Analysis of the Decrement of Renal Weights in Adult Male Rats after Long Term Lithium Carbonate Ingestion

Tazeen Kohari [1], Syed Meesam Iftikhar Hussain Rizvi[2], Asma Basharat Ali [3]

Abstract

Objective: This analysis was aimed at evaluation of the effects of prolonged ingestion of Lithium carbonate on renal weights in rat models.

Methods: In our experimental analysis, twenty healthy male rats of age sixty-five days were randomly divided in two groups. Group A (n =10) and Group B (n=10) was given Lithium carbonate. Group A, which was the control group, was further divided into two subgroups according to time duration Group A1 (n=5) and Group A2 (n=5). The control group rodents were fed a lab diet consisting of vegetables, flour pellets and water for a period of 2 and 6 weeks, whereas Group B (n=10) was the Lithium-treated group which also contained five animals in each group. In the treated Group B the animals were divided according to time duration in B1 (2 weeks), Group B2 (6 weeks). Group B rodents along with the lab diet were given Lithium. At the end of the period, animals were sacrificed, and the skin, fascia, and intestines were separated and removed. The red oval kidney was weighed on Digital Weighing Balance at 2 and 6 weeks in all the Groups and recorded. Statistical Analysis was performed on SPSS version–16.

Results: The renal weights in grams of both groups were documented and it was found that Groups B1 and B2 treated with Lithium carbonate showed statistically highly significantly decreased p-value <0.001 of renal weights as compared to the Control Groups A1 and A2 which were on Lab diet. There were statistically highly significantly decreased renal weights at 6 weeks in group B2 than in Group B1, A1, and A2.

Conclusion: This analytical research has proved that renal damage occurs due to decreased renal weights in rat models due to prolonged intake of Lithium carbonate.

Keywords: Bipolar disorder, Lithium, Psychosis, Bipolar disorder, hepatorenal disorder.

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Introduction

Kidneys are paired retroperitoneal organs, situated on each side of the posterior abdominal wall. In males, they typically weigh between 120g -130g to 140g to 150g grams while in females; their weight ranges between 120g to 135g. The urinary system (kidneys) is located one on the right and the other on the left of the spinal cord measuring in length, 5 to 5.7 cm in wide, and 5 to 5.5 cm in thickness. The superior poles are located medial and posterior in relation to the lower poles. Each kidney is related to the suprarenal glands (adrenal glands) superiorly, the right suprarenal gland which is pyramidal in shape is placed on the top of the right kidney and the left suprarenal gland is present superiorly and medially on the left kidney. Anteriorly, the right kidney is related to the colic flexure, to the second part of the duodenum, coils of the small intestine and the liver, the hepatorenal recess separates it from the surrounding structures and anterior-related structures of the left kidney are suprarenal gland, pancreas, descending colon, it is situa-

[1]Department of Anatomy, Bahawalpur Medical & Dental College (BMDC),
[2,3] Department of Anatomy, Jinnah Medical & Dental College (JMDC)

Correspondence: Dr. Tazeen Kohari
Department of Anatomy, Bahawalpur Medical & Dental College (BMDC),
Email: tazeenk67@gmail.com

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ted adjacent to the greater curvature of the stomach, and left upper pole adjacent to the spleen and it is connected by a splenorenal ligament. Each kidney is covered in its upper part by the diaphragm posteriorly and the 12th rib is present at the upper pole. The muscle present medial to the renal organ is the psoas muscle and laterally is the Quadratus Lumborum. The renal ureters pass over the psoas muscle on their way to the bony pelvis. Embryological development of the mammalian kidney is from the intermediate mesoderm. Initially, nephrogenesis occurs as the pronephros, the vestigial excretory units or nephrotomes originate at the fourth week of development and regresses by the end of the fourth week. As the initial kidney pronephros regresses, the mesonephros arises from the intermediate mesoderm basically from thoracic to upper lumbar segments. Mesonephric tissue comprises of excretory units that grow in length and take the shape of a loop, then capillaries arise and give rise to a renal corpuscle (glomerulus surrounded by Bowman's capsule). The collecting duct receives the excretory tubule termed the Mesonephric or Wolffian duct. Kidneys are the two bilateral organs that are developed by approximately the sixth week[1].

