The Clinical Importance of Total Drug Monitoring in Reducing the Toxicity Associated with Valproic Acid in Epileptic Children in Taif City

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Abstract

Background: Epilepsy is a group of neurological disorders that are characterized by an epileptic seizure. An epileptic seizure can last for seconds and may last for a longer time of fewer than five minutes. An epileptic seizure may cause physical harm; therefore, its management is necessary. Epilepsy requires long-term epileptic treatment. Children with epilepsy can be managed by valproic acid, which is the very commonly used antiepileptic drug in clinical practice. However, chronic usage of valproic acid is associated with adverse effects, especially among children. These adverse effects involve hepatotoxicity, coagulation disorders, and pancreatitis. Therapeutic drug monitoring (TDM) is effective in adjusting the dosage of the drug to obtain the optimum concentration in order to reduce toxicities associated with the medication.

Aim: To investigate the effects of TDM in assessing liver injury associated with valproic acid treatment for epileptic children.

Methods: This study is a cohort study that was conducted on epileptic children treated with valproic acid monotherapy at least one month after using TDM at the children hospital in Taif. Liver enzymes, serum creatinine, total bilirubin, direct bilirubin, and dose of valproic acid adjusted by TDM were estimated. Statistical analysis was performed using SPSS software version 21.

Results: A total of 126 epileptic children were involved in our study; 68 were involved in the TDM group, and 58 were involved in the non-TDM group. There were significant differences between the two groups regarding the mean of AST (P=0.0001), ALT (P=0.048), and total bilirubin (P=0.0001). There was a significant negative association between valproic acid levels determined by TDM and ALT (r=-0.256, P=0.035), whereas the correlation was positive with serum creatinine (r=0.414, P=0.0001). Logistic regression model showed significant association between TDM usage and elevated AST, OR=0.033, 95% CI=0.004-0.2 (P=0.001).

Conclusion: TDM has a significant impact in reducing liver injury and maintaining good hepatic function among epileptic children treated with valproic acid. TDM is also can be used to monitor renal function and correct renal injury by adjusting the valproic acid dose.

Keywords: TDM, Valproic acid, Toxicity, Liver injury

1. Introduction

Epilepsy is a group of neurological disorders that are characterized by epileptic seizures (Alsharif *et al.*, 2017) [6]. Epileptic seizure causes from abnormal electrical activity in the brain (Lee, 2010) [51].

Epilepsy is one of the most common neurological diseases and very common in the world; it affects more than 50 million individuals (Scott *et al.*, 2001) [80] and contributes 1% of the disease's burden (Rabie *et al.*, 2016) [74]. The prevalence of epilepsy is higher in growing countries compared to developed ones (Ropper *et al.*, 2009) [78]; almost 90% of epileptic patients alive in low and middle-income countries (Ngugi *et al.*, 2010) [69].

Epilepsy incidence is expected to increase with time as life expectancy increases globally as well as the advances in healthcare that led to the survival of epileptic patients (Horaib *et al.*, 2021) [38]. The etiology of epilepsy is not known among almost 60% of all cases (Alsharif *et al.*, 2017) [6].

Epilepsy is the very common recurrent neurologic disease among children, and it has become a major public health problem (Rabie *et al.*, 2016) [74]. The frequency of epilepsy among children is 4-8 cases/1000 children (Annegers, 1994) [7]. However, the prevalence may increase and reach 57/1000 children based on epidemiologic studies (Al Rajeh *et al.*, 2001) [2]. In Saudi Arabia, epilepsy prevalence is 6.54/1000 population (Al Rajeh *et al.*, 2001) [2].

Epilepsy has potential negative impacts on the life of an individual; individuals with epilepsy experience difficulties with education, social relationships, and employment (Alaqeel & Sabbagh, 2013) [4]. Epilepsy can significantly affect the quality of life of the patient due to the need for regular medications, side effects of medications, and chronicity of the disease (Alaqeel & Sabbagh, 2013) [4]. Uncontrolled epileptic seizure affects the life of the patient as it results in poor outcomes on the motor, cognition, and language development (Bombardieri *et al.*, 2010) [11]. The clinical efficacy of epilepsy treatment is commonly determined by a remarkable reduction in seizure frequency or seizure freedom (Kerr *et al.*, 2011) [45]. Standard treatment of epilepsy is a mono-therapy antiepileptic drug (AED) or adjunctive therapy if mono-therapy has not resulted in seizure control (Kerr *et al.*, 2011) [45].

It has been reportef that valproate has the broadest spectrum of anticonvulsant activity compared to all available AEDs in adults and children with epilepsy (Löscher, 2002). Due to the broad spectrum of valproate, it is a mainstay of AED for a wide range of epileptic syndromes and seizures (Romoli *et al.*, 2019) [77].

Valproate was presented in clinical practice 50 years ago, and its efficacy and acceptability profiles have been reported (Romoli *et al.*, 2019) [77]. It is the first choice of drug nowadays for the treatment of several epileptic and non-epileptic diseases. The scientific name of Valorpic acid (VPA) is N-dipropylacetic acid (Romoli *et al.*, 2019) [77]. VPA is the chosen drug for the treatment of children recently diagnosed with epilepsy, atonic seizure, juvenile myoclonic seizures, idiopathic generalized epilepsy, and multiple seizure types (Mehndiratta *et al.*, 2016) [63].

VPA is generally well tolerated; however, it is associated with adverse effects such as sleep disturbances, abdominal pain, rash, and weight gain. It is also associated with toxicities, including hepatotoxicity, mitochondrial toxicity, and aplastic anemia(Mehndiratta *et al.*, 2016) [63].

Therapeutic drug monitoring (TDM) refers to the individualization of drug dosage by maintaining the concentration of the drug in the plasma within a targeted therapeutic limit or window (Birkett, 1997) [9]. TDM involves the measurement of drug concentration in different biological fluids and the interpretation of these concentrations regarding relevant clinical parameters (Kang *et al.*, 2009) [44]. AEDs have been the most popular drugs for which TDM was performed. TDM has been traditionally applied for first-generation AEDs, including VPA, carbamazepine, and phenytoin (Krasowski, 2010) [47].

2. Epilepsy in children

Epilepsy is a type of complicated and progressive disorders characterized by epileptic seizures of crippling and intermittent nature (Mohamed *et al.*, 2020) [64]. The primary cause of epilepsy is unknown in more than one-half of cases (Mohamed *et al.*, 2020) [64], but some inherited conditions and genetics such as severe brain injury, complications from previous illness, and stroke may result in epilepsy with the involvement of both causes in many patients (Alonazi *et al.*, 2018) [5].

Epilepsy is the most common neurological and non-infectious disease in the world (Mohamed *et al.*, 2020) [64], and its incidence is potentially greater in developing nations compared with developed nations (Ropper *et al.*, 2009) [78]. Epilepsy is the most faced condition in pediatric neurology clinics, especially in developing countries (Noebels *et al.*, 2012) [70]. This is due to poorer public hygiene, poorer perinatal care and standards of nutrition, greater risk of cerebral infection, and brain injury (Saad, 2014) [79]. It was estimated that childhood epilepsy is approximately 0.5% (Giussani *et al.*, 2014) [32]. The prevalence of epilepsy among children less than ten years of age was reported to be 6/1000, and up to 5% of children will have a febrile seizure in the first five years of life (Abo Melha & Al- Rajeh, 1987) [1].

In the developed world, the average epilepsy prevalence among children is around 50/100000 children annually (Neubauer *et al.*, 2008) [68]. The latest reports showed that the highest incidence of epilepsy was recorded among infants with age less than one year and those with an age of one to 12 years at a rate of 102/100000 cases annually, whereas the rate among children with the age of 11-17 years was reported to be 21-24/100000 (Lv *et al.*, 2017).

A study from Turkey included 1625 students with age 6-14 years, the prevalence of epilepsy was 1.35%, and only 22 students had epilepsy. The rate of epilepsy among males and females was reported to be 4.9/1000 and 12.4/1000, respectively, with a total rate of 8.6/1000. The risk factors for epilepsy progression included family history of epilepsy, febrile convulsion, antenatal/postnatal problems, history of head trauma, history of neonatal jaundice, and serious maternal illness during pregnancy (Huseyinoglu *et al.*, 2012). Another Turkish study conducted on 10742 students with age of 7-17 years showed that 83 students were diagnosed with epilepsy, with a raw prevalence among males and females estimated to be 6/1000 and 9/1000, respectively, and active prevalence estimated to be 7/1000, 4/1000, and 6/1000 among males, females and both genders, respectively. The risk of epilepsy was increased by 2.6 times regarding premature birth,

3.3 and 1.6 times due to average and poor family income levels, respectively. The risk of epilepsy greatly increased by 15.1 times due to a history of febrile convulsion (Canpolat *et al.*, 2014) [13].

