# Serum levels of lithium in patients of a psychiatric center in Manaus, Amazonas

***Níveis séricos de lítio em pacientes de um centro psiquiátricos em Manaus, Amazonas***

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**ABSTRACT**

Lithium is the medication of choice for bipolar disorder maintenance therapy and is also used in the treatment of mania, recurrent depression and in patients at risk for suicide. Therapeutic concentrations fluctuate between 0.5 and 1.2 mmol/L, obtained with maintenance of between 900 and 2,400mg/day. This article presents preliminary data of a study on treatment with lithium in patients at a public psychiatric center in the city of Manaus, Amazonas, Brazil. Data were obtained on the posology prescribed, co-medication, ingestion of other substances and the serum lithium concentration was determined to evaluate the adhesion to the lithium treatment and the risk of toxicity or poor efficacy, due to inappropriate levels. It was found that only 26.98% of the patients presented therapeutic concentrations. The possible causes of this low prevalence are: inadequate lithium doses prescribed (60.32%) and patients who did not take the prescribed doses, or did not take them properly with regard to daily frequency. The latter two situations characterize a lack of adhesion to treatment with lithium, which demands a specific study to enable understanding the phenomenon of this group of patients.

***Key Words:*** Lithium Carbonate; Drug Monitoring; Bipolar Disorder.

**RESUMO**

O lítio é o medicamento de escolha na terapia de manutenção do transtorno do humor bipolar e também é usado no tratamento da mania, depressão recorrente e em pacientes sob risco de cometer suicídio. A faixa de concentração terapêutica varia entre 900 a 2.400mg/dia. Este artigo apresenta dados preliminares de um estudo sobre o uso de lítio por pacientes de um centro psiquiátrico público na cidade de Manaus, Amazonas, Brasil. Foram coletadas informações sobre a posologia prescrita, uso de co-medicações e ingestão de outras substâncias, sendo determinada a concentração sérica de lítio para avaliar a adesão ao tratamento, risco de toxicidade ou ineficácia do mesmo devido a níveis séricos inapropriados. Os resultados revelaram que apenas 26,8% dos pacientes apresentavam concentrações séricas dentro do intervalo terapêutico. As possíveis causas para esta baixa prevalência são: prescrição inadequada (60,32%) e não ingestão das doses prescritas ou dificuldade em tomar o medicamento com frequência. As duas últimas situações caracterizam a falta de adesão ao tratamento com lítio, que demanda um estudo específico que permita a compreensão de tal fenômeno neste grupo de pacientes

***Palavras-chave:*** Carbonato de Lítio; Monitoramento de Medicamentos; Transtorno Bipolar.

## INTRODUCTION

Lithium is the medication of choice for long term maintenance treatment of bipolar disorder, in spite of increasing alternative proposals, including various new anticonvulsant and antipsychotic agents (Busby & Sajatovik, 2010; Laolakkana & Wannawitchate, 2008; Young, 2009). It is also used in the treatment of mania, recurrent depression, in patients at risk for suicide and its efficacy is directly related to its therapeutic concentrations (Sproule, 2002).

Inappropriate doses of lithium may result in weak control of symptoms or potentiation of dose-dependent adverse effects such as: nauseas, diarrhea, polyuria, polydipsia, fine hand tremor, muscle weakness, in addition to toxicity risks and chronic renal failure (Sproule, 2002). Thus, serum lithium monitoring must be associated with the therapeutic scheme (Aronson & Reynolds, 1992; Vega *et al*., 2011), as this indicates adhesion to treatment, facilitates the adjustment of dose, detects variations due to medicamentous interactions and conditions of intoxication (Rosa *et al.*, 2006).

Treatment may begin with an attack dose that is afterwards adjusted by means of monitoring therapy. Prophylactic maintenance doses range between 900 and 1,500 mg/day (Anderson *et al.*, 2002; Kook *et al.*, 1985; Lobeck, 1988), and may be increased to up to 2,400mg/day (Carson, 1992).

In patients chronically treated with lithium, monitoring demands blood samples collected at the time of day when the concentration is at its lowest; that is to say 12 hours after the last dose, or immediately before the following dose of the medication (trough level) and when the pharmacokinetic state of equilibrium has been reached, 5 or 7 days after treatment has started (Anderson *et al.*, 2002; Carson, 1992; Lobeck, 1988).

This trough level must be maintained between 0.8 and 1.5 mmol/L in acute conditions of mania or hypomania and between 0.6 and 1.2 mmol/L for prophylaxis of bipolar disorder (Lobeck, 1988; Sproule, 2002). By virtue of the toxic effects of lithium, it is suggested that the maintenance levels for prophylaxis should be kept below 0.9 mmol/L (Sproule, 2002). Baumann *et al.* (2004) considered lithium a medication whose therapeutic monitoring is mandatory and as consensus adopts the concentrations of 0.5 to 1.2 mmol/L as therapeutic interval.

