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Curtailing Teratogenic Effects of Valproic Acid - A Mini Review

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ABSTRACT

VPA is the most widely used drug for the therapy as an anticonvulsant and mood-stabilizing. It is prescribed for the alone or with the combination in the treatment of epilepsy. However, the VPA has side effects on the developing fetus and affecting several signaling pathways which cause various other side effects. Though, VPA was known as a potent teratogen causing birth defects via interfering the folate metabolism and oxidative stress, and histone deacetylase inhibition. However, the present article aims to explore the adverse consequences of VPA and the substances which are significantly curtailed its side effects which are Vitamins, S-adenosyl methionine (SAM) and others herbal products such as Curcumin, etc. This will be providing information for focusing too on its therapeutic use in future because of none of any such other alternative of VPA.

Keywords: Valproic acid, Epilepsy, Anticonvulsant, Birth defects, Oxidative stress

INTRODUCTION

Valproic acid (VPA) has widely prescribed antiepileptic drugs worldwide for long-term epilepsy. It also used for controlling several others neurological disorders including tonic-clonic and idiopathic generalized seizures, juvenile myoclonic epilepsy and migraines, etc. [1,2]. Due to causing birth defects it is known teratogenic agent and classified as a Type 'D' category which indicating human fetal risk [3]. The study revealed that the administration of VPA during pregnancy may induce neural tube defects, most notably spina bifida (in human), as well as also caused cardiovascular, urogenital, craniofacial and digital abnormalities. In laboratory animals experimentation showed a variety of malformations in mice [4,5], rats [6], rabbits [7] and rhesus monkeys [8]. However, the birth defects reported due to VPA exposure are major three premises, i.e., folate deficiencies, generation of oxidative stress and histone deacetylase inhibition. It interferes with folate metabolism chiefly inhibiting the production of one-carbon units which involve in the DNA synthesis and methylation [9]. So, gynecologist doctors, a prescribed daily dose of 4-5 mg folic acid during pregnancy for reducing the incidences of spontaneous abortion [10,11]. first time reported that HDAC inhibition as factors for teratogenicity. After that Gurvich et al. [12] worked on Xenopus and zebrafish embryos and he explained VPA induced teratogenicity via changing gene expression [12]. Role of oxidative stress also reported that they involve in embryonic metabolism or bio-activation drugs or chemicals, which produced ROS, inducing cellular damage or altered signaling and finally teratogenesis [13,14]. Many others work has reported that the levels of catalase, superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) are played a very important role during organogenesis period embryos [15-17].

TOXICITY OF VPA AND THEIR CURTAILING EFFECTS

Several previous work has been reported that induction of oxidative stress by VPA cause teratogenicity. Various metabolites such as 4-ene VPA, 2-ene VPA and 2, 4-diene VPA interacts with GSH and down their levels and disturb the balance of cellular oxidative levels. So, they worked also have provide the evidence the by supplementation with natural or synthetic antioxidants such as vitamins or catalases or curcumin as antioxidant which compensate its oxidative stress 18-20]. Bourgeois [1] and Elmazar et al. [21] reported in mice the reducing incidences of spina bifida

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occulta, exencephaly, palate and rib malformations by administration of combination of the three vitamins (Folic acid, vitamin B6 and vitamin B12) and in other by the modification on glutathione homeostasis (GSSG/GSH ratio) along with the inhibiting Hoxa2 gene induced teratogenesis prohibited after pre-administration of ascorbic acid [21] .However, in my previous work revealed that on administration VPA (300 mg per kgbwt) significantly reduced the levels of GSH, SOD and catalase and remarkably increased the levels of ROS, TBARS. Along with these also induced the mRNA expression of the CYP2C9 enzyme known for enhancing the formation of the (E)-2,4-diene-VPA, a toxic metabolite of VPA involve in the oxidative stress generation.

Though curcumin, a potent known antioxidant, co-administration (100, 150 and 200 mg per kgbwt.) along with VPA, demonstrated noteworthy increase GSH, SOD and catalase levels and ROS, TBARS levels reduced. However, the level of CYP2C9 level also reversed. Yet, this work endorses the antioxidant effects of curcumin affording dose-dependent ameliorative effects against the anomalies in fetus induced by VPA [1,21]. A number of resources with Folic acid, vitamins and various others plant products in various form now used as the protective, prophylactic or ameliorative form.

CONCLUSION

In light of all these above-mentioned works and considering ongoing overview it seems that although the work on against the protection of birth defects is inadequate, scanty. The published work showed on VPA caused oxidative stress and damage during the organogenesis period of fetal development which leads to induced teratogenesis and any others toxicity. So, furthermore, studies need to be required to explore the curtailing its oxidative damage and the anti-teratogenic substances interactions in signaling pathways that reduced VPA generation toxicity or its metabolites formation which involved in the defects in developing embryo as birth defects.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

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