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RESEARCH ARTICLE

EFFECT OF CARBAMAZEPINE ON FETAL KIDNEY

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Abstract

Aims and Objectives: - Carbamazepine is one of the most widely used anti-epileptic drugs among women of child bearing age. This study aims to investigate the morphological and histopathological teratogenic effects of carbamazepine use during pregnancy.

Material and Method:-The healthy pregnant female mice were divided into two groups. The control group received equivalent quantity of distilled water by intraperitoneal route on 7th day of gestation. Second group received 30mg/kg of carbamazepine by intraperitoneal route on 7th day of gestation. Fetuses were delivered on the 18th day of gestation by hysterectomy. Each fetus was assessed for histopathological changes of kidney.

Results:-Kidney of fetal mice showed edematous changes. Glomeruli appeared to be atrophied and degeneration of epithelial lining of most tubules was evident.

Conclusion:-Histopathological changes in kidney of fetus are due to carbamazepine administered to the pregnant mice.

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Introduction:-

Few drugs when administered during pregnancy may cause structural or functional alteration, reversible or irreversible, which may interfere with the normal growth, differentiation and development of the growing embryo, such phenomenon is called teratogenicity and such drugs are known as teratogens. Teratogens induce major morphological changes during embryonic period because it is the stage of rapid cellular division and differentiation (organogenesis), this effect has been laid to genetic factors, associated with the pathology itself (Macara, 2000). The effect of teratogen ranges from no effect to malformation or intrauterine fetal death depending upon the dose (Harden et al. 2009). Systems differentiation at the time of exposure determine pattern of congenital anomalies (Perucca, 2005). The mechanism of teratogenicity and human teratogenesis can be predicted by doing animal experiments in different animal species.

Some drugs are safe during pregnancy. There are five FDA (United States Food And Drug Administration) categories for drugs used during pregnancy. Carbamazepine is one of the most widely used anti-epileptic drugs among the women of child bearing age. It is highly effective for cryptogenic, symptomatic partial seizures, generalized tonic-clonic seizures, trigeminal neuralgia and mood disorders. It is a tricyclic anticonvulsant, neutral, lipid soluble compound that can easily pass the blood brain barrier and other membranes in the body (Hiremath et al., 2006).

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Off springs born to mothers with epilepsy are subject to a double risk, that is, to both epilepsy and the anti-epileptic drugs. The effects of neonatal direct toxicity and a high potential for behavior sequelae, related to language and learning capacity, are added to the teratogenic effects resulting from the anti-epileptic drugs exposure during pregnancy (Adab et al.,2001).Although the highest index of malformation in child born to mothers with epilepsy is associated to the mother exposure to anti-epileptic drugs, the interruption of the treatment may allow the convulsive fits and consequent fetal risks due to intrauterine hypoxia (Kaaja et al.,2004).

The aim of this study is to investigate developmental toxicity of carbamazepine for microstructure of vital organs.

Materials and Methods:-

The present study was conducted in the Department of Anatomy, of our institution after getting permission from ethical committee of university. The healthy female mice of 6-8 weeks of age, weighing 20-25g were subjected for the study. These animals were obtained from animal house of Department Of Anatomy, of our institution. The animal house was maintained at ambient temperature of $25\pm 2^{\circ}\text{C}$ and 50-60 % relative humidity with 12:12 hour light: dark cycle.

For mating female albino mice were kept overnight with the male mice in a single plastic cage in the ratio of 2:1 (female: male=2:1). The mating and pregnancy success was approved by appearance of vaginal plug which was considered as day zero of the pregnancy. The pregnant mice were caged separately and allocated randomly into two equal groups. The first was control group: each pregnant mouse received 1ml of distilled water by intraperitoneal route on 7th day of gestation and the second group received 30mg/kg of carbamazepine by intraperitoneal route on 7th day of gestation. Carbamazepine was in the tablet form (100mg) which was dissolved in distilled water and desired quantity of drug was administered.

On the 18th day of gestation, all animals were killed by cervical dislocation and fetuses were delivered by hysterectomy. Each fetus was examined for gross malformation and euthanized by decapitation. Chest and abdominal viscera were exposed and removed by midline incision. After gross examination viscera were preserved in 10% neutral formalin solution for further histopathological studies. The tissue was processed and embedded in paraffin. Five micron thin sections were cut using rotary microtome and slides were prepared. Haematoxylin and eosin (H&E) stained used for general histological study. The slides were examined under light microscope.

Results:-

The results indicated that carbamazepine administration during pregnancy, in the dosage of 30 mg/kg reduced weight gain in pregnant rats but it has not significantly changed the percentage of pre-implantation and post-implantation losses.

The carbamazepine administration in the dosage of 30 mg/kg, during rats' pregnancy period, has not occasioned significant alteration in the external measures of the morphological parameters of the fetuses. Absence of syndactily and cleft palate and also no alteration related to eyes and ears were evident.

Kidney when examined grossly showed reduction in size of kidney of foetuses exposed to Carbamazepine, as shown in Fig.1. Light microscopic examination of the H&E stained slides of kidney of the first (control) group showed normal renal structure of both cortex and medulla (fig.2). But mice kidney of the second group (treated) showed edematous changes. Glomeruli appeared to be atrophied and degeneration of epithelial lining of most tubules was evident (Fig.3).



