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Hepatotoxicity of Valproate on Fetal Mice Liver

Medical Science

KEYWORDS : Valproate, Cytotoxic effect, Fetal mice liver, Teratogenic effect

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ABSTRACT

Valproic acid is an antiepileptic drug. It acts by elevating GABA level in the CNS. It exerts therapeutic effects in a broad range of seizure (tonic-clonic, myoclonic, absence, partial) and bipolar disorder.

The present work was carried out in the Department of Anatomy, IMS, BHU, Varanasi to evaluate the cytotoxic effect of valproate on fetal mice liver. Pregnant mice were exposed to single dose (8th gestational day) of Sodium valproate (200 mg/kg dose) intraperitoneally and fetuses were collected on 18th gestational day.

The liver was smaller in size in valproate treated groups. Histologically, liver showed dilated central vein, breakage of endothelial lining of central vein, oedema and loss of normal architecture of liver parenchyma. Valproate was found teratogenic at 200 mg/kg dose in mice fetus.

INTRODUCTION-

Teratology is the science that studies the causes, mechanisms and patterns of abnormal development. The term teratology has been derived from the Greek word 'Teras' meaning 'monster' and 'Logos' meaning 'the study of'. The word monster is derived from Latin word 'monsterum' which means something providing for knowledge of coming events. Geottroy Saint Hilaire coined the term 'Teratology' (studying serious deviations from the normal type) to designate the science of monsters.

Valproic acid was first synthesized in 1882 by B.S. Burton. Valproic acid is also known as 2-propylvaleric acid. Valproic acid acts by elevating GABA level in the central nervous system. Valproic acid presently the most widely used antiepileptic drug (AED), due to its antiepileptic effectiveness in alleviating a broad range of seizure types: tonic-clonic, myoclonic, absence and partial[1]. In addition to providing antiepileptic effects, valproic acid has shown to be therapeutically active in bipolar disorder[2], migraine[3] and neuropathic pain[4] and is currently being thoroughly trialed to focus on new indications predominantly Alzheimer's disease, HIV and cancer therapy[5].

Use of valproate during pregnancy may result in limb abnormalities, neural tube defects, heart defects, cleft palate, developmental delay, behavioural problems, craniofacial abnormalities, learning difficulties. These all abnormalities together constitute the foetal valproate syndrome (FVS).

However, the reports on valproate teratogenicity at 200 mg/kg dose is limited in literature so the present study was designed to assess the teratogenic effects of valproate in fetuses of mice.

Aim of this research article is to study the macro and microscopic effect of Valproate on developing liver.

MATERIALS & METHODS-

The present work was carried out in the Department of Anatomy, IMS, BHU, Varanasi. In present study, pregnant swiss albino mice were exposed to single dose (8th gestational day) of Sodium valproate (200 mg/kg dose) by intraperitoneal route. Equal volume of normal saline was administered to control mice through same route. Pregnant dams of both the groups were sacrificed on 18th day of gestation by cervical dislocation and fetuses were collected. The liver were dissected out from the fetuses, observed for any gross abnormality and then fixed in 10% formalin for 48 hours for histological study.

OBSERVATIONS-

On gross examination of liver, reduction in size was seen in fetuses exposed to Sodium valproate in comparison to control group.

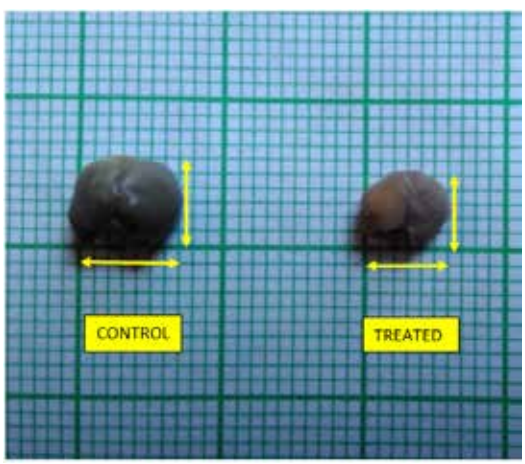

Figure 1- Reduction in size of fetal mice liver treated by Valproate in comparison to control fetal mice liver

On histological examination, following microscopic features has been observed in single dose treated group as compared to control-

Figure 2- Control, H&E, 1000X showing intact endothelial lining of central vein (←—)

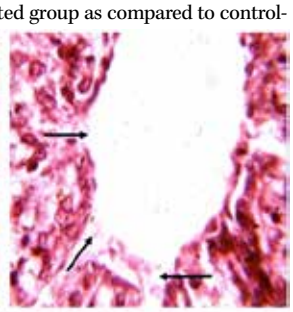

Figure 3- Single dose treated, H&E, 1000X showing destruction of endothelial lining of central vein(←—)

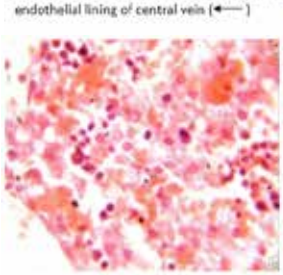

Figure 4- Control, H&E, 1000X showing normal architecture of developing liver

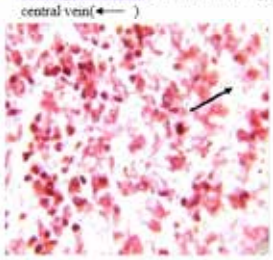

Figure 5- Single dose treated, H&E, 1000X showing loss of normal architecture and oedematous appearance (←—) of liver parenchyma

DISCUSSION-

Present study reveals the hepatotoxicity of valproic acid. This hepatotoxicity may be due to teratogenic effects of valproic acid. Due to valproic acid administration, degenerative changes in placenta can cause reduced maternoembryonic gaseous exchange and lack of transport of sufficient nutrients to the fetus which may lead to oxidative stress. It may lead to hepatotoxic changes in fetus exposed to valproate.

There are only few study conducted on liver of mice fetus. Various authors worked on valproate treated adult mice liver. Stephens et al[6] (1992) showed that depakene can cause liver damage and cause pancreatitis which occasionally progress to bleeding and death. Treating mice with valproic acid induces fatty degeneration of hepatocyte, swelling and increased number of kupffercells. Prolonged time of administration produced inflammation of portal tract, necrosis and cirrhosis (Raza et al. 2000)[7]. Khan et al[8] (2005) reported that steatosis and necrosis of hepatocyte are the main histopathological changes in liver of albino rat induced by toxic dose of valproic acid.

A study on valproate treated adult mice, conducted by Ibrahim[9] in 2012 revealed distortion of liver architecture, accompanied with vacuolar degenerative changes seen focally in hepatocytes. Focal areas of necrosis were also described. Scattered focal aggregates of inflammatory cells seen in between hepatocytes.

Findings of liver histology of our study corroborate with the finding of Shrestha et al[10] (2014). Shrestha et al conducted a study on liver of valproate treated mice fetuses. Marked distortion of typical hepatic laminar pattern, dilated sinusoids were detected. The hepatocytes showed marked degeneration. Many of the cells were vacuolated and ruptured with exudation of the intracellular contents in the intercellular matrix. The nuclei showed pyknosis, karyolysis and karyorrhexis. The cells were irregularly arranged around the portal triad.

CONCLUSION-

Various authors worked on valproate treated adult mice liver. There are only few study conducted on liver of mice fetus.

Present study concludes that valproate is teratogenic drug and it also has potential to cause hepatotoxicity. So it's use in human pregnancy should be avoided if possible.

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