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Brief Report

The Effect of Lithium Carbonate on the Circadian Rhythm of Sleep in Normal Human Subjects

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INTRODUCTION

One characteristic of patients with bipolar depression may be a desynchronization of circadian rhythms (Tupin, 1970; Moody and Allsop, 1969). These patients may manifest rapid free-running circadian rhythms (Pflug *et al.*, 1976; Kripke *et al.*, 1978). Kripke *et al.* (1978) suggested that a therapeutic effect of lithium could be to slow the circadian oscillators in such patients. Lithium slows circadian rhythms in rodents, cockroaches, and Kalanchoe, a plant possessing a prominent circadian rhythm (Engelmann, 1973; Engelmann *et al.*, 1976; Hofmann *et al.*, 1978).

Factors such as light intensity, which slow circadian rhythms in free-running models, generally delay circadian rhythm phase in the presence of external synchronizers (Aschoff, 1965; 1969). These factors cause the peak and trough of the rhythm to occur later relative to the external synchronizer (e.g., light and dark). This effect was described by Engelmann *et al.* (1976) with lithium. Since pharmacologic studies of humans in isolation are difficult, we studied lithium's effect on the circadian rhythm of sleep in a normal social environment to see if lithium delays circadian rhythms.

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METHODS

As part of a larger investigation of the effects of lithium carbonate on healthy, normal subjects, sleep reports were gathered from 22 paid volunteers (mean age 24), screened and selected as previously reported (Judd *et al.*, 1977). A double-blind, randomized, split-half cross-over procedure was used. Subjects were maintained for 14 days each on lithium carbonate and on inactive placebo. Lithium dosages were adjusted to achieve a mean serum level of 0.89 meq/liter (range 0.7 to 1.3 meq/liter). Sham dosage adjustment procedures were used during placebo administration. Nine subjects in the lithium-first and 13 in the placebo-first groups completed the study. Sleep logs dividing each 24-hr period into 15-min intervals were filled out daily by subjects to record the precise intervals when they had slept. The Stanford Sleepiness Scale (Hoddes *et al.*, 1973) was used to establish subjects' alertness upon awakening. Two subjects were dropped from the analysis because of incomplete data.

Data were analyzed by two statistical methods. First, the median points of nocturnal sleep were calculated for each of the last 7 nights during the lithium and placebo conditions. These median points were averaged for each subject to obtain separate mean midsleep points for lithium and for placebo administration. Second, best-fitting 24-hr cosine curves were computed from the sleep log data for the last 7 days of lithium and for placebo, using the least-squares method. The peak of the fitted curve (the acrophase) was selected as an estimate of the peak of the sleep-wake 24-hr rhythm. Both methods agreed closely. Daytime naps influenced the cosine fits but were ignored in computing nocturnal sleep medians, and the methods weighted nocturnal awakenings differently. Using a least-squares procedure, equations of the best-fitting lines connecting the midsleep points were obtained in order to evaluate the slopes and determine any trends. Finally, both awakening and sleep-onset times were examined for the last 7 days of the two maintenance periods using paired t tests.

RESULTS

There were no order effects for lithium and placebo administration. On lithium maintenance, subjects' median point of sleep was 14.2 min later than the median point on placebo (paired t test, $t = 2.38$; df = 19; $p = 0.027$, 2-tail). Similarly, the 24-hr acrophases were 3.64° later during lithium than placebo administration (paired t test, $t = 2.37$; df = 19; $p = 0.029$, 2-tail), where 3.64° corresponded to approximately 14.6 min. Closely identical significance values were obtained using the nonparametric Wilcoxon Signed Rank test. Since all midsleep points and acrophases were grouped in the early morning hours, a linear model was justified, and the hypothetically circular distribution of these data could be ignored. Nine subjects reported daytime naps which averaged a

total of 19 min a day. Nap duration was not significantly different during the lithium and placebo conditions. Analysis of variance of the midsleep points revealed no significant interactions between the sequential days in each condition and the drug-condition factors, although an overall lithium effect and an overall sequence effect were found. Both sleep onsets and awakenings were later in the lithium condition than with placebo, but these contrasts were not significant, nor were the progressive trends in sleep time different for lithium and placebo.

No differences between lithium and placebo were found in amplitudes of fitted 24-hr cosines (a measure reflecting both napping and midsleep awakenings); in mesors of the cosines (a measure of total 24-hr sleep duration); or in sleepiness scores upon morning awakening.

DISCUSSION

In contrast with the placebo condition, lithium appeared to cause small, but significant delays (14.2 min or 3.64°) in the sleep-wake circadian rhythm of these subjects, and the sleep-wake phase delay appeared related to lithium's effect upon endogenous biological oscillators, since neither quality nor quantity of sleep and napping were affected. Since these data were derived from self-reported questionnaires rather than from empirical observations, the results were subject to inadvertant errors of recall, and studies with objective recording are needed. However, our preliminary data are fully consistent with the prospective hypotheses.

Even though the phase shifts which we have observed are small, there have been studies indicating that shifts of this magnitude have profound effects. Elliott (1976) found that a change in the 24-hr light-dark cycle of only 36 min was sufficient to initiate gonadal development and testosterone output in golden hamsters.

The effects in human subjects of phase shifts of this nature are not fully known, particularly if such shifts are maintained over a long term as in therapeutic lithium treatment regimens. This is to our knowledge the first report of lithium's potential effect upon circadian rhythms in a sample of normal human subjects, and results are promising enough to warrant further investigation using a more traditional methodology for the study of biological rhythms in man.

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