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Research Article

Study of the Teratogenic Potentials of Lamotrigin in Rat Fetus

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Abstract

Introduction: Lamotrigine (LTG) is a second generation antiepileptic drug, widely used in the treatment of epilepsy and bipolar disorder. It is a phenyltriazine 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 [1]. Lamotrigine crosses the placenta easily and rapidly. The present study has been carried out to evaluate the teratogenic effects of LTG on fetal rat.

Materials 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. The experimental group of rats were administered LTG in the dose of 1, 1.5 and 2 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 terms of induced abortion, reduction in litter size, reduction in weights and/or length of fetuses and pups, resorptions and any gross malformation.

Results: The weight gain of lamotrigine treated pregnant rats showed a significant decrease of 13.2, 18.3 and 25.6% as compared to control group animals. About 78.0% of lamotrigine treated pregnant rats reached full term pregnancy as compared to 90% in controls. The incidence of abortion in treated animals was 8.1 and 9.3% as compared to none in controls. Mean number of pups delivered by treated animals (6.8 1.27, 7.50 2.26, 7.0 0.91) showed a highly significant decrease of 15.4, 26.6 and 29.5% as compared to controls (8.8 6.36). Mean weight of pups from treated animals (5.97 0.124, 4.86 0.112, 4.21 0.086 gm) showed a highly significant decrease of 17.12, 26.75 and 38.8% as compared to controls (5.93 0.067 gm). Mean CRL of pups from treated animals (36.4 0.670, 33.1 0.092, 61.4 0.515 mm) showed a highly significant decrease of 18.42, 26.63 and 29.5% as compared to controls (47.93 0.276 mm). There were no resorptions in control group. Treated group A, B and C had incidences of 9.7, 31.6 and 38.4% resorptions respectively. No gross structural malformation was found in control or any of the treated groups.

Conclusion: In conclusion we report that lamotrigine proved to be fetotoxic/embryotoxic when administered during gestation to female albino rats. The higher costs of the newer AEMs may inhibit their wider use, especially in poorer countries [2]. LTG teratogenicity has been reported in animals, although results from human studies have proven inconclusive. There is a need to appraise the possibility of minimizing foetal toxicity caused by drugs. To achieve this, an elaborate prospective evaluation is warranted. This present study is an attempt to elucidate and establish a viable LTG safety profile for use during pregnancy, so that risks of foetal malformations can be minimized.

Keywords: *Fetus; Lamotrigine; Rat; Teratogen*

Introduction

Lamotrigine (LTG) is a second generation antiepileptic drug, widely used in the treatment of epilepsy and bipolar disorder. It is a phenyltriazine 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 [1]. Lamotrigine crosses the placenta easily and rapidly, therefore, the maternal treatment leads to a considerable fetal exposure [3-6]. 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.

Chemical structure

The International Union of Pure and Applied Chemistry (IUPAC) name of lamotrigine is 6-(2,3-dichlorophenyl)- 1,2,4-triazine-3,5-diamine and the empirical formula is C9H7Cl2N5; while the molecular mass is 256.091 g/mol [7].

Pharmacodynamics

As described by Brunton., *et al.* the mechanisms underlying the broad spectrum of actions of LTG are not completely understood [8]. One possibility involves LTG's inhibition of glutamate release in rat cortical slices treated with veratridine, a Na+ channel activator. This raises the possibility that LTG inhibits synaptic release of glutamate by acting on Na+ channels [8]. Tierny., et al. described that LTG is thought to interfere with neuronal sodium channels and inhibit the release of excitatory amino acids, glutamate and aspartate [9]. A decrease in glutamate release has also been reported as a mechanism of action [10].

Pharmacokinetics

LTG is absorbed in the gastrointestinal tract and hence oral administration is employed. It is metabolised primarily by glucuronidation (Major metabolite: LTG 2-N-glucuronide) and the plasma half-life of a single dose (antiepileptic) is 15 - 30 hours [8,11]. Its antiepileptic doses are 100 - 500/day, bid. However, it must be noted that therapeutic range and optimum drug level have not been established [9,10,12].

To study and compare the effects of Lamotrigine administration during gestation on offspring of albino rats in terms of induced abortion, reduction in litter size, reduction in weights and/or length of fetuses and pups, resorptions and any gross malformation.

