Effects of Chronic Lithium Treatment on the Peripheral Nervous System

Carlo Faravelli, M.D.; Milena Di Bernardo, M.D.; Valdo Ricca, M.D.; Paola Benvenuti, M.D.; Mario Bartelli, M.D.; and Oscar Ronchi, M.D.†

Background: Although lithium carbonate is widely used in the treatment of mood disorders, symptoms suggesting toxic effects on the peripheral nervous system may emerge even in subjects whose serum lithium levels remain within the recommended therapeutic range.

Method: Electroneuronographic (ENG) parameters (motor nerve conduction velocity of peroneal and median nerves, sensory nerve conduction velocity of sural and median nerves, amplitude of motor potential of peroneal and median nerves, and amplitude of sensory action potential of the median nerve at the wrist and the sural nerve) were investigated in 2 groups (N = 34) of patients suffering from bipolar affective disorder (DSM-III-R, DSM-IV) undergoing maintenance treatment with lithium carbonate for at least 1 year (mean = 2.06 years) in monotherapy. For 12 patients, ENG results were compared with pretreatment values, whereas in the other 22 cases, only data relevant to posttreatment were available. Fifty-four healthy subjects and 20 patients with recurrent major affective disorder (unipolar and bipolar) never treated with lithium made up the comparison groups.

Results: Compared with the 2 comparison groups, patients on chronic lithium treatment showed significant reduction of motor nerve conduction velocity of peroneal and median nerves, sensory nerve conduction velocity of sural and median nerves, amplitude of motor potential of peroneal and median nerves, and amplitude of sensory action potential of the median nerve at the wrist and the sural nerve. The comparison with the assessment made prior to lithium treatment also showed significant changes; after a period of treatment with lithium varying from 2 to 8 years (mean = 5.2 years), significant reductions were found on motor and sensory nerve conduction velocity and on amplitude motor potentials and sensory action potentials.

Conclusion: Chronic maintenance treatment with lithium affects the peripheral nerves, even if the impairment rarely is such as to warrant discontinuation of treatment. Monitoring of ENG results could be useful for the early detection of neurotoxicity of lithium.

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Received March 6, 1998; accepted Aug. 6, 1998. *From the Unit of Psychiatry (Drs. Faravelli, Bernardo, Ricca, and Benvenuti) and the Unit of Neurology (Drs. Bartelli and Ronchi), Department of Neurological and Psychiatric Sciences, University of Florence, Florence, Italy.*

†Deceased.

Reprint requests to: Carlo Faravelli, M.D., Dipartimento di Scienze Neurologiche e Psichiatriche, Università degli Studi di Firenze, V.le Morgagni 85, 50134 Firenze, Italy.

In recent years, the use of lithium has become widespread in the treatment of an ever growing number of conditions, including nonpsychiatric ones.[1,2] However, side effects on the renal,[3] cardiac,[4] gastroenteric,[5] metabolic,[5] and thyroid[6] functions have been reported on several occasions. It has also been frequently observed that patients treated with lithium complain of fatigue and tiredness accompanied by paresthesias, which can lead in some cases to actual myasthenia-like loss of motor performance.[7] Tremors, usually distal, are other frequently reported symptoms.[8,9] The peripheral nervous system (PNS) involvement manifested by polyneuropathy of varying severity has also been reported in lithium intoxication.[10] Several articles report evidence of actual peripheral nerve damage during lithium intoxication.[10–13] In animals, Samples and Seybold[14] and Ebara and colleagues[15] showed that, after chronic treatment with lithium, the caudal nerve conductibility in the rat diminished when toxic levels of lithium were reached, while at nontoxic levels conductibility remained within the normal range. Licht et al.[16] found that the axon caliber in the sural nerve of the rat is reduced after chronic treatment with lithium.

Few authors have studied the effects of chronic maintenance lithium treatment at therapeutic doses on the PNS in humans. Girke et al.[17] first recorded abnormal nerve conduction velocity (NCV) in both manic-depressive patients treated with lithium salts and in asymptomatic volunteers receiving lithium. They reported that 30% of the patients on prophylactic treatment with lithium showed a reduction of the NCV and of the duration of the single motor unit potential of the peroneal nerve. Manocha et al.[18] also noted reduction of the amplitude of evoked action potentials in patients on chronic lithium therapy. Chang et al.[19] found a negative linear correlation between motor and sensory NCV and serum lithium levels. Podnar et al.[20] demonstrated subclinical involvement of motor and sensory axons in affective patients that was only

slightly more pronounced in lithium-treated patients, suggesting that lithium is just one among the factors leading toward minor axonopathy in psychiatric patients.

