The Effect of Lithium Carbonate on the Cognitive Functions of Normal Subjects

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• **The responses of 24 normal male subjects were compared after two weeks of placebo administration and two weeks of lithium carbonate administration (mean serum lithium level, 0.9 mEq/liter) on a series of tasks of intellectual function, aesthetic judgment, and semantic creativity. This was a placebo-controlled, split-half crossover, double-blind design. There were no significant changes on semantic creativity or aesthetic perception measures following lithium carbonate maintenance. There were lithium carbonate-related performance deficits on three of five performance tasks concerned with cognitive and/or motor functions. The deficit is probably due to a lithium carbonate-induced slowing of performance, consistent with our previous report of subjective effects in normal subjects. The implications of slowing on possible behavioral mediating mechanisms by which lithium carbonate exerts its clinical effects are discussed.**

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In a recent study reported elsewhere in this issue (p 346), we examined the effects of therapeutic maintenance doses of lithium carbonate on dimensions of affect, mood, and personality in normal male subjects. Among the effects of lithium carbonate reported by the subjects was a subjective sense that their capacity to concentrate and focus their thinking was impaired. We were also anecdotally impressed that the subjects receiving lithium carbonate appeared slower in response to interpersonal stimuli, were less interesting, and less apt at spontaneous problem solving. We were stimulated to determine whether these impressionistic observations could be demonstrated in a more formalized assessment of cognitive and intellectual functioning.

To date, previous research findings have been somewhat contradictory. Schou et al[1] reported a dose-dependent (ie, approximately 1,850 mg/day) lithium carbonate impairment of subjectively experienced capacity to concentrate, comprehend, and memorize. Linnoila et al[2] found significant slowing of reaction time in normal subjects after 14 days' maintenance at therapeutic serum lithium levels, but they reported no effect due to lithium carbonate on motor coordination. Demers and Heninger[3] elicited a lithium carbonate-related performance deficit in six manic-depressive patients on the Digit Symbol Subtest of the Weschler Adult Intelligence Scale (WAIS), but not on the Bender Gestalt test. Aminoff et al[4] also reported a significant deterioration in the IQ (mean decrease of 8.2) in nine mentally subnormal patients with Huntington chorea who were receiving lithium carbonate. However, Bech et al (unpublished data) report no significant changes due to lithium carbonate on several independent performance measures associated with simulated car driving.

This study focuses on the effects of lithium carbonate on more complex cerebral integrative functions such as capacity to abstract, problem solving, linguistic ability and creativity, general intellectual functioning, and aesthetic perception. We therefore sought to compile an experimental testing battery with a broad range of instruments and tasks, which could potentially assess the effect in normal subjects of lithium carbonate at therapeutic dose levels on more complex human functions.

SUBJECTS AND METHODS

Subjects

Twenty-four normal, paid, male volunteers were chosen and screened as reported elsewhere in this issue (p 346). The subject sample consisted primarily of college students who ranged in age from 21 to 31 years (mean, 24 years).

Protocol

The details of the procedure and research design have been reported elsewhere (p 346); therefore, only a brief summary will be presented here for the reader's orientation. A double-blind, randomized, split-half crossover procedure was used for lithium carbonate and inactive lithium carbonate placebo administration (14 days of each). Serum lithium levels were monitored with twice-weekly assays and adjusted by an independent physician blind to the experiment. Serum lithium levels on testing days ranged from 0.7 to 1.4 mEq/liter. There were three identical testing sessions: a baseline and two experimental sessions each at the end of a 14-day placebo and lithium carbonate maintenance period. The sessions began at approximately 1 PM and lasted three to four hours, with a midpoint break to minimize fatigue.

Test Instruments.—*The Otis Quick-Scoring Mental Ability Test.*—This is a standardized paper-and-pencil IQ instrument that correlates highly with lengthier adult IQ tests.[5] It involves a series of logical, linguistic, and mathematical tasks and is available in multiple equivalent forms for repeated trials.

The Meier Art Test: Aesthetic Perception and Art Judgment.—This test assesses ability to appreciate or judge qualitative levels of creativity in the visual aesthetic realm.[6] Given our previous

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Table 1.—Comparison of Cognitive and Motor Performance Tests Comparing Scores From Lithium Carbonate and Placebo Conditions*

Testing Instrument	Mean Score: Placebo	Mean Score: Lithium Carbonate	t	P (One-Tailed)
Otis IQ Test (IQ Score)	120.75	118.54	2.25	.018
WAIS† Block Design Test	14.38	14.42	−0.05	NS
WAIS† Digit Symbol Test	15.09	12.91	2.02	.028
Halstead-Reitan Trail Making A (time in seconds)	20.15	22.31	−1.82	.041
Halstead-Reitan Trail Making B (time in seconds)	49.04	52.28	−1.14	NS
Meier Aesthetic Perception Test	36.67	35.00	1.00	NS
Meier Art Judgment Test	48.42	48.21	0.16	NS

*N = 24; *df = 23*.
†Weschler Adult Intelligence Scale.

findings that lithium carbonate produced considerable mood shifts and promoted a sense of blunted perceptions, we wished to examine whether these alterations actually influenced the subjects' capacity for aesthetic perception. The test has been standardized and consistently discriminates among and ranks individuals with various levels of artistic abilities.