A study from Egypt showed that the prevalence of epilepsy among children less than 18 years in Upper Egypt was 9.7/1000, with a higher prevalence noted among children younger than 12 years old, where the prevalence was 10.8/1000. Also, 59.4% of epileptic children had idiopathic epilepsy (Farghaly *et al.*, 2018) [28].

Inherited neurological disorders such as epilepsy and genetic epilepsy syndrome are more common in Saudi Arabia due to the high rate of consanguineous marriage (El-Hazmi &

Warsy, 1996) [24]. In a study conducted on 1230 Saudi students with age six to 18 years, the prevalence of epilepsy was 5.5%, with consanguinity between parents as a significant factor for having epilepsy. Also, family history had a major impact on the prevalence of epilepsy (Alsharif *et al.*, 2017) [6]. Another Saudi study from the Aseer region included 2500 students from primary, preparatory, and secondary schools, reported that 20 cases were detected to suffer epilepsy (0.8%). The most important risk factors included consanguinity, febrile convulsion, family history, and head trauma (Rabie *et al.*, 2016) [74].

3. Types of seizures

Seizures are the clinical symptoms of an electrical surge which is cerebral in origin and can be broadly characterized as motor and non-motor. The manifestation of the seizures are govern by the part of the brain is the origin such as motor strip seizure that are presented with muscle jerks, and occipital lobe seizure that are present with visual phenomena. The manifestations are further dictated by the source of these seizure, whether the source is both cerebral hemispheres or just a part of the brain (Magazi *et al.*, 2018) [58].

3.1 Motor seizure

This category of seizure is the most rapidly identifiable of the seizure and involves eight types; tonic, myoclonic, clonic, tonic-clonic, atonic, automatisms, hyperkinetic, and epileptic spasms (Magazi *et al.*, 2018) [58].

3.1.1 Tonic seizure

This type of seizures is presented with a spasm of the body with different limbs and may results in backward arching of the back followed by loss of consciousness (Vignoli *et al.*, 2017). The spasms occurred due to the rapid onset of increased tone in the extensor muscles (Saad, 2014) [79]. It lasts for seconds to at most a few minutes, and frequently begins with tonic spasm of the muscles in the neck leading to fixation of the head in an erect position, with opened eyes, and mouth opening or jaw clenching. The contraction of abdominal and respiratory muscles often follows and may lead to brief period of apenea and high-pitched cry. Irregular tonic seizures vary from a slight rotation of the head to a tonic contraction of all the muscles of one side of the body (Magazi *et al.*, 2018) [58].

The occurrence of this type in isolated manner is rarely occur especially in childhood onset syndromes such as the Lennox Gestaut; this syndrome progress into adolescence and continue to adulthood (Vignoli *et al.*, 2017), and tonic seizures are the most common types of seizure among patients with this syndrome (Saad, 2014) [79]. Tonic seizures are recognized symptoms of frontal lobe epilepsy especially originating in the supplementary motor cortex (Jobst *et al.*, 2000).

Patients with tonic seizures generally show quite abnormal electroencephalogram consisting of the background with bursts of irregular spike and wave activity as well as multifocal spikes, and sharp waves. The ictal electroencephalogram usually consists of two-sided synchronous spikes of 10 to 25 Hz of medium to high voltage with a frontal accentuation (Saad, 2014) [79]. Focal dystonia is a mimicker of these seizures but it would not affect consciousness of the patients and wouldn't cause abnormal ictal electroencephalography (Magazi *et al.*, 2018) [58].

3.1.2 Myoclonic seizure

This type involves brief jerky movements of the muscle with preserved consciousness (Magazi *et al.*, 2018) [58]. They are described by sudden brief irregular and shock like contractions that lasts of less than 350 milliseconds and may be generalized or confined to the trunk and face or to one or more limbs or even to specific muscles or group of muscles (Saad, 2014) [79]. Myoclonic seizure can be repetitive or single and range in severity from almost imperceptible twitch to a serious jerking; also, they can be symmetric or asymmetric (Saad, 2014) [79]. This type of seizure tended to occur near the onset of sleeping and upon awakening from sleep (Saad, 2014) [79].

They are common in isolation conditions and often they are coexisting with other types of seizures and as a result manifest with loss of consciousness due to presence of other types (Magazi *et al.*, 2018) [58]. When myoclonic seizure occur with other clusters, they may evolve into tonic- clonic seizures and as a result loss consciousness and postical confusion (Saad, 2014) [79].

This type of seizure can be a feature of some idiopathic generalized epilepsies such as infantile spasm (Saad, 2014) [79]. There are other distinct epilepsy syndromes that present with myoclonic seizure such as progressive myoclonic epilepsies like Baltic myoclonus/ Unverrichet- Lundborg, the juvenile myoclonic epilepsy, and mitochondrial cytopathies like myoclonus epilepsy and ragged- red fibers (Magazi *et al.*, 2018) [58].

Myoclonic seizure can be negative or positive; negative myoclonus refers to the brief loss of postural tone when the body part is held against the gravity. The ictal electroencephalogram pattern of myoclonic seizure is characterized by generalized polyspikes and wave discharges which corresponds to myoclonic jerk (Tamber & Mountz 2012; Rudzinski *et al.* 2013) [88, 79].

3.1.3 Clonic seizure

This type of seizures is typically observed among neonates and young children and it is characterized by repetitive rhythmic clonic jerks of1-2 Hz with short post- ictal phase and impairment of consciousness (Saad, 2014) [79]. Clonic seizures involve sustained muscle contractions which could have a generalized or focal presentation, based on the involvement of brain surface area (Magazi *et al.*, 2018) [58]. They can lead to a clonic- tonic- clonic seizure and it is thought that the repetitive discharges return to rhythmic excitatory discharges from the cortex. The ictal electroencephalogram show waves discharges and generalized polyspikes or generalized fast activity (Tamber & Mountz 2012 ofX; Rudzinski *et al.* 2013 ofX) [88, 79].

3.1.4 Tonic-clonic seizures

It is the classic form of epileptic seizures and the most common form of seizures with a tonic phase that is followed by a clonic phase (Saad, 2014; Magazi *et al.*, 2018) [79]. This type involves loss of consciousness, sphincter control and post ictal confusion beside experiencing muscle stiffness and jerks (Magazi *et al.*, 2018) [58]. Therefore this type of seizures involves changes in consciousness followed by tonic extension and then clonic convulsive movements that affect the four limbs (Saad, 2014) [79].

Generalized tonic- clonic seizures are the most common type of seizures in infant. The onset may appear at any time after the neonatal period and it may be a symptom of primary

generalized epilepsy following focal seizure with a focal onset or alternating with other forms of seizures (Saad, 2014) [79]. One study from Saudi Arabia reported that 76.2% of 341 epileptic patients had generalized tonic clonic seizures (Hamdy *et al.*, 2014) [37].
During seizure in the tonic phase, there are generalized repetitive spikes shown by electroencephalogram, then in the clonic phase, periodic spikes are shown (Saad, 2014) [79].

3.1.5 Atonic seizure
This type of seizure is not common, but is a distinct manifestation of the Lennox Gestaut syndrome. This type is characterized by the loss of body tone with falling of patient to the ground in a limp form (Vignoli *et al.*, 2017) [90]. This type may reveal as the classic drop attack, as all postural tone is suddenly changed or unexpectedly lost such as a slight head drop or bowing at the knees. The loss of body tone involves the sudden loss of muscle tone such as the neck resulting in a drop of the head or it may involves all muscles of the trunk leading to fall down to the ground. Due to lack of tone which may occur, injuries often reported as patients have no means of self-protection. During the fall, consciousness is impaired; however, the patient may regain awareness immediately once hitting the ground. On electroencephalogram, an electro decremental reaction results in a sudden generalized drop in amplitude of the electroencephalogram and this pattern may develop into slow spike and wave complexes or diffuse polyspikes (Saad, 2014) [79].

3.1.6 Automatisms
These are less or more coordinated movements associated with an ictus which occur with consciousness disturbance such as being disruptive or walking aimlessly. There is usually an amnesia for these events when patients come around (Magazi *et al.*, 2018) [58].

3.1.7 Hyperkinetic seizure
This type is characterized by an agitated movement of a body part similar to pedaling of the feet (Magazi *et al.*, 2018) [58].