Although consistent in detecting abnormal NCV in patients on chronic lithium treatment, all these studies allowed concomitant treatments, namely carbamazepine, haloperidol, sulpiride, clothiapine, fluphenazine, and thioridazine. Since concomitant haloperidol or carbamazepine therapy has been found to endanger patients on lithium treatment to lithium intoxication,[21,22] one could suspect that the long-term effects on the PNS reported in these studies are due to the combination of treatments rather than to lithium alone.

In the present study, we have therefore investigated the electromyographic changes in affective patients undergoing chronic prophylactic monotherapy with lithium carbonate.

METHOD

Several years ago, a prospective study with bipolar patients was started by one of the authors (O.R.) to investigate the potential neurotoxicity of chronic lithium treatment. In 12 patients suffering from bipolar disorder according to DSM-III-R,[23] an electroneurographic (ENG) assessment was made immediately before the commencement of lithium therapy, and a follow-up was planned after 5 years of treatment. Unfortunately, because of the death of our colleague, the study was interrupted and not restarted until 1996. Those 12 patients previously assessed were reevaluated after 2 to 8 years (mean ± SD = 5.2 ± 2.4 years), during which they were maintained on chronic lithium monotherapy according to the original protocol. There were 4 men and 8 women, with a mean ± SD age (at the time of the second examination) of 45.4 ± 12.5 years (range, 21–64).

To reach a consistent number of probands, 22 more patients were included in the study. All the patients satisfied the DSM-IV[24] diagnosis of bipolar affective disorder and were chosen among those who had been treated with lithium alone for at least 1 year. Fifteen were women and 7 were men, with a mean ± SD age of 46.5 ± 13.5 years (range, 21–65) and a mean ± SD height of 172.4 ± 16.7 cm. The duration of lithium treatment ranged from 1 to 10 years (mean ± SD = 4.8 ± 1.6), whereas the duration of the illness ranged from 2 to 15 years (mean ± SD = 8.7 ± 1.4).

For both groups, no concomitant treatment was prescribed since the start of lithium therapy. The dosage of lithium was titrated in order to maintain serum concentration within the range of 0.50–1.0 mEq/L, and we checked for lithemia monthly. None of the patients showed clinical signs of disturbances of the peripheral nerves before treatment.

Twenty patients (13 women, 7 men) with recurrent major affective disorder (including unipolar and bipolar) who matched the lithium patients for sex, age, body weight and height, and duration of illness and who had never been treated with lithium were used as control group. Ages varied from 24 to 69 years (mean ± SD = 45.7 ± 15.2). The duration of illness ranged from 1 to 5 years (mean ± SD = 3.2 ± 1.5), during which these patients received a variety of drugs (mainly antidepressants, benzodiazepines, and antiepileptics), but never lithium.

There were no significant differences between these 3 patient groups regarding age, sex, age at onset, duration of illness, or number of episodes. A further control group was made up of 54 healthy subjects (32 women, 22 men) aged 18 to 63 years (mean ± SD = 42 ± 9.2 years).

The ENG parameters considered as indicators of possible damage of the peripheral nerves were the following:

1. Motor NCV of peroneal and median nerves
2. Sensory NCV of sural and median nerves
3. Amplitude of motor action potential of peroneal and median nerves
4. Amplitude of sensory action potential from the sural nerve and the median nerve at the wrist

The tests were performed after the subject had been resting for at least 45 minutes in a room where the temperature was constant at 22°C–23°C. Values within 2 standard deviations of the values obtained in the healthy group were considered normal. All of the subjects were given detailed information on the examination and gave their written consent. Data were analyzed using parametric tests, including the t test and univariate analysis of variance (ANOVA). The Tukey test was used for post hoc pairwise comparison.

RESULTS

The 2 groups on lithium therapy did not show differences on any of the ENG parameters investigated. These 2 groups were therefore combined into a single group of patients receiving lithium. This group's ENG results were compared with the affective patients never treated with lithium and with the healthy subjects control group (Table 1).

The ANOVA tests showed significant differences in the motor NCV (peroneal nerve), the sensory NCV (sural and median nerve), the motor action potential amplitude (peroneal nerve), and the sensory action potential amplitude (sural and median nerve); post hoc tests showed that the differences were due to the lithium group in all the comparisons. In the patients on lithium therapy, the ENG figures were in fact generally below the normal standards. In no case, however, was the impairment such as to justify a clinical diagnosis of PNS abnormality (no value outside 2 standard deviations of the healthy comparison group).

