European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 1999; 3: 63-69

Lithium safety in the prophylaxis of bipolar disorders: a study with plasma levels

M.C. MAURI, V. LAINI, M.E. SCALVINI, L.S. VOLONTERI, M.S. FERRARI, G. PANZA

Department of Clinical Psichiatry, Clinical Neuropsychopharmacology Unit, University of Milan, IRCCS, Ospedale Maggiore – Milan (Italy)

Abstract. – From many decades efficacy of lithium salts, as mood stabilizers, has been largely recognized, but their tolerability, in particular during intermediate or long-term treatments is still discussed. The most frequently described side effects can affect several organs.

Aim of the study was to evaluate lithium carbonate tolerability after a "brief" (1 month-4 years), "intermediate" (5-9 years) and "long-term" (10-21 years) treatment of patients affected by Bipolar Disorders (BD). 27 patients (14 males, 13 females), aged from 20 to 78 years (mean 49.03 years ± 14.61 SD), affected by BD, type I, according to DSM IV criteria were included into the study.

Our data suggest a good tolerability of lithium salts without significant differences among the three different periods of treatment.

Key Words:

Lithium safety, Bipolar disorders, Prophylaxis, Plasma levels.

Introduction

From many decades lithium efficacy, as mood stabilizer, has been recognized. Currently, lithium salts represent the principal therapy in the treatment of Bipolar Disorders (BP), manic/hypomanic episodes and the prophylaxis of BD[1-3].

Moreover, their tolerability is still discussed, most of all in intermediate and long-term treatment[21].

Low therapeutic index of lithium salts must be considered to evaluate their tolerability: plasma levels ranging between 0.5 and 1 mEq/l are retained therapeutic during brief term treatments, while 0.4-0.9 mEq/l are considered the optimal therapeutic levels in maintenance therapy[4].

The most frequent side effects of lithium salts may affect several organs.

About renal function, polyuria and hyperalbuminuria are described in intermediate and long-term treatments. According to some authors[5], albuminuria depends on treatment duration and it may be exacerbated when lithium salts are associated with neuroleptics, while other authors[6] substain that it depends on patient age, previous lithium intoxications, previous nephropatis and lithium administration in several doses in a day.

A reduction of iodine organification, an inhibition of fT3 and fT4 release and TSH increase are the most frequent side effects on thyroid function. In some cases they may cause goiter, while hyperthyroidism is less frequent (thyroiditis or Graves' disease). In this sense, some authors hypothesize that a long-term treatment may exacerbate a pre-existent autoimmune disorder[7]. About parathyroid function, hyperparathyroidism is described in intermediate and long-term treatments and it seems to depend on lithium mechanism of action[8].

In some cases, a reduction of glucose tolerance is described in long-term treatments (rarely Mellitus Diabetes) and it seems to be due to an inhition of insulin pancreatic secretion.

About cardiac function, ripolarization alterations (T wave flattening and inversion, ST line prolongation) are described; arrhythmias are less frequent (sinusal tachyarrythmias, atrial and ventricular extrasystoles, sinusal bradycardia). These side effects are reversible with treatment interruption and they are due to lithium interference with the Na^+/K^+ pumps

and lithium action on cellular membranes of myocardium and conduction system.

Cognitive impairment is described during chronic treatments (reduction of learning and creative capacities, reduction of concentration and amnesia)[4,9].

A weight increase is frequent in the first 6-12 months of therapy.

About hepatobiliary function, literature data are laking[10,11].

The most frequent hematologic side effects are neutrophil leukocytosis with relative lymphopenia and thrombocytopenia[12].

Aim of the study was to evaluate lithium carbonate tolerability in a "brief" (1 month-4 years), "intermediate" (5-9 years) and "long term" (10-21 years) treatments in patients affected by BD. In particular, a possible correlation between age of patients or duration of treatment and lithium plasma levels or lithium salts side effects were searched.

