

Research Article

Effects of lithium carbonate on the microanatomy of thyroid gland of albino rats

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ABSTRACT

Background: Lithium is routinely used to treat mania and other psychiatric disorders. It prevents the mood swing changes in bipolar disorders and the treatment is usually prolonged. Aim of current study was to observe histological changes in the thyroid gland of lithium carbonate treated albino rats.

Methods: Sixty albino rats were taken and divided into two groups, group A (control group) of 15 animals, were fed with normal diet and group B of 45 animals, were fed normal diet along with lithium carbonate at the dose of 30mg/kg body weight daily. The animals were sacrificed at four, eight and twelve week's interval, 5µm sections prepared and stained with haematoxylin and eosin stain.

Results: Microscopic changes in thyroid gland of albino rats were evident after 8 weeks of drug administration which include marked pleomorphism, shrinkage in size of thyroid follicles, excess of colloid and marked vacuolations in acini. At 12th week of study, follicles were found both macro and micro follicular, with variable lining epithelium and hyperchromatic nuclei. Lining epithelium of some follicles was disrupted. The stroma was infiltrated with lymphocytes and eosinophils and there were some interfollicular hemorrhages.

Conclusions: Lithium given over prolonged period will cause macro and micro follicular goiter with hyperplastic epithelium and hyper chromatic nuclei, hyperplasia of stroma with increased vascularity, sometimes hemorrhages and finally may lead to thyroiditis like picture. So, it is advised that patients on lithium therapy should be periodically evaluated for thyroid dysfunction

Keywords: Lithium carbonate, Microanatomy, Thyroid gland, Albino rats

INTRODUCTION

Lithium (Greek, meaning Stone) was discovered by Arfwedson in 1811.¹ Lithium carbonate (Li₂CO₃), salt form of lithium, is commonly used as a psychiatric medication for the treatment of mania, both acutely and in the long term.^{2,3} The therapeutic uses of lithium also include use as an augmenting agent in depression, schizoaffective disorder, aggression, impulse control disorder, eating disorders, attention deficit disorder and in certain subsets of alcoholism. Lithium has been used in many medical disorders, especially cluster headache and

dermatological disorders (seborrheic dermatitis, eczematoid dermatitis, genital herpes).⁴ Initially, lithium was used to treat Urinary calculi and gout with little success,⁵ till Cade J. (1949),⁶ reported its antimanic effect. Lithium belongs to alkali group of metals, having atomic no.3 and atomic weight of 6.93. It is water soluble, non protein bound and is distributed in all body fluids.⁷ Lithium is readily absorbed after oral administration and its peak level is reached in 2-4 hrs. About 95% of absorbed lithium carbonate is excreted in urine; about 1% in feces and 4-5 % in sweat.^{2,8} Lithium binds poorly to high and low molecular weight plasma

proteins but binds strongly to very low molecular weight ligands.⁹ As it moves slowly from extracellular compartment to intracellular space, it may require 6-8 days to reach steady blood concentration and desired therapeutic responses.²

Distribution of lithium in the human organs is almost uniform; it is concentrated in tissues like brain, kidney, thyroid, bone, liver, and muscle cells against concentration gradient.² Lithium becomes widely distributed in the central nervous system and interacts with a number of neurotransmitters, decreasing norepinephrine release and increasing serotonin synthesis. It has been reported that lithium can alter the glucose metabolic set point¹⁰ and inhibits the phosphoglucosyltransferase.¹¹ An increase in fructose 2, 6-biphosphate levels had been observed with lithium treatment but it does not affect the cytochrome P-450.¹²

