Original Article

Changes in Organ-Body Weight Relationship After Withdrawal of Chronic Lithium Administration in Rabbits

Nazreen Sharif, Ansa Rabia and Omar Iftikhar

Background: There is widely increasing use of lithium in psychiatric patients. Its chronic use has various side effects on the body. These effects are more severe if drug is withdrawn suddenly, affecting not only body weight but also other organs of the body disturbing hypothalamic-hypophyseal axis.

Objective: To document changes in organ-body weight relationship after withdrawal of chronic Lithium administration in rabbits

Material and Methods: Thirty adult male rabbits were divided into two groups, control and experimental. Each group was further divided into three subgroups. Lithium Carbonate powder 34.2 mg per kg body weight was administered daily by oral route in the form of capsule for four weeks to experimental group whereas control group was given empty capsules and normal diet. Animal weight and serum lithium levels were measured at the beginning of the experiment and thereafter checked weekly. After four weeks, one third of the animals in each group were sacrificed and their liver, kidney, thyroid and pituitary were weighed to see the effect of drug. Second and third groups were sacrificed one and two weeks after lithium withdrawal, respectively.

Results: The mean serum lithium levels gradually dropped after one week and significant fall was seen after 2 weeks of withdrawal but it did not touch the baseline. After 4 weeks of lithium consumption, hypothalamic-hypophyseal axis showed exaggerated response reflected by statistically significant increase in thyroid weight and statistically significant fall in that of pituitary along with decrease in weight of animal and kidney.

Conclusion

Abrupt withdrawal of drug set hypothalamic-hypophyseal axis at a new level as reflected by increase in thyroid and pituitary weight. Weight gained by body might be on account of other reasons.

Key Words: Chronic lithium, abrupt withdrawal, rabbits, hypothalamic-hypophyseal axis.

Introduction

Affective disorders are extremely common in general medical practice as well as in psychiatry. It covers an extraordinarily broad range from normal grief to sometimes fatal psychosis. The lifetime risk of suicide in major affective disorders is about 10-15%.[1] Lithium has been used since the late eighteenth century in different parts of the world for the treatment of bipolar disease. It was used for the first time to treat the bipolar patients in the 1870's by Carl Lange and William Hammond in Denmark and New York respectively.[2] Lithium carbonate lowers up to 7 folds in rate of suicidal acts and 2.7 folds in morbidity, whereas there is an increase of up to 14 times in fatalities after its discontinuation in manic depressive patients.[3] Non psychiatric uses are limited, however, it had been used in prophylaxis of cluster headaches (trigeminal autonomic cephalgias) and in neuro-degenerative diseases like amyotrophic lateral sclerosis.[4] Lithium however has a narrow therapeutic index of 0.6 to 1.2 meq/lit which makes its blood serum monitoring absolutely essential to avoid intoxication. Levels above 2 meq/lit are usually toxic.[5]

Chronic lithium usage had been shown over the years to produce a number of side effects. A lot of research had been focused on studying the harmful effects of lithium on various organs such as the kidney, thyroid, brain and liver.[6,7] However another common effect of such use was noticed to be weight gain.[8]

Lithium is a drug which is concentrated in various tissues like brain, kidney, thyroid, bone, liver and muscle cells against concentration gradient, causing increased lithium ratio.[9] Inside the cell its concentration may affect various functions and metabolism of the cells[10] so when the drug is withdrawn, unexpected response occurs.[11,12,13] These effect are more severe with abrupt rather than with

Table-1: Lithium therapy given to albino rabbits.

Groups	Subgroups	Rabbits	Treatment	Duration	Serum lithium level done & Sacrificed
Group "A"	A 1	5	Normal diet & empty capsule	4 weeks	29th day
	A2	5	Normal diet & empty capsule	4 weeks	After one week of withdrawal 36th day
	A3	5	Normal diet & empty capsule	4 weeks	After two week of withdrawal 43th day
Group "B"	B1	5	Normal diet & lithium 34.2mg/kg	4 weeks	29th day
	B2	5	Normal diet & lithium 34.2mg/kg	4 weeks	After one week of withdrawal 36th day
	B3	5	Normal diet & lithium 34.2mg/kg	4 weeks	After two week of withdrawal 43th day

of lithium being prescribed around the world, the present study was designed to highlight its effect not only on body weight but also on different organs of the body especially in relation with hypothalamic-hypophyseal axis.