Figure 1:- Reduction in size of kidney of fetuses exposed to Carbamazepine.

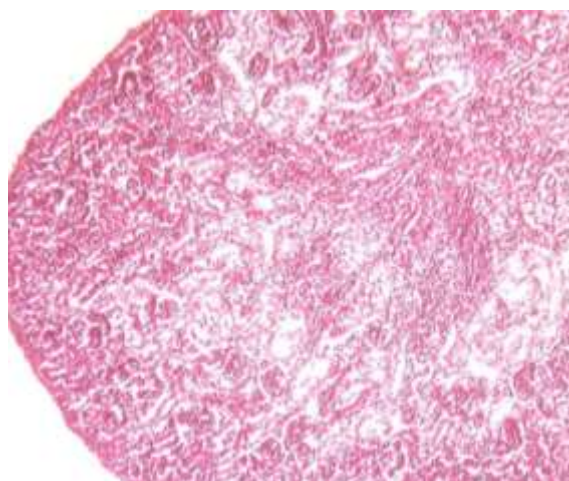


Figure 2:- Photomicrograph of control kidney shows normal developing nephrons in the outer cortex, fully developed nephron in inner cortex and loops of Henley in medulla (H & Ex100).

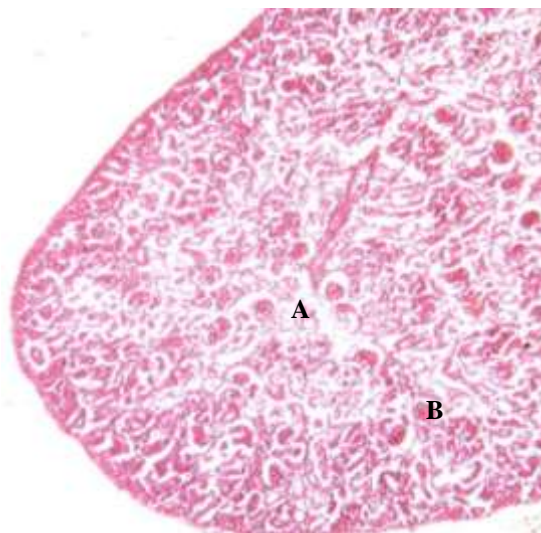


Figure 3:- Kidney of mice exposed to carbamazepine showing(H & E X100) that shows edematous appearance of kidney (A) and clumping of Bowman's capsule (B).

Discussion:-

Pregnant mice were exposed to Carbamazepine on gestational days 7th, 8th and 9th, in low dose and high dose. Foetuses were collected on GD18.

Carbamazepine is efficacious in treatment of a variety of CNS disorders, as well as epileptic seizures. CBZ is usually well tolerated and therefore is also used in pregnant women (Eva Maňáková et al., 2011).

Carbamazepine is used as a monotherapy anticonvulsant agent for treating epilepsy. It is associated with better seizure control and seizure rating score. It is considered as mood stabilizer also. The dosage of carbamazepine for adult ranged from 600–1600 mg/day. The starting dose is 200 mg twice /day and increased by 200 mg/day every 3 to 5 days. Samren et al., (2003), Briggs et al., (2008) recommended that carbamazepine is the drug of choice in pregnant women who requires anticonvulsant therapy for the first time. It may cause harm to the foetus because it crosses the placenta and then there is a high risk for use of carbamazepine during pregnancy.

The children of mothers taking antiepileptic drugs during pregnancy are at the increased risk of teratogenicity. The antiepileptic drugs cause anatomical and behavioural effects by interacting with the genotype. Occurrence of defects depends upon susceptibility of genotype (Finnel et al., 1987).

The risk of birth defects due to antiepileptic drug exposure is higher in the first trimester in human and 6th to 15th day in rodents (Manson and Kang, 1994). None of the available antiepileptic drugs are completely safe during pregnancy (Dean et al., 2002, Mawer et al., 2002, Morrow et al., 2006).

The mechanism by which CBZ exerts its teratogenicity is largely unknown. The study on Swiss albino mice indicated that similar to Phenytoin, CBZ could be biotransformed to a reactive teratogenic metabolite that might be responsible for the observed fetotoxicity (Finnel et al., 1995). The primary pathway of metabolism for CBZ involves the oxidative formation of carbamazepine-10,11-epoxide, which is thought to be responsible for the teratogenicity of the parent drug (Lindhout et al., 1984). This was confirmed in a study on pregnant mice where carbamazepine-10,11-epoxide treatment significantly increased the incidence of malformations in foetuses (Bennett et al., 1996).

The result of this study referred to atrophy of renal glomeruli, degeneration of epithelial lining of renal tubules. These results are consistent with Okada, (2005), who confirmed that atrophy of glomeruli and degeneration of renal tubules leads to retarded renal growth. According to, Tatsunori (2010), concentrations of carbamazepine and its metabolites are much higher in the brain, lung, liver and kidney than its concentration in the blood. This suggests that the drug is retained in organ tissues and then this fact explains toxic effect of carbamazepine in kidney which represents as histopathological changes.

Conclusion:-

Histopathological changes of kidney due to developmental toxicity of carbamazepine represents as morphological changes and congenital anomaly of this organ depending on dosage of carbamazepine. Carbamazepine should be used cautiously during pregnancy, better restricted as much as possible during pregnancy. Further researches in human should be performed to verify these results.

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