Original Article

Lithium Induced Toxicity

A Comparative Analysis of Lithium Induced Cerebellar Cortical Toxicity in Albino Rats

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ABSTRACT

Objective: To compare the thickness of cerebello cortical gray matter of albino rats after chronic ingestion of Lithium carbonate.

Study **Design:** Prospective experimental study

Place and Duration of Study: This study was carried out in Animal House affiliated with atomy department BMSI, JPMC, Karachi from April 2012 to June 2012.

Materials and Methods: Thirty male albino rats of 100-200 grams were selected and divided into two major groups A and B. Each major group consisted of 15 animals and my study was conducted according to the time period of the study which was 2 weeks, 6 weeks and 12 weeks. The control group purpose was served by Group A which was given lab diet and B was the Lithium treated group. Lithium carbonate (ADAMJEE PHARMACEUTICALS) was given at a dose of 20mg/kg/day for 2, 6 and 12 weeks. Cerebellar Gray matter thickness was measured at 2nd, 6th and 12th weeks in the normal healthy control group and Lithium treated group.

Results: Group B showed a progressive decrement of gray matter as the time period of study advance.

Conclusion: The present study concluded that Lithium carbonate causes a significant decrease of cerebello cortical gray matter.

Key Words: cerebellum, Lithium carbonate, Gray matter.

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INTRODUCTION

Lithium is the most abundant element in nature[1]. It was discovered by Johan August Arfwedson (1772-1841)[2], and was first used in the treatment of gout[3] in 19th century. Lithium carbonate was also used to prevent depression around 1870[4]. Now for the past five decade Lithium salts are used to treat neurological disorder[5] such as schizophrenia[6], cycloid cyclosis[7] major depression[8]. Bipolar affected disorder symptoms include feeling of hopelessness.[9] In 1970 Lithium was approved as favourable treatment for mania. As time passed the medicinal world accepted Lithium as a prime treatment for manic depression[10]. At present in the medicinal world $Li_2 Co_3$ is considered as an anti-manic drug but in many parts of the world, it is still considered as a mood stabilizing agent[11]. Lithium carbonate used for long term treatment has been reported to cause cerebellar degeneration in rat, [12] and the primary target organ in human is the central nervous system[13]. Muscular weakness and renal failure are the other side effects of Lithium therapy [14]. There is growing evidence that Lithium can induce long lasting neurological sequelae, the most frequent clinical feature is a permanent cerebellar syndrome[15]. Therefore cerebellar toxicity has been recognized as a potential irreversible consequence of lithium therapy[16]. Various studies have approved that lithium cause's damage at multiple sites in the nervous system but cerebellar feature tend to be most prominent[17].

Several studies have been carried out to ascertain the deleterious effect of acute Lithium ingestion on various organs but my present study is designed to evaluate and analyze the cerebellar cortical atrophy due to chronic Lithium administration.

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MATERIALS AND METHODS

This prospective study was carried out in the Animal House, Jinnah Postgraduate Medical Center (JPMC), Karachi. For this study 30 albino rats of 100-200 grams of weights were selected for study. They were kept under observation for 7 days prior to commencement of study. The animals were randomized into two experimental groups each comprising of 15 rats. Group A animals were put on laboratory diet (control group) and group B animals were administered Lithium carbonate at a dose of 20mg/kg/day[18, 19, 20, 21] in powder form mixed in flour pellets given at fixed meal time i.e. 10AM. The albino rats were decapitated, and the brain of each rat was removed by parietal bone approach. The cerebellum was separated from the rest of the brain. Formal saline fixed three micrometers thick sections of the tissue were prepared. The thickness of the gray

matter was measured by optical micrometer and the results were recorded at 2, 6th and 12th weeks in control A group and Lithium treated group. The observations were compared among the group at weekly interval and also comparison between both the major groups was done. Data collected was analyze using student's "T" test. Results were expressed as mean, SEM P<0.001 was considered statistically highly significant. All calculation was done by utilizing computer software SPSS 16 through Microsoft excel in windows.

RESULTS

Group A (Animal on Normal Diet): There was a highly significant (P-<0.001) increase in the mean values of thickness of the gray matter of control group A at 2nd weeks was 347.8 ± 1.84 at 6th weeks 363.4 ± 2.24 and at 12th weeks 381.2 ± 2.42 the results showed that the mean values of the thickness of the gray matter was highly significantly (p<0.001) increased at 12th weeks than 6th and 2nd weeks.