Material and Methods

Chemical: Lithium carbonate powder by Fluka Chemic AG. CH-9470 Buchs Company, made in Switzerland was obtained from the medical store of Postgraduate Medical Institute, Lahore and was used for the study.

Animals: Thirty adult male albino rabbits were used for the experiment. They were kept at the Animal House of Postgraduate Medical Institute, Lahore and were allowed 2 weeks for acclimatization in optimal light and temperature and had free access to water and seasonal vegetables. Animals were randomly divided into 2 main groups; control A and experimental B, each with further subgroups A1, A2, A3 & B1, B2, B3, each having 5 animals. Lithium carbonate powder was given orally in a dose of 17 mg/kg calculated from chronic oral consumption of 1200 mg/day for an average of 70 kg given to man.[7] The weighed quantities of Li_2CO_3 in double the therapeutic dose 34.2 mg/kg body weight, once daily in capsules was given **(Table 1)**. The control group animals were given empty capsules. Serum lithium levels were recorded by using FP 10 & IT 20 Flame Photometer at the beginning of experiment and then weekly till the end of the experiment **(Table 1)**. The animals were also weighed and sacrificed on different days; their thyroid, liver, pituitary and kidneys were removed from the body and were weighed (mean weight of both kidneys was used for statistical analysis). The results were analyzed using statistical variance appropriate to the experimental design.

Results

No serum lithium levels were detected in control group animals as they did not receive lithium. The mean serum lithium levels gradually dropped after one week of withdrawal in B2 but it was not statistically significant when compared with B1(p value=0.732). However, statistically significant decrease was seen in subgroup B3 when compared with subgroups B1 and B2 (p values=0.000 and 0.001 respectively) i.e. after 2 weeks of withdrawal of drug; b

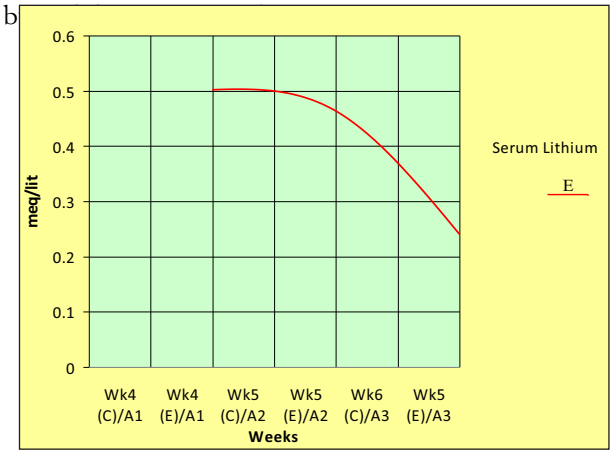

Figure I: Graph showing mean serum lithium levels with chronic lithium therapy and after its withdrawl in different experimental groups.