In cases of suspected toxicity, determination of the serum concentration is performed at the maximum peak absorption of the drug, 2 to 4 hours after ingestion of the dose (peak

level). Serum concentrations of over 1.5 mmol/L are associated with signs of toxicity, such as: Coarse hand tremor, persistent gastrointestinal effects, muscle hyperirritability, slurred speech, confusion, stupor, convulsions, hyperreflexia, irregular pulse and coma. Serum lithium concentrations above 2 mmol/L denote severe toxicity (Anderson, 2002). There are some methods for estimating the adjustment of the adequate dose in the beginning of treatment, based on determination of the lithium serum concentration (Carson, 1992), which may be performed in the maintenance stage by the calculation (serum concentration observed = dose)/(serum concentration desired = new dose) (Rosa *et al.*, 2006).

However, even at serum concentrations considered as therapeutic, a small portion of patients may develop symptoms of intoxication although they are using low doses of lithium. Another important fact is that some patients present signs of lithium toxicity after long periods of taking the same dose (Kehoe & Mender, 1992) that is why it is important to implement therapeutic monitoring in patients submitted to this medication therapy.

The purpose of this article, part of a study about treatment with lithium in psychiatric patients, was to evaluate the serum lithium concentrations in patients at the psychiatric center "Centro Psiquiátrico Eduardo Ribeiro" (CPER), one of the main public services providing ambulatory attendance to psychiatric patients in the city of Manaus, Amazonas, Brazil, in order to evaluate the adhesion to treatment and the risk of toxicity or poor efficacy of the treatment, due to inappropriate plasma levels.

## METHOD

This research was approved by the Ethics Committee of the Federal University of Amazonas (Brasil) in 2010/11/22 (protocol number 0408.0.115.115-10) and included ambulatory patients attended at "Centro Psiquiátrico Eduardo Ribeiro", in the city of Manaus, Amazonas, who were under treatment with lithium in the period from January to March 2011. Recruitment of the research participants was performed daily, without previous contact, and they were approached in order of arrival for their bi-monthly consultation. After the patient gave their formal consent, the interview was held about the treatment data and use of lithium and other substances.

Serum lithium concentration was determined at a private laboratory, accompanied by researchers, by means of the ion selective electrode technique, widely used by clinical analysis laboratories, due to lower cost and providing fast results (Aliasgharpour & Hagani, 2009). The equipment used was an ion detector AVL Model 9180, Roche brand, with a dynamic band between 0.1 and 6.0 mmol/L. The participants provided blood samples for lithemia, at the time of trough level and being a minimum of 7 days after treatment began, or of a dose adjustment. Serum concentrations between 0.5-1.2 mmol/L were considered as being within the therapeutic range (Baumann *et al*., 2004).

To characterize the studied population descriptive statistics were used. For comparison of the serum lithium concentration means, between the groups, the t-test for comparison of 2 means and the Kruskal-Wallis test for independent groups were used, according to the case, with a level of significance of 5%.

## RESULTS

Serum lithium levels were determined in 63 patients from CPER. Table 1 presents the distribution of the studied population according to social, demographic, therapeutic data and the comparison of the mean serum lithium concentration (mmol/L) according to the group of patients

The majority of the patients had been diagnosed with bipolar mood disorder (77.78%) and only 26.98% of them were found to have therapeutic serum lithium levels. The majority, 57.14%, were found to have sub-therapeutic levels and 15.87% presented no detectable levels of lithium, indicating that they were not complying with the prescribed therapy. No patient presented toxic levels of serum lithium. Medicamentous interactions with lithium were present in 60.32% of the patients (risperidone, olanzapine, haloperidol, carbamazepine, valproic acid, captopril and hydrochlorothiazide), and the maintenance doses fluctuated between 300 and 1200mg/day.

Table 1

Distribution of the studied population according to social, demographic, therapeutic data and the comparison of the mean serum lithium concentration according to the group of patients (mmol/L).