Mechanism of action - lithium and thyroid gland

The thyroid gland is highly vascular organ. Lithium gets highly concentrated in thyroid gland against concentration gradient and interferes with thyroxine synthesis and metabolism.¹³ The pathway of thyroid hormone synthesis, transport of secretion in the circulation and their metabolism offer numerous targets for drug interaction.¹⁴ Lithium inhibits the coupling of iodotyrosine residues in the formation of thyroxine (T₄) and triiodothyronine (T₃), and subsequent release of these iodothyronines.¹⁵ Although the precise mechanism for this process is still uncertain, it may decrease the pinocytosis of colloid from the follicular lumen, leading to inhibition of colloid droplet formation as well as the blockade of cellular events mediated by cyclic adenosine monophosphate (cAMP), either by directly inhibiting adenyl cyclase as a substitute for cationic enzymatic co-factors (e.g. Na⁺ or K⁺), or through the blockade of cAMP at any step in the cellular microenvironment.^{16,17} Lithium may affect deiodinase activity, which is a group of enzymes that can either activate thyroid hormones by promoting the conversion of T₄ to T₃, or inactivate hormones by converting either T₄ to reverse triiodothyronine (rT₃) or T₃ to inactive diiodothyronine (T₂).¹⁸ Particularly, lithium has been shown to inhibit the type II deiodinase enzyme (5'-monodeiodinase), which is responsible for the peripheral conversion of T₄ to T₃.¹⁸ In addition, lithium can increase intrathyroidal iodine content, which inhibits the release of T₄ and T₃ through a feedback mechanism.¹⁹ The inhibition of organic iodine formation and inhibition of thyroid hormone secretion is responsible for the initial fall in serum T₄ and T₃ within hours of iodide therapy.²⁰ Since lithium is also concentrated in the pituitary gland and hypothalamus there may be an effect on the hypothalamo-pituitary axis.²¹ Patients on lithium therapy may develop goiter, hypothyroidism and hyperthyroidism which on histological examination manifests as macro or micro-follicular goiter.²²

Aim of the study

Lithium carbonate is widely used to treat manic depressive psychosis. As the therapy is prolonged one, it is unlikely to be without undesirous side effects on various organs including thyroid gland. The present study is aimed to analyze the histological changes that occur in thyroid gland on prolonged use of Lithium in Albino rats and try to correlate these findings to human beings.

METHODS

After Institutional Animal Ethics Committee approval, 60 Albino Rats (average weight 150 gm) were housed under uniform husbandry conditions. The rats were divided in two groups: group A (control group) of 15 rats were fed with routine diet and water ad. Libitum, group B: this group of 45 rats was fed with routine diet, water and pellets of flour mixed with lithium carbonate. The animals of two groups were kept in different cages labelled (A) and (B).

Dose of the drug: Dose of the drug was calculated by converting adult human therapeutic dose (600-2400mg/day) to animal dose.^{7,23} The average dose of lithium carbonate amounted to 30mg/kg of weight of rats per day.

To study the effects of the drug, five rats from group (A) i.e. control group and 15 rats from group (B) i.e. drug treated group were sacrificed at intervals of four, eight and twelve weeks. The animals were anesthetized with chloroform, a midline incision was given on the anterior aspect of neck, small strap muscles retracted, thyroid gland excised, put in between blotting papers and preserved in 10% formalin. The tissues were processed by standard histological technique; 5µm thick sections were prepared, stained with Haematoxylin and Eosin stain, observed under compound light microscope and observations recorded.

RESULTS

Control group

Microscopic examination of sections from control group showed the same normal histological structure, which included thyroid follicles of variable sizes and their lumens contained colloid. The follicles were lined by simple cuboidal epithelium and surrounded by stroma (connective tissue).

Lithium treated group

Histological examination (Table 1) showed intact capsules and architecture. Microscopic changes were evident after eight weeks of drug treatment. Thyroid gland of drug treated animals showed follicles of varying size and shape; some were large, some small; some shrunk and in some colloid was depleted resulting in

vacuolation of the follicles (Figure 1). Vacuolations or scaploid appearance of follicles was observed in 20% animals at 8 weeks, which increased to 60% animals at 12 weeks. Many sections showed irregular follicles with papillary folding projecting into the follicular lumens. Some follicles showed detachment of lining epithelium and detached follicular cells were found in the follicular colloid. Papillary folding and follicular cell detachment was observed more at 12 weeks of drug treatment. The follicles were lined with hyperplastic epithelial cells with large hyperchromatic nuclei.

Table 1: Microscopic findings of thyroid gland at 4, 8 and 12 weeks of lithium treatment.