3.1.8 Epileptic spasms
The main characteristic is sudden flexion of truncal muscle and limb and usually occur in series. They are a feature for the West syndrome which presents in infancy and continue to early childhood (Magazi *et al.*, 2018) [58].

3.2 Non-Motor seizures
This category involves five types of seizures; absences, cognitive, emotional, sensory, autonomic, and behavioral arrest (Magazi *et al.*, 2018) [58].

3.2.1 Absence seizures
Absence seizures involve brief episodes that last for 4-20 seconds, they are described by blank stare, rapid onset behavioral arrest, and unresponsiveness (Saad, 2014; Magazi *et al.*, 2018) [79, 58]. They typically occur in childhood or adolescent periods and have a generally good prognosis (Magazi *et al.*, 2018) [58]. This is true of typical absence which does not have post- ictal phenomena and are brief; atypical presentation involves longer absence duration (Magazi *et al.*, 2018) [58].
Atypical absence seizures have been related tone changes of the body and head and myoclonic components. The electroencephalogram of absence seizures is pathogenomic; they occur as bilateral synchronous and symmetric paroxysms of spike and wave complexes at a frequency of 3 Hz appears simultaneously with the clinical seizure. Hyperventillation is a potential activator for typical absence seizure; it almost always

activates with the discharge. Failing to induce an absence seizure with several trials of hyperventilation of 3- 5 minutes duration in an untreated patient makes the diagnosis of absence seizure is unlikely (Saad, 2014) [79].

3.2.2 Cognietive and emotional seizures
A wide range of psychological and mental phenomena could be the prominent presentation of certain seizures; these include illusions like out of body experience, hallucinations and delusions. Further signs could include forced thinking and mood changes such as anxiety, depression and fear. Forced thinking involves intrusive thoughts for example, a rapid recollection of past life experiences (Stephani & Koubeissi, 2017) [85]. This type of seizures often originates in the temporal lobe including the limbic structures (Magazi *et al.*, 2018) [58].

3.2.3 Sensory seizures
They include various hallucinations that overlap with what could have been categorized as cognitive. Their presentation is not infrequent with the manifestations often being auras before motor phenomena. There could be negative sensory phenomena with decreased appreciation of the specific senses (Magazi *et al.*, 2018) [58]. Seizures can be triggered by taking hot shower, reading, and listening to the voice of a particular radio presenters (Stefan & Theodore, 2012) [84].

3.2.4 Autonomic seizure
Autonomic seizure manifest with sensations such as gastric phenomena like palpitation, borborygmi, piloerection causing goose bumps. Certain syndromes have manifestations of autonomic seizure as one of the defining characteristics such as Panayiotopoulos syndrome which is an early onset epilepsy. There is a hypothesis about the possible cause of rapid unexpected death in epilepsy being partly from dysautonomia from the compromised cardiorespiratory function (Moseley *et al.*, 2013) [66].

4. Challenges of diagnosing epilepsy
Under reporting of seizurs is common because there is a need to recognize the manifestations for what it is (Elger & Hoppe, 2018). The patient often had no insights about the phenomenology of the ictal events and the diagnosis of the patient is often based on narration of events which are a challenge for sometimes, especially if the seizurs are atypical (Magazi *et al.*, 2018) [58].
Electroencephalography is a diagnostic tool for epilepsy, and it is sparsely distributed in many low-income nations with a concentration in the cities with the resultant of long waiting time. Many patients are not able to afford its cost and this is a challenge for patients (McLane *et al.*, 2015) [62]. Electroencephalography is also infrequently lack proper expertise to use and has a potential to contribute to a high rate of enormous results (Birbeck, 2010). The same applies to the availability of other brain tools such as imaging facilities including the computed tomography scan and magnetic resonance imaging (McLane *et al.*, 2015) [62].

5. Treatment of epilepsy in children

Children with epilepsy are managed by pediatric neurologists; many medications may be useful for the managing of epilepsy, such as first-line or adjunctive drugs. However, the choice of medication can be affected by the side effects of the drug and may be performed in conjunction with a neurologist (Claassen *et al.*, 2015) [17]. Epilepsy requires long-term AED therapy (Maksoud *et al.*, 2016) [60, 61].

Failure of treatment and poor adherence is very popular among patients experiencing adverse effects of AEDs, and this leads to treatment discontinuation among almost 25% (Perucca *et al.*, 2009; Uijl *et al.*, 2009) [73]. Some studies demonstrated that epileptic patients treated with AEDs are more likely to suffer bone abnormalities such as abnormal dentition, osteomalacia, rickets, and short stature (Guo *et al.*, 2001).

5.1 Valproic acid (VPA) for the treatment of epilepsy and associated toxicity

Valproic acid (VPA) is effective for the management of epilepsy, and it is among the most commonly used AEDs in clinical practice (Espinosa *et al.*, 2008) [26]. VPA has been available for therapy more than 50 years; it is a broad spectrum anti-seizure medication (ASM), and it is one of the old generation of ASM (Tomson *et al.*, 2016) [50]. The efficacy of VPA in epilepsy syndrome, focal and generalized epilepsy, especially in the pediatric population, has been accurately and widely validated with randomized controlled trials and observational studies (Glauser *et al.*, 2013; Guerrini, 2006) [33, 35]. Also, various clinical trials consistently proved the high efficacy of VPA among patients with typical and atypical absence seizures among both children and adults showing like seizure control using VPA or other AEDs (Maheshwari & Jeavons; 1975; Villarreal *et al.*, 1978; Davis *et al.*, 1994).

General information about the adverse effects of VPA, especially severe adverse effects, must be given to the patients and their parents before the initiation of VPA treatment (Gerstner *et al.*, 2008) [30]. VPA is associated with adverse effects, including weight gain, headache, fatigue, drowsiness, tremor, and nausea (Star *et al.*, 2014; Esfahani *et al.*, 2019) [83, 25], whereas the most serious adverse drug effects include hepatotoxicity, coagulation disorders, encephalopathy, bone marrow suppression, and pancreatitis (Star *et al.*, 2014; Esfahani *et al.*, 2019) [83, 25]. These complications may be associated with other factors such as dose and age (Esfahani *et al.*, 2019) [25].

Coagulopathies were reported among children cured with VPA. More than 4% of children treated with VPA experience this pathology. Symptoms of this disease include thrombocytopenia, von Willebrandt disease, platelet disfunction, hypo-fibrinogenemia, factor XIII deficiency, and vitamin K-dependent factors insufficiency (Gerstner *et al.*, 2006) [30]. Thrombocytopenia and platelets dysfunction could be explained through two hypotheses. The first stated that VPA has immediate toxicity on bone marrow, leading to a reduction in the production of erythrocytic and neutrophilic marrow, whereas the second one includes the inclusion of VPA into the platelet membrane. This leads to modification of the membrane, which could reason autoimmunity, due to the production of immunoglobulin (M) antibody directed against circulating thrombocytes, but this alteration might also result in simple alteration of the properties of the membrane, which could clarify the observation of thrombocytopenia without the reduction in the platelet count (Chateauvieux *et al.*, 2010) [14].

In a study involving epileptic children below 18 years of who were treated with VPA mono-therapy and those administrating VPA poly-therapy, it was found that incidence of thrombocytopenia was not varied between mono-therapy or poly-therapy. However, a greater proportion of thrombocytopenia was associated with a duration of VPA longer than two years (Indrayati *et al.*, 2020) [41].

In Saudi retrospective study involved 50 children below two years of age treated with VPA; it was shown that 64% had more than 50% seizure improvement after treatment with VPA, and 22% were seizure-free. There were no remarkable defects in blood count indices or ammonia through the treatment period, but there was an asymptomatic moderate rise in glutamate dehydrogenase noted in 18% of patients. The study revealed that VPA treatment for pediatric less than two years of age could be considered an effective and safe option for epilepsy among this age group (Muthaffar *et al.*, 2021) [67].

The use of VP among children less than two years is restricted by its potential hepatotoxicity, especially when used in high dosage or as polytherapy (Muthaffar *et al.*, 2021) [67]. Hepatotoxicity usually appears within the first six months of VPA treatment initiation (Romoli *et al.*, 2019) [77]. The clinical features of hepatotoxicity include somnolence, anorexia, apathy, vomiting, seizure worsening, and jaundice (Romoli *et al.*, 2019) [77]. The incidence of hepatotoxicity among patients treated with VPA is less than 1% per 20000 patients; however, hepatotoxicity is age dependent. Its risk was reported to be higher in children below two years of age, mainly if suffering from acute seizure disorders or other neurological diseases such as cognitive impairment and brain damage (Bryant & Dreifuss, 1996) [12].