The Aesthetic Perception Test includes 50 reproductions of classic art. For each reproduction, four alternative versions are shown: the unchanged original and three subtly altered versions designed to be aesthetically less pleasing. The subject ranks the four versions in terms of aesthetic merit.

The Art Judgment Test is similar in concept, but involves 100 pictures, each with two versions. The subject is told how the two versions are different, eg, "treatment of foreground" or "arrangement of lighting and picture," and required to choose the better of the two.

For our purposes each subtest was split into two equivalent forms.

Selected tests From the Wechsler Adult Intelligence Scales.—The subtests selected measure visual-spacial and nonlinguistic aspects of intelligence and problem solving[7]: the Digit Symbol Test and the Block Design.

Trail Making Tests A and B.—These neuropsychological tests from the Halstead-Reitan Battery are simple pencil-and-paper tests in which the subject connects as quickly as possible a sequence of numbers, or numbers and letters, arranged out of order on a page.[8] The amount of time in seconds needed to complete the task is the performance score used.

The Guilford-Christensen Fluency Tests.—These tests utilize linguistic materials to assess semantic fluency as a measure of creativity.[9] There are very few psychometric tests of creativity; even though this battery relies exclusively on verbal performance, it has undergone some attempt at standardization. At the very least, we hoped that these tests would potentially assess levels of cognitive response capacity to new demands and problem situations.

There are four timed pencil-and-paper subtests: Word Fluency, Ideational Fluency, Associational Fluency, and Expressional Fluency. The number of correct responses given in the allotted time is scored. Matched versions helped avoid learning effects.

Following completion of the study, the code for the lithium carbonate-placebo condition was broken and the data analyzed by matched or correlated *t* tests. One-tailed levels of significance were used when research findings previously described in the literature indicated a confirmed lithium carbonate effect on performance measures.[1-4] Statistical interactions significant at the .05 level or greater are reported.

RESULTS

Initially, the data were analyzed for differences between the initial drug-free baseline testing session and the placebo condition session. There were no significant differences, indicating no placebo effect. Therefore, only data comparing the lithium carbonate and the placebo sessions are reported.

Table 2.—Scores From the Fluency Battery Comparing the Lithium Carbonate and Placebo Conditions*

Testing Instrument	Mean Score: Placebo	Mean Score: Lithium Carbonate	t	P (One-Tailed)
Christensen-Guilford Word Fluency	20.57	19.86	−0.55	NS
Christensen-Guilford Ideational Fluency	25.93	23.98	0.89	NS
Christensen-Guilford Expressional Fluency	4.64	3.88	1.49	NS
Christensen-Guilford Associational Fluency	15.43	14.43	0.72	NS

*N = 14; *df = 13*.

Next, order and learning effects were assessed since this was a repeated measures design. Significant learning effects were discovered on the Digit Symbol and Block Design (WAIS subtests), and Trails A and B (Halstead-Reitan Battery). Learning-correction factors were calculated for each of these by holding lithium carbonate and placebo conditions constant while calculating the learning effect change score. This learning effect correction factor was then applied to the performance scores. These corrected performance scores were then used in comparing results from the placebo and the lithium carbonate conditions.

The data in Table 1 compare the scores achieved on the psychometric tests and tasks from both the placebo and lithium carbonate testing sessions. Three of the seven possible aggregate performance scores derived from these tasks reflect effects from the 14 days of lithium carbonate maintenance. In each case, where a statistically significant interaction is present, a performance deficit occurred during the lithium carbonate condition. There was a slight reduction, approximately two points, in overall IQ score while on lithium carbonate therapy ($P = .018$). The WAIS Digit Symbol performance also declined while on lithium carbonate therapy ($P = .028$). In the less complex of the two Trail Making Tests (Trail A) there was also a deficit, in which the subjects took longer to complete this test during lithium carbonate maintenance ($P = .041$).

Unfortunately, complete data from the Christensen-Guilford Fluency Tests were obtained from only 14 of the 24 subjects. While this is sufficient for statistical purposes, it should be noted, and the data are reported separately in Table 2. Lithium carbonate did not influence the performance of these subjects on this aspect of the testing battery.