Findings	4 th week (n=15; %)	8 th week (n=15; %)	12 th week (n=15; %)
Capsule	Intact	Intact	Intact
Architecture	Preserved	Preserved	Preserved
Pleomorphism	Absent	Present +	Present ++
Size of follicles	Both Macro and micro follicular	Both Macro and micro follicular	Both Macro and micro follicular
Vacuolations	Absent	Present (n=3; 20%)	Present (n=9; 60%)
Papillary folding	Absent	Present (n=3; 20%)	Present (n=6; 40%)
Detachment of follicular cells	Absent	Absent	Present (n=3; 20%)
Interstitial Haemorrhages	Absent	Present +	Present ++
Lymphocytic infiltrations	Present +	Present ++	Present +++
Eosinophilic infiltrations	Absent	Absent	Present +

Some follicles were lined with simple squamous epithelium; others were lined with cuboidal or tall columnar epithelium. There was marked epithelial cell pleomorphism and pronounced nuclear changes at 12 weeks of drug treatment (Figure 2).

The interfollicular stroma was hyper cellular and congested at 8 weeks of drug treatment, which changed to frank interstitial hemorrhages at 12 weeks (Figure 2). The stroma was observed to be infiltrated with lymphocytes from the beginning of the study but the infiltration increased as the duration of drug treatment increased (Figure 1). At the end of the study, some specimens showed mild eosinophilic infiltrate.

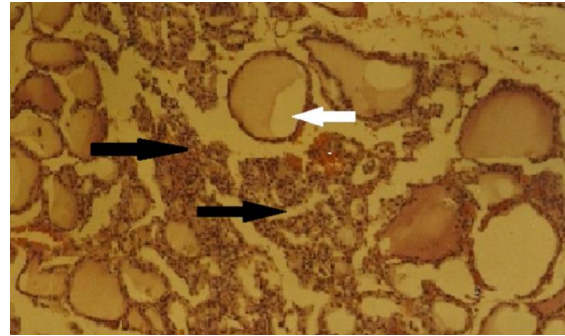


Figure 1: Photomicrograph of thyroid gland of Albino rat after 12 weeks of lithium therapy, showing vacuolations of thyroid follicles (white arrow), lymphocytic infiltrations (black arrow) and pleomorphic epithelium with hyperchromatic nuclei (red arrow) (H and E x 100).

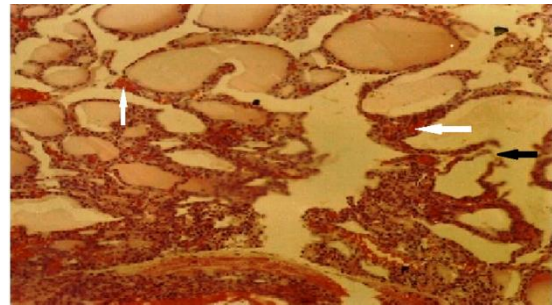


Figure 2: Photomicrograph of thyroid gland of albino rat after 12 weeks of lithium administration showing interfollicular hemorrhages (white arrow), follicular disruption (black arrow) and detached follicular epithelium cells in the colloid (small white arrow). (H and E x 100).

DISCUSSION

Lithium carbonate is routinely used in the treatment of manic depressive psychosis, in addition to other psychiatric disorders.^{3,4} Structural and functional effects of lithium carbonate have been studied by various workers from time to time.^{1,6} Lithium gets concentrated in the thyroid gland against concentration gradient by active transport.¹³ It was observed that thyroid gland showed formation of goiter of both macro and micro-follicular type in all the drug treated animals.. The formation of goiter is due to proliferation of thyrocytes due to activation of the proliferative tyrosine kinase and Wnt/beta-catenin signaling pathways.²² The follicles were lined with hyperplastic epithelial cells with hyperchromic nuclei. Similar findings were also reported by Tseng H. Len (1971),²⁴ Helte (1973),²⁵ Schou M et al. (1968)¹ and Faurndt L (1981).²⁶ The effects of lithium on thyroid gland are enhanced if there was pre-existing subclinical thyroid disorder.⁹ Studies have shown that majority of patients who developed hypothyroidism after lithium therapy have either thyroid peroxidase antibodies and/or an exaggerated stimulation of TSH.^{27,28} Other studies

showed fluctuations in antibody titers over the course of lithium treatment, negating the possibility that that lithium increases these antibodies.²⁹ In the present study, it was observed that there was increased vascularity and occasional interfollicular hemorrhages in the stroma. Such findings have not been reported by any other worker. The increased vascularity may be due to increase in size of the thyroid gland as goiter formation occurs. Increased inflammation due to infiltration of lymphocytes results in hemorrhages in the stroma.