Materials and Methods

Twenty-seven patients (14 males, 13 females), aged from 20 to 78 years (mean 49.03 ± 14.61 SD), affected by BD, type I, according to DSM IV criteria[13] were included into the study. Lithium salts were administered at a dose ranging from 300 to 1200 mg/die (mean 847.90 mg/die ± 218.9 SD). No patients assumed other drugs apart hypnotics (benzodiazepines) for brief periods, only in case of dire necessity.

Patients affected by Mellitus Diabetes, preexistent disorders of thyroid, urogenital, parathyroid, cardiovascular and neurological functions were not included into the study.

The population sample has been divided into 3 groups according to the duration of treatment:

– the first group (Group 1) included 9 patients (2 males, 7 females), aged between 20 and 57 years (mean 36.66 years ± 13.02 SD) with a mean weight of 72 kg ± 26.94 SD (Table I). They assumed lithium salts from 1 month to 4 years (mean 2.05 years ± 1.42 SD) at a mean dose of 791.30 mg/die ± 198.08 SD;

– the second group (Group 2) included 9 patients (5 males, 4 females) aged between 36 and 78 years (mean 50.55 years ± 12.49 SD) with a mean weight of 76.5 kg ± 10.48 SD (Table I). They assumed lithium salts from 5 to 9 years (mean 8.22 years ± 1.20 SD) at a mean dose of 911.88 mg/die ± 231.10 SD;

– the third group (Group 3) included 9 patients (6 males, 3 females), aged between 49 and 73 years (mean 59.88 years ± 7.83 SD) with a mean weight of 70.05 kg ± 9.40 SD (Table I). They assumed lithium salts from 10 to 21 years (mean 16.22 years ± 3.41 SD) at a mean dose of 819.82 mg/die ± 201.08 SD.

Thyroid function (fT3, fT4, TSH), renal function (creatinine and urea plasma levels, creatinine clearance) hepatobiliary functions (alanine aminotransferase-ALT, aspartate aminotransferase-AST, γ-glutamyl transferase-γGT, cholinesterase, alkaline phosphatase, total and direct bilirubinemia), creatinine phosphokinase-CPK, lactate deydrogenase-LDH, electrolytes (natremia, kalemia, phosphatemia, chloremia, calcium and magnesium serum values), total proteinemia and albumin plasma levels were evaluated for each patient at the end of every period of lithium assumption. Moreover, glycemia, uric acid and cholesterol levels, triglyderides, amylasemia, hemochrome and body weight had been evaluated. All patients underwent ECG at the same times.

After this, for each patient lithium plasma levels has been evaluated at the begining of treatment, then every 6 months (up to 144 months-12 years-for the patients of Group 3) by Atomic Absorption (AA) method.

Mini-Mental State Examination (MMSE)[14] and Wechsler Memory Scale Examination (WMSE)[15] were administered to evaluate patients cognitive mnesic functions.

Statistical analises included descriptive methods, analysis of variance (ANOVA), multifactor analysis of variance (Tukey' Test), Chi-square and regression analysis.

The results are expressed as mean ± SD.

Results

No clinical relapses were described during the study.

TSH mean plasma levels were significantly higher in the second group of patients, but they were within the normal range (Table I).

Table I. Mean values and significativity of variables.

