OPEN ACCESS

Scholars International Journal of Anatomy and Physiology
Abbreviated Key Title: Sch Int J Anat Physiol
ISSN 2616-8618 (Print) | ISSN 2617-345X (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Review Article

Comparative Teratogenic Effects of Antiepileptic Drugs

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DOI: https://doi.org/10.36348/sijap.2024.v07i09.002 | **Received:** 07.10.2024 | **Accepted:** 12.11.2024 | **Published:** 21.11.2024

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Abstract

Epilepsy requires a constant medication during pregnancy. Maintaining, monitoring and a stability of pregnant women with epilepsy between restricting seizures and reducing fetal exposure to the antiepileptic drugs are essential. Major and minor malformations were presented in children subjected to the antiepileptic drugs during pregnancy. This review article aimed to highlight some of antiepileptic drugs as potential teratogen to understand the associated congenital malformation risks with these drugs, differences in hazards between several selection treatment are essential to safe both mother and fetus.

Keywords: Epilepsy, Antiepileptic Drugs, Congenital Malformations.

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INTRODUCTION

Epilepsy is one of the most disabling chronic neurological conditions. This disease is characterized by the recurrent seizures, loss of consciousness and the control of bowel function [1]. Antiseizure medications previously described as antiepileptic or anticonvulsant drugs. Antiepileptic drugs are used for prevention and control of the epileptic seizures. In addition, they are approved treatments in nonepileptic illness, including migraine, neuropathic pain, bipolar disorder, and the generalized anxiety disorder the most concerning problem in the epileptic pregnant women is the development of tonic-clonic seizures, which can be very dangerous to fetus such as intracranial hemorrhage, transient hemorrhage and heartbeat irregularities [2, 3]. It is essential to use these drugs for epileptic women during pregnancy because epileptic attack can cause harmful effects to both mother and fetus. Counselling is recommended concerning teratogenic risks when the drug is written for a woman of childbearing age and when considering pregnancy [4]. Pregnant epileptic women require a balance between controlling seizures and reducing fetal exposure to the potential antiepileptic teratogenic effects. Several reports suggested that the risk of adverse fetal effects varies in relation to the type of antiepileptic drugs (Figure 1) and for the daily dose. Crucially, major congenital malformations are principally correlated with the first trimester of gestation but impacts on cognitive and behavioral development could extend throughout pregnancy [5]. Careful selection of antiepileptic drugs can decrease the possible harmful effects; therefore, this article is mainly concerned with the teratogenic risks of antiepileptic drugs in pregnancy.

Valproic Acid

Valproic acid is principally used in the treatment of epilepsy due to the wide-ranging activity against general and partial seizure [6]. It is an anticonvulsant drug and is efficient as a mood stabilizer and against several types of epilepsy and it is used to increase the level of Gamma amino butyric acid in the brain. Gamma amino butyric acid is crucial inhibitor of seizures, and the reduction of GABA levels could potentiate seizures. Valproic acid is demonstrated as a human teratogen that causes birth defects [7]. And highly contraindicated when administered during the first trimester of pregnancy [8]. The prospective research in humans have reported that the prenatal exposure to valproic acid increases the risk of congenital malformations in a dose-dependent method [9]. The timing of exposure to valproic acid and the exposed concentration is a fundamental in influencing the type and extent of teratogenicity.

Teratogenesis, particularly by valproic acid has been reported as major congenital malformations and neurodevelopmental anomalies. Valproic acid has been revealed to cross the placenta and accumulate in the foetal circulation with higher concentration than that in

the maternal blood, causing teratogenicity. Major congenital malformations were reported such as neural tube defects as spina bifida, fused vertebrae, fused rib, cleft lip/palate, cardiac abnormalities, urinary tract defects or malformation of limbs.

