      | 277   | 280    |
| 9       | 13     | 324   | 600    |
| 10      | 12     | 387   | 288    |
| 13      | 11     | 520   | 329    |

Ref range 3-14 10^9/L 150-450
Mean 9.8142 9.6172 358.32 369.4
Variance 14.9 8.8 18257.9 15521.6
SD 3.86 2.97 135.12 124.59
P(T<=t) 2-tail 0.747031 0.58563866
considered. More studies and a better understanding of VPA-related age pharmacokinetics and epigenetics are recommended.

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