Group	Variable (normal range)	Mean ± SD	Significance
	TSH		
I (<5 yrs)	(0.32-4.30 mcU/ml)	2.17 ± 0.55* mcU/ml	
II (5-9 yrs)		4.10 ± 2.38 mcU/ml	*p = 0.03 I vs II
III (≥ 10 yrs)		2.43 ± 1.58 mcU/ml	
	fT4		
I	(0.8-2.0 ng/dl)	1.23 ± 0.30 ng/d	
II		1.89 ± 2.44 ng/dl	NS
III		1.24 ± 0.25 ng/dl	
	fT3		
I	(3.8-6.8 pg/ml)	4.23 ± 0.57 pg/ml	
II		4.89 ± 0.64 pg/ml	NS
III		4.24 ± 0.80 pg/m	
	Na^+		
I	(135-145 mmol/l)	135.50 ± 0.83* mmol/l	
II		138.50 ± 1.04 mmol/l	*p = 0.0002 I vs II
III		139.22 ± 1.78 mmol/l	*p = 0.0003 II vs III
	Ca		
I	(8.1-10.4 mg/dl)	9.20 ± 0.60* mg/dl	
II		9.06 ± 0.54* mg/dl	*p = 0.04 I vs III
III		9.90 ± 0.62 mg/dl	*p = 0.02 II vs III
	Total bilirubina		
I	(< 1.0 mg/dl)	0.42 ± 0.12* mg/dl	
II		0.74 ± 0.39 mg/dl	*p = 0.05 I vs II
III		0.80 ± 0.25 mg/dl	*p = 0.0007 I vs III
	Cholesterol		
I	(0-200 mg/dl)	182.25 ± 46.28 mg/dl	NS
II		207.33 ± 44.73 mg/dl	
III		225.33 ± 33.44 mg/dl	
	γGT		
I	(7-32 U/l)	18.28 ± 11.23 U/l	NS
II		29.83 ± 34.24 U/l	
III		32.22 ± 25.72 U/l	
	Weight		
I		72.00 ± 26.94 kg	NS
II		76.55 ± 10.48 kg	
III		70.05 ± 9.40 kg	
	WMSE		
I	(90-109)	106.31 ± 12.38	NS
II		101.05 ± 20.24	
III		94.83 ± 14.02	

NS = No Significant.

fT3 and fT4 plasma levels resulted within the normal range in the three groups of patients (Table I).

Cholesterol plasma levels resulted higher than standard range in the second and third group of patients (Table I). Tryglicerides were higher in the third than in the second and first group, but their values remained within the standard range (mean 136.71 ± 138.10 mg/dl; 165.16 ± 89.20 mg/dl; 167.55 ± 83.42 mg/dl).

Amylasemia showed higher values in the third group of patients (mean 140.66 ± 48.65 U/L; 141.40 ± 59.11 U/L; mean 191 ± 133.76 U/L).

Total bilirubinemia was significantly higher in the third group of patients (Table I). Direct bilirubinemia was also higher in the third group (mean 0.12 ± 0.07 mg/dl; 0.18 ± 0.12 mg/dl; 0.23 ± 0.07 mg/dl).

AST plasma levels were higher in the first group (mean 33.75 ± 34.95 U/L; 20.28 ± 3.86 U/L; 24.66 ± 8.60 U/L); ALT values were higher in the third group of patients (mean 25.87 ± 17.42 U/L; 20.42 ± 8.71 U/L; 31.55 ± 15.24 U/L).

γGT plasma concentrations were higher in the third group and over the standard range (Table I). Alkaline phosphatase plasma levels remained within the standard range, but, in the second and third group, their values were higher than the first one (mean 162.57 ± 52.30 U/L; 198.28 ± 57.71 U/L; 197.11 ± 61.50 U/L).

CPK plasma levels resulted over the standard range in the first two groups (mean 435.62 ± 904.79 U/L vs 301.33 ± 520.17 U/L), while in the third group they were within the standard range (mean 84.88 ± 68.75 U/L).

Natremia was significantly higher in the third group than in the first group (Table I).

Calcium plasma levels were significantly higher in the third group than in the second and in the first one (Table I). Phosphatemia was higher in the first group (3.42 ± 0.60 mg/dl) than in the second (2.80 ± 0.14 mg/dl) and in the third ones (2.95 ± 0.61 mg/dl).

Acid uric plasma levels were higher in the third group (3.41 ± 1.80 mg/dl; 4.56 ± 1.41 mg/dl; 5.36 ± 1.26 mg/dl).