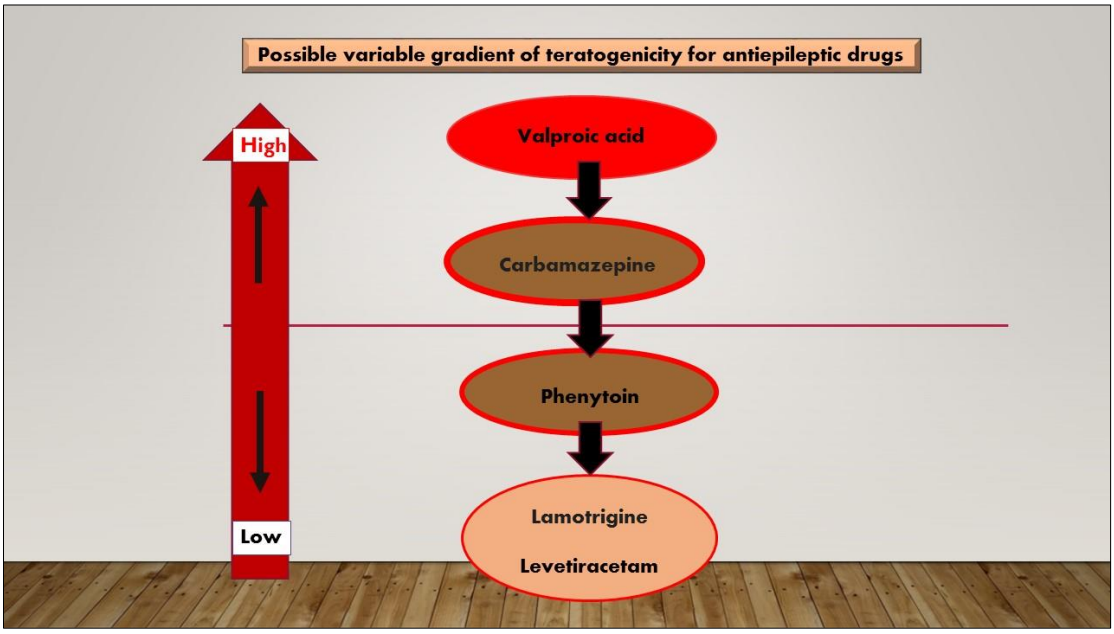

Figure1: Comparative teratogenic risks of antiepileptic drug

Neurodevelopmental anomalies mainly to children exposed to valproic acid *in utero* caused reduced cognitive function might have lower verbal IQ levels, reduced language and or learning development and probable autism [10]. Several animals research was demonstrated to mimic the special effects of the valproic acid on the human to explain the mechanism of its teratogenic action [11]. Previous studies suggested that Valproic acid produces its teratogenic effects due to induction of the oxidative stress, DNA damage and increased of apoptosis leading to imperfect histogenesis of the fetal tissues. It is demonstrated that valproic acid causes a pathological rise of apoptosis causing an imbalance between the cell proliferation and cell death, the final consequence of which is malformation [12]. Valproic acid effects are due to decrease the cell viability through enhancement of the oxidative stress with overproduction of the reactive oxygen species that leads to lysosomal and mitochondrial dysfunction [13].

Several studies in chicken embryos exposed to valproic acid showed embryonic malformations to the limbs and eyes through inhibition of angiogenesis, stimulation of oxidative stress, inhibition of histone deacetylase. In addition, some genes involved in tissue development such as reduction in Pax2 and Pax6, downregulation of superoxide dismutase and retinol binding protein 4 [14]. In rat, valproic acid administration to pups prenatally or early postnatally causes alterations in the number of neurons and synapses of the cerebellum [15, 16].

Carbamazepine

Carbamazepine is used as drug for epilepsy and bipolar disorder and counted as one of a human teratogen that leads to minor and major abnormalities in fetuses and infants such as developmental problems, neural tube defects, growth retardation and abnormal IQ. A decrease of fetal head circumference of offspring of epileptic pregnant women treated with carbamazepine were reported. Teratogenic effect of Carbamazepine use during pregnancy were reported in the mice such as growth retardation and neurodevelopmental toxicity [17]. Carbamazepine was administrated intraperitoneally to the pregnant albino rats during pregnancy and noticed that the maternal carbamazepine changes fetal neuroendocrine-cytokines axis and these developmental alteration were dose-dependent [18].

Phenytoin

Phenytoin is a well-recognized human/animal teratogen. Previous studies of prenatal exposure to phenytoin suggested a group of developmental abnormalities that was named “fetal hydantoin syndrome” This syndrome includes abnormal head and facial development, including microencephaly, short nose, low nasal bridge, cleft palate, epicanthal fold, wide mouth, low hairline, and abnormal ears [19]. Several research reported the mechanism of phenytoin toxicity is thought to act as a potential to cause embryonic bradycardia/arrhythmia and hypoxia-related damage during a limited developmental period via the oxidative stress. Embryonic hypoxia with vascular disorder and tissue necrosis resulting in-utero death or teratogenicity [20]. Significantly, longer duration of hypoxia result in

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the embryonic death while shorter duration of severe hypoxia result in the growth retardation, orofacial clefts, distal digital reduction, and the cardiovascular defects [21]. Phenytoin was injected to female rats from day 6 to day 18 of gestation. The oxidative stress indices are significantly increased in maternal plasma, tissues and in the pup tissue with decrease in the body weight, length, and number of pups. Maxillary hypoplasia and skeletal anomalies were also noticed [22]. Moreover, Gestational administration of phenytoin produced degenerative changes on the cerebellar development in rat offspring [23].

Lamotrigine

Lamotrigine, a phenyltriazine derivative, is second-generation of an antiepileptic treatment used for partial and generalized seizures. While its use in pregnancy is associated with risk of seizure deterioration because its clearance is accelerated in pregnancy [24, 25]. Monotherapy of Lamotrigine during pregnancy is supposed to be relatively safe, but its teratogenic results have been reported [26]. Also, Brain Teratogenicity Induced by Lamotrigine in Rat fetuses [27].

Levetiracetam

levetiracetam is a second-generation antiepileptic drugs [28], and has high efficiency, safety, and promising profile with low prevalence of harmful effects [29]. Giving levetiracetam to pregnant and lactating female rats had a negative impact on the body weight and cerebella of the offspring [30].

CONCLUSION

Optimal use of antiepileptic treatment in epileptic women during pregnancy, a detailed understanding of the teratogenic influences of antiepileptic drugs and knowledge of the differences in hazards between various treatment alternatives are required. Future research in vitro and animal research on mechanisms of teratogenicity of antiepileptic drugs is required to develop safer medications and appropriate prevention policy.

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