Lithium and Lecithin in Tardive Dyskinesia: An Update


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Abstract. Psychiatric inpatients with tardive dyskinesia (TD) were treated with either lithium alone (n = 9) or with a combination of lithium and lecithin (n = 9) for 5 weeks in a double-blind, placebo-controlled experiment. A statistically significant but clinically unimportant improvement of TD occurred during both treatments. The addition of lecithin to lithium had no effect.

Key Words. Tardive dyskinesia, lithium, lecithin.

The hypothesis of striatal cholinergic deficit in tardive dyskinesia (TD) is based on a number of observations summarized by Jeste and Wyatt (1982). Some studies reported beneficial effects on TD of acetylcholine precursors such as choline (Growdon et al., 1977) or lecithin (LEC) (Growdon et al., 1978; Jackson et al., 1979).

We were unable to replicate the effect of LEC on TD (Anderson et al., 1982). However, we reported that combined treatment with lithium (Li) and LEC elicited a modest improvement of TD in a group of nine patients (Anderson et al., 1983). Li enhances the rate of acetylcholine synthesis in the rat brain (Jope, 1979), and choline accumulation in the red blood cells develops during Li treatment in humans (Jope et al., 1978). These observations appeared to provide a theoretical basis for the clinical effect of the combined Li-LEC treatment for TD.

Li alone has also been tried as a treatment for TD, with several reports suggesting beneficial effects (Prange et al., 1973; Ehrensing, 1974; Gerlach et al., 1975; Reda et al., 1975; Pickar and Davies, 1978). However, two relatively large studies (Simpson et al., 1976; Jus et al., 1978) failed to report consistent effects of Li on TD. The purpose of this study was to replicate our clinical observation of Li plus LEC effects in a larger patient sample.

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Methods

Eighteen chronic psychiatric inpatients with the diagnosis of persistent TD served as subjects. After the diagnosis of TD was established based on the criteria of Schooler and Kane (1982), the patients were evaluated weekly for at least 2 months with the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976) to assess the stability of TD before the experimental treatment was started. For each patient, the stability of TD was assessed by a coefficient of variation of AIMS ratings over the 2-month observation period. Neuroleptic treatment was kept constant during this evaluation period as well as during the experimental treatment. Five patients were on thioridazine, two on fluphenazine, two on thiotixene, one on haloperidol, one on perphenazine, and one on another (unknown) neuroleptic. Three patients were on various antidepressants, and one was receiving no psychoactive medication during the trial. No patient received more than one psychoactive drug during the trial. Blood samples for neuroleptic levels were drawn in a subset of patients (n = 10) at the end of study weeks 3, 6, 8, and 10 (Table I). Neuroleptic levels were measured using gas chromatography (haloperidol, chlorpromazine, and thioridazine), high performance liquid chromatography (perphenazine), or radioimmunoassay (fluphenazine).

The subjects were assigned to treatment groups A or B (Table I) in a way which resulted in an approximate balancing of these groups on patients' age and sex. Group A had six males and three females (average age 48.6 years); group B consisted of five males and four females (average age 50.7 years).

The dose of active Li was varied individually to maintain a serum level around 0.6 mEq/l. LEC dose was 0.714 g/kg/day. The preparation used was NC 95, a soya-bean extract supplied by the American Lecithin Company. LEC was blended in a milkshake drink; milkshake alone served as placebo. The dosages and methods of administration conformed to our previous experiments (Anderson et al., 1983). AIMS ratings were videotaped weekly and tapes were later presented in random order to a pair of raters. Double-blind procedures were followed. Items 1-7 on the AIMS scale were summed, and the final rating was obtained by averaging these sums between the two raters. The correlation coefficients between raters ranged between 0.70 and 0.99; the median was between 0.87 and 0.92.