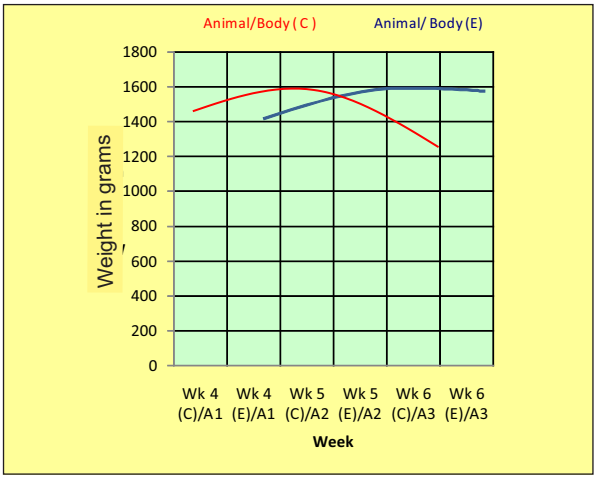

Figure II: Graph showing comparison of weight of

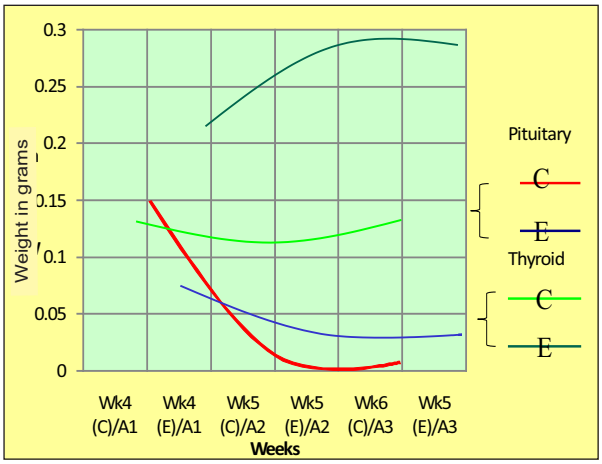

Figure III: Graph showing comparison of weight of thyroid and pituitary in control (C) and experimental (E) groups.

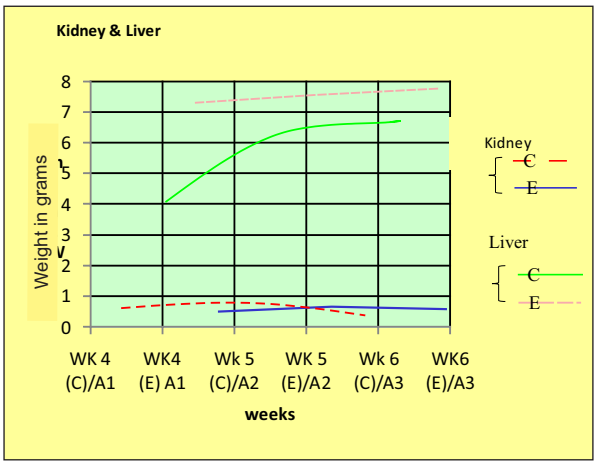

Figure IV: Graph showing comparison of weight of kidney and liver in control (C) and experimental (E) groups.

Animals gained body weight both in groups A and B. There was a statistically significant weight gain in B3 when compared with A3 (p value=0.030) i.e. after 2 weeks of withdrawal of drug **(Figure II).**

The weight of thyroid increased both in groups A and B. There was a statistically significant increase in weight of thyroid in subgroup B1 when compared with subgroup A1 (p value=0.035) i.e. after 4 weeks of Lithium therapy and also in subgroup B3 when compared with subgroup A3 (p value=0.043). There was no statistically significant change in weight of pituitary when subgroups of group B were compared with comparable subgroups of A (p values=0.051; 0.523 and 0.0223 at week 4, 5 and 6 respectively) as shown in **(figure III).**

The weight of liver increased both in groups A and B. There was a statistically significant increase in weight of liver in subgroup B1 when compared with subgroup A1(p value=0.017) i.e. after 4 weeks of Lithium therapy. There was no statistically significant change in weight of kidney when subgroups of group B were compared with comparable subgroups A (p value=0.736; 0.271 and 0.508 at week 4, 5 and 6 respectively **(Figure IV)**.

Discussion

In the present study, after 4 weeks of chronic lithium therapy, there was a statistically significant rise in serum lithium levels in group B1 as was also observed by Javaid[16] and Sharif.[17] Animals gained body weight both in groups A1 and B1 but it was more so in group A1 as compared to group B1. However, this difference in weight was not statistically significant. Individual variation in response to Lithium had been largely reported. [18] Lithium did not affect appetite in normal individuals,[19,20] whereas other workers had reported weight gain despite reduced appetite which might be due to an altered resting metabolic rate.[21] Combining anti-psychotics with mood stabilizers had lead to a greater weight gain than treatment with one or two mood stabilizers.[22]

