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Research Article

Effects of Valproic Acid on Pregnancy in Epilepsy Patients

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Abstract

Valproic acid has long proven to be an effective drug for treating epilepsy and has been prescribed to pregnant women with epilepsy ever since. There are only few prospective studies regarding this drug during pregnancy, however several cohort studies have shown that women taking it during the first trimester have an increased risk of congenital disorders such as spina bifida, craniosynostosis, cleft palate, hypospadias, and more. Valproic acid also has a postnatal developmental disorder effect such as ADHD and ASD in children who were exposed to it before birth. Concerns about valproic acid and its teratogenic risks has led many women to discontinue their antiepileptic medication either before pregnancy or early in their pregnancy Even though it is highly recommended to minimize or even discontinue valproic acid use in pregnancy, but in some cases, the risks of discontinuing this drug may outweigh the benefits. When valproic acid was discontinued in the first trimester (the most teratogenic period) it was associated with a significantly higher incidence of generalized tonic-clonic seizures than when it was continued (33% *vs* 16%). Furthermore, if valproic acid is substituted for another antiepileptic drug, seizure incidence could increase by 29%. Using valproic acid during pregnancy for epilepsy patients is a growing problem where patients and doctors will be faced with a situation where they must consider in detail the benefits and risks of using this drug.

Keywords: Valproic acid; Epilepsy; Pregnancy

Introduction

Since its anticonvulsant qualities were discovered more than 5 decades ago, valproic acid has been proven to be a successful treatment for epilepsy [1]. The Food and Drug Administration (FDA) authorized valproic acid in 1978 as a monotherapy and as an additional therapy for various types of seizures which can also be used to treat bipolar disorder and prevent migraines [2]. Valproic acid's effectiveness in treating epilepsy has been extensively studied in various observational and RCT (Randomized Controlled Trials) studies which stated that because of its broad-spectrum action against practically all types of seizures, valproic acid is more superior and preferable to other antiepileptic medications [3,4]. Despite the fact that it is not the sole anti-epileptic medication that is presently most frequently administered, valproic acid still remains one of the most effective medications. This medication is strongly recommended when other anticonvulsants are inadequate, and also as a first-line treatment for complex partial seizures. It is also used in emergency situations to control focal and generalized seizures [5].

Epilepsy is a neurological condition that is often found in pregnant women with a prevalence of 0.5%-1% [6]. In Indonesia, there is no definite data regarding the incidence of epilepsy in pregnancy. But in the United States, it is said that around 3-5 out of 1,000 births are delivered by women with epilepsy. Meanwhile, of all the pregnant women, it was found that between 0.3%-0.5% were women with epilepsy [7]. A study in the United Kingdom showed that out of all antiepileptic drugs that have been prescribed to pregnant women, about 25% are valproic acid [8]. Various studies stated that valproic acid does have a fairly high teratogenic risk. Over the past decade, new facts have emerged concerning the risks of congenital abnormalities and postnatal developmental problems in children exposed prenatally to valproic acid. These risks raise concerns about the efficacy of valproic acid as a first-line therapy for epilepsy in females of reproductive age. Despite being aware of its teratogenic risk, valproic acid was still prescribed to 20% of pregnant epileptic women between the year 1999 and 2004, according to data from EURAP (International Registry of Anti-Epileptic Drugs and Pregnancy) [9,10]. In 2018, the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency advised against using valproic acid during pregnancy unless the mother has a kind of epilepsy that is resistant to other anti-epileptic medications.

Women of reproductive age who are not involved in a program for preventing pregnancy should also not be given this medicine [11].

Concerns about valproic acid and its teratogenic risks has led many women to discontinue their antiepileptic medication either before pregnancy or early in their pregnancy. However, in some cases this is not recommended because it can greatly increase the chance of experiencing a seizure. Therefore, this review article will provide an overview of the potential risks and benefits of the use of valproic acid among pregnant or prospective pregnant women with epilepsy.

