



## 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,

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

## Introduction:

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

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**) and contributes 1% of the disease's burden (**Rabie et al, 2016**). The prevalence of epilepsy is higher in growing countries compared to developed ones (**Ropper et al, 2009**); almost 90% of epileptic patients alive in low and middle-income countries (**Ngugi et al, 2010**). 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**). The etiology of epilepsy is not known among almost 60% of all cases (**Alsharif et al, 2017**).

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

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**). 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**). 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**). The clinical efficacy of epilepsy treatment is commonly determined by a remarkable reduction in seizure frequency or seizure freedom (**Kerr et al, 2011**). 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**).

it has been reported 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**).

Valproate was presented in clinical practice 50 years ago, and its efficacy and acceptability profiles have been reported (**Romoli et al, 2019**). It is the first choice of drug nowadays for the treatment of several epileptic and non-epileptic diseases. The scientific name of Valproic acid (VPA) is N-dipropylacetic acid (**Romoli et al, 2019**). 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**).

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**).

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**). 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**). 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**).

## Literature review

### 1. 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**). The primary cause of epilepsy is unknown in more than one-half of cases (**Mohamed et al, 2020**), 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**).

Epilepsy is the most common neurological and non-infectious disease in the world (**Mohamed et al, 2020**), and its incidence is potentially greater in developing nations compared with developed nations (**Ropper et al, 2009**). Epilepsy is the most faced condition in pediatric neurology clinics, especially in developing countries (**Noebels et al, 2012**). This is due to poorer public hygiene, poorer perinatal care and standards of nutrition, greater risk of cerebral infection, and brain injury (**Saad, 2014**). It was estimated that childhood epilepsy is approximately 0.5% (**Giussani et al, 2014**). 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 & AlRajeh, 1987**).

In the developed world, the average epilepsy prevalence among children is around 50/100000 children annually (**Neubauer et al, 2008**). 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**).

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**).

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**). 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**). 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**).

## **2.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**).

### **2.1Motor 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**).

### **2.1.1 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**). 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 apnea 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**).

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**). 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**). 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**).

### **2.1.2 Myoclonic seizure:**

This type involves brief jerky movements of the muscle with preserved consciousness (**Magazi et al, 2018**). 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**). 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**). This type of seizure tended to occur near the onset of sleeping and upon awakening from sleep (**Saad, 2014**).

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**). 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**).

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

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**).

### **2.1.3 Clonic seizure:**

This type of seizures is typically observed among neonates and young children and it is characterized by repetitive rhythmic clonic jerks of 1-2 Hz with short post- ictal phase and impairment of consciousness (**Saad, 2014**). 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**). 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**).

#### **2.1.4 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). This type involves loss of consciousness, sphincter control and post ictal confusion beside experiencing muscle stiffness and jerks (Magazi et al, 2018). 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).

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). One study from Saudi Arabia reported that 76.2% of 341 epileptic patients had generalized tonic clonic seizures (Hamdy et al, 2014).

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). **2.1.5 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). 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).

#### **2.1.6 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).

#### **2.1.7 Hyperkinetic seizure:**

This type is characterized by an agitated movement of a body part similar to pedaling of the feet (Magazi et al, 2018).

#### **2.1.8 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).

#### **2.2 Non-Motor seizures:**

This category involves five types of seizures; absences, cognitive, emotional, sensory, autonomic, and behavioral arrest (Magazi et al, 2018).

##### **2.2.1 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). They typically occur in childhood or adolescent periods and have a generally good prognosis (Magazi et al, 2018).

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**).

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. Hyperventilation 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**).

### **2.2.2Cognitive 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**). This type of seizures often originates in the temporal lobe including the limbic structures (**Magazi et al, 2018**).

### **2.2.3Sensory 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**). Seizures can be triggered by taking hot shower, reading, and listening to the voice of a particular radio presenters (**Stefan & Theodore, 2012**).

### **2. 2.4Autonomic 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**).

## **3. Challenges of diagnosing epilepsy:**

Under reporting of seizures 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 seizures are atypical (**Magazi et al, 2018**).

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**). 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**).

## **4. 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**). Epilepsy requires long-term AED therapy (**Maksoud et al, 2016**).

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**). 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**).

#### **4.1 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**). 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**). 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**). 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**). VPA is associated with adverse effects, including weight gain, headache, fatigue, drowsiness, tremor, and nausea (**Star et al, 2014; Esfahani et al, 2019**), 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**). These complications may be associated with other factors such as dose and age (**Esfahani et al, 2019**).

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 dysfunction, hypo-fibrinogenemia, factor XIII deficiency, and vitamin K-dependent factors insufficiency (**Gerstner et al, 2006**). 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**).

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**).

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**).

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**). Hepatotoxicity usually appears within the first six months of VPA treatment initiation (**Romoli et al, 2019**). The clinical features of hepatotoxicity include somnolence, anorexia, apathy, vomiting, seizure worsening, and jaundice (**Romoli et al, 2019**). 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**).

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; Wangeet al, 2020**).

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**). 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**).

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**). 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**).

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**).

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**).

Hyperammonemia state also can occur with VPA treatment(**Romoli et al, 2019**). 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 2039mg/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**).

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**).