Animals belonging to control group A1 showed an increase in weight of organs like kidney and pituitary but liver and thyroid did not show any rise. There was a decrease in weight of thyroid and increase in weight of pituitary in animals belonging to control group showing that there was normal functioning of hypothalamic-hypophyseal axis. Not only this, it also explained decrease in BMR which was reflected by increase in body weight and decrease in the weight of liver. An increase in kidney weight seemed to follow that of body weight. In experimental group B1, the hypothalamic-hypophyseal axis showed an exaggerated response which was reflected by an increase in thyroid weight with a concomitant decrease in weight of pituitary, causing an increase in BMR reflected by increase in liver weight and a fall in body weight. Kidney followed weight change as that of body. Chatterjee et al (1990) observed marked weight loss in the experimental animals after three weeks of lithium consumption in therapeutic dose. Chronic lithium therapy had been reported to cause mild microscopic changes but no effect on weight of the kidney [17] whereas functional changes related to oxidative stress had been reported.[24] Lithium is a known anti-thyroid drug[1] and goiter associated with lithium therapy was suggested to be a compensatory reaction to its anti-thyroid effect.[10] Mild to moderately

enlarged thyroid on gross examination with mild to moderate follicular hyperplasia and increased vascularity on microscopic examination had been noted earlier.[25] Similar findings suggestive of goiter had been reported earlier.[7] Inflammatory, congestive changes[26] and bile duct proliferation[16] had been reported on histological examination of liver from animals treated with chronic lithium therapy which might be responsible for this weight gain. An increase in hepatic glycogen with such therapy causing a weight gain had also been observed.[27] Chronic lithium therapy had been known to induce oxidative stress in liver.[24]

At week 5 i.e. one week after withdrawal of chronic lithium therapy, a fall in serum lithium level was observed in B2 but it was statistically insignificant when compared with that of B1. However, a post withdrawal rise in serum lithium levels, attributed to redistribution of lithium from its stored tissues like brain, kidney, liver and thyroid had been reported.[28] In control group A2, there was a fall in weight of thyroid and pituitary; however, only fall in pituitary weight in A2 was statistically significant when compared with that of Al. So it seemed to follow hypothalamic-hypophyseal axis. But due to decrease in BMR, there was an increase in body weight followed by kidney and liver in control group A2. In experimental group B2, hypothalamic-hypophyseal axis was disturbed as sudden withdrawal of lithium had reset the hypothalamic-hypophyseal axis to a higher level so that basal and TRH stimulated response of pituitary was exaggerated causing central hyperthyroidism[10] which was shown by an increase in weight of both thyroid and pituitary along with those of body, liver and kidney, but no value was statistically significant when compared with those of A2. So it was observed that there was a sustained effect of drug on weight of animal and its various organs after one week of sudden withdrawal of chronic lithium therapy. Thyroid gland had been reported to be moderately enlarged with prominent isthmus and mild congestion after sudden withdrawal of chronic lithium therapy on gross & microscopic examination respectively.[25] This exaggerated response might be due to unmasking of anti-thyroid antibodies by lithium withdrawal leading to rebound phenomenon.[7,29] Mild focal changes in renal architecture without congestion had been observed but without effecting weight of the organ.[17] This prolonged excretion pattern of lithium might be related to tissue storage, particularly in bones[30,31] and its gradual release from there into blood.[30]

Two weeks after withdrawal of chronic lithium therapy, there was a statistically significant fall in lithium level (B3). but it did not reach the baseline. Normally after withdrawal of the drug the serum lithium levels usually reach baseline in 10-14 days.[1] Margo and McMahon and Delva et al observed similar effect of withdrawal on the serum lithium levels.[11,12] However, such unpredictable responses in various individuals could be due to genetically determined lithium ratio, erythrocyte lithium/serum lithium, which is different even in mono-dizygotic twins.[32] Hypothalamic-hypophyseal axis was normal as weight of thyroid was increased with significant fall in weight of pituitary, suggesting an increase in BMR as reflected by fall in body weight, followed by statistically significant fall in kidney weight. There was an increase in liver weight suggesting an increased metabolism. An age-related decrease in pituitary weight had been reported earlier.[33] In experimental group (B3), hypothalamic-hypophyseal axis was set at a new level. This was suggested by an increase in weight of pituitary and thyroid when compared with those of A3. However, body weight and weight of thyroid in B3 was statistically significant more than those of A3 which could be supported by Sharif (2006) who reported thyroid gland to be grossly enlarged with marked congestion 2 weeks after withdrawal of chronic lithium therapy on gross and microscopic examinations.[25] It had been reported that changes appearing one week after lithium withdrawal persisted at week 2.[17] When the drug was discontinued suddenly, it gave rise to unexpected results. Regression analysis suggested that there was dose dependent gradual increase in weight which became significant after 2 weeks of withdrawal. Raised erythrocyte ratio in rabbits as compared to humans, caused sustained effect on various tissues like muscles, liver and fat cells, leading to increase weight even after the withdrawal.[4] It may be either due to its insulin like effect on carbohydrate metabolism, leading to increase in glucose uptake and glycogen synthesis in muscles, adipose tissue and brain; accompanied by depletion in liver glycogen[10,35,36] or due to persisting edema.[28]