Pharmacology

Mechanism of action

In general, the mechanism action of valproic acid as a therapy for epilepsy can be explained in several ways, such as affecting the levels of GABA (Gamma-Aminobutyric Acid) in the Central Nervous System (CNS), inhibit histone deacetylase enzymes and blocking voltage-gated ion channels [2]. Gamma-Aminobutyric acid (GABA) is an important neurotransmitter that plays a role in specific brain areas associated with seizures. Valproic acid has an effect on the production of GABA, which causes an increase in the levels of this neurotransmitter in the brain which can prevent seizures. In addition, valproic acid is also considered to be able to enhance the effects of GABA that are already present in the receptor area. Various studies stated that the mechanism action of valproic acid mimics/resembles the action of GABA, thereby reducing the risk of seizures [12]. The Tricarboxylic Acid (TCA) cycle produces GABA from α-ketoglutarate, which is subsequently converted by GABA transaminase and succinic semialdehyde dehydrogenase into succinic semialdehyde and succinic acid, respectively. According to earlier research, valproic acid inhibits succinic semialdehyde dehydrogenase and GABA transaminase, preventing the breakdown of GABA and therefore raising its concentration [2]. There is further speculation that voltage-gated sodium and calcium channels are crucial for the role in the action of valproic acid. Valproic acid can reduce Ca2+ ion activity and prolong the recovery of voltage-gated Na+ channels. However, the role of valproic acid on K+ channel conductance is still controversial. Although the exact methods are not yet clearly established, observational studies suggest that these pathways in the brain are likely to impact the onset of some types of seizures, especially absence seizures [2,11].

These numerous mechanisms can provide an explanation for its extensive spectrum activity, its other indications besides for epilepsy, namely for migraines and mood disorders, as well as its potential use for new indications such as cancer therapy and prevention, which are currently being studied [13].

Pharmacokinetics

Valproic acid is well absorbed after oral administration, with a bioavailability of over 80%. Peak levels are reached within 2 hours (1 hour to 4 hours). Food can slow absorption and will decrease toxicity if the drug is administered after meals. Valproic acid has a pKa of 4.7 so it ionizes completely at physiological pH plasma. The drug also binds 90% to plasma proteins, but the amount of binding decreases when blood concentrations exceed 150 μg/ml. Because valproate is completely ionized and binding to plasma proteins, it is dispersed in extracellular water with a Vd (volume of distribution) of about 0.15 L/kg. Valproic acid is fully ionized and binds to plasma proteins, so it is dispersed in extracellular water with a Vd (volume of distribution) of approximately 0.15 L/kg. Valproic acid is mostly (95%) metabolized in the liver and less than 5% is excreted in its original form. Valproate clearance is considered very slow, with a half-life of around 9 hours-18 hours. Clearance of valproate is dose-dependent when at a completely excessive blood levels. About 20% of the drug is directly excreted as valproate conjugate. The remainder is converted into various compounds metabolized by beta and omega oxidants, which eventually be conjugated and excreted [14].

Valproic Acid Dosage and Toxicity

The starting daily dose of valproic acid is generally 15 mg/kg. At a weekly interval this starting dose may be increased by 5 mg/kg to 10 mg/kg, but still not to exceed 60 mg/kg which is its maximum daily dose. In some patients, doses of 25 mg/kg-30 mg/kg daily are sufficient, while others may require doses of 60 mg/kg or more. Valproate has a therapeutic concentration of 50 μg/ml to 100 μg/ml. Data from several efficacy studies indicate that drug administration should not be discontinued until peak morning levels are atleast 80 μg/mL. However, some patients require and tolerate peak levels above 100 μg/mL [14]. The most common side effects of valproic acid are gastrointestinal symptoms which includes anorexia, nausea, vomiting that occurs in about 16% of patients. Other CNS effects include sedation, ataxia, and tremors. These symptoms are rare and usually decrease as the dose is reduced. Rashes, alopecia, and appetite stimulation may also occur occasionally. Valproic acid has some effects on liver function, with up to 40% of patients having elevated plasma liver enzymes, which are often asymptomatic during the first few months of treatment [15]. This hepatotoxic effect is generally reversible when treatment is discontinued. However, this can get worse, so it is necessary to monitor liver function when using valproic acid. In addition, another rare idiosyncratic response can occur, namely thrombocytopenia [14].