Weight gain is a well-known adverse effect that happens among 40% of children (**Corman et al, 1997**), and it is the major cause for discontinuation of VPA treatment (**Biton et al, 2001**). 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**).

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**).

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**).

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**).

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**).

### **5. 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**).

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**). 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**).

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**).

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**).

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**).

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 nonrandomized 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**).

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

Shaikh 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 subtherapeutic 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**). 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**).

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**). 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.

### **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 .

### **Hypothesis**

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

### **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).

### **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  $\leq 0.05$  is considered significant.

## 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  $\pm$  SD of TDM was  $64.3 \pm 34.3$ , 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.

**Table1: Characteristics Comparison between both groups (exposure and control group) (Retrospective Cohort study)**

	TDM group (n=68)	Non-TDM group (n=58)	P value
<b>TDM(50-100)uq/ml Range</b>	6.3 - 143.3		
Mean $\pm$ SD	$64.3 \pm 34.3$		
Median (IQR)	55.5 (41.6 - 84.5)		
<b>TDM</b>			
< 50	29 (42.6)		
50-100	27 (39.7)		
> 100	12 (17.6)		
<b>Age (years)</b>			
Range	2.8 - 11.8	2.3 - 12	
Mean $\pm$ SD	$8.4 \pm 2.5$	$7.2 \pm 2.7$	
Median (IQR)	9.2 (6.5 - 10.4)	7.1 (4.7 - 9.4)	<b>0.014@</b>
<b>Age (years)</b>			
< 6	14 (20.6)	18 (31)	<b>0.014*</b>
6-9	19 (27.9)	25 (43.1)	
> 9	35 (51.5)	15 (25.9)	
<b>GENDER</b>			
Male	46 (67.6)	43 (74.1)	0.425*
Female	22 (32.4)	15 (25.9)	
<b>DURATION OF USED</b>			
Range	1 - 10	1 - 11	
Mean $\pm$ SD Median (IQR)	$6.2 \pm 2.5$ 6.5 (4 - 8)	$5.5 \pm 2.4$ 5 (4 - 7)	0.096@
<b>DURATION OF USED</b>			
1-5	25 (36.8)	32 (55.2)	<b>0.039*</b>
> 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 ( $P=0.2$ ).

**Table2: 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
<b>AST(0-41)U/L Range</b>	12 - 43	18.6 - 52	
Mean $\pm$ SD Median (IQR)	28.2 $\pm$ 7.2 29 (22.9 - 33.7)	34.2 $\pm$ 10 33.9 (25.2 - 42.9)	<b>0.000*</b>
<b>ALT(0-41)U/L Range</b>	3.8 - 33.5	7 - 44	
Mean $\pm$ SD Median (IQR)	16 $\pm$ 8 15.9 (10.1 - 20.9)	19.6 $\pm$ 9.8 18.9 (11.4 - 25)	<b>0.048 @</b>
<b>DIRECT BILIRUBIN(0-5.1)umol/L Range</b>			
Mean $\pm$ SD Median (IQR)	0.4 - 5 1.9 $\pm$ 1 1.9 (1.1 - 2.2)	0.3 - 7 2.2 $\pm$ 1.6 2.1 (0.9 - 2.7)	0.561 @
<b>TOTAL BILIRUBIN(0-21)umol/L Range</b>	1.5 - 12.5	2 - 15	
Mean $\pm$ SD Median (IQR)	5.9 $\pm$ 2.7 5.9 (3.6 - 6.8)	7.7 $\pm$ 2.7 7.7 (5.7 - 10.2)	<b>0.000*</b>
<b>SCR(35-53)umol/L Range</b>	10 - 51	10 - 74	
Mean $\pm$ SD Median (IQR)	29.7 $\pm$ 9.8 30 (23 - 36)	28.5 $\pm$ 11 26 (22 - 33)	0.289 @

\*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).

**Table3: Comparison between the two groups regarding the elevation of parameters**

Variables	TDM group (n=68)	Non-TDM group (n=58)	P value*
<b>AST</b>			
Elevated	1 (1.5)	18 (31)	<b>0.000</b>
Not elevated	67 (98.5)	40 (69)	
<b>ALT</b>			
Elevated	0 (0)	4 (6.9)	<b>0.042</b>
Not elevated	68 (100)	54 (93.1)	
<b>DIRECT BILIRUBIN</b>			
Elevated	0 (0)	4 (6.9)	<b>0.042</b>
Not elevated	68 (100)	54 (93.1)	
<b>TOTAL BILIRUBIN</b>			
Not elevated	68 (100)	58 (100)	....
<b>SCR</b>			
< 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.

**Table4: 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	<b>-0.256</b>	<b>0.035</b>
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	<b>0.414</b>	<b>0.000</b>

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).

**Table5: Logistic regression model to explore predictors of elevated AST**

Variables	P-value	OR	95% C.I.for OR
TDM usage	<b>0.001</b>	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

**Table6: 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

## 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**). 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**).

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**). 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**). 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**). 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**). 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**). 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**).

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 nonTDM 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).

Previous studies (Shaikh et al 2018; Mohsen et al 2009) 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.

### 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.

### 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.

**Place:** Taif

**Date:** April 2022

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