Conclusions

After 4 weeks of lithium consumption, hypothalamic -hypophyseal axis showed exaggerated response reflected by statistically significant increase in thyroid weight and statistically significant fall in that of pituitary causing an increase in BMR, leading to increase in liver metabolism and decrease in weight of

of animal and kidney.

2 weeks after sudden withdrawal of drug, hypothalamic-hypophyseal axis was set at a new level as reflected by increase in thyroid and pituitary weight, but weight gained by body might be on account of other reasons as explained earlier.

It is suggested that abrupt withdrawal of chronic lithium therapy could have unexpected side effects. Therefore, in order to find the level of disturbance of hypothalamic-hypophyseal axis, we should explore microscopic picture of pituitary, hypothalamus and liver alongwith their biochemical analysis.

Department of Anatomy
CMH/Medical and Dental College, Lahore
theesculapio@hotmail.com
www.sims.edu.pk/esculapio.html

References

1. Goodman L, Gillman AG. Thyroid and antithyroid drugs. In: The Pharmacological Basis of Therapeutics. 9th Edition. McGraw Health Professions Division New York. 1996;446-49.
2. Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J.Decreased risk of suicides and attempts during long-term lithium treatment:a meta-analytic review. Bipolar Disord 2006;8: 625–39.
3. Lithium slows ALS progression In Study. muscular dystrophy Association. 2008; Available from URL: Http://www.als-mda.org/research/news/080204Lithium_slows_ALS.html. Retrieved 2009.
4. Groleau G. Lithium toxicity. Emerg Med Clin North Am 1994;12:511-31.
5. Clarke WB, Clarke RM, Olson EK, Barr RD, Downing RG. Binding of lithium and boron to human plasma proteins. Biol Trace Elem Res 1998;65(3):237-49.
6. Rosser R. Thyrotoxicosis and lithium. Br J Psych 1976; 128: 61-6.
7. Barbara S, Fleischhacker WW, Kaschka WP. Psycho neuroimmun. 2001. Karger Publishers, p. 2. ISBN 380557262X.
8. Okusa MD, LIT Crystal. Clinical manifestations and management of acute lithium intoxication. Am J Med 1994; 97:383-9.
12. Lazarus JH. The effects of lithium therapy on thyroid & thyrotropin releasing hormone. Mary Ann Liebert. Inc 1998;8:10.
13. Margo A. McMahon P. Lithium withdrawal triggers psychosis. Brit J Psych 1982;141:407-10.
14. Delva NJ, Letemendia FJJ, Prowse AW. Lithium withdrawal trial in chronic schizophrenia. Br J Psych 1982; 141:401-6.
15. Lapierre YD, Gagnon A, Kokkinidis L. Rapid recurrence of mania following lithium withdrawal. Biol Psych 1980; 15:859-64.
16. Baldessarini RJ, Tondo L, Floris G. Reduced morbidity after gradual discontinuation of lithium treatment for bipolar I and II disorders: A replication study. Am J Psych 1997; 154:551-3.
18. Yuce M. Difficulty in stopping lithium prophylaxis. Br Med J 1979; 1020.
19. Javaid S. A study of lithium induced toxicity in rabbit. M. Phil Thesis Pathology Department, University of the Punjab. Lahore;1985.
17. Sharif N, Hussain N, Raza TA. Role of chronic lithium therapy and its withdrawal on rabbit kidney-a histological study. Pak Postgr Med J 2003; 14(2) :100-3.
20. Jensen GL. Drug-induced hyperphagia: what can we learn from psychiatric medications. J Parenter Enteral Nutr 2008; 32(5): 578-81.
21. Chen Y, Goodal ER, Silverstone T. The effects of lithium on body weight and food intake in normal subjects a pilot study. Int Clin Psychopharmacol 1992;7(l):51-4.
22. Oerlinghausen BM, Psychological effects, compliance and response of long-term lithium. Brit J Psychiatry 1982 ;141:411-9.
23. Ruetsch O, Viala A, Bardou H, Martin P, Vacheron MN. Psycho-tropic drugs induced weight gain: a review of the literature concerning epidemiological data, mechanisms & manage-ment. Encephale 2005;31 :507-16.
24. Correll CU. Weight gain and metabolic effects of mood stabilizers and antipsychotics in pediatric bipolar disorder: a systematic review and pooled analysis of short-term trials. J Am Acad Child Adolesc Psychiatry