Valproic Acid in Epilepsy

Valproic acid has been proven to be an effective therapy for generalized epilepsy, and is considered the first-line drug for nearly all epilepsy syndromes unless there are specific contraindications. In a one large study of adults and children with generalized or unclassified epilepsy, the efficacy and tolerability of valproic acid was significantly better than that of lamotrigine or topiramate [16]. Status epilepticus can also be treated with valproic acid and despite its lack of high-quality trial research, the evidence that is currently available implies that for patients with status epilep-

ticus who cannot be treated with benzodiazepines, valproic acid can be given as an effective and a safe treatment option [17].

Pregnancy in Epilepsy Patients

Pregnancy is related to physiological, endocrine and psychological changes that can lead to a decrease in the seizure threshold [18,19]. The concept of seizure threshold holds that everybody has a stability among excitatory and inhibitory forces within side the brain. A low seizure threshold makes epilepsy to develop easily and less harder for a person to elicit a seizure. The opposing outcomes of oestrogen (proconvulsant) and progesterone (anticonvulsant) on seizure threshold were proven in animal and human studies. Oestrogen has also been proven to decrease the seizure threshold [20]. The frequency of seizures in pregnancy can increase because of multiple reasons such as changes in oestrogen and progesterone levels, increased water and sodium retention, stress related with pregnancy, changes in the pharmacokinetics of anti-epileptic drugs and physiological factors such as sleep deprivation. One of the factors that can predict the amount of seizures that can happen during pregnancy, is the frequency of seizures that occurred 1 year before pregnancy [18].

Concentrations of antiepileptic drugs in plasma can vary due to physiological changes such as in the absorption process, hepatic clearance, increased renal clearance and plasma volume distribution and also induction of liver enzymes. In pregnancy, drug absorption can be impaired because of reduced gastric tone and motility. Changes in the activity of enzymes in the liver that play a role in drug metabolism, blood flow, and drug transporters can affect the hepatic clearance of antiepileptic drugs. This is very important because some antiepileptic drugs are metabolized by Nicotinamide Adenine Dinucleotide Phosphate (NADPH) cytochrome P450 reductase, Uridine Diphosphatase Glucose (UDP) glucuronosyltransferase, and then excreted *via* the kidneys [21]. The risk of death from pregnancy in a woman is ten times greater for those who have a history of epilepsy than for those who don't. Aside from that, it has been reported that as many as 12 out of 14 cases of maternal death that occurred from 2009 to 2012, were classified as a Sudden Unexpected Death in Epilepsy (SUDEP) with uncontrolled seizures being the main cause [6].

Therefore, out of consideration of their own health and that of their child, women who have a history of epilepsy are strongly advised to continue their treatment with antiepileptic drugs during their pregnancy. According to a study conducted by Schmidt and Schachter which stated that although about two-thirds of pregnant women with epilepsy do not have seizures during their pregnancy, the dosage of anti-epileptic drugs need to be adjusted as pregnancy goes on, particularly if seizures occur during the first 3 months of pregnancy [5].

DiscussionEffects of valproic acid in pregnancy

There are only few prospective studies on the effects of valproic acid during pregnancy, however many cohort studies have demonstrated a 7-fold increased risk of congenital malformations in women using this medication during the first trimester of pregnancy [22]. When compared to individuals who were not receiving antiepileptic medications, patients who received valproic acid as a monotherapy in the first trimester had a significantly higher risk of spina bifida, craniosynostosis, cleft palate, hypospadias, atrial septal defect, and polydactyly [23,24]. According to estimates, these risks affect 10%–11% of newborn from women with epilepsy, compared to just 2%-3% of the general population. The causes of these teratogenic reactions are not fully elucidated, but may include epigenetic alterations, such as inhibition of histone dehydrogenase with associates with alterations in gene expression, heightened oxidative stress, or inhibition of folate, which is necessary for DNA synthesis [25,26].