The incidence of hepatotoxicity caused by VPA among children is higher compared to adults, with a ratio of 1:5000 compared to 1:40000, respectively. The proposed mechanism for hepatotoxicity includes defects of oxidative phosphorylation, inhibition of gluconeogenesis, and reduction of intracellular CoA (Koenig *et al.*, 2006; Wange*et al.*, 2020) [46].

A comprehensive review of 37 cases of fetal hepatotoxicity among patients receiving VPA showed that the risk of hepatotoxicity was higher among pediatric less than three years of age, patients with signs of developmental delay, and patients on poly-therapy (Dreifuss *et al.*, 1987) [21]. A review published in 2014 and used the WHO global individual case safety reports (ICSRs) found that a total of 156 fatalities were related with hepatotoxicity, and its risk is greater among children with the age of six years and younger (Star *et al.*, 2014) [83].

Tenderness and abdominal pain, independent from abdominal distension, diarrhea, vomiting, apathy, and lethargy, should be considered as warning signs for potential pancreatitis, especially in the pediatric population (Romoli *et al.*, 2019) [77]. The first report on the potential association of acute pancreatitis and VPA treatment was in 1979 by Bataladen and coauthors. (Batalden *et al.*, 1979). VPA-caused pancreatitis was postulated in almost 13% of children with acute pancreatitis (Houben *et al.*, 2005) [39].

Encephalopathy was demonstrated to be an extremely uncommon complication of VPA treatment, and it was described mostly among patients with inborn metabolic problems; however, it also was described among patients

with no metabolic defect. It was shown that the risk of encephalopathy is increased due to VPA when VPA is mixed with topiramate (Longin *et al.*, 2002) [54].

There are four forms of encephalopathy related with VPA; encephalopathy as a straight effect of VPA, another with elevated levels of serum VPA, but normal ammonia, hyperammonemia encephalopathy, encephalopathy with hepatopathy, but with regular ammonia, and encephalopathy with reduced liver function and hyperammonemia (Gerstner *et al.*, 2008) [30].

Hyperammonemia state also can occur with VPA treatment(Romoli *et al.*, 2019) [77]. One study was conducted on 60 epileptic children with ages ranging between 3 months to 12 years on VPA mono-therapy for at least three months. The study divided patients into two groups based on the VPA dose; one group included patients on a low dose of 20-39mg/Kg/d, and the other group involved patients on a high dose of 40-46mg/Kg/d. It was found that blood ammonia level was significantly associated with both doses and serum levels of VPA, and all children suffering from hyperammonemia were asymptomatic (Sharma *et al.*, 2011) [82].

Postural tremor is a different side effect of VPA and often mimics essential tremor. Memory problems, dizziness, nystagmus, and dizziness have been described as common adverse effects that generally resolve with drug dose modifications or discontinuation. In addition, confusion, headache, drowsiness, and tiredness have also been associated with VPA(Romoli *et al.*, 2019) [77].

Weight gain is a well-known adverse effect that happens among 40% of children (Corman *et al.*, 1997) [18], and it is the major cause for discontinuation of VPA treatment (Biton *et al.*, 2001) [10]. BMI tends to rise during the first 16 months of treatment and then tend to stabilize, resulting in a rise from 6.9% to 16% in the proportion of young children in the clinical category of overweight, whereas, in older children, the change to higher weight category is 14% (Chateauvieux *et al.*, 2010). VPA also is associated with changes in serum cholesterol, triglycerides, and fasting blood glucose (Chateauvieux *et al.*, 2010) [14].

One study was conducted on 25 children recently diagnosed with epilepsy and was on VPA mono-therapy for at least one year, and another group of control children included 25 children with a history of simple febrile spasms. The study found a potential increase in weight and BMI with a significant reduction of height centiles among epileptic patients at six months and one year. On the other hand, no major change was noted regarding serum calcium at any time (Maksoud *et al.*, 2016) [60, 61].

One study included 209 epileptic children from Iran with a mean age of 7.02 years and was on a low therapeutic dose of VPA mono-therapy found that 53.1% of children gained weight, and decreased appetite was prevalent among 11% of children, and it was significantly common among younger patients. The study also reported various side effects, but less common, and they included abdominal pain (16.3%), headache (5.7%), nausea/vomiting (2.4%), diarrhea (1.4%), tremor (1.4%), and each of constipation, dizziness, abnormal color vision, and myoclonus represented (1%), whereas bruxism was prevalent among 0.5%. Thrombocytopenia and impaired liver function, each was experienced by 1%. The study revealed that a low dose of VPA mono-therapy resulted in side effects, but these side effects weren't life-threatening (Esfahani *et al.*, 2019) [25].

VPA is associated with alopecia; which is due to the telogen shedding, and it occurs within three months of treatment beginning. VPA also induces thinning of the hair, transient alopecia, hair texture changes, and hair color differences. However, alopecia can be prevented by the administration of zinc and selenium-containing vitamin as it does not depend on VPA dose (Develioglu *et al.*, 2008) [20].

VPA inhibits the hepatic metabolism of drugs and replaces other highly-bound drugs from their plasma protein-binding places. therefore, co-administrated medications that are highly protein-bound or metabolized in the liver may need dosage adjustment (Gerstner *et al.*, 2008) [30].

6. Therapeutic drug monitoring (TDM)

Therapeutic drug monitoring (TDM) is described as the clinical use and measurement of plasma/serum or saliva drug concentrations to modify the dosage of a drug for each patient and thus schedule to each patient individual therapeutic requirement (Johannessen Landmark *et al.*, 2020) [72].

Regarding epilepsy management, there are 27 AEDs available internationally, and there is a marked pharmacological variability, where at present pharmacokinetic variability is the most simply measurable and can be monitored for it (Johannessen Landmark *et al.*, 2020) [72]. Genetic, environmental, and physiological factors also provide to the extensive variability in the blood serum concentrations obtained from any given AED. furthermore, adherence plays a role in the total estimation of the AED treatment (Johannessen Landmark *et al.*, 2020) [72].

There are many factors that contribute to the pharmacological inconsistency within and between patients, such as pharmacokinetics inconsistency in general and in special groups of patients. There are significant physiological and pathological changes that occur during the transition from childhood to adolescence, then to adulthood, and to an older age. These differences contribute to the pharmacokinetics of AEDs(Johannessen Landmark *et al.*, 2020) [72].

Pharmacokinetics during early childhood are affected and changed by physiological alteration. For most AEDs, the clearance is high-level, and as a result, the elimination half-life is at a low level, especially from six months to about six years of age. The clinical effect is that young children and infants often require a greater dosage per kilogram body weight than older children and adolescents. This extensive pharmacokinetic inconsistency during growth makes it difficult to predict the optimal dose of therapy, and therefore TDM may be useful among this age group of patients(Johannessen Landmark *et al.*, 2020) [72].

Although there are several AEDs available for the treatment of epilepsy, 50% of patients do not respond to the first AED one-third is still considered as being treatment-resistant. Furthermore, many of them have several convulsion types (Chen *et al.*, 2018; Kwan & Brodie *et al.*, 2000). The choice of the proper AED for different types of seizures is of paramount significance as some AEDs are specifically effective for certain types of seizures (Glauser *et al.*, 2013; Nunes *et al.*, 2012). Therefore, TDM may be a valuable tool to individualize, optimize and monitor AED treatment in patients with refractory epilepsy with a difficult management and seizure incidence (Johannessen Landmark *et al.*, 2020) [72].

TDM is used to optimize dosage decisions to prevent toxicity of the therapy and maximize its efficacy (Eilers, 1995). Limited randomized studies reported a positive effect of

TDM on the clinical outcomes among epileptic patients; however, evidence from non- randomized studies and everyday clinical practice indicated that implementation of TDM for older and newer AEDs may best be used to guide patient management, and provided that concentrations of the drug in the serum are measured strong indication and clinical interpretation (Patsalos *et al.*, 2008) [72].

The first-generation AEDs, consist of VPA, exhibit extensive interpatient pharmacokinetic variability, so TDM has been utilized for these drugs (Landmark *et al.*, 2016) [50]. TDM is useful for AEDs for the selection of the optimum therapy and helps the evaluation of non-compliance (Shaikh *et al.*, 2018) [81]. Monitoring of VPA is helpful when its efficacy and toxicity are doubtful. The clearance of VPA is not constant due to inter- individual variability of pharmacokinetics and concentration-dependent plasma protein binding pharmacokinetic of VPA(Reith *et al.*, 2001; Evans *et al.* 1992; Fattore *et al.*, 2006) [76, 27, 29].

