Research Article

Effect of Lamotrigine on Fetal Rat Brain

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Abstract:

Studies on the effect of lamotrigine on fetal brain are limited. The present experimental study was conducted to explore any macroscopic or microscopic changes in fetal brain induced by lamotrigine. Pregnant albino wistar rats received 1.5 mg oral lamotrigine on day 9 to 11 of pregnancy and the pups were harvested on day 20. The mean body weight and length were lower and brain weight and volume were higher of the pups exposed to lamotrigine. However, the differences were not statistically significant. Some of the experimental pups had exencephaly and haemorrhages over the body. Histology of the brain revealed that in lamotrigine treated group, the lateral ventricles were dilated and the plexiform layer of the cerebral cortex was relatively less differentiated.

Key Words: Lamotrigine, Teratogenicity, Rat fetus, Brain defect.

Introduction:

Lamotrigine (LTG) is a second generation antiepileptic drug, widely used in the treatment of epilepsy and bipolar disorder. It is a phenyl triazine derivative and the mechanism of action is related to the blockade of voltage dependent sodium channels which stabilises presynaptic membranes and inhibit excitatory neurotransmitter release (Messenheimer 1995). Lamotrigine crosses the placenta easily and rapidly, therefore, the maternal treatment leads to a considerable fetal exposure (Myllynen et al, 2003; Ohman et al, 2000; Rambeck et al, 1997; Tomson et al, 1997). Though considerable numbers of pregnant women are exposed to LTG, sufficient data is not available concerning its teratogenicity. The present study has been carried out to evaluate the teratogenic effects of LTG on fetal rat with special reference to brain development.

Material and Methods:

Albino wistar rats weighing between 150-200 gm were used. Females showing proestrus at 17.00 hrs were caged overnight with males of the same stock. When spermatozoa were found in the vaginal smear in the next morning at 09.00 hrs, it was taken as day 0 of gestation. The pregnant animals were kept individually in separate cages under controlled environmental conditions. The experimental group of rats were administered LTG in the dose of 1.5 mg orally using nasogastric tube on day 9, 10 and 11 of pregnancy. The control rats received only tap water. Pregnant rats were sacrificed on day 20 of gestation and the fetuses were collected after noting the resorption sites and dead fetuses. The live fetuses were cleaned, blotted, weighed and were examined under dissecting microscope for various external malformations. The fetal brain was dissected from the cranial cavity and was preserved in formal saline for histological examinations.

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Results:

Sixty pups delivered from 12 rats in the experimental group and thirty delivered from 6 rats in the control group were studied. The values of the morphometric parameters are shown in Table 1. Though the mean body weight and length of the LTG treated pups were lower as compared to the control group, the difference was not statistically significant. Similarly, the mean brain weight and volume of the LTG exposed rats was higher, but statistically it was comparable to control values.

Some of the LTG exposed rat foetus had well defined dark brown swellings over parieto-occipital region of head (exencephaly). Hemorrhages of various sizes were found over the body; especially over the cervicothoracic junction. None of these findings were found in the control fetuses.

The ventricles of the experimental pups were larger than that of the control pups (Fig.I & II). Histologically, the plexiform layers in the experimental rat pups were relatively less clearly defined (Fig. III).

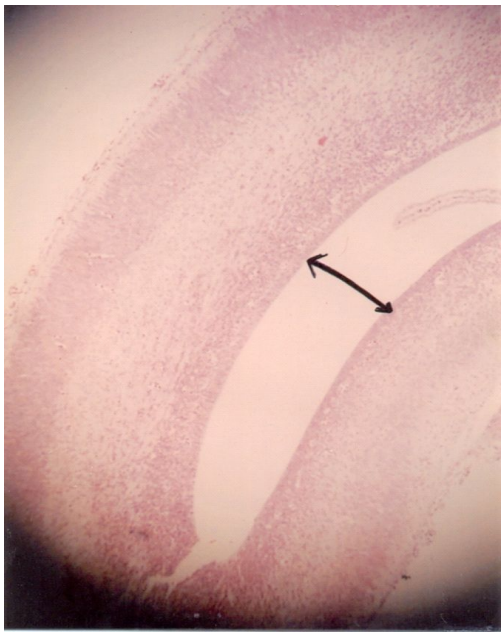

Fig.I: Lateral ventricle (arrow) is larger in Lamotrigine treated rat fetus as compared to control (H & E x 40).