Kidneys play a pivotal role in many homeostatic functions. These functions encompass the elimination of metabolic waste products such as ammonia, regulation of fluid and electrolyte balance, maintenance of metabolic acid-base equilibrium, and homeostasis of calcium. Additionally, the kidneys are responsible for the synthesis of hormones, regulating blood pressure and red blood cell synthesis[2].

Kidneys are highly vascularized organs; they receive around 20% of the cardiac output via the renal arteries. This blood passes from the afferent arterioles, into the filtration capillaries, known as glomeruli, and then exits via the efferent arterioles. This process is known as glomerular filtration. The renal corpuscles, which constitute the glomerulus and its encasing Bowman's capsule along with the renal tubules, are responsible for the filtration, reabsorption, and secretion function of the kidney[3]. The structural and functional unit of the renal system is the nephron. The nephron is composed of the tubular system which is the proximal convoluted tubule (PCT), loop of Henle, and distal convoluted tubule (DCT). The renal cortex consists of the proximal convoluted tubule, glomeruli, and initial parts of the distal convoluted tubule, the medulla contains the loop of Henle and collecting ducts. The functions of the body homoeostasis and blood pressure are basically maintained by nephron. Hence, nephron pathologies tend to be as complex as its structure. Each segment of the nephron is susceptible to damage from different toxins and infectious agents. Many toxins can affect more than one section of the nephron[4]. Lithium is advised in many neurological disorders but it acts as a toxin which has been implicated in previous studies to cause kidney damage or nephrotoxicity. Researchers in 2021 found that the gold standard anti-psychiatric drug usage for an extended time period developed impaired urinary functions, chronic renal disease and they had documented that the prevalence of renal functional loss was greater in patients given continued Lithium therapy[5]. The clinical presentation of Bipolar disorder is quite extensive. Patients present with signs and symptoms similar to mental disorders, including anxiety disorders, stress, dementia, and schizophrenia. First, a record of ancestors having of psychotic disorders is positively suggestive of a mental disorder. Second important consideration are signs and symptoms of emotional collapse and recklessness, and other nervous exhaustion presentation. Third, the relationship between emotional disruption and personality must be considered in making the diagnosis of mood disorder. Clinically, manic disorders include bipolar disorder and it is always considered in the differential diagnosis of patients with depression, The degrees of bipolar disorder vary among the affected population a large percentage is found to be mild, and severe bipolar disorder subjects were large in number and presented with increased, severity of the manic behavior and psychological disabilities, functional impairment, higher rates of abuse, disruption of neural functioning. Lithium is a monovalent cation used in the management of a wide spectrum of psychiatric disorders. It is used as the first-line mood-stabilizi-

ng drug for bipolar disorder and severe depression, especially in patients with suicidal tendencies. It has also been used as a protective drug in neurological diseases such as acute neuronal injury, chronic degenerative disorders, Alzheimer's disease, and certain conditions like hepatitis, leucopenia and certain cancers. It is readily absorbed from the gastrointestinal tract reaching peak plasma concentration in 2-4 hours. Distribution occurs throughout the extracellular fluid. The elimination half-life of Lithium is estimated at 24 hours and more than ninety percent of the dose of this lightweight metal is excreted in the urine. Renal clearance is only twenty percent and it is actively reabsorbed in the proximal tubule at sites normally used for conservation of sodium[6]. Humans are exposed to lithium in small doses from the water, food intake, and environment. Among the affected patients a high percentage belonged to occupations like mine handlers and battery manufacturers. Within the affected group of patients, the highest percentile suffered from urinary, skin, neuronal, and endocrinal complications. Many studies have been conducted and proven the harmful effects of lithium on the renal, nervous, endocrine (thyroid), integumentary, and circulatory systems. Research has also proven Lithium to be teratogenic in nature as it can cross placental barriers[7]. The adverse effects of lithium linked with prolonged use frequently cause polyuria and polydipsia[8]. Psychiatric patients who require chronic treatment with lithium have reported nephrotoxicity by a decrease in glomerular filtration and creatinine clearance[9]. Other studies have shown lithium causing polyuria with a decrease in renal weights[10].