Shaikl and coworkers studied TDM for VPA; the study involved a total of 206 samples of plasma of epileptic patients using VPA. It was found that 29% of the tests were in sub-therapeutic levels, 13% of the samples had toxic levels, and more than one-half (58%) of all tests had VPA levels in the therapeutic range. It was revealed that VPA concentration in plasma changed with gender and age group. The authors suggested careful attention to specific gender and particular age group in order to obtain the desired clinical response (Shaikh *et al.*, 2018) [81]. Another study assessed the possible correlation between the serum concentrations and the clinical response of VPA through TDM. The study included 18 epileptic patients, and a bad correlation was found between the plasma concentration of VPA and its therapeutic effects. The study proved that TDM of VPA is useful only when patients aren't responsive to treatment or vulnerable to adverse drug reactions with normal doses (Mohsen *et al.*, 2009) [65].

One study was conducted on 30 epileptic patients managed by VPA with a mean age of

7.93 years. The study found that less than one-half of patients (46.33%) had serum levels of VPA within the therapeutic range, whereas 56.66% were below the therapeutic range. There was a bad correlation between the daily dose concentration and therapeutic level. The authors also suggested different monitoring of liver function tests and blood urea nitrogen (Kumar *et al.*, 2011) [48]. However, there is a lack in the number of studies that investigated the role of TDM in VPA treatment among children. Moreover, there was no study that reported the role of TDM in reducing the toxicity associated with VPA among epileptic children.

7. Objectives of the study

Investigate the effects of TDM on epileptic children leading to pro inflammatory changes and development of liver injury associated with chronic valproic acid treatment in epileptic patient.

8. Hypothesis

Tdm will make a significant different change on valproic acid related toxicity

9. Subjects and methods

This study was a Cohort study that was conducted on 126 epileptic children at the children hospital in Taif at least after one month after using TDM. The study included children who have been prescribed for VPA mono-therapy with an age range of 0-12 years old, whereas those more than 12 years old or patients who were on a combination therapy regimen were excluded.

The included children were divided into two groups; the control group included 58 patients with epilepsy and treated with VPA without TDM, and the exposure group included 68 epileptic patients treated with VPA with TDM.

They included children who have been prescribed for VPA mono-therapy were compared for liver enzymes (ALT, AST), bilirubin (direct and total), and kidney function test (SCR).

10. Statistical analysis

Statistical analysis was performed using SPSS software version 21. Simple descriptive was done for the presentation of the collected data; all values were expressed as mean and standard deviation. Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Fishers's test as a post hoc test for comparison between groups. P-value of≤0.05 is considered significant.

11. Results

In the current study, a total of 126 individuals were included in the study; 68 were involved in the TDM group, whereas 58 participants were included in the Non-TDM group. The mean ± SD of TDM was 64.3±34.3, and there were only 12 (17.6%) recorded with more than 100 uq/mL. There was a significant difference between the two groups regarding the mean age (P=0.014) and the age groups (P=0.014), whereas there was no significance regarding gender distribution (P=0.4). Also, there was no significant difference between the two groups regarding the mean duration of usage (P=0.09), but there was a significant difference regarding the groups of the duration of usage (P=0.039), table1.

Table 1: Characteristics Comparison between both groups (exposure and control group) (Retrospective Cohort study)

	TDM group (n=68)	Non-TDM group (n=58)	P value
TDM(50-100)uq/ml			
Range	6.3 - 143.3		
Mean ± SD	64.3 ± 34.3		
Median (IQR)	55.5 (41.6 - 84.5)		
TDM			
< 50	29 (42.6)		
50-100	27 (39.7)		
> 100	12 (17.6)		
Age (years)			
Range	2.8 - 11.8	2.3 - 12	
Mean ± SD	8.4 ± 2.5	7.2 ± 2.7	
Median (IQR)	9.2 (6.5 - 10.4)	7.1 (4.7 - 9.4)	**0.014@**
Age (years)			

< 6	14 (20.6)	18 (31)	**0.014***
6-9	19 (27.9)	25 (43.1)	
> 9	35 (51.5)	15 (25.9)	
GENDER			
Male	46 (67.6)	43 (74.1)	0.425*
Female	22 (32.4)	15 (25.9)	
DURATION OF USED			
Range	1 - 10	1 - 11	
Mean ± SD	6.2 ± 2.5	5.5 ± 2.4	
Median (IQR)	6.5 (4 - 8)	5 (4 - 7)	0.096@
DURATION OF USED			
1-5	25 (36.8)	32 (55.2)	**0.039***
> 5	43 (63.2)	26 (44.8)	

*Chi-square test, @Mann Whitney test

The comparison between the two groups regarding the laboratory parameters measured is shown in table2. There were significant differences between the two groups regarding the mean level of AST (P=0.0001), ALT (P=0.048), and total bilirubin (P=0.0001), whereas there were no significant differences regarding direct bilirubin (P=0.5), and SCR (P=0.2).

Table 2: AST, ALT, DIRECT BILIRUBIN, TOTAL BILIRUBIN, and SCR Comparison between both groups (exposure and control group)

Variables	TDM group (n=68)	Non-TDM group (n=58)	P value
AST(0-41)U/L			
Range	12 - 43	18.6 - 52	
Mean ± SD	28.2 ± 7.2	34.2 ± 10	
Median (IQR)	29 (22.9 - 33.7)	33.9 (25.2 - 42.9)	**0.000***
ALT(0-41)U/L			
Range	3.8 - 33.5	7 - 44	
Mean ± SD	16 ± 8	19.6 ± 9.8	
Median (IQR)	15.9 (10.1 - 20.9)	18.9 (11.4 - 25)	**0.048 @**
DIRECT BILIRUBIN(0-5.1)umol/L			
Range	0.4 - 5	0.3 - 7	0.561
Mean ± SD	1.9 ± 1	2.2 ± 1.6	@
Median (IQR)	1.9 (1.1 - 2.2)	2.1 (0.9 - 2.7)	
TOTAL BILIRUBIN(0-21)umol/L			
Range	1.5 - 12.5	2 - 15	
Mean ± SD	5.9 ± 2.7	7.7 ± 2.7	
Median (IQR)	5.9 (3.6 - 6.8)	7.7 (5.7 - 10.2)	**0.000***
SCR(35-53)umol/L			
Range	10 - 51	10 - 74	0.289 @
Mean ± SD	29.7 ± 9.8	28.5 ± 11	
Median (IQR)	30 (23 - 36)	26 (22 - 33)	

*t-test, @Mann Whitney test

The assessment of elevated and non-elevated parameters between the two groups is shown in table3. A significant elevation was observed regarding AST (P=0.0001), ALT (P=0.042), and direct bilirubin (P=0.042).

Table 3: Comparison between the two groups regarding the elevation of parameters

Variables	TDM group (n=68)	Non-TDM group (n=58)	P value*
AST			
Elevated	1 (1.5)	18 (31)	**0.000**
Not elevated	67 (98.5)	40 (69)	
ALT			
Elevated	0 (0)	4 (6.9)	**0.042**
Not elevated	68 (100)	54 (93.1)	
DIRECT BILIRUBIN			
Elevated	0 (0)	4 (6.9)	**0.042**
Not elevated	68 (100)	54 (93.1)	
TOTAL BILIRUBIN	68 (100)	58 (100)	….
Not elevated			
SCR			
< 35	46 (67.6)	44 (75.9)	0.275
35-53	22 (32.4)	13 (22.4)	
> 53	0 (0)	1 (1.7)	

*Chi-square test

The correlation between TDM levels with liver and kidney function showed a significant negative correlation with ALT level (r=-0.25, P=0.03) and a significant positive correlation between SCR (r=0.4, P=0.0001), table4.

Table 4: Correlation between TDM level with liver & kidney functions

Variables	TDM	
	r	P
Age (years)	-0.037	0.765
Duration of Used	-0.018	0.887
AST(0-41)U/L	0.114	0.356
ALT(0-41)U/L	-0.256	0.035
Direct Bilirubin (0-5.1)umol/L	0.191	0.119
Total Bilirubin (0-21)umol/L	0.103	0.405
SCR(35-53) umol/L	0.414	0.000

The logistic regression model showed that TDM usage was a significant predictor of elevated AST (P=0.001), with odds of 0.033 (table5), whereas there were no significant predictors for elevated ALT (table6).