Neuropsychological tests (MMSE and WMSE) scores resulted within the standard range, even if WMSE scores were lower in the third group (Table I).

Lithium oral doses were significantly higher in the second group than in the first group and they were significantly lower in the third group than in the second one (Table II).

Lithium plasma levels resulted significantly lower in the first group than in the second and in the third ones (Table II, Figure 1).

Coefficient variation (CV) of lithium plasma levels resulted higher in the first group than in the other groups (42.79; 31.18; 33.66) (Figure 1).

Lithium plasma levels resulted positively correlated to the age of patients (r= 0.62, p= 0.001) (Figure 2), while there was no correlation between lithium dosage (mg/kg) and lithium plasma levels.

No abnormalities in the values of LDH, cholinesterase, total proteinemia, albumin plasma levels, creatinine plasma levels, urea, creatinine clearance, kalemia, chloremia, magnesium plasma levels, leukocyte count, glycemia were observed in the three groups.

No ECG variations were observed in the three groups of patients.

Discussion

Brief, intermediate and long-term treatments with lithium salts may produce some effects on organ functions, but usually, the benefits of the therapy out-weight the drawbacks, provided that the treatment is given in proper dosage and appropriate range plasma concentrations, even if our study has not provided an evaluation of clinical outcome.

Our study has focused some minimal toxic effects of long-term treatment with lithium salts.

About thyroid function, TSH values were significantly more elevated in the patients treated for 5-9 years, even if they were within the normal range. These results agree with lilerature data according to which lithium therapy may cause an increase of TSH values during long term treatment[16,17]. This result has been explained hypothesizing a response of TSH to a decrease of T3 and T4 that has been observed in the patients initially treated with lithium salts. The phenomenon has not

Table II. Lithium doses and plasma levels mean values.

Group	Variable (normal range)	Mean ± SD	Significance
	Dose		
I (< 5 yrs)		791.30 ± 198.08* mg/die	
II (5-9 yrs)		898.13 ± 237.38* mg/die	*p = 0.046 I vs II
III (≥ 10 yrs)		819.82 ± 201.58 mg/die	*p = 0.0005 II vs III
	Plasma levels		
I	(0.5-1.0 mEq/l)	0.46 ± 0.20* mEq/l	
II		0.61 ± 0.19 mEq/l	*p = 0.0005 I vs II
III		0.61 ± 0.20 mEq/l	*p = 0.0005 I vs III