The comparisons between the prelithium ENG results and the test performed during chronic lithium treatment in

Table 1. Electroneuronographic Values (Mean ± SD) in Patients Undergoing Lithium Therapy, Affective Patients, and Controls[a]

Variable	Lithium Patients	Affective Controls	Healthy Controls	Analysis F (df = 2,105)	p
Number of cases	34	20	54		
Motor NCV peroneal nerve	51.7 ± 4.9	54.4 ± 5.0	53.9 ± 4.6	8.781	< .05
Motor NCV median nerve	59.1 ± 4.9	58.9 ± 6.5	57.6 ± 6.7	2.367	NS
Sensory NCV sural nerve	50.4 ± 5.2	55.7 ± 6.5	55.9 ± 7.1	11.678	< .001
Sensory NCV median nerve	59.3 ± 5.5	66.0 ± 6.9	67.7 ± 6.4	21.392	< .001
MAP amplitude peroneal nerve	9.7 ± 3.5	10.4 ± 3.7	10.6 ± 3.9	9.893	< .05
MAP amplitude median nerve	11.2 ± 4.1	12.1 ± 4.6	13.0 ± 4.4	4.935	NS
SAP amplitude sural nerve	20.6 ± 6.8	26.3 ± 8.2	27.2 ± 8.5	18.975	< .001
SAP amplitude median nerve	36.9 ± 12.6	54.6 ± 17.2	58.5 ± 18.4	12.737	< .001

[a]Abbreviations: MAP = motor action potential, NCV = nerve conduction velocity, NS = not significant, SAP = sensory action potential. NCV values given in m/s.

Table 2. Electroneuronographic Values (Mean ± SD) of 2 Measurements in Patients Before and During Lithium Therapy[a]

Variable	Pretreatment	During Treatment	Analysis t	p
Number of cases	12	12		
Motor NCV peroneal nerve	53.0 ± 3.7	48.0 ± 3.6	3.28	< .01
Motor NCV median nerve	58.7 ± 6.2	56.6 ± 7.1	0.78	NS
Sensory NCV sural nerve	52.1 ± 4.0	47.9 ± 4.2	4.35	< .001
Sensory NCV median nerve	60.4 ± 3.9	57.4 ± 2.9	2.07	< .02
MAP amplitude peroneal nerve	10.3 ± 3.9	9.6 ± 3.8	3.13	< .05
MAP amplitude median nerve	12.0 ± 4.4	11.3 ± 4.5	1.79	NS
SAP amplitude sural nerve	26.1 ± 7.5	21.0 ± 7.3	4.15	< .001
SAP amplitude median nerve	53.8 ± 11.2	41.4 ± 12.0	4.12	< .001

[a]Results from the original 12 subjects only. Measurements taken before lithium therapy and 5.2 ± 2.4 years (range, 2–8 years) into chronic lithium therapy. NCV values given in m/s.

the 12 patients of the original study are summarized in Table 2. Compared to pretreatment values, the following measures were significantly reduced: peroneal motor NCV, sural and median sensory NCV, motor action potential amplitude of the peroneal nerve, and sensory action potential amplitude of the sural and median nerve. None of the posttreatment ENG figures had significant correlations either with the duration of lithium treatment or with the age of the subjects.

DISCUSSION

Several patients on maintenance treatment with lithium showed or complained of mild-to-moderate signs of motor retardation, tiredness, tremor, and fatigue. The clinical impression is that lithium may impair peripheral nerve function, even though the neurologic examination does not show clear signs of abnormality. Our results seem to confirm the clinical impression of subthreshold damage to the PNS. In fact, the peripheral nerve conduction and action amplitudes were generally reduced in patients on chronic lithium treatment, though in no case was this impairment severe enough to justify a clinical diagnosis of peripheral nerve damage.

In this sense, our study confirms the few but consistent findings previously reported by other authors. However, our study gives further strength to this conclusion because of 2 peculiarities: first, in our patients no other chronic treatment but lithium was allowed; second, in a subsample of cases the study was prospective, with pretreatment measurements. Previous studies on PNS function during chronic lithium therapy were performed with patients concomitantly receiving carbamazepine or antipsychotic drugs and without any assessment prior to treatment.[19–22]

There are limitations in our study, since its original design was modified because of the death of the chief electromyographist. For 12 patients, the original design of prospective follow-up was maintained, whereas other patients were recruited later among those who attended the lithium clinic of our department. In these cases, no prelithium ENG values were available. On one hand, however, the 2 groups on lithium therapy had the same postlithium values. On the other hand, the subsample for whom pretreatment ENG results were obtained had values in the same range as in the healthy subjects.