Table 5: Logistic regression model to explore predictors of elevated AST

Variables	P-value	OR	95% C.I.for OR		
TDM usage	**0.001**	0.033	0.004	-	0.270
Age (years)	0.750	0.957	0.728	-	1.257
Gender (Males VS Females)	0.144	0.405	0.120	-	1.362
DURATION OF USED	0.299	0.844	0.613	-	1.162

OR= odds ratio, **CI**= confidence interval

Table 6: Logistic regression model to explore predictors of elevated ALT

	P value	OR	95% C.I.for OR		
TDM usage	0.997	0.000	0.000	-	.
Age (years)	0.654	0.874	0.484	-	1.578
Gender (Males VS Females)	0.084	0.122	0.011	-	1.326
Duration of Used	0.627	0.845	0.428	-	1.667

OR= odds ratio, CI= confidence interval

12. Discussion

Epileptic attacks of convulsion can vary potentially between patients. An epileptic seizure is a condition of manifestations attributed to excessive, irregular, and synchronous neural activation in the brain (Mac *et al.* 2007). Some last for seconds and others may last for a longer time of fewer than five minutes. Also, they can affect one arm or one leg, while others can affect the whole body (Huff & Fountain, 2011). An epileptic seizure may cause physical harm, especially if the seizure includes all of the body, making the whole body uncontrolled (Raspall-Chaure *et al.*, 2008).

Antiepileptic drugs (AEDs) are effective for the treatment of epileptic patients; however, treatment failure and poor adherence to medication are very common among patients experiencing side effects of AEDs, and almost 25% of patients experiencing adverse effects stop medication (Perucca *et al.*, 2009; UijL *et al.* 2009) [73, 89]. Valproic acid is an effective medication for the therapy of all epileptic types; it is the most commonly used AED in clinical practice (Espinosa *et al.* 2008) [26].

However, valproic acid has been linked with various adverse effects and toxicities. It was recommended to use valproic acid with caution in children patients with epilepsy (Maksoud *et al.* 2016) [60, 61]. The incidence of side effects is elevated in children patients compared to the adult population due to changes in pharmacokinetic parameters and pharmacodynamic reactions that occur with development throughout childhood (Lee 2019; Sven *et al.* 2016) [53]. Similar impacts can be induced by slower rates of liver metabolism in children and the higher rates of hepatic microsomal enzymes, especially among those with age between 2-4 years, due to the relatively bigger size of the liver in comparison to the total body weight, which needs higher maintenance dose compared to adults (Wanger *et al.* 2019). Therefore, we conducted this study to investigate the impact of TDM on liver injury and pro-inflammatory changes associated with chronic use of valproic acid treatment among epileptic children.

It was stated that few randomized studies demonstrated a positive effect of TDM on the clinical outcome of epilepsy (Johannessen Landmark *et al.*, 2020) [72]. However, this is the first study conducted on the impact of TDM among epileptic children regarding valproic acid-associated toxicity.

A previous study conducted on pediatric less than two years of age and managed by valproic acid showed that there was a slight elevation in the mean of AST after using valproic acid compared to before usage; however, this elevation was not significant. Also, there was an asymptomatic moderate increase in glutamate dehydrogenase noticed among 18% of patients. The study demonstrated that valproic acid is safe to be used among pediatric less than two years of age (Muthaffar *et al.* 2021) [67]. On the other hand, in a review included 268 individual case safety reports from 25 countries since 1977, it was found that a total of 156 fatalities were associated with hepatotoxicity due to valproic treatment; hepatotoxicity was reported to be a considerable problem for epileptic children treated with valproic acid (Star *et al.* 2014) [83]. Hepatotoxicity due to valproic acid may be attributed to the exposure of the liver to valproic acid degradation products, especially in young children (Chateauvieux *et al.*, 2010) [14].

In the current study, there were significant differences between the TDM group and the control group regarding liver function (ALT, AST) and total bilirubin. Patients in the non-TDM group significantly experienced higher levels of AST, ALT, and total bilirubin. Higher values of liver enzymes reflect toxicity effect and hepatocyte injury. Further investigation to identify the percentages of patients who experienced elevated levels of laboratory parameters showed that almost all patients in the TDM group did not experience an elevation in AST, ALT, or direct bilirubin, whereas significant proportions of patients in the non-TDM group experienced elevations in the previous parameters. On the other hand, there was no significant difference in serum creatinine (SCR), and none of both groups experienced a significant elevation in total bilirubin.

Therefore, TDM has a significant impact in reducing liver injury and maintaining good hepatic function among epileptic children treated with valproic acid.

The correlations between TDM with liver and kidney functions showed that TDM is positively associated with serum creatinine. Hence, an increase in TDM can be a predictor of elevation in serum creatinine which is an indication of unfavorable kidney function. Therefore, adjusting the dose of valproic acid by using TDM can be an indication of kidney function. Regarding liver function, there was a significant negative correlation between TDM and

ALT; however, logistic regression analysis showed that there was no association between TDM and elevated ALT, but there was a significant association between TDM and elevated AST with an odds of 0.03. This indicates that the increase in
TDM usage carries an odd of elevated AST estimated to be 0.033. Therefore adjusting the treatment dose through TDM can predict good hepatic function and avoid liver injury associated with treatment. On the other hand, any increase in TDM can be a predictor of elevation in AST, and therefore liver inflammation can be predicted.
A previous systematic review demonstrated that TDM might enhance clinical care if optimally implemented for AEDs (Al-Roubaie *et al.*, 2020) [3].
Previous studies (Shaikh *et al.* 2018; Mohsen *et al.* 2009) [81] focused on the efficacy and impact of TDM of valproic acid to detect the therapeutic range of valproic acid if it is optimum, below, or in the toxic range. However, the previous studies determined the proportion of patients administrating valproic acid at a toxic level but didn't report the usefulness of TDM in prediction and monitoring toxicity through blood parameters.

13. Conclusion

Valproic acid used for the management of epilepsy is associated with liver inflammation and toxicity among epileptic children. This toxicity can be observed through the elevation in liver enzymes (AST & ALT) and total bilirubin. However, the implementation of TDM for valproic acid resulted in improving liver function and reducing liver toxicity by adjusting the dose of valproic acid. Moreover, TDM could predict the elevation in AST level and, in turn, predict liver inflammation among epileptic children using valproic acid. TDM is also can be used to monitor renal function and correct renal injury by adjusting the dose.

14. Strength, weakness, limitations of the study, and recommendations

This study focused on the effect of TDM on epileptic children regardless of adult and included the diversity of the samples, which are considered as strong points of the study. And the first study reporting the impact of TDM in reducing and predicting liver injury caused by valproic acid for epileptic children as there was no previous study conducted on this subject On the other hand, the weak points of the study included small sample size, and only one center in Taif city was available for data collection.
The limitation of the study is that the study included a small sample size also there is no protocol to using the TDM,. studies are recommended to investigate the impact of TDM on different toxicities caused by valproic acid. Also, a larger sample size is recommended to be involved in further studies.