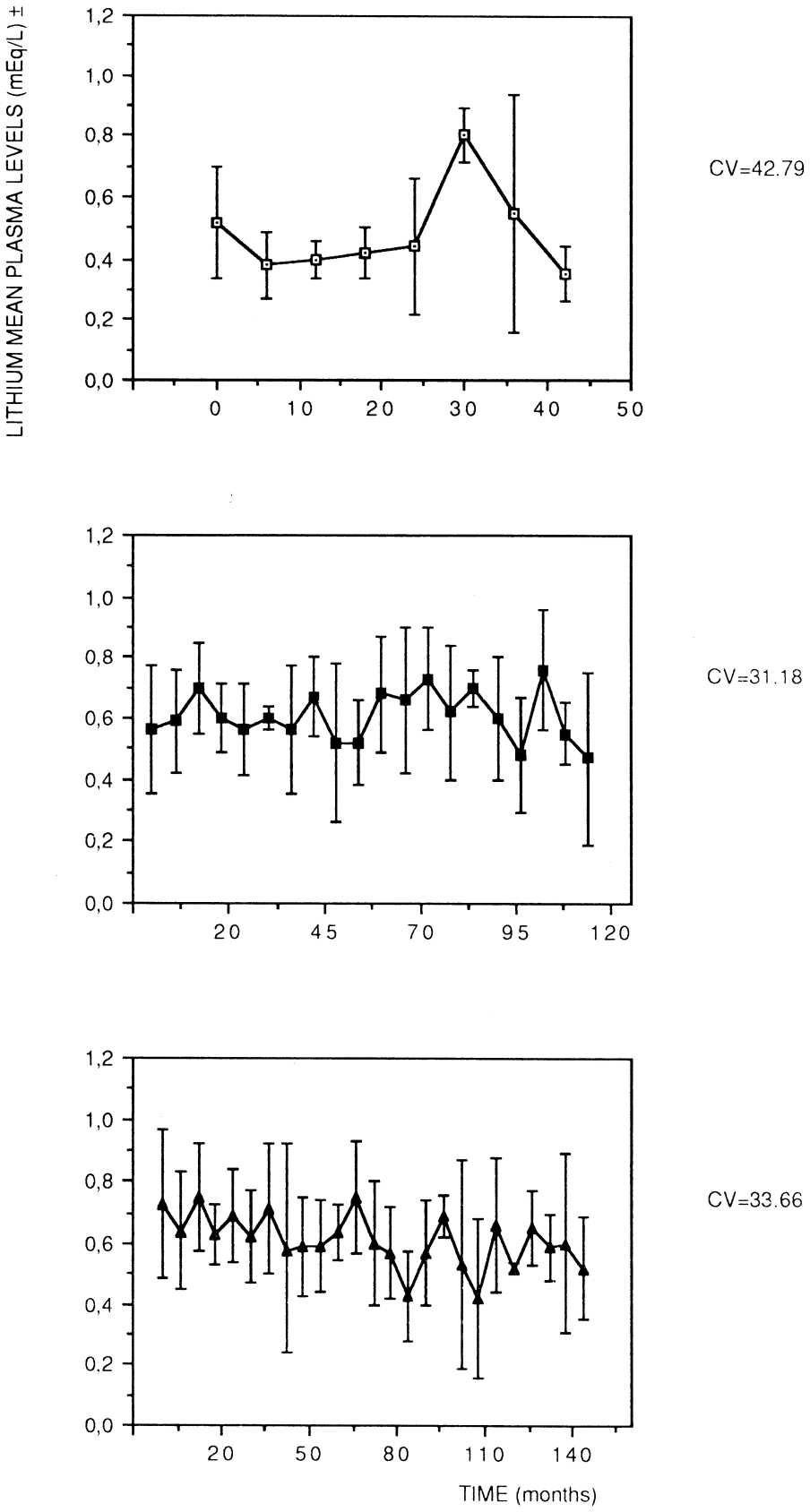

Figure 1. Lithium plasma levels in the three groups of patients.