Materials 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, 1.5 and 2 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 terms of induced abortion, reduction in litter size, reduction in weights and/or length of fetuses and pups, resorptions and any gross malformation

The pregnant rats were divided in four groups:

- Group A contained 10 pregnant rats. They received 1 mg orally on day 9, 10 and 11 of pregnancy.
- Group B contained 10 pregnant rats. They received 1.5 mg orally on day 9, 10 and 11 of pregnancy.
- Group C contained 10 pregnant rats. They received 2 mg orally on day 9, 10 and 11 of pregnancy.
- Group D contained 10 pregnant rats, behaved as control group and received distilled water orally for the same period.

The pregnant rats were observed for duration of pregnancy, weight gain, abortions and number of pups given birth. The obtained pups were weighed and their crown rump length noted. They were then examined under dissecting microscope for any structural malformations. Subsequently they were processed in the lab: for measurements of bones. In the present study the data was subjected to students 't' test. By this test the statistical significance of the difference between two means of various parameters between control and experimental groups was evaluated.

Results

The weight gain of lamotrigine treated pregnant rats showed a significant decrease of 13.2, 18.3 and 25.6% as compared to control group animals. About 78.0% of lamotrigine treated pregnant rats reached full term pregnancy as compared to 90% in controls. The incidence of abortion in treated animals was 8.1 and 9.3% as compared to none in controls. Mean number of pups delivered by treated animals (6.8 1.27, 7.50 2.26, 7.0 0.91) showed a highly significant decrease of 15.4, 26.6 and 29.5% as compared to controls (8.8 6.36). Mean weight of pups from treated animals (5.97 0.124, 4.86 0.112, 4.21 0.086 gm) showed a highly significant decrease of 17.12, 26.75 and 38.8% as compared to controls (5.93 0.067 gm). Mean CRL of pups from treated animals (36.4 0.670, 33.1 0.092, 61.4 0.515 mm) showed a highly significant decrease of 18.42, 26.63 and 29.5% as compared to controls (47.93 0.276 mm). There were no resorptions in control group. Treated group A, B and C had incidences of 9.7, 31.6 and 38.4% resorptions respectively. No gross structural malformation was found in control or any of the treated groups.

Groups	Maternal body weights		
	Gestational day-1	Gestational day-20	Weight gain/loss
A	173.7 ± 8.961	230.4 ± 9.044	55.0 ± 8.173
B	172.9 ± 6.941	225.5 ± 4.567	47.5 ± 3.147
C	187.0 ± 9.657	237.3 ± 8.614	44.3 ± 8.843
D (Control)	187.5 ± 9.055	248.8 ± 6.627	62.3 ± 2.044

Table 1: *Comparison of mean maternal body weight (gm) gain/loss between gestational day 1 and 20 in different group of rats.*

** Mean + standard error.*

Groups			Animals		
		Non-pregnant	Non-pregnant Pregnant		Pregnant
	Total used	Pseudopregnent (%)	Infertile (%)	Abortion (%)	Full term (%)
A Lamotrigine Dose I	10	1 (10)	1 (10)	0	8 (80)
B Lamotrigine Dose II	11	2 (18.1)	0	1 (9.1)	8 (72.8)
C Lamotrigine Dose III	14	1 (7.1)	2 (14.2)	1 (7.1)	10 (71.4)
D Lamotrigine Control	22	2 (9.1)	0	0	20 (90.9)

Table 2: *Average number of Pregnancy and non-pregnancy.*

Groups	Dose	Average number	Gain/loss as compared to control
A Lamotrigine	I	8.1 ± 0.54	15.40%
B Lamotrigine	II	7.50 ± 0.26	22.60%
C Lamotrigine	III	7.0 ± 0.21	28.70%
D Control	-	9.3 ± 0.36	-

Table 3.

** Mean + standard error.*

Groups	Dose	Average number	Gain/loss as compared to control
A Lamotrigine	I	5.37 ± 0.124	17.82%
B Lamotrigine	II	5.36 ± 0.112	25.95%
C Lamotrigine	III	3.61 ± 0.086	38.68%
D Control	-	5.43 ± 0.037	-

Table 4: *Comparison between average weight (gm) of pups in different experimental groups at birth.*

** Mean + standard error.*

Groups	Dose	Average crl	Gain/loss as compared to control
A Lamotrigine	I	36.4 ± 0.100	18.42%
B Lamotrigine	II	35.1 ± 0.092	25.63%
C Lamotrigine	III	33.4 ± 0.115	27.50%
D Control	-	46.3 ± 0.076	-

Table 5: *Comparison between average crown rump length (mm) of pups in different experimental groups at birth.*