15. References

1. Al-Rajeh, Abo Melha AMS. The pattern and type of seizure disorders among a selected group of Saudi children. Saudi Medical Journal. 1987; 8:583-591.
2. Al Rajeh S, Awada A, Bademosi O, Ogunniyi A. The prevalence of epilepsy and other seizure disorders in an Arab population: A community-based study. Seizure. 2001; 10(6):410-414.
3. Al-Roubaie Z, Guadagno E, Ramanakumar AV, Khan AQ, Myers KA. Clinical utility of therapeutic drug monitoring of antiepileptic drugs: Systematic review. Neurology: Clinical Practice. 2020; 10(4):344-355.
4. Alaqeel A, Sabbagh AJ. Epilepsy; what do Saudi's living in Riyadh know?. Seizure. 2013; 22(3):205-209.
5. Alonazi NA, Alnemri A, El Melegy E, Mohamed N, Talaat I, Hosny A, *et al*. Clinical characteristics and aetiology of early childhood epilepsy: a single centre experience in Saudi Arabia. Sudan J Paediatr. 2018; 18(1):57-62.
6. Alsharif MM, El-Fetoh NMA, Ali GY, Alanazi KF, Alanazi AN, FalahAlanazi O, *et al*. Epilepsy as a health problem among school children in Turaif, Northern Saudi Arabia, 2017. Electronic physician. 2017; 9(8):5036.
7. Annegers JF. Epidemiology and genetics of epilepsy. Neurol Clin; 12: 15-29. Batalden PB, Van Dyne BJ, Cloyd J.(1979). Pancreatitis associated with valproic acid therapy. Pediatrics. 1994; 64: 520-2.
8. Birbeck GL. Epilepsy care in developing countries: part I of II. Epilepsy currents. 2010; 10(4):75-79.
9. Birkett DJ. Pharmacokinetics made easy: therapeutic drug monitoring. Aust Prescr. 1997; 20:9-11.
10. Biton V, Mirza W, Montouris G, Vuong A. Weight change associated with valproate and lamotrigine monotherapy in patients with epilepsy. Neurology. 2001; 56:172-7.
11. Bombardieri R, Pinci M, Moavero R, Cerminara C, Curatolo P. Early control of seizures improves long-term outcome in children with tuberous sclerosis complex. Eur J Paediatr Neurol. 2010; 14:146-149.
12. Bryant AE, Dreifuss FE. Valproic acid hepatic fatalities. III. U.S. experience since 1986. Neurology. 1996; 46(2):465-469.
13. Canpolat M, Kumandas S, Poyrazoglu HG, Gumus H, Elmali F, Per H. Prevalence and risk factors of epilepsy among school children in Kayseri City Center, an urban area in Central Anatolia, Turkey. Seizure. 2014; 23(9):708-716.
14. Chateauvieux S, Morceau F, Dicato M, Diederich M. Molecular and therapeutic potential and toxicity of valproic acid. Journal of Biomedicine and Biotechnology, 2010.
15. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30- year longitudinal cohort study. JAMA neurology. 2018; 75(3):279-286.
16. Christianson AL, Zwane ME, Manga P, Rosen E, Venter A, Kromberg JG. Epilepsy in rural South Africa childrenprevalence associated disability and management. S Afr Med J. 2000; 90:262-6.
17. Claassen J, Riviello JJ, Silbergleit R. Emergency Neurological Life Support: Status Epilepticus. Neurocrit Care. 2015; 23(2):S136-42.
18. Corman CL, Leung NM, Guberman AH. Weight gain in epileptic patients during treatment with valproic acid: a retrospective study. Can J Neurol Sci. 1997; 24:240-4.
19. Davis R, Peters DH, McTavish D. Valproic acid. A reappraisal of its pharmacological properties and clinical efficacy in epilepsy. Drugs. 1994; 47(2):332-372.
20. Develioglu H, Özgören Ö, Nalbantoglu M, Eren K, Göze F. Histo- pathological evaluation of drug allergy observed with gingival overgrowth induced by phenytoin: A case report. Balkan Journal of Stomatology. 2008; 12(3):166-169.

21. Dreifuss FE, Santilli N, Langer DH, Sweeney KP, Moline KA, Menander KB. Valproic acid hepatic fatalities: a retrospective review. Neurology. 1987; 37(3):379-379.
22. Eilers R. Therapeutic drug monitoring for the treatment of psychiatric disorders. Clinical use and cost effectiveness. Clin Pharmacokinet. 1995; 29:442-450.
23. Elger CE, Hoppe C. Diagnostic challenges in epilepsy: seizure under- reporting and seizure detection. The Lancet Neurology. 2018; 17(3):279-288.
24. El-Hazmi MAF, Warsy AS. Genetic disorders among Arab populations. Saudi Med J. 1996; 17:108-123.
25. Esfahani PN, Nasiri J, Badihian S, Yaghini O. Short-term side effects of low dose valproate monotherapy in epileptic children: a prospective study. Iranian Journal of Child Neurology. 2019; 13(2):37.
26. Espinosa PS, Salazar JC, Yu L, Baumann RJ. Lack of valproic acid-associated weight gain in prepubertal children. Pediatr Neurol. 2008; 39:177-80.
27. Evans WE, Schentag JJ, Jasko WJ. Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring. 3rd ed. Lippincott Williams & Wilkins, 1992.
28. Farghaly WM, Abd Elhamed MA, Hassan EM, Soliman WT, Yhia MA, Hamdy NA. Prevalence of childhood and adolescence epilepsy in Upper Egypt (desert areas). The Egyptian journal of neurology, psychiatry and neurosurgery. 2018; 54(1):1-7.
29. Fattore C, Messina S, Battino D, Croci D, Mamoli D, Perucca E. The influence of old age and enzyme inducing comedication on the pharmacokinetics of valproic acid at steady-state: A case-matched evaluation based on therapeutic drug monitoring data. Epilepsy Res. 2006; 70:153-160.
30. Gerstner T, Bell N, König S. Oral valproic acid for epilepsy-long-term experience in therapy and side effects. Expert opinion on pharmacotherapy. 2008; 9(2):285-292.
31. Gerstner T, Teich M, Bell N, Longin E, Dempfle CE, Brand J, *et al*. Valproate-associated coagulopathies are frequent and variable in children. Epilepsia. 2006; 47(7):1136-1143.
32. Giussani G, Cricelli C, Mazzoleni F, Cricelli I, Pasqua A, Pecchioli S, *et al*. Prevalence and incidence of epilepsy in Italy based on a nationwide database. Neuroepidemiology. 2014; 43:228-232.
33. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kälviäinen R, *et al*. and ILAE Subcommission on AED Guidelines. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2013; 54(3):551-563.
34. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kälviäinen R, *et al*. Guidelines, I.S.A. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2013; 54(3):551-563.
35. Guerrini R. Valproate as a mainstay of therapy for pediatric epilepsy. Paediatr. Drugs. 2006; 8(2):113-129.
36. Guo CY, Ronen GM, Atkinson SA. Long-term valproate and lamotrigine treatment may be a marker for reduced growth and bone mass in children with epilepsy. Epilepsia. 2001; 42:1141-7.
37. Hamdy NA, Alamgir MJ, El Gamri EM, Khedr MH, Fazili S. Profile of epilepsy in a regional hospital in Al qassim, Saudi Arabia. International journal of health sciences. 2014; 8(3):247.
38. Horaib W, Alshamsi R, Zabeeri N, Al-Baradie RS, Wahab MMA. Quality of Life and the Perceived Impact of Epilepsy in Children and Adolescents in the Eastern Province of the Kingdom of Saudi Arabia. Cureus, 2021, 13(12).
39. Houben ML, Wilting I, Stroink H, Van Dijken PJ. Pancreatitis, complicated by a pancreatic pseudocyst associated with the use of valproic acid. Eur J Paediatr Neurol. 2005; 9:77-80
40. Huff JS, Fountain NB. Pathophysiology and definitions of seizures and status epilepticus. Emerg. Med. Clin. North Am. 2011; 29(1):1-13.
41. Huseyinoglu N, Ozben S, Arhan E, Palanci Y, Gunes N. Prevalence and risk factors of epilepsy among school children in eastern Turkey. Pediatr Neurol. 2012; 47(1):13-8. Indrayati L, Nur FT, Soebagyo B. Platelet counts in epileptic children receiving valproic acid. Paediatrica Indonesiana. 2020; 60(1):13-7.
42. Jobst BC, Siegel AM, Thadani VM, Roberts DW, Rhodes HC, Williamson PD. Intractable seizures of frontal lobe origin: clinical characteristics, localizing signs, and results of surgery. Epilepsia. 2000; 41(9):1139-1152.
43. Johannessen Landmark C, Johannessen SI, Patsalos PN. Therapeutic drug monitoring of antiepileptic drugs: current status and future prospects. Expert Opinion on Drug Metabolism & Toxicology. 2020; 16(3):227-238.
44. Kang JS, Lee MH. Overview of therapeutic drug monitoring. The Korean journal of internal medicine. 2009; 24(1):1.
45. Kerr C, Nixon A, Angalakuditi M. The impact of epilepsy on children and adult patients' lives: development of a conceptual model from qualitative literature. Seizure. 2011; 20(10):764-774.
46. Koenig SA, Buesing D, Longin E, Oehring R, Häussermann P, Kluger G, *et al*. Valproic acid– induced Hepatopathy: nine new fatalities in Germany from 1994 to 2003. Epilepsia. 2006; 47(12):2027-2031.
47. Krasowski MD. Therapeutic drug monitoring of the newer anti-epilepsy medications. Pharmaceuticals. 2010; 3(6):1909-1935.
48. Kumar SV, Radhika Y, Kumar GV. Therapeutic drug monitoring of valproic acid in pediatric epileptic patients. Int Bull Drug Res. 2011; 1:11-18.
49. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000; 342:314-319.
50. Landmark CJ, Johannessen SI, Tomson T. Dosing strategies for antiepileptic drugs: from a standard dose for all to individualised treatment by implementation of therapeutic drug monitoring. Epileptic Disorders. 2016; 18(4):367-383.
51. Lee GP. Neuropsychology of Epilepsy and Epilepsy Surgery. 1st edition . Oxford University Press, Oxford, UK, 2010.
52. https://global.oup.com/academic/product/neuropsychology-of-epilepsy-and-epilepsy- surgery-9780195372502?cc=in&lang=en&.
53. Lee J. Antiepileptic drugs in children: current concept. J Korean Neurosurg Soc. 2019; 62:296-301.
54. Longin E, Teich M, Koelfen W, Koenig SA. Topiramate