Table No.1: Mean* value of the thickness of the gray matter of cerebellum (µm) in control group at weekly interval.

Group	2nd week		6th week		12th week	
	Mean	SEM	Mean	SEM	Mean	SEM
A (ND)	347.8	1.84	363.4	2.24	381.2	2.42

Mean* ± SEM

Statistical analysis of the thickness of the gray matter at weekly interval in control group animals

Group	2wk VS 6wk	2wk VS 12wk	6wk Vs 12wk
B vs. A	0.006	0.001	0.002

Highly Significant***

Group B (Lithium Intoxicated Animals): The mean values of the thickness of the gray matter in lithium treated group animals B at 2nd weeks was 275.5 ± 3.19 at 6th weeks 257.3 ± 2.96 at 12th weeks 239.8 ± 6.51 the above results shows a highly significant (P<0.001) decreased in the thickness of the gray matter at 2nd weeks than 6th weeks and 12th weeks and a moderately significant (P<0.001) decreased in the thickness of the gray matter at 12th weeks than 2nd weeks and 6th weeks and an insignificant (>0.05) decreased of the thickness of the gray matter was observed at 12th weeks when compared 6th weeks.

Mean* value of the thickness of the gray matter of cerebellum (µm) in Lithium treated group B animals at weekly intervals

Group	2nd week		6th week		12th week	
	Mean	SEM	Mean	SEM	Mean	SEM
B(Li)	275.5	3.19	257.3	2.96	239.8	6.51

Mean* ± SEM

Statistical analysis of the thickness of the gray matter at weekly interval in Lithium treated group B animals

Group	2wk VS 6wk	2wk VS 12wk	6wk Vs 12wk
B vs. A	0.001	0.011	0.093

Insignificant Moderately significant**
Highly Significant***

Major Group Comparison: On major group comparison it was found that there was a highly significant (P<0.001) decreased thickness of the cerebellar gray matter of group B lithium intoxicated animals than the control group A

Statistical analysis of the mean value of the thickness of gray matter between group B and group A

Group	P-value
B vs. A	< 0.001 ***

Highly Significant***

DISCUSSION

The cerebellum is the largest part of the hindbrain is dorsal to the pons, and the elemnt of the cerebellar cortex posses a precise geometric order consisting of three male layers. Molecular, Purkinje cell and granular layer or the gray matter and its constituent cell [22]. Many studies reveal severe cerebellar atrophy of the internal granule and Purkinje cell layer due to chronic Lithium use[23]. Observations of our study report that lithium carbonate when used for increasing time period causes a highly significant decrease of gray matter in lithium treated group B, than control group A. the same result were recorded by Gomez and Lucas (2010)[24.] They in their study report that lithium causes severe neurological manifestation and this may be due to the reason that lithium causes inhibition of glycogen synthase kinase-3 leading to an increase in neuronal apoptosis. Inhibition of GSK-3 causes increase translocation of T cells c3/4 (NFAT c3/4) transcription factors to the nucleus, leading to increased Fas ligand (FasL) levels activation. Fas initiates apoptosis by binding to its surface receptor Fas as a consequence there is sequential activation of caspases-3 and release of cytochrome C from mitochondria which causes cellular degradation and death[25]. This neurological apoptosis causes a decrease in the thickness of the molecular layer Purkinje cell layer and internal granular layer[26]. Thus leading to a decrease in the cerebello cortical gray matter this is in accordance with the observations of our study also many studies conducted on the detrimental effect of lithium carbonate in Albino rats record the same results this is in agreement with Tathagat[27] (2011) and Kandovich-Bellin O, (2009)[28].

The results of our study are also in agreement with Bhalla et al.,(2007), they in their study had recorded that Lithium intoxication causes an increase imbalance in antioxidant enzymes which are superoxide dismutase (SOD), Catalase (CAT) and glutathione synthetase (GST), [29] there by leading to excessive generation of free radicals hence resulting in enhanced oxidative stress.[30] Increased oxidative stress leads to cell damage and cell death. [31] the magnitude of atrophy was highest in cerebellum[32]

CONCLUSION

The present suggest that chronic lithium carbonate ingestion causes highly significant deterioration of cerebello cortical tissue and its used should be monitored carefully.

Conflict of Interest: The study has no conflict of interest to declare by any author.

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