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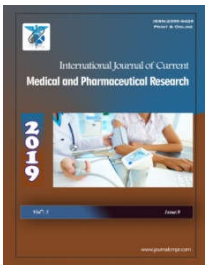

TERATOGENIC EFFECTS OF VALPROIC ACID AND STRAGIES FOR REDUCING RISK IN GIRLS AND WOMEN OF CHILD BEARING AGE

Pem Tamang

Department of Pharmacy Practice, Sri Venkateshwara College of Pharmacy, RVS Nagar, Chittoor, India

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ABSTRACT

Conventional studies with evidence regarding the teratogenic effects of valproate was established which demonstrated that valproic acid is more teratogenic than other antiepileptics. Prenatal exposure of valproic acid in the first trimester of pregnancy is associated with an increased risk of congenital abnormalities and autism spectrum disorder and childhood autism. Use of valproic acid should be avoided or should take minimum effective doses if women are intolerable to others antiepileptics. It is recommended that higher standards of prenatal counselling and prescribing pattern with regard of valproate use should be followed. Women should to understand the risk of valproate and the choice of effective contraceptive methods should be reassessed and folic acid supplementation should be initiated.

INTRODUCTION

Valproate is fatty acid indicated for the treatment of epilepsy, manic occurrence associated with bipolar disorder, and prophylaxis of migraine headaches. If we study in regard to its use in epilepsy, valproate in epilepsy acts by increasing Gama-Amino Butyric Acid levels by altering properties of sodium channels. The prevalence of epilepsy in adults is 5-10 per 1000, and is influenced by many factors, both genetic and environmental [14]. One risk factor for seizure activity is estrogen, hence pregnancy can increase the seizure rate [15].

US Food and Drug Administration (FDA) approved valproic acid in 1978 which was discovered in early 1960s as one of the potent antiepileptics, until 1980s when valproate was confirmed to be the most teratogenic drug [1]. Prescribing pattern for valproate remained same amongst women of child bearing age in United states notwithstanding with the fact of potential teratogenic risk [6].A European Union review recommended to avoid valproate exposure in pregnancy post examining the effectiveness of evidence of previous regulatory action, hence the we study the teratogenic effect of valproic acid and its relative measures to prevent risk and enhance the safetyamongst the women of reproductive potential in the light of European regulatory made in March 2018.

French National Agency for the Safety of Medicine and Health Products (ANSM) prosecuted prohibition on use of sodium valproate in pregnancy as a result of teratogenicity[10].

UK Royal College of Obstetricians and Gynecologists implemented guidelines in 2016 suggest to terminate the use of this drug in any woman of child-bearing potential considering previous NICE guideline[11]. In February 2018, the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency commended that valproate should not be used in pregnancy unless the patient is inefficient or intolerable to other anti-epileptic drugs, and also that the drug should not be prescribed for women of childbearing age who are not enrolled in a pregnancy prevention programme [12]. In April 2018, the UK Medicines and Healthcare Devices Regulatory Agency endorsed this recommendation [13].

Studies reveals significant risk of neurodevelopmental disorders (neural tube defects), congenital malformations (polydactyly, cleft palate, hypospadias, cardiac defects), low IQ,increase risk of autism, limb defects to fetus as a consequences of utero exposure to valproate in first trimester of gestation[2]. Research with compelling evidence states that teratogenicity to fetus with maternal exposure during first trimester with valproic acid is observed to be dose-dependent[7] and use of combination therapy is associated with increased risk of congenital abnormalities or when used as adjuvant with other antiepileptics [8]. Risk and benefits should be considered and assessed carefully prior prescribing, and ensure women of child bearing potential understands the risk of use during pregnancy and necessities for use of effective contraceptives throughout treatment.

Corresponding author:* **Pem Tamang
Department of Pharmacy Practice, Sri Venkateshwara College of Pharmacy, RVS Nagar, Chittoor, India

The estimated mean daily dose of antiepileptic was calculated by formula of total amount of antiepileptic drug filled 30days before pregnancy to birth divided by number of days within same interval. The defined daily dose drug assumed to be average maintenance dose per day is used for evaluating high or dose of antiepileptic drug[5]. Dose more than or equal to 1000mgs of valproate pose higher teratogenic risk (21.9%) than 2.5% of lower/divided doses and the risk rate elevate fourfold with antiepileptic polytherapy[3]. Valproate is associated with teratogenic risk of 6.3%compared with carbamazepine (2.4%), lamotrigine (2.7%) and lithium (0.1%) [4].

Congenital Malformation in New Born

High risk of serious congenital malformations with fetal exposure to valproic acid was discovered in 1981 with the report of first Spina Bifida[9]. Several studies confirmed increased in risk in utero exposure. Study by Janneke Jentink et. al combined data from previous cohort studies observed congenital abnormalities in offspring among women who had consumed valproate during first trimester, as cohort had limited capacity to detect rare and excessive risk of malformation in large population Case-control study was employed to assess association between valproate and malformations by applying European Surveillance of Congenital Anomalies (EUROCAT) antileptic study database derived from population based congenital anomaly registries. Information was obtained from hospital records. The reason for its teratogenicity is not fully understood but assumed to be epigenetic effects including inhibition of histone deacetylase, associated with gene expression [16], increase in fetal oxidative stress or inhibition of folate needed for DNA synthesis [17]. Frequency of maternal use of valproate was 2 per 1000.