2007;46(6):6X7-700.
25. Chatterjee S, K Roden, TK Banerji. Morphological changes in some endocrine organs in rats following chronic lithium treatment. Anat Anz Jena 1990; 170:3 1-7.
26. Nciri Rr Allagui MS, Vincent C, Murat JC, Croute F, El Felki A. The effects of subchronic lithium administration in male Wistar mice on some biochemical parameters. Hum & Exp Tox 2009;2X(1 0): 64 1 -6.
27. Sharif N. Raza TA. Histological study on withdrawal of chronic lithium therapy on rabbits thyroid. Annals 2006; 12(3): 450-4.
28. Loghin F, Olinic A, Popa DS. Socaciu C. Leucuta SE. Effects of long-term administration of lithium and hydrochlorothiazide in rats. Met Based Drugs 1999; 6(2):X7-93.
29. Bosch F, Rodriguez-Gill JE, Hatzoglou M, Gomez-Foix AM, Hanson RW. Lithium inhibits hepatic gluconeogenesis and phosphoenolpyruvate carboxykinase gene expression. J Biol Chem 1992 Feb 15;267(5):2888-93.
30. Morton AW, Sonne SC, Lydiard RB. Lithium side effects in the medically ill. Inf LJ Psych Med 1993;23(4):357-X2.
31. Todd J, TC Jerram. Thyrotoxicosis during lithium treatment. PASTIC 197X;32:201-3.
32. Laurence DR, Bennett PN. Central nervous system In: Clinical Pharmacology. 7th edition. ELBS with Churchill Livingstone, Singapore 1992;293-5.
33. Birch NJ. Metabolic effect of lithium. Proceedings of the first British Lithium Congress University of Lancaster, England In: Johnson FN, Johnson S editors. Lithium in medical practice. MTP. Lancaster, England 1977;X9-111.
34. Lee CR, C Paschalis. Metabolism as guide to the solution of patients for lithium. therapy. Proceedings of the first British Lithium Congress University of Lancaster England In: Lithium in Medical Practice. Johnson FN. Johnson S (ed). MTP. Lancaster, England 1977;365-79.
35. Ikram MF, Sajjad Z, Shokh I, Omair A. Pituitary height on magnetic resonance imaging observation of age and sex related changes. J Pak Med Assoc 2008 May;58(5):261-5.
36. Laurence DR. Bennett PN. Central Nervous System In: Clinical Pharmacology. 7th Edition. ELBS with Churchill Livingstone, Singapore 1992; 293-5.
37. Plenge P. Lithium effects on rat brain glucose metabolism in long term: Lithium treated rats. Proceedings of the first British Lithium Congress University of Lancaster, England In: Johnson FN, Johnson S, editors. Lithium in medical practice. MTP. Lancaster, England 1977; 145-52.
38. Vendsborg P. Lithium and Glucose Tolerance. Proceedings of the first British Lithium Congress University of Lancaster. England In: Lithium in Medical Practice Johnson FN. Johnson S (ed). MTP. Lancaster, England