Since lithium is generally used in psychiatric disorders that require prolonged treatment, the results recorded in this investigation have revealed that if antimanic drugs like Lithium Carbonate are prescribed to maniac patients they develop nephrotoxicity[11,12]. The damaging effect of Lithium on renal weight was evident in the treated group in this study when compared with the untreated group of rodents.

Clinicians and authors of the same in their recently published investigation have raised concern over the scarcity of the literature that determines the injurious effects of lithium on the renal system. Therefore, the course of our study recorded and analyzed deviations of the urinary organ which was decreased organ (Kidney) weights in interventional groups of animals treated with lithium for extended time-periods and the decrease in weight of renal organ provides evidence of abnormal morphological change. The aim of this study is to evaluate the decline in organ weights (parameter) after oral doses of lithium for prolonged time period.

Methodology

This experimental study was conducted at Basic Medical Sciences Institute, Medical Centre Karachi after approval was taken from the university's animal ethical committee. This study was completed in six weeks from 5th May to 15th June year 2017. Pre-study sample size for animal study in which sacrifice is required is minimum six and we selected twenty animals that is ten in two groups. Each group comprised of ten adult male Wistar albino rats, 10-11 weeks in age and 250-300 grams in weight. They were retrieved from Charles River Breeding Laboratories, Brooklyn, and Massachusetts. Only healthy adult male rats aged 10-11 weeks and weights between 250-300 grams were included and at any time period of the study, any animal that felt sick during the acclimatization or study period was excluded from the research. The Randomization was achieved by allotting identification numbers. The numbers were then drawn in a lottery manner and the animals were randomly assigned to the two different groups in a logical manner. The two major groups A and B were then divided into four groups according to time period: A1, A2, B1, and B2, with five animals in each. They were housed in cages under controlled temperature and lighting conditions. The rodents were given a lab diet, consisting of green leafy vegetables and water and libitum. They were acclimatized for a week prior to study in a 12-12-hour day-night routine. Group A1 and A2 animals were

given only a healthy diet and served as Control groups, while the experimental groups, Group B1 and B2 animals were given Lithium carbonate 20mg/kg obtained by the name of Lithobid in powder form mixed in flour pellets daily at 10 a.m. in addition to their lab diet and water[13]. At the end of 2 weeks, Group A1 and B1 animals were sacrificed after anesthetizing them with ether. The abdominal wall of the animals was dissected and kidneys were identified and removed completely. The organs were weighed on a digital weighing machine, Beurer GS203, and the renal weights were recorded for both groups. At the end of 6 weeks, Group A2 and B2 animals were sacrificed in the same way and their kidneys were weighed and the observed data for two and six weeks in all groups were documented. The change measured of decreased kidney weights in treated Group B was observed. Five readings were taken in each group that is A1, A2, B1, B2 and the mean was calculated for each group. The original renal weights in all groups were compared and analyzed statistically using SPSS version 2016.

Results

Table 1. Comparison of weight (gms) ± standard deviation of Kidneys of Albino rats.