Results

The coefficients of variation of AIMS ratings during the 2-month observation period preceding the start of the trial ranged between 9% and 25% (average 16%). The principal results are summarized in Table 1. The AIMS in period I represents the average of the three weekly ratings performed in that period. These averages were used as (baseline) scores in eight analyses of variance (ANOVAs) which were performed separately for weeks 4, 5, 6, 7, 8, 9, 10, and 11. Each of these eight analyses was a two-way ANOVA with time (baseline, week n) as a repeated measure, and treatment as an independent group measure (Li plus placebo LEC, Li plus LEC). Time X group interactions were also computed. The effect of time (footnoted in Table 1) was highly significant in week 5 (F = 12.9, df = 1/16, p = 0.002) and tended to be significant in weeks 6 (F = 3.9, p = 0.067) and 7 (F = 4.5, p = 0.051). There were no significant effects of group membership (attributable to the lecithin treatment). No interactions were statistically significant. In addition to the formal statistical analyses, we inspected the course of AIMS changes over time in each of the 18 subjects in an effort to detect individual responders to the treatments. Only one patient seemed to show a beneficial response; she was in the Li plus LEC group.
Table 1. Treatment schedule and results

<table>
<thead>
<tr>
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<th>Period I</th>
<th>Period II</th>
<th>Period III</th>
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<tbody>
<tr>
<td></td>
<td>Week 1 Week 2 Week 3 (average)</td>
<td>Week 4 Week 5 Week 6 Week 7 Week 8</td>
<td>Week 9 Week 10 Week 11</td>
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<tr>
<td>Group A</td>
<td>Treatment PL Li + PL LEC</td>
<td>Li + PL LEC</td>
<td>PL Li + PL LEC</td>
</tr>
<tr>
<td></td>
<td>AIMS: 11.6</td>
<td>12.0</td>
<td>11.6</td>
</tr>
<tr>
<td>Group B</td>
<td>Treatment PL Li + PL LEC</td>
<td>Li + LEC LEC</td>
<td>PL Li + PL LEC</td>
</tr>
<tr>
<td></td>
<td>AIMS: 12.0</td>
<td>10.8</td>
<td>11.6</td>
</tr>
<tr>
<td>Average</td>
<td>AIMS: 11.2</td>
<td>10.9</td>
<td>10.4</td>
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PL = placebo. Li = lithium. LEC = lecithin. AIMS = Abnormal Involuntary Movement Scale.

1. $p < 0.01$, by analysis of variance (see text).
2. $p < 0.1$, by analysis of variance (see text).

The groups did not differ in their average Li plasma levels during period II (0.64 and 0.65 mEq/l, respectively, for groups A and B).

To explore the possibility that the reduction of AIMS ratings associated with Li administration was mediated by an increase of neuroleptic blood levels (Nemes et al., 1986), correlation coefficients between the change of AIMS and change of neuroleptic level were computed. The change of AIMS was defined as the absolute difference between the ratings at weeks 3 and 6. The change of neuroleptic level was defined as the relative difference (percentage of change) between weeks 3 and 6. The correlation coefficient was not significant ($r = -0.21$, $n = 10$).

Discussion

Our results do not support the hypothesis that the combined Li-LEC treatment has any effect on TD. However, both treatment groups (LEC and placebo LEC) showed a modest, but statistically significant decrease of AIMS severity during period II. This effect is most likely attributable to Li, since this is the only period during which Li was administered. We cannot exclude the possibility that the Li effect on TD was mediated by an increase in neuroleptic levels, but our data do not support that hypothesis.

It is possible that our previous positive results with the Li-LEC combination (Anderson et al., 1983) were due primarily to Li; the design we used in that study was not ideally suited for the separation of the effects of these two substances.

The improvement of TD we observed was minimal and therefore clinically unimportant. This is clearly a negative study which follows a pattern set by previous attempts at TD treatment: Encouraging results observed in pilot studies cannot be replicated in rigorously designed experiments. Useful treatments for TD will probably remain elusive until a better understanding of its basic mechanism is achieved.

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References


