

## Original Research Article

# Levels of serum lithium in manic depressive patients with mild persistent bronchial asthma

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### ABSTRACT

**Background:** Lithium, widely used in manic depressive (MD) patients, might protect the airways against constrictor stimuli in bronchial asthma (BA), through its effects on cell signal transduction and ion transport pathways.

**Methods:** Serum lithium levels were studied in MD patients with better controlled mild persistent BA (group A) and MD patients with not so well controlled BA (group B).

**Results:** Serum lithium levels were highly significantly more in group A compared to lithium levels in group B.

**Conclusions:** Lithium may inhibit the contractile response of airway smooth muscle and can be used in treatment / monitoring of BA.

**Keywords:** Bronchial asthma, Lithium, Manic depressive

### INTRODUCTION

Bronchial asthma (BA) is an inflammatory disease of the airways characterized by airway obstruction and increased airway responsiveness.<sup>1</sup> There is a noticeable increase in health care burden from BA in several areas of the world.<sup>2</sup>

BA is very common and is a disturbing yet increasing cause of mortality and morbidity throughout the world and also in India. Mild asthma includes intermittent and persistent mild asthma, according to the Global Initiative for Asthma (GINA) classification and affects between 50% and 75% of asthma patients.<sup>3</sup>

BA results from complex interactions between inflammatory cells, their mediators, airway epithelium and smooth muscle, etc.<sup>4</sup> Acute and chronic inflammation can affect not only the airway caliber but also underlying

bronchial hyper-responsiveness, which enhances susceptibility to bronchospasm.<sup>5</sup>

The role of calcium via its second messengers, IP<sub>3</sub> (inositol triphosphate) and DAG (diacylglycerol) in airway smooth muscle (ASM) contraction is well known. But both sodium and potassium also have important parts in ASM contraction, mediated through their respective mechanisms.

Lithium is considered to be a drug of choice in the therapy of manic depression but lithium has been used in other conditions.<sup>6</sup> It was anticipated that lithium, through its effects on cell signal transduction and ion transport pathways, would be likely to protect the airways against constrictor stimuli.<sup>7</sup> So, the levels of lithium in manic-depressive (MD) patients with mild persistent BA was studied to evaluate whether there was any possible beneficial effect of lithium on BA symptoms.

## METHODS

This was a cross sectional study conducted in the Biochemistry, Psychiatry and Chest departments of a tertiary care medical college of West Bengal.

### Inclusion criteria

MD patients in the age range 25-50 years with mild persistent BA. The study was conducted from June 2018 till May 2019.

### Exclusion criteria

None of the patients were current smokers, and none had smoked within the previous two years, no patient had any bronchial or respiratory tract infection during the month preceding the test. Patients were excluded from the study if they had had a severe exacerbation of asthma requiring hospitalization during the month preceding the study, if they had taken systemic corticosteroids in any form during the previous two months, or if they had inhaled corticosteroids during the previous month, before the test.

At the time of this study approximately 200 patients with MD (and mild persistent BA) were registered at the Psychiatry department but records from about 40 patients were excluded or could not be used for the following reasons: poor attendance by the patient at the clinic, the patient was apparently not taking the lithium tablets regularly, the patient had recently started taking lithium and the dosage had not yet been stabilized, the patient had taken lithium only a few hours before attending the outpatient department.

In an effort to ensure that blood samples were taken about 12 hours after lithium ingestion, patients had been routinely instructed to take their 'last' tablet(s) on the night before attending the outpatient department. The 158 patients who were included in this study had been receiving the same dose of lithium for at least 3 months.

The following information was extracted from the department register: age and sex of patient, diagnosis, daily lithium dose, proprietary brand of lithium prescribed, other drugs prescribed, clinical assessment and any indication of lithium side effects. Consensus diagnosis by two psychiatrists was made for each patient, according to proper criteria.<sup>8</sup> The patients had been treated with lithium carbonate for at least 5 years (5-22 years, mean 14.3 years) and attended the same outpatient clinic for the entire period of lithium administration.

From 158 patients, 73 patients who were better controlled with respect to their BA status were chosen as group A, and 64 age and sex matched patients whose BA control status was not as good as compared to group A, were included as group B. The patients were from Murshidabad district of West Bengal. The study was approved by the Ethics Committee of the medical

college. All subjects gave their written consent after receiving a full explanation of the nature of the procedures.

Venous blood sample was collected from each subject after 12 hours of fasting. All samples were coded and assayed in a blind fashion by an investigator who was unaware of the subjects' clinical status. Serum lithium was assayed by ion selective electrode and statistical analysis of the data was performed by using Statistical Package for Social Sciences (SPSS version 16) and inferences were drawn.  $P < 0.05$  was considered to be significant.

## RESULTS

Mean (+ SD) serum lithium levels (in mmol/L) in group A and group B were 0.68 (+0.09) and 0.63 (+0.08) respectively and the difference was found to be extremely significant ( $p = 0.0008$ ) i.e. subjects with better degree of BA control had higher levels of lithium, which was statistically highly significant, compared to subjects with BA not so well controlled.  $p$  value and statistical significance: two-tailed  $p$  value equals 0.0008. By conventional criteria, this difference is considered to be extremely statistically significant. Confidence interval: The mean of Group A (0.68 mmol/L) minus Group B (0.63 mmol/L) equals 0.0500. 95% confidence interval of this difference: From 0.0211 to 0.0789.