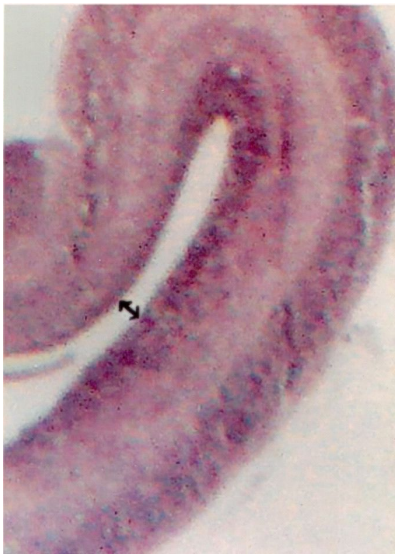

Fig.II: Control rat fetus showing normal sized ventricles (arrow) (H & E x 40).

Table 1: Morphometric parameters (Mean ± S.D.) of the rat pups.

Parameters	Experimental	Control n = 60	p-value n = 30
Body weight (g)	2.29 ±0.25	2.34±0.34	0.39
Body length (cm)	2.77±0.40	2.93±0.5	0.90
Brain weight (g)	0.12±0.024	0.11±0.024	0.34
Brain volume (ml)	0.15±0.03	0.14±0.03	0.19

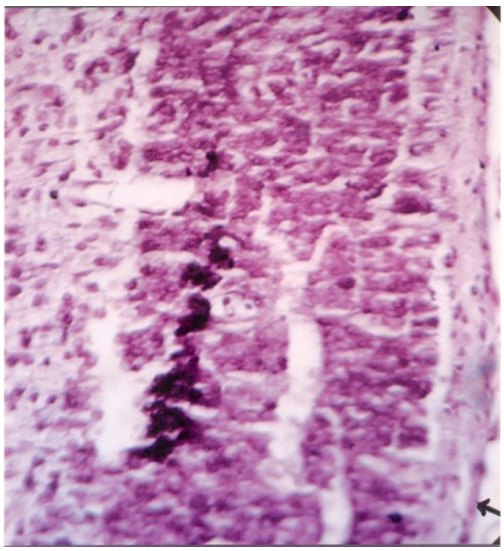

Fig.III: Histological section of cerebral cortex showing less clearly defined plexiform layer in Lamotrigine treated rat fetus (H & E X 400).

Discussion:

In our experimental study, offsprings of LTG treated rat demonstrated relatively lower body weight and length with higher brain weight and volume. Some of these fetuses had exencephaly and haemorrhages over the body. Histologically, the ventricular size was larger in LTG exposed rat fetus with less differentiated plexiform layer. de Marchi et al (2001) treated pregnant rats with four times the recommended human dose of LTG during the period of organogenesis and reported low birth weight and altered brain structure which included increased volume and diameter of the cerebral structure, increased density of the subcortical layer and ventricle dilatation. Padmanabhan et al (2003) reported that administering LTG as single dose of 50-200 mg/kg body weight can induce intrauterine growth retardation in mice, whereas multiple doses of 25, 50, 75 mg/kg body weight caused a dose dependant increase in embryonic resorption and craniofacial malformations. Rahmani et al. (2006) studied the teratogenic effects of lamotrigine on mouse fetus and noted reduction of body weight and height with increased malformations of vertebral columns and limbs. Rats receiving up to 0.5 times an equivalent human dose of 500 mg/day produced offspring with decreased folate concentrations, an effect known to be associated with teratogenicity in human and animals (Iqbal et al, 2001). However, the authors did not find teratogenic effects in animals by using increasing doses up to 1.2 times the human dose.

The data derived from human studies remains inconclusive. However, most of the human pregnancy registry studies could not reveal clear cut evidence of a relationship between LTG and teratogenesis. They concluded that LTG monotherapy during pregnancy to be relatively safe (Gentile, 2006; Ornoy, 2006; Richens, 1994; Vajda et al, 2006). However, major congenital malformations like neural tube, cardiac, gastrointestinal, hypospadias/genitourinary defects and other defects has been reported in offspring of women treated with LTG in pregnancy and most of them were receiving LTG in significantly higher dose as compared to those without major congenital malformations (Meador et al, 2006). Similar was the observations of Perucca (2005) who identified a positive correlation between maternal dose and frequency of major congenital malformations. Several authors suggested that LTG may be less teratogenic to humans as compared to other antiepileptic drugs (Sabers et al, 2004; Tatum, 2006; Tomson et al, 1997) and most of the major malformations were similar to that in the general population (Morrow et al, 2006).

Results obtained from animal study may not be directly applicable to human beings. One of the various factors that influence outcome is the dose. In most animal studies, the dose used was higher than that in human. Secondly, the metabolism in human body may be somewhat different from animals. Though this animal study does not show significant gross morphometric effect of LTG, some histological changes were observed. Therefore, LTG should not be regarded totally safe drug during pregnancy until its safety is established in a large scale randomised study with long term follow-up.

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