COMMENT

We have previously discussed in detail the methodological problems of the research design, such as bias from a paid "normal" subject sample and the absence of an active placebo (p 346). The issue, specific to this study, is the selection of the testing instruments utilized. They represent a stylistic choice; obviously, other instruments could have been selected. In the area of verbal creativity and

aesthetic judgment, there is a distinct paucity of psychometric instruments available, and we therefore selected the best and in one case the only instrument available. We were interested in obtaining a broad range of performance data that could be done fairly quickly and were varied enough to sustain interest during the three hour testing period. Thus, we believe that the testing battery assembled is representative and has demonstrated promise in assessing aspects of more complex mental functioning that might be altered by various psychoactive drugs.

The 14 subjects on whom we have complete data performed equally well on all of the Christensen-Guilford tasks whether they were receiving lithium carbonate or placebo. While semantic fluency is only one aspect of the creative process, lithium carbonate did not influence our subjects' performance on these tasks. In addition, the drug did not influence their abilities of aesthetic perception and judgment, which implies that lithium carbonate is not likely to influence one's capacity for aesthetic appreciation. Although the subjects may have felt that aspects of their perceptions of their environment may have been blunted, their performance on these specific tasks was unaffected. This may be particularly significant, since there has been considerable discussion about the interactional interface between "mania" and "creativity" and the role of psychotropic drugs in influencing each of these processes. To the opinions that have already been expressed, we would add our own impressions, based on data from these two relatively narrow inventories, to state that it does not appear that lithium carbonate, in and of itself, influences verbal creativity or the capacity to judge artistic efforts in normal subjects.

In three of the performance tests the subjects (N = 23) demonstrated a small but definite decrement in performance levels while receiving lithium carbonate. During the lithium carbonate condition, performance was impaired by a factor of approximately 10% on both the Digit Symbol and the Trails A, and IQ was affected by approximately a two-point decrease. It is noteworthy that our data on these tests involving a normal subject sample are consistent with two prior studies that utilized different subject samples. Specifically, we demonstrated a lithium carbonate-related performance deficit on the Digit Symbol test similar to that of Demers and Heninger[3] and a small but consistent IQ deficit similar to that reported by Aminoff et al.[4] In addition, we found a performance deficit in the Trail Making A test, the less complex of the two Trails tests, which is more likely to be indicative of a slowdown of motor speed rather than cognitive performance. In another report (p 346) we did indicate that lithium carbonate delayed normal subjects' reaction time on the Holtzman Inkblot Technique by 4.65 seconds ($P = .048$). While alone this was seen to be of little significance concerning personality, in light of the indication of lithium carbonate-induced slowing of performance, it may be a further confirmation of slowing derived from a timed "nonperformance" test.

These findings are consistent with those of Linnoila et al,[2] who reported a slowing in the reaction time of normal subjects after 14 days' maintenance on lithium carbonate. These results are not consistent with the findings of Bech et al (unpublished data), but there does appear to be a thread of commonality across three different studies, ours (p 346) and two others.[1,3] Each used different experimental populations and different experimental conditions, and each has implicated some type of motor or cognitive slowing secondary to lithium.

In this issue (p 346) and previously,[10] we reported that normal subjects receiving lithium carbonate subjectively felt their levels of cognitive and motor performance were impaired. This was not apparent to independent trained raters, but it was discernible to other raters who were well acquainted with the subjects. This impairment is now confirmed in the present study by objective performance data, in which some performance levels were subtly but definitely altered while the subjects were receiving lithium carbonate.

It appears to us that those tests where performance was adversely altered by lithium carbonate were those in which the time component was a particularly crucial scoring variable. Thus, in looking at the data, we believe that there is some indication that the performance deficit may be due more to a lithium carbonate-induced slowing than to a performance disruption resulting in reduced levels of accuracy. While the evidence is not conclusive, both our data and those of others tend to suggest it.

It is our feeling that the locus of lithium carbonate's effect in impairing performance is an important issue. Is it due to simple motor slowing, or is it an effect that has more to do with a slowing in thinking or information processing? If the latter were true, it would reveal something hitherto unnoticed about the overall effects of lithium carbonate, in addition to its known influence in stabilizing mood. If lithium carbonate does influence cerebral processing, this may be a crucial aspect of an underlying behavioral mechanism by which desirable clinical changes in lithium carbonate-responsive patients occur.

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Nonproprietary Name and Trademarks of Drug

Lithium carbonate—*Eskalith, Lithane, Lithotabs, PFI-Lithium.*

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