enhances the risk of valproate associated side effects in three children. Epilepsia. 2002; 43:451-4.
55. Löscher W. Basic pharmacology of valproate: a review after 35 years of clinical use for the treatment of epilepsy. CNS Drugs. 2002; 16(10):669-694.
56. Lv RJ, Wang Q, Cui T, Zhu F, Shao XQ. Status epilepticus-related etiology, incidence, and mortality: A meta-analysis. Epilepsy Res. 2017; 136:12-17.
57. Mac TL, Tran DS, Quet F, Odermatt P, Preux PM, Tan CT. Epidemiology, etiology, and clinical management of epilepsy in Asia: A systematic review. Lancet Neurol. 2007; 6:533-543.
58. Magazi DS, Nkohla S, Mmako MT. Epilepsy seizure types, classification and treatment. South African Family Practice. 2018; 60(4)22-27.
59. Maheshwari MC, Jeavons PM. Proceedings: The effect of sodium valproate (Epilim) on the EEG. Electroencephalogr. Clin. Neurophysiol. 1975; 39(4):429.
60. Maksoud HMA, El-Shazly SM, El Saied MH. Effect of antiepileptic drug (valproic acid) on children growth. Egyptian Pediatric Association Gazette. 2016; 64(2):69-73.
61. Maksoud HMA, El-Shazly SM, El Saied MH. Effect of antiepileptic drug (valproic acid) on children growth. Egyptian Pediatric Association Gazette. 2016; 64(2):69-73.
62. McLane HC, Berkowitz AL, Patenaude BN, McKenzie ED, Wolper E, Wahlster S, *et al*. Availability, accessibility, and affordability of neurodiagnostic tests in 37 countries. Neurology. 2015; 85(18):1614-1622.
63. Mehndiratta MM, Thomas SV, Baheti NN, Bansal AR, Bhoi S, Dubey D, *et al*. Valproic Acid: A Summary of Indian Epilepsy Society-Consensus Document. International Journal of Epilepsy. 2016; 3(01):028-032.
64. Mohamed THE, Alanazi AOZ, Alshammari TMF, Alshammari ANM, Alenezi OML, Alruwili WAO, Almatrafi SKF. Epilepsy in Saudi Arabia: Prevalence in Different Regions, Causes, Risk Factors, and Management: A Systematic Review. International Journal of Pharmaceutical and Phytopharmacological Research. 2020; 10(6):92-99.
65. Mohsen F, Amir Hooshang M, Naser Vahdati M, Mohammad Hassanzadeh K, Mahmood Reza A, Naghmeh M, *et al*. Therapeutic drug monitoring of valproic acid in patients with monotherapy at steady state, 2009.
66. Moseley B, Bateman L, Millichap JJ, Wirrell E, Panayiotopoulos CP. Autonomic epileptic seizures, autonomic effects of seizures, and SUDEP. Epilepsy & Behavior. 2013; 26(3):375-385.
67. Muthaffar OY, Almahmudi SM, Alrabghi MO, Mahfouz MMB, Alfawaz NS. Valproic acid for children below 2 years of age with epilepsy. Neurosciences Journal. 2021; 26(4):357-365.
68. Neubauer BA, Gross S, Hahn A. Epilepsy in childhood and adolescence. Dtsch Arztebl Int. 2008; 105(17):319-328.
69. Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Estimation of the burden of active and life-time epilepsy: A meta-analytic approach. Epilepsia. 2010; 51(5):883-90.
70. Noebels J, Avoli M, Rogawski M, Olsen R, Delgado-Escueta A. Jasper's Basic Mechanisms of the Epilepsies. Oxford University Press, 2012, 466-70.
71. Nunes VD, Sawyer L, Neilson J, Sarri G, Cross JH. Diagnosis and management of the epilepsies in adults and children: summary of updated NICE guidance. Bmj, 2012, 344.
72. Patsalos PN, Berry DJ, Bourgeois BF, Cloyd JC, Glauser TA, Johannessen SI, *et al*. Antiepileptic drugs-best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008; 49(7):1239-1276.
73. Perucca P, Carter J, Vahle V, Gilliam FG. Adverse antiepileptic drug effects: toward a clinically and neurobiologically relevant taxonomy. Neurology. 2009; 72(14):1223-9, 3.
74. Rabie FM, Al Asmari AH, Al-Barak SA, Al-Rashed FM, Mare N. Prevalence and Determinants of Epilepsy among School Children in Aseer Region- KSA. Journal of Education and Practice. 2016; 7(21):149-153.
75. Raspall-Chaure M, Neville BG, Scott RC. The medical management of the epilepsies in children: conceptual and practical considerations. Lancet Neurol. 2008; 7(1):57-69.
76. Reith DM, Andrews J, McLaughlin D. Valproic acid has temporal variability in urinary clearance of metabolites. Chronobiol Int. 2001; 18:123-129.
77. Romoli M, Mazzocchetti P, D'Alonzo R, Siliquini S, Rinaldi VE, Verrotti A, *et al*. Valproic acid and epilepsy: from molecular mechanisms to clinical evidences. Current neuropharmacology. 2019; 17(10):926-946.
78. Ropper AH, Adams RD, Victor M, Samuels MA. Ropper AH. Adams and Victor's principles of neurology. 9th ed. New York: McGraw-Hill Medical, 2009.
79. Rudzinski LA, J Jerry, JJ Shih. New drug classes for the treatment of partial onset epilepsy: Focus on perampanel. Therapeutic Clin. Risk Manag. 2013; 9:285-293. Saad, K. (2014). Childhood epilepsy: an update on diagnosis and management. American Journal of Neuroscience, 5(2), pp.36-51.
80. Scott RA, Lhatoo SD, Sander JW. The treatment of epilepsy in developing countries: where do we go from here? Bulletin of the World Health Organization. 2001; 79:344-51.
81. Shaikh AS, Liu H, Li Y, Cao L, Guo R. Therapeutic drug monitoring of valproic acid. Pakistan Journal of Pharmaceutical Sciences. 2018; 31(4 SI):1773-1777.
82. Sharma S, Gulati S, Kabra M, Kalra V, Vasisht S, Gupta YK. Blood ammonia levels in epileptic children on 2 dose ranges of valproic acid monotherapy: A cross-sectional study. Journal of Child Neurology. 2011; 26(1):109-112.
83. Star K, Edwards IR, Choonara I. Valproic acid and fatalities in children: a review of individual case safety reports in VigiBase. PLoS One. 2014; 9(10):p.e108970.
84. Stefan H, Theodore WH. eds. Epilepsy, Part I: Basic Principles and Diagnosis, 2012.
85. Stephani C, Koubeissi M. Hypercognitive seizures-Proposal of a new term for the phenomenon forced thinking in epilepsy. Epilepsy Research. 2017; 134:63-71.
86. Sven C, van Dijkman, Ricardo Alvarez-Jimenez, *et al*. Pharmacotherapy in pediatric epilepsy: from trial and error to rational drug and dose selection – a long way to go. Expert Opin Drug Metab Toxicol. 2016; 12:101143-1156.

87. Tomson T, Battino D, Perucca E. Valproic acid after five decades of use in epilepsy: time to reconsider the indications of a time-honoured drug. Lancet Neurol. 2016; 15:210-218.
88. Tamber MS, JM Mountz. Advances in the diagnosis and treatment of epilepsy. Seminars Nuclear Med. 2012; 42:371-386.
89. Uijl SG, Uiterwaal CS, Aldenkamp AP, Keizer K. Adjustment of treatment increases quality of life in patients with epilepsy: a randomized controlled pragmatic trial. Eur J Neurol. 2009; 16(11):1173-7.
90. Vignoli A, Oggioni G, De Maria G, Peron A, Savini MN, Zambrelli E, *et al*. Lennox–Gastaut syndrome in adulthood: Long-term clinical follow-up of 38 patients and analysis of their recorded seizures. Epilepsy & Behavior. 2017; 77:73-78.
91. Villarreal HJ, Wilder BJ, Willmore LJ, Bauman AW. Hammond EJ, Bruni J. Effect of valproic acid on spike and wave discharges in patients with absence seizures. Neurology. 1978; 28(9Pt 1):886-891.
92. Wagner JL, Mueller M, Kellermann T, *et al*. Vulnerabilities to antiepileptic drug (AED) side effects in youth with epilepsy. Epilepsy Behav. 2019; 97:22-8.
93. Wang Y, Hu W, Li Z. Influence of age and co-medication on the concentration and efficacy of valproic acid in Chinese epilepsy children. Pak J Pharm Sci. 2020; 33:537-542.