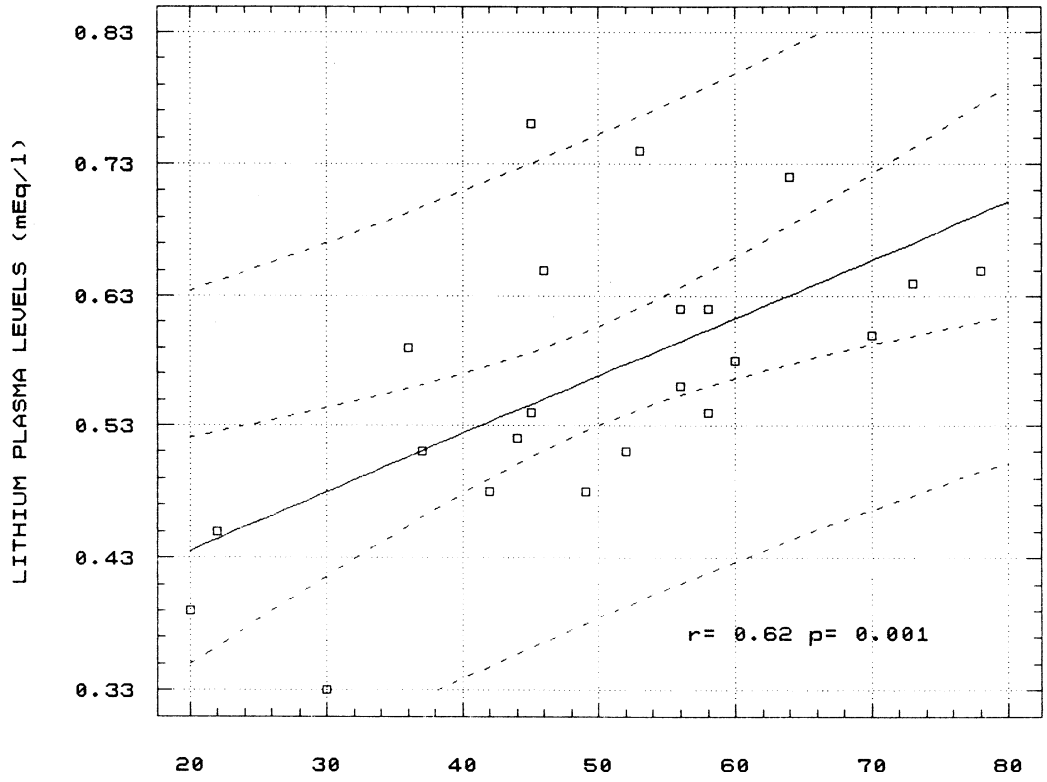

Figure 2. Correlation between lithium plasma levels and age.

been observed in our sample population probably because pituitary stimulation was sufficient to remedy the T3-T4 deficiency provoked by lithium salts[18].

There was a trend to higher values of electrolytes (Na^+, Ca^{++} and K^+) in the third group of patients. In particular, considering Na^+ values, although higher values have been observed in the third group, they were within the standard range. In any case, we may hypothesize that Na^+ elevation was due to the exchange between Na^+ and lithium in Na^+-K^+ pump. Calcium presented lower values in the first group of patients, while it was higher in the second and third ones. This may be explained by a long-term lithium effect on parathyroid, even if clinical hyperparathyroidism evidences were not observed. In fact, calcium values remained in the standard range and, moreover, they were not associated to alterations of phosphatemia and magnesium plasma levels, that, usually, characterize an hyperparathyroidism picture[8].

Hepatic functions seemed to be influenced by long-term lithium therapy: ALT, γGT, cholesterol and triglycerides were more elevated in the third group of patients; in particular, cholesterol and γGT showed values over the normal range. In any case no patients showed clinical disturbances. This supports literature data, according to which it is not demonstrated that lithium may provoke or exacerbate hepatic disorders[10].

Lithium doses resulted more elevated in the first group of patients probably because there was the tendency of clinicians to maintain more elevated dosages of lithium salts for a long period. Lithium plasma levels showed an higher variation of mean values in the first group as underlined from CV values; CV values were lower in the second and third group of patients, confirming that during long-term treatment we can assist to a stabilization of lithium plasma levels ranging in the normal range: 0.51-0.76 mEq/l/0.48-0.74 mEq/l (vs 0.33-0.65 mEq/L in the first group).

There was no correlation between lithium plasma levels and all reported effects of long term treatment with lithium, including the twenty year of continuation therapy with lithium salts. There was a positive correlation between age and lithium plasma levels; in fact, more aged people showed a reduced di-

stribution volume, so lithium salts might be more concentrated. Age is the only factor studied among which might cause changes in the distribution of lithium in the body[19] and this indicate more attention in the lithium therapy of elderly patients.

Additionally, cognitive-mnesic abilities evaluation does not present significant differences in the three groups of patients. However, there was a trend to lower values of WMSE in the third group of patients, according to literature data indicating that, in sensitive patients, lithium may induce memory impairment and prolonged reaction time[20].

In conclusion, our data suggest a good tolerability of lithium salts maintened in the normal range of concentrations also during a long-term treatment. In fact, relevant clinical consequences on different organs have not been observed and patients cognitive-mnesic functions are not significantly compromised.