Another limitation is that the aim of the study was to explore the effect of lithium alone, without allowing for the interference of any other treatment. This means that the subjects investigated were all good responders to lithium. The 22 patients who were evaluated during treatment were in fact selected among those who received lithium alone during all the course of the illness. All the 12 cases selected for the prospective study also showed a general well-being along the entire period of treatment, with minor mood fluctuation that did not require adjunctive treatments. This unusual rate of efficacy is likely attributable to the criteria of inclusion. Since the study was aimed at studying patients who could be treated with lithium carbonate alone, only typical bipolar patients were selected; cases where the probability of good response was lesser (rapid cyclers, schizoaffective, patients with mood-incongruent manic symptoms, etc.) were excluded.

Our result shows that bipolar patients on chronic lithium therapy had a reduction in the conductibility of the peripheral nerves that could impair both motor and sensory functions. Motor peroneal NCV and sensory NCV of the median nerve were affected the most. The motor NCV peroneal nerve reduction could be connected to the greater vulnerability of this nerve, owing to the fact the nerve is made up of axons that are anatomically far

away from their trophic center. As far as the sensory afferents of the median nerve are concerned, an explanation can be found in the reduced diameter of the nonfusal sensory afferents compared with the diameter of the motor efferents.

Since no other treatment was prescribed, the impairment of the PNS can be due to either the lithium therapy or the illness. Including a randomized control group of patients with bipolar disorder taking placebo would have resolved the question. Obvious ethical reasons did not allow such a design to be implemented. The closest approximation was that of choosing a population of people affected by mood disorder, theoretically candidates for lithium, who were not treated with it because of various reasons. These reasons include somatic contraindications (e.g., inadequate kidney, heart, or thyroid functionality), refusal to undergo chronic therapy, or different therapeutic strategies on the part of the treating physician. Unfortunately, we could not retrace a sufficient number of bipolar patients, so we had to also include some unipolar patients. Since the ENG parameters do not distinguish this group from the healthy subjects, one could conclude that the influence of the illness per se on nerve conduction is negligible. It could be objected that the matching with the lithium-treated group is not perfect, at least as far as the type of illness is concerned. However, as the proportion of bipolar patients is substantial (> 50%), if there had been an effect of bipolar disorder, it should have reduced the ENG values of the group. Instead, means and standard deviations are almost the same as those of the normal population. Moreover, when bipolar and unipolar patients within this group were compared, no difference emerged. This suggests that the subthreshold impairments of the PNS that we found are entirely due to the lithium therapy. As said above, however, the impairment never was such as to necessitate discontinuation of treatment.

We did not find any statistical correlation between the length of treatment and PNS changes. This does not necessarily mean that this effect is time independent. At least 2 other possibilities remain open: (1) the interindividual variability is such to obscure the effect of time, and (2) in those cases where the PNS is negatively affected by lithium, this effect manifests itself relatively early and remains stable thereafter. This second interpretation is supported by the fact that the changes of ENG are evident when we considered only those patients who had been on lithium for 2 years or less.

Since this study is predominantly clinical-naturalistic, we cannot answer several questions raised by the findings. A prospective follow-up study with repeated measures would give more definite information. The evaluation of ENG change after discontinuation of lithium would also offer information on the reversibility of this effect.

A speculative issue raised by this study is whether the hypofunction of peripheral nerves is simply an unwanted side effect of lithium or if it is implicated in the antimanic effect of this drug. On one hand, the hypothesis of an overall lithium-induced hyporeactivity of the nervous system would be fascinating in the light of the "kindling theory" of bipolar illness.[25] On the other hand, Licht et al.[26] showed that chronic lithium affects the peripheral nerves,[16] but not the neocortex in rats.

As a result of our research, we may conclude that long-term chronic therapy with lithium, although universally considered the treatment of choice for recurrent bipolar illness, does affect the PNS. So far, we do not know the clinical relevance of this effect. However, we can suspect the following: (1) with longer periods of treatment (e.g., 15–20 or 30 years), the reduction of PNS conduction becomes clinically significant; (2) PNS changes might be early indicators of central nervous system toxicity; and (3) this effect may be greater when bipolar disorder is comorbid with other conditions that also influence the PNS (e.g., diabetes or alcoholism).

While the issue deserves better understanding, it is our opinion that monitoring PNS function, in addition to the kidney, thyroid, and, sometimes, heart functions, would seem a good clinical policy during long-term treatment with lithium.

Drug names: carbamazepine (Tegretol and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), thioridazine (Mellaril and others).

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