In addition to its teratogenic effects, valproic acid can cause various problems after birth. Some studies say that between 30% and 40% of children who has been exposed to valproic acid since the second and the third trimester of pregnancy can lead to cause alterations in cognitive functioning and behaviour, and also a higher chance of having neurological disorders, particularly ADHD and ASD [27]. According to research conducted in Denmark, the probability of ASD in children exposed to valproic acid is 3 times-5 times higher than in the general population. Cohen et al. also identified the chance of developing Attention Deficit Hyperactivity Disorder (ADHD) in 21% of children ages 6 years and above who had been exposed to prenatal valproic acid [28,29]. Furthermore, in a 2004 retrospective study, it was concluded that prenatal intake of valproic acid may have an impact on the intellectual development of children where these children had significantly lower verbal intelligence (IQ) scores than those exposed to carbamazepine, phenytoin, or those who were never expose to any antiepileptic drugs [30]. Several factors may contribute to the clinical effect for mothers and children expose to valproic acid, namely the frequency and duration of seizures, the need for additional drug treatments to control epilepsy, the use of drugs and alcohol, comorbidities, sociocultural factors, and also the stage of pregnancy the woman is in [5].

It is recommended to discontinue treatment with valproic acid during pregnancy, particularly during the initial trimester. Nevertheless, there are some potential risks associated with the discontinuation of this drug in patients with well controlled epilepsy [5]. The EURAP study showed that the discontinuation of therapy in the initial trimester (the most teratogenic trimester) was associated with significantly higher rates of generalized tonic-clonic seizure (33%) compared to the continuation of treatment (16%). It is even more concerning to note that the prevalence of seizures may be increased (29%) when valproic acid is switched to another anti-epileptic drug [31]. The prevention of major birth defects in the fetus can be achieved by administering folic acid supplements, but in the case of women with epilepsy, there is still not enough data to determine its effectiveness. However, giving folic acid is still recommended for all women of reproductive age with or

without epilepsy before conception and during pregnancy at a dose of 0.4 mg per day [32].

In users of valproic acid it is also recommended to check serum alpha-fetoprotein levels (at week 14-16 of pregnancy), ultrasound examination (at week 16-20 of pregnancy) and amniocentesis to check levels of alpha-fetoprotein and anticholinesterase in amniotic fluid [21]. If there are abnormalities in any of the examinations above, continuing the pregnancy or not has to be considered thoroughly. Use of the lowest possible daily dose divided into 3 doses to minimize fluctuations in serum valproic acid levels can also lower the risk of fetal harm. It has been observed that higher daily doses of 1000 mg or more, as well as combination with other therapy (polytherapy), are related to a greater risk of teratogenicity. Additionally, it has been observed that certain other antiepileptic drugs may enhance the teratogenicity of valproic acids. Therefore, if it is necessary to use valproic acid during pregnancy, the most effective dosage should be prescribed in 2 to 3 doses, and ideally as a monotherapy [25].

Conclusion

Using valproic acid in pregnant women with epilepsy is a growing problem. Valproic acid has the highest teratogenic risk compared to other antiepileptic drugs. Not only that, postnatal abnormalities in the form of cognitive and behavioural abnormalities can also be experienced by foetuses exposed to valproic acid. In summary, it is highly recommended to minimize or even discontinue valproic acid use in pregnancy, but in some cases, the risks of discontinuing this drug may outweigh the benefits. Therefore, patients and doctors will be faced with a situation where they must consider in detail the benefits and risks of using this drug.

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Conflict of Interest

Authors have no conflict of interest to declare.

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