Analyses of case in exposure to valproate compared to control without exposure during pregnancy resulted in association with increase risk of atrial septal defect 0.5%, cleft pallet 0.3%, hypospadias 0.7%, polydactyly 0.2%, craniosynostosis 0.1% and spina bifida 0.6%, as shown in table 1[26].

Table 1 Absolute risk of congenital malformation with sodium valproate (adapted from Jentink)

Condition	Odds ratio (median and range) in offspring of mothers who took valproate in pregnancy	Absolute risk
Spina bifida	12.7 (7.7-20.7)	0.6%
Atrial septal defect	2.5 (1.4-4.4)	0.5%
Cleft palate	5.2 (2.8-9.9)	0.3%
Hypospadias	4.8 (2.9-8.1)	0.7%
Polydactyly	2.2 (1.0-4.5)	0.2%
Craniosynostosis	6.8 (1.8-18.8)	0.1%

Risk of former five conditions was 2-7 times higher for exposed fetus and for later was 12-16 times more depending on control group. Additionally, researches demonstrated higher the dose of drug were associated with increased risk of abnormalities[18]. Polytherapy was traditionally considered to increase risk[19], however it is not a consistent framework. Vajda and colleague asseverated that fetal abnormalities of polytherapy depends on exposure to valproate than other antiepileptics[20]. Data from NAAPR suggested prevalence of fetal malformations was 9.1% for lamotrigine with valproate compared with lamotrigine monotherapy 1.9%, 15.4% for carbamazepine with valproate compared with carbamazepine monotherapy 2.9% [21].

Risk of Autism Spectrum Diorder and Childhood Autism

Autism is a serious behavioral disorder characterized by, increased repetitive or stereotypic activity, higher anxiety, and decreased level of social interaction. A study was conducted by Tomasz Schneider and Ryszard Przewtocki, which demonstrated similarities between behavioral patterns in valproate exposed rats and autistic patients. Experiment on female Wistar rats was carried out with single intraperitoneal injection of 600mg/kg sodium valproate on the 12.5 day of fertilization. The result showed the rats exposed to valproate exhibit long term and selective effects on postnatal behavior which was observed in autistic patients. Brain autopsy and imaging results manifested similarities in abnormalities of Valproate exposed rats and autistic patients. Results also indicates resemblance of alteration of behavioral pattern and disturbed behavior in valproate exposed rats and person with autism[23].

The autism spectrum disorders include Asperger syndrome, atypical autism, childhood autism and unspecified insidious developmental disorders with most severe being childhood autism, manifesting at least one of following symptoms related to1) stereotyped pattern of behavior, 2) impaired social interaction and 3) impaired communication before 3 years of life[22].

large population-based cohort study was conducted in Denmark from 1996 to 2006 by Jakob Christensen et.al to evaluate association between maternal use of valproate during pregnancy and the risk of autism spectrum disorder and childhood autism in the newborn, children of women who used valproate during pregnancy had a higher risk of autism spectrum disorder and childhood autism compared with children of women who did not use valproate. Their risks were also higher for children of women who previously used valproate but stopped before their pregnancy. The risk of autism spectrum disorder and childhood autism was increased in women who filled valproate prescription in first trimester than women who filled in later pregnancy. Higher risk was also established in women who used high dose (>750 mg/d) of valproate than women who used low does (<750mg/d) for autism spectrum disorder and childhood autism. The sex ratio (boys to girls) for valproate exposed children was higher than children not exposed[24].

As autism is a lifelong condition even a moderate risk may have major health implication its important to consider when prescribing valproate in pregnancy [24].

Valporate Pregnancy Prevention Programme

Standards were established which was to be followed prior prescribing Valproate from previous audits guided by NICE [24] as follows;

- There should be clinical evidence for women of child bearing age prior prescribing valproate.
- There should be subsequent discussion after review of women prescribed valproate.
- There should provision of effective contraception which must be discussed.
- General practitioner should be informed about the clinical discussion.
- Women exposed to valproate in pregnancy should be given periconceptional folic acid and followed up in a high-risk pregnancy.

- Yellow monitoring forms should be used for recording information delivered to patients and filed in their case notes.

Effective Contraceptive Methods

- In women or girls of childbearing age, pregnancy should be prohibited prior initiation of valproate or must use highly effective contraception. Various methods of contraception were initiated which includes, long acting reversible contraceptives (LARC), copper intrauterine device (Cu-IUD), levonorgestrel intrauterine system (LNG-IUS) and progestogenoly implant (IMP) sterilization which have failure rate of less than 1%.
- User dependent barrier methods such as condoms, cap, diaphragm, oral contraceptive pills (Combine or progesterone only), these methods are least effective since it incorporates user failure risk.
- For patients without capacity to make informed decision are advised on effective methods of contraception and risk advocated with the use of valproic acid to their offspring.
- Individual circumstances should be evaluated when selecting appropriate contraceptive method to ensure patient's engagement and compliance with selected method.

Prenatal Supplementation of Folic Acid Reduces Risk of Autism Spectrum Disorders

Numerous studies states that the prenatal consumption of 400 µg Folic Acid from 4 weeks before to 12 weeks after conception with history of neural tube defect and 800 µg with no history of neural tube defect is associated with reduced risk of autistic disorder in valproate exposed offspring [25].

CONCLUSION

Prenatal exposure of valproate was associated with a significant teratogenicity in offspring. Valproate is associate with high risk of teratogenesis compared with other types of antiepileptics drugs. Various strategies are established for prescribing valproate, further caution against the use of valproate among women of childbearing potential are taken.

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