The mechanism of the effect of lithium on the thyroid gland is not fully understood. Lithium gets concentrated in the thyroid gland five times than other organs.³⁰ It is possible that lithium reduces iodine uptake by the thyroid gland, impairs coupling of iodotyrosinase and interferes with the release of hormone from the gland.³¹ Elbakery et al. (2009)³² reported detachment and desquamation of follicular cells into the colloid, as was found in the present study. In the present study, in some specimens there was lympho - eosinophilic infiltrates, which resembles the picture of Hashimoto thyroiditis. Similar findings were also reported by other workers which called these eosinophilic infiltrates as Hurthle cells.³³ Hurthle cells are characterized as enlarged epithelial cells with abundant eosinophilic cytoplasm as a result of altered mitochondria. These cells are commonly present in Hashimoto's thyroiditis which may change into adenoma which has potential to become malignant.³⁴ Cellular infiltrations observed in the present study is consistent with autoimmune thyroiditis, as some studies have reported a higher incidence of thyroid antibodies in the blood of some patients treated with lithium.³⁵

Clinical correlation

In clinical studies, the most common abnormality associated with lithium administration is goiter. The incidence is estimated to be 40-50% of the patients treated with lithium.²² Lithium is associated with a 7% (2-15%) increase of clinical hypothyroidism, 5% risk of goiter and rarely (0.7%) hyperthyroidism.¹³ Subclinical hypothyroidism (approximately 19%) is considered more common than clinical hypothyroidism, and minor elevation of thyroid stimulating hormone (TSH) may normalize without treatment. Chemical hypothyroidism with lithium is around 50%.¹³ Lithium is highly concentrated in the thyroid gland against a concentration gradient, probably by active transport. Lithium interferes with glandular release of thyroid hormones (T₄ and T₃) by decreasing the endocytosis of thyroid hormone-laden thyroglobulin on the luminal side of the thyroid follicle; this causes a transient thyrotropin elevation in more than a third of lithium carbonate-treated patients.³⁶ The glandular release inhibition is mediated by cyclic adenosine monophosphate (cAMP) within the thyrocyte.³⁷ Lithium at higher doses may block iodine uptake and organification within the thyroid. Lithium was found to stimulate cell proliferation in the absence of thyrotropin stimulation; but under thyrotropin

stimulation, lithium diminished thyrocyte proliferation, especially when used at higher concentrations.³⁸ Lithium affects many aspects of cellular and humoral immunity *in vitro* and *in vivo*. Prevalence of specific thyroid antibodies among lithium-treated patients varies across studies. Women are known to express thyroid autoimmunity more frequently than men, and it is more in the middle age range. So also thyroid autoimmunity has been found associated with affective disorders, irrespective of lithium use. So it is unclear as to whether lithium *per se* can induce thyroid autoimmunity.³⁹

There is evidence that females, patients with rapid cycling and patients with an underlying autoimmune thyroiditis are more prone to lithium-induced hypothyroidism.⁴⁰ A study showed that 74% cases of hypothyroidism developed in the first two years of treatment.³⁸ Lithium-induced goiter is usually characterized by small, smooth and nontender nodules; in some cases, nodules may regress over time. The cause of lithium-induced thyrotoxicosis is not clear; some authorities have speculated that lithium may directly stimulate autoimmune reactions.³⁸

CONCLUSION

From our study, we conclude that lithium given to rats over prolonged period will cause macro and micro follicular goitre with hyperplastic and hyper chromic epithelium, disruption of follicles, hyperplasia of stroma with increased vascularity, sometimes hemorrhages and finally may lead to thyroiditis like picture. It is suggested that before starting lithium, thyroid functions have to be assessed (the determination of thyroid hormones, thyroid stimulating hormone (TSH) and baseline antithyroid antibody). Subsequently, monitoring of thyroid function should be done every 6 to 12 months.

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