** Mean + standard error.*

Group Animals		Foetuses					
	Alive	Dead (%)	Premature (%)	Total	Resorption (%)	Total implantation	Foetal mortality
Lamotrigine A 10	72 (97.2)	0	2 (2.7)	73	2 (2.3)	83	.5
Lamotrigine B 10	64 (95.5)	1 (1.4)	2 (2.9)	68	5 (5.7)	85	8.0
Lamotrigine C 10	61 (88.2)	3 (4.4)	5 (7.3)	68	15 (15.3)	96	18.3
Control D 30	250 (100)	0	0	250	0	250	0

Table 6: *Detail of foetuses and pups of rats.*

Groups	Dose	Average weight of placenta	Average weight of liver
A Lamotrigine	I	0.42 ± 0.016	0.59 ± 0.013
B Lamotrigine	II	0.40 ± 0.018	0.46 ± 0.013
C Lamotrigine	III	0.52 ± 0.012	0.44 ± 0.016
D Lamotrigine	-	0.71 ± 0.007	0.49 ± 0.014

Table 7: *Comparison between mean weight (gm) of placenta and liver of pups in different experimental groups.*

** Mean + standard error.*

Groups	Dose	Humerus	Ulna	Femur	Tibia
A Lamotrigine	I	4.93 ± 0.076	4.83 ± 0.047	4.45 ± 0.039	4.40 ± 0.055
Blamotrigine	II	4.77 ± 0.037	4.63 ± 0.044	4.61 ± 0.046	4.85 ± 0.042
C Lamotrigine	III	4.43 ± 0.056	4.21 ± 0.062	4.25 ± 0.059	4.39 ± 0.067
D Control	-	6.24 ± 0.076	6.50 ± 0.074	6.49 ± 0.079	6.70 ± 0.087

Table 8: *Comparison of mean intact bone length (mm) in control and treated albino rat pups.*

** Mean + standard error.*

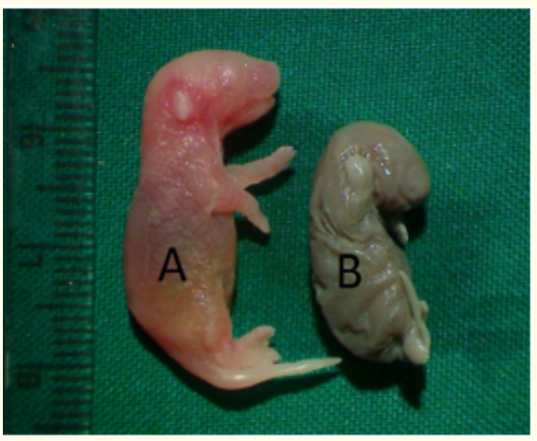

Figure 1: *A) Normal fetus. B) Abnormalities of the fetal extremities of sharing of lamotrigine.*

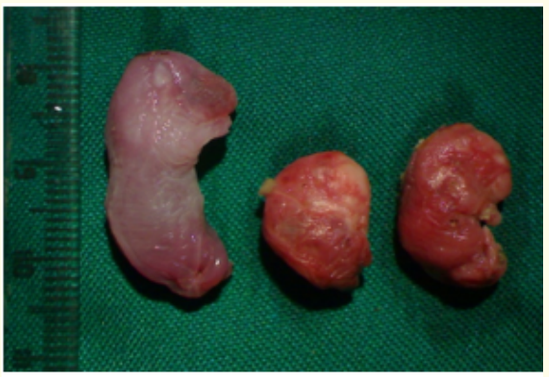

Figure 2: *Incidence of kyphosis and defect of the extremity in fetuses sharing of lamotrigine.*

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. de Marchi., *et al.* [13] treated pregnant rats with four times the recommended human dose of LTG during the period of organogenesis and reported low birth weight. Padmanabhan., *et al*. [14] 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*. [15] 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 [16]. However, the authors did not find teratogenic effects in animals by using increasing doses up to 1.2 time the human dose. 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 [17-20]. 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 [21] 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 [6,22,23] and most of the major malformations were similar to that in the general population [24-26].

Conclusion

In conclusion we report that lamotrigine proved to be fetotoxic/embryotoxic when administered during gestation to female albino rats. The higher costs of the newer AEMs may inhibit their wider use, especially in poorer countries [2]. LTG teratogenicity has been reported in animals, although results from human studies have proven inconclusive. There is a need to appraise the possibility of minimizing foetal toxicity caused by drugs. To achieve this, an elaborate prospective evaluation is warranted. This present study is an attempt to elucidate and establish a viable LTG safety profile for use during pregnancy, so that risks of foetal malformations can be minimized.

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