**Table 1: T test of serum lithium levels (in mmol/l) of group A and group B including the significance in difference.**

	Group A	Group B
Mean	0.68	0.63
SD	0.09	0.08
SEM	0.0105	0.01
N	73	64

N.B. SD= Standard deviation, SEM= Standard error of mean, N=number of subjects

Number of subjects in group A and group B were respectively 73 and 64. At the time of this study approximately 200 patients with MD (and mild persistent BA) were registered at the Psychiatry department but records from 42 patients were excluded; so actually records of 158 subjects were used for the study. Intermediate values used in calculations:  $t = 3.4159$ ,  $df = 135$ , standard error of difference = 0.015

## DISCUSSION

In ASM the role of calcium is as follows: Interaction of contractile agonists with their G protein-coupled receptors leads to activation of phospholipase C- $\beta$ , which hydrolyzes phosphatidylinositol 4, 5-bisphosphate (PIP<sub>2</sub>), thus producing the two second messengers IP<sub>3</sub> and DAG. IP<sub>3</sub> binds to its receptor on the sarcoplasmic reticulum, thereby releasing calcium (Ca<sup>2+</sup>) that activates Ca<sup>2+</sup>-

calmodulin-dependent myosin light chain kinase (MLCK). MLCK phosphorylates myosin light chain, leading to ASM contraction.<sup>9</sup> In-vitro studies have shown that lithium partially inhibits the contractile response of airway smooth muscle, possibly by an effect on the inositol phospholipid-derived second messenger system.<sup>10</sup> This finding is supported by the fact that improvement in asthma control during the course of lithium therapy has been recorded, and a double-blind trial of short-term lithium therapy in patients with asthma has shown an improvement in airway responsiveness.<sup>11</sup>

On the other hand, Ca<sup>2+</sup> influx via the reverse-mode of the sodium calcium exchanger (NCX) plays a substantial role in excitation-contraction coupling and the refilling of the sarcoplasmic reticulum in ASM.<sup>12</sup> Thus, the inhibition of the Na/K pump, which appears to be associated with atopy, may contribute to airway dysfunction by elevating cytosolic levels of sodium, thereby promoting Ca<sup>2+</sup> influx via reverse-mode NCX activity and increasing tone.<sup>13</sup> Potassium also plays an important role in ASM. ASM cells express various types of potassium (K<sup>+</sup>) channels which play a key role in determining the resting membrane potential, a relative electrical stability and the responsiveness to both contractile and relaxant agents. In addition, K<sup>+</sup> channels are also involved in modulation of neurotransmitter release from airway nerves. Lastly, K<sup>+</sup> channel openers are able to induce hyperpolarization of ASM cells, bronchodilation, suppression of airway hyperresponsiveness, and inhibition of neural reflexes.<sup>14</sup> Concurrently, there is evidence that lithium may influence intracellular concentrations of potassium, calcium and sodium.<sup>15</sup> Logically, this mechanism might help lithium to improve symptoms in asthmatics, a finding which has been proved by studies.<sup>11</sup>

In BA there are phenotypic transitions of bronchial epithelial cells, smooth muscle cells, and fibroblasts. Human bronchial fibroblasts (HBFs) derived from patients with BA display predestination towards TGF- $\beta$ -induced phenotypic switches. The interference between TGF- $\beta$  and GSK-3 $\beta$  signaling contributes to pathophysiology of BA. The inhibition of GSK-3 $\beta$  by Lithium attenuates TGF- $\beta$  1-induced myofibroblast transition (FMT) in HBF of BA. Cytoplasmically sequestered  $\beta$ -catenin, abundant in TGF- $\beta$  1/LiCl-stimulated asthmatic HBFs, most likely interacts with and inhibits the nuclear accumulation and signal transduction of Smad proteins. These data may explain recurrence of BA symptoms upon the discontinuation of lithium therapy in certain psychiatric diseases.<sup>16</sup>

In present study also, subjects with better degree of BA control had higher levels of lithium, which was statistically highly significant, compared to subjects with BA not so well controlled (Table 1). Combination of all or some of the above mentioned evidence might explain the findings of present study, i.e. lithium may inhibit the contractile response of airway smooth muscle, possibly by an effect on the inositol phospholipid-derived second messenger system;

lithium may influence the intracellular concentrations of potassium, calcium and sodium; inhibition of GSK-3 $\beta$  by Lithium attenuates TGF- $\beta$  1-induced myofibroblast transition (FMT) in HBF of BA, etc.

The study has limitations; firstly, the sample size is low. But with so many exclusion and inclusion criteria, it could not find more patients having both MD and mild persistent BA at the same time. The research with larger sample size is required to extrapolate the findings to the general population. Serum lithium was estimated with ion selective electrodes. Lithium can be estimated by various methods, but the present method was employed as it is a time tested and standard method. Patients were taking a number of medications (other than diuretics, ACE inhibitors, theophylline, caffeine, and acetazolamide, etc) to control MD and BA. However, these treatments are characteristic of patients with BA and do not affect serum lithium levels. The present study was conducted in a tertiary care hospital. However, in our country, most people visit district, subdivisional, and lower-tier hospitals for treatment. Hence, results of the study might not reflect the true picture of the population as a whole. Probably, a multicentric study on a larger population would be better in revealing the actual statistics.

## CONCLUSION

Despite these limitations, and taking into consideration the findings of the study, the study results point toward using lithium estimation as an important, potential parameter for BA treatment and/or monitoring. Still, more research is needed to confirm the findings. It was concluded that the problem of pathogenesis of BA should be further investigated, and other similar biological parameters to determine pathophysiology, and therefore treatment options, should also be assessed.

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