Groups	Intervention	Weeks	Weight (gms) Mean ± SD	Groups Comparisons
A1 (n=5)	Control	2	0.602 ± 0.636	p<0.001
A2 (n=5)	Control	6	0.783 ± 0.936	p<0.001
B1 (n=5)	Lithium-treated	2	0.569 ± 0.036	p<0.001
B2 (n=5)	Lithium-treated	6	0.478 ± 0.006	

The mean values of renal weights (Table 1) in Group A1 and Group A2 were 0.602 ± 0.836 gms, at 2 weeks and 0.783 ± 0.936 gms, at 6 weeks respectively. The mean values of kidney weights in treated Group B1 and Group B2 were 0.569 ± 0.036 gms at 2 weeks and 0.478 ± 0.006 gms at 6 weeks respectively (Table - 1).

The p-value (p<0.001) in Lithium lithium-treated group (Group B2) was found to be highly significantly decreased at 6 weeks compared to 2 weeks (Group B1) and also highly significantly decreased as compared to Group A1 and Group A2. The p-values in Group A1 and Group A2 (at 2 and 6 weeks) were found to be highly significantly increased at both 2 and 6 weeks as compared to Group B.

Hence there were statistically highly significant differences between groups using an independent sample t-test (p<0.001).

In this experimental investigation, the results showed statistically significant differences between groups. A comparison of the observed values has shown a highly significant decline in kidney weights due to the prolonged oral intake of Lithium carbonate at 2 and 6 weeks in Group B1 and Group B2 respectively.

The comparative analytical results of this study among control and treated groups are in agreement with the fact that the long-term intake of antipsychotic drugs leads to organ damage which is the main objective of my study.

Discussion

Bipolar disorder is personal and social deprivation. Maniac patients need pharmacological intervention and acute depressive disorders usually need treatment; patients suffering from bipolar disorder need long-term treatments with high dosage intake of lithium, to improve human and professional living. Therapeutic treatment is required to improve physical illnesses, metabolic disorders, maniac, and personality disturbances. Varied drug therapies for treatment of psychosis and management of patients suffering from anxiety, disorder is introduced by clinicians. Among the antipsychotic drugs, Lithium is the most commonly used drug due to its antimanic properties, this antipsychotic drug is popularly prescribed as it decreases relapses and causes decline in personality disorders. The drug of choice for personality disorders introduced 70 years ago, Lithium has been popularly used to treat mental disorders. Among Psychiatric disorders and personality disturbances, the common includes manic depressive disorder or Bipolar Disease (BD) also BSD short for Bipolar spectrum disorder are included under the umbrella of BD. Studies have recorded the different types with percentage of, BD-I being 3.1 percent, BD-II, almost 1.5 Percent affec-

ted, and subthreshold BD to be globally 1.6 percent, respectively. BD is a disease that includes range of moods of mania, hypomania, and depression. The disease is continuous and the intensity of depression increases along with mood swings. It has been observed that if psychiatric disorders are not treated they become complicated and patients appear with recurrences, for all these reasons medical management of bipolar disorder is a challenge. Medicinal history has proved that Li is the most favorable drug for mania but in today's clinical practice, its prescriptions have declined, due to the fact that it caused excretory apparatus damage as reported by John Cade in 1950 and the same review with chronic longitudinal treatment due to lithium resulted in nephrological pathogenesis as was studied in this comparative study[14-16].

Clinicians and researchers found that patients given this drug suffered from multiple organ injuries. Similarly, experiments with long-term Lithium administration showed unfavorable side effects of Lithium, like renal impairment, and gastrointestinal, neural, metabolic, and cardiovascular disorders. The damaging effects of Lithium increased in parallel with increasing time period. The most important negative effect of long-term lithium therapy is interstitial nephropathy. Many systematic clinical trials with this drug had documented that damage was due to decreased glomerular filtration. After oral intake of the drug, it is widely spread throughout the body within a few hours. Lithium is not absorbed and it is expelled entirely along with the waste matter from the body in urine. Approximately, 80% of lithium is filtered by the glomerulus and is reabsorbed: 60% by the proximal tubule and 20% by the thick ascending limb of the loop of Henle and collecting ducts. It causes renal dysfunctions due to tubular dysfunction, and its intoxication eventually results in a diseased renal state like nephrogenic Diabetes Insipidus and a decrease in the glomerular filtration rate, as reported by Liu YH, Tsai KF[17]. This may induce a reduction of renal weights and the same was reported by our prospective study.