| | n | % | Mean | Standard Deviation | Statistics | p-Value |
|---|---|---|---|---|---|---|
| Patients | 63 | 100.00 | | | | |
| Gender | | | | | | |
| Male | 16 | 25.40 | | | | |
| Female | 47 | 74.60 | | | | |
| Diagnosis reported | | | | | | |
| Epilepsy | 1 | 1.59 | \| | | | |
| Schizophrenia | 10 | 15.87 | \| | | | |
| Panic Syndrome | 3 | 4.76 | 0.50* | 0.31 | t=0.5450 | p>0.50 |
| Bipolar Mood Disorder | 49 | 77.78 | 0.45 | 0.28 | | |
| Use of tobacco | | | | | | |
| Yes | 6 | 9.52 | 0.33 | 0.13 | t=1.1367 | p>0.20 |
| No | 57 | 90.48 | 0.48 | 0.29 | | |
| Use of alcoholic beverages | | | | | | |
| Yes | 4 | 6.35 | 0.22 | 0.10 | t=1.5896 | p>0.10 |
| No | 59 | 93.65 | 0.48 | 0.28 | | |
| Use of caffeine | | | | | | |
| Yes | 47 | 74.60 | 0.45 | 0.29 | t=0.6849 | p>0.20 |
| No | 16 | 25.40 | 0.51 | 0.28 | | |
| Daily Dose of Lithium | | | | | | |
| 300mg | 9 | 14.29 | 0.27 | 0.14 | | |
| 600mg | 29 | 46.03 | 0.37 | 0.20 | H=11.1995 | p<0.005 |
| 900mg | 23 | 36.51 | 0.61 | 0.30 | | |
| 1200mg | 2 | 3.17 | 1.04 | 0.01 | | |
| Type of medicamentous interaction | | | | | | |
| None | 25 | 39.68 | 0.54 | 0.30 | | |
| ↑ Levels of Li and ↓ Levels of Li | 1 | 1.59 | 0.42** | 0.27 | t=1.6576 | p>0.10 |
| ↑ Levels of Li - pharmacokinetic | 3 | 4.76 | \| | | | |
| ↑ Levels of Li - pharmacokinetic | 34 | 53.97 | \| | | | |
| Serum Lithium Level | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Not detected | 10 | 15.87 | | | | |
| Subtherapeutic | 36 | 57.14 | 0.31 | 0.10 | t=11.0931 | p<0.001 |
| Therapeutic | 17 | 26.98 | 0.81 | 0.23 | | |
| Toxic | 0 | 0 | | | | |

* Mean of patients with disorders other than bipolar mood disorder.
** Mean of patients with some medicamentous interaction with lithium.

## DISCUSSION

Plasma lithium levels may be influenced by medicamentous interactions, use of alcoholic beverages or tobacco, and particularly the ingestion of coffee, as found by Mester *et al.* (1995).

However, when we compared the means of these groups, which fluctuated between 0.22 to 0.51 mmol/L, no significant difference was found between the group that drank coffee and the group that did not, probably because the ingestion here related, fewer than 4 cups/day, classified these patients as weak coffee drinkers, differing from the heavy coffee drinkers studied by Mester *et al.* (1995). It was also observed that there was no significant difference between alcohol drinkers and non drinkers, or between smokers and non smokers.

As regards medicamentous interactions, although there was co-medication, which is known to be capable of influencing the pharmacokinetics of lithium, no significant difference was found between the groups with and without interaction.

With regard to the daily dose received, it was observed that there was significant difference; patients with doses of 300 and 600 mg/day presented mean serum concentrations at sub-therapeutic levels, and patients with doses of 900 and 1200 mg/day were shown to have therapeutic levels.

Indeed, the recommended maintenance doses fluctuated between 900 and 2,400mg/day (Anderson *et al.*, 2002; Aronson & Reynolds, 1992; Kook *et al.*, 1985; Lobeck, 1988). The data, therefore, revealed that the patients with doses of 300 and 600 mg/day (60.32%) were found to be underdosed and this is why they probably presented a mean serum concentration at sub-therapeutic levels.

Resuming the analysis of patients distributed according to serum lithium levels, whether they were therapeutic or not, the proportion of patients who did not present detectable serum lithium levels (15.87%) or presented sub-therapeutic concentrations (57.14%) is

alarming, as they are patients who are certainly not being benefited by the effects of lithium for the treatment of their disorders.

The probable causes why the patient does not attain therapeutic levels is that they have not been prescribed adequate doses of lithium, as has been previously mentioned, and non compliance with therapy as reported by Cruz *et al*. (2011); that is to say, patients did not take the prescribed doses properly, since other factors, such as interactions were discarded.

Adjustment of the dose calculated for patients at sub-therapeutic levels led to theoretical doses of 900 to 3600mg/day, which could not be safely implemented, raising the hypothesis that the patients were not complying with the posology prescribed at present. Thus, the attempt to correct the dose was prejudiced, because only the certainty that therapy is complied with, will allow the implementation of therapy monitoring in the service, with the corresponding individual adjustment of the dose, which will contribute to a better follow up of patients and success of the therapy.

## CONCLUSION

The results found indicate an apparent non compliance with therapy by the patients at CPER as regards treatment with lithium. This is a situation related to lack of adhesion to therapy, the causes of which involve attitudes and beliefs. It requires a more detailed study, complementary to the present study, in order to understand the phenomenon in this group of patients and to identify the factors that influence it. So that it will allow measures to be taken to increase adhesion and favor better results to be obtained from the treatment with lithium.

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