References

1) KECK PE, MCELROY SL. Outcome in the pharmacologic treatment of bipolar disorder. J Clin Psychopharmacol 1996; 16 (Suppl1): 15S-23S.

2) POST RM, KETTER TA, PAZZAGLIA PJ ET AL. Rational polypharmacy in the bipolar affective disorders. Epilepsy Res Suppl 1996; 11: 153-180.

3) CALABRESE JR, BOWDEN C, WOYSHVILLE MJ. Lithium and the anticonvulsants in the treatment of bipolar disorders. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: the fourth generation of progress. New York: Raven Press, 1995: 1099.

4) SCHOU M. Lithium prophylaxis: myths and realties. Am J Psychiatr 1989; 146: 573-576.

5) WALKER RG. Lithium nephrotoxicity. Kidney Int Suppl 1993; 42: 93-98.

6) JENSEN HV, HEMMINGSEN L, HOLM J, CHRISTENSEN EM, AGGERNAES H. Urinary excretion of albumin and retinol-binding protein in lithium-treated patients: a longitudinal study. Acta Psychiatr Scand 1992; 85: 480-483.

7) SADOUL JL, KEZACHIAN B, FREYCHET P. Therapeutique par lithium et hyperthyroidie: pathologie causée ou facilitée par le lithium? Reune de la litérature à propos d'un cas où l'hyperthyroïdie transitoire. Ann Endocrinol 1994; 54: 353-358.

8) BROCHIER T, ADNET-KESSOUS J, BARILLOT M, PASCALIS JG. Hyperparathyroidie sous lithium. Encephale 1994; 20: 339-349.

9) VANHOOREN G, DEHAENE I, VAN ZANDYCKE M et al. Polineuropathy in lithium intoxication. Muscle Nerve 1990; 13: 204-208.

10) VIEGUT V, JEFFERSON JW. Lithium and the liver. Lithium 1990; 1: 9.

11) JEFFERSON JW. Lithium and hyperbilirubinemia. J Clin Psychopharm 1992; 12: 141-142.

12) COLLINGS S. Thrombocytopenia associated with lithium carbonate. BMJ 1992; 305: 159.

13) AMERICAN PSYCHIATRIC ASSOCIATION. Diagnostic and Statistical Manual of Mental Disorders. 4th ed (DSM IV). Washington DC: American Psychiatric Association, 1994.

14) FOLSTEIN MF, FOLSTEIN SE, MCHUGH PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189-198.

15) WECHSLER D. Wechsler memory scale. Firenze: Manuale Ed Italiana OS, 1981.

16) SOUZA FGM, SOUZA VBN. Effects of lithium on TSH and T4 levels in affective disorders evaluated by meta-analysis. In: Xth World Congress of Psychiatry 1996. Madrid: August 23-28: 1174.

17) YOUNG RC, MEYERS BS. Psychopharmacology. In: Sadavoy J, Lazarus LW, Jarvick LF, Grossberg GT, eds. Comprehensive review of geriatric psychiatry II. Washington DC: American Psychiatric Press, 1996: 755.

18) DENIKER P, EYQUEM A, BERNHEIM R, LOO H, DELARUE P. Thyroid autoantibody levels during lithium therapy. Neuropsychobiology 1978; 4: 270-275.

19) AMDISEN A. Serum level monitoring and clinical pharmacokinetics of lithium. Clin Pharmacokinet 1977; 2: 73-92.

20) SCHOU M. Lithium. In: Dukes MNG, ed. Meyler's side effects of drugs. 13th Edition. Amsterdam: Elsevier 1996: 81.

21) MAURI MC, PERCUDANI M, REGAZZETTI MG, ALTAMURA AC. Alternative prophylactic treatments to lithium in bipolar disorders. Clin Neuropharmacol 1990; 13 (Suppl 1): 590-596.