Metals inhibit enzyme activity in humans and the most targeted key enzyme is a serine/threonine protein kinase (GSK-3â) which functions in a number of cell growths. If GSK-3â is inhibited by Lithium as discovered, then synaptic activity is delayed resulting in cell apoptosis and a decreased number of the renal tubules and inducing a decline in the weights of kidneys[18]. The same results of decreased renal weights were documented in our research.

Studies conducted on the effects of Lithium inhibiting Glycogen synthase kinase-3beta (GSK-3â) have been done and the same results of renal toxicity were found due to the reason that the antipsychotic drug leads to mitochondrial damage causing oxidative stress and cell death resulting in decreased organ weights[19-21]. This is in agreement with our study.

Clinical literature by Davis J, Desmond M, & Berk, have reported that long-term lithium treatment leads to permanent nephrotoxicity[21]. They related their experiment to the effect of the mood stabilizer lithium and reported that the adverse effects of the antimanic drug increased with increasing age and concluded that monitoring of patients is necessary so as to decrease the nephropathies. It was observed that intake of our experimental drug had resulted in renal cell death resulting in kidney disease due to prevention of glycogen synthetase activity as GSK 3 is essential for mitochondrial synthesis[22]. Glycogen synthetase kinase is a serine protein kinase required for cell processes and hormonal signaling which is affected by prolonged intake of this soft alkali which eventually induces oxidative stress. Increased oxidative stress generates high quantities of reactive oxygen species resulting in nuclear collapse and, it has been documented that extended use of lithium results in obliteration of cell metabolic activities which leads to cellular death due to mitochondrial clumping and diseased organs state the same was observed by us, clinical observations of lithium oral doses had proved that this drug is associated with cytotoxicity because it causes DNA impairment which produces plasma membrane loss and inhibition of cellular fu-

nctions resulting in apoptosis and decreased organ weights, the same decreased organ weights were found in our work and it may be due to the reason that this antipsychotic drug use produces denaturation of nuclear proteins[8,23].

Hedya and Swoboda reported in their study that Lithium was allowed for the treatment of psychosis by the U.S. Drug Administration (FDA) but its acute to chronic ingestion produced weight loss of the organs, they have also mentioned in their research that chronic lithium therapy resulted in diminished renal excretion due to glomerular loss and reduced renal capacity[24]. It was also observed that this antimanic drug in the population was the agent related to Diabetes Insipidus. Studies conducted on Lithium resulting in Nephrogenic Diabetes Insipidus had reported that this lesion occurred due to loss of responsiveness to antidiuretic hormone. Researchers found that Lithium led to the destruction of excretory organ structure and influenced renal cell degradation which eventually showed decreased excretory organ weights. From being the most popular drug for various mental illnesses it is highly recommended in major depression and Mood disorders with non–oncological status of patients but clinically it has its limitations and should not be prescribed in comorbid patients with cognitive slowing and patients suffering from renal failure.

Our descriptive work at two and six weeks on the oral doses of Lithium the old but still famous mood stabilizer is in accordance with the above-mentioned researches and showed a decline in renal weights.

The small sample size is the limitation of the study. It is recommended that further studies must be conducted on a longitudinal basis with more intervention in order to establish the drug effects. However, our experimental research has proved that being the favorable mood-stabilizing drug Lithium causes renal damage and it should be prescribed with caution in the population as its long-term use causes several structural organ damage. The psychiatrists prescribing Lithium should advise patients for regular follow-up in O.P.D. to monitor Lithium levels and different organ functions.

Conclusion

This analytical research has proved that renal damage occurs due to decreased renal weights in rat models due to prolonged intake of Lithium carbonate.

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