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TRIAL OF LITHIUM CARBONATE IN THE PREMENSTRUAL TENSION SYNDROME

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INTRODUCTION

Good results with the use of Lithium salts in the premenstrual tension syndrome have been reported (Sletten and Gershon, 1966; Rossman 1969). These observations however await confirmation. The value of Lithium is suggested by its known capacity to affect water and electrolyte balance which are implicated in the pathophysiology of the syndrome, and its efficacy in psychiatric disorders characterised by periodicity. (Gjessing, 1967; Schou, 1968, Forssman and Walinder, 1969; Hanna *et al.*, 1972). We therefore undertook a controlled study on the efficacy of lithium in the syndrome.

Methods

The study compared lithium with placebo, was double-blind with multiple random cross-over, and involved 19 Chinese out-patients. It lasted up to 8 menstrual cycles for each patient. The first cycle involved open lithium for dosage adjustment; thereafter the allocation to either lithium or placebo for a cycle was randomized so that a patient did not necessarily have equal numbers of lithium and placebo periods. Lithium was dispensed in capsules of 250 mg (6.8 mEq) of the carbonate salt. Dosage was flexible, ranging from 750–1000 mg daily and aiming at maintaining serum concentration at 0.8 – 1.3 mEq/1. Lithium estimation by flame photometry was carried out at least once a month when patients were interviewed. Dosage was regulated by the interviewing psychiatrist on the basis of serum lithium values reported to her from the laboratory, true values for the lithium periods and fictitious values within the same range for the placebo periods.

Patients were selected on the basis of symptoms being temporarily related to the menstrual period – marked emotional tension (irritability, anxiety, depression) and various somatic features, as originally described by Frank (1931). They had also to promise not to become pregnant during the trial.

They were not permitted to take diuretics or hormones, excepting oral contraceptives; other psychiatric medication including antidepressants (8 patients) and tranquillizers (18 patients) was maintained at fixed levels throughout. Excluded from the study were patients with brain damage, active somatic disease, alcoholism, character disorders, as well as those in whom lithium therapy was for one reason or another contraindicated. The majority (17) of the subjects had, at onset of trial, moderate to severe symptoms of premenstrual tension which had either not responded to medication or whose slight response had stabilised for long periods. Their ages ranged from 20 to 44 years (mean 32.3)

Concomitant psychiatric conditions were diagnosed in accordance with the U.K. Glossary of

Mental Disorders, 1968, as follows: Affective psychoses – depressed type, 2 cases, manic type 1; Neuroses – anxiety 2, depressive 1, hysterical 1. 5 were remitted schizophrenics. 7 patients had no psychiatric conditions apart from the premenstrual tension. The study was begun in November 1971 and completed in August 1972.

Results

There were 5 dropouts, one due to pregnancy and 4 to exacerbations of symptoms or side-effects requiring review of management; their assessments before the dropout were retained. 105 cycles were completed; the assessments of 15 of these were excluded because they were associated with serum lithium levels below 0.6 mEq/1 and those of another 11 because lithium was present in serum whilst the patients were supposedly on placebo. Of the remaining 79 cycles subjected to final assessment, 33 were treated with lithium and 46 placebo. Patients were rated on a Global Clinical Scale (GCS), which scored illness from 0 = asymptomatic to 3 = severely ill; a Target Symptoms Scale (TSS), which rated 9 symptom parameters from 0 = absent to 3 = severe; and a Self-Rating Scale (SRS) which scored overall condition from 0 = asymptomatic to 3 = severe. Initial scores obtained just before the trial were compared with post-cycle scores at the end of each cycle, the differences between these were the score changes, which when positive signified improvement.

GCS. The mean initial score was 2.26. The mean score changes were: with lithium, 1.35, with placebo 1.24 ($t = 0.673$, $P > .05$).

TSS. The mean initial score was 7.58. The mean score changes were: with lithium, 5.59, with placebo 5.13 ($t = 0.871$, $P > .05$).

The scores of the items were, given in the order of mean initial score, and mean lithium score change *vs* mean placebo score change, as follows: irritability – 1.68, 1.91 *vs* 1.80; depression – 1.42, 1.12 *vs* 1.28; headache – 1.16, 0.85 *vs* 0.61; abdominal distension – 1.00, 0.73 *vs* 0.78; anxiety – 0.74, 0.67 *vs* 0.54. dysmenorrhoea – 0.58, 0.15 *vs* 0.11; breast pain – 0.21, 0.30 *vs* 0.26 swelling of ankles – 0.11, 0.09 *vs* 0.09; swelling of face, 0.0, 0.03 *vs* 0,0. Significant differences at the .05 level or greater were not obtained on any of the items of the TSS.

SRS. The mean initial score was 2.26. The mean score change with lithium was 1.44 and with placebo 1.22 ($t = 0.995$, $P > .05$).

Overall, patients made good improvement with lithium and with placebo; they did slightly better with lithium but the differences were not significant.

The main adverse reactions noted in a minority of cases, were tremor, weakness of limbs, nausea, vomitting and abdominal discomfort. One patient became acutely confused. The pregnant patient who dropped out of the trial had a full-term delivery of a normal male infant.

DISCUSSION

Our experiences with lithium treatment of the premenstrual tension syndrome would appear to differ from those of Sletten and Gershon. One possible reason is the way in which lithium was administered. Sletten and Gershon gave a fixed dosage of 27 milliequivalents per day for ten days before menstruation. We adjusted dosages (range 20–27 milliequivalents per day) according to the serum lithium concentration and gave treatment throughout the month. It does not seem likely that these small differences could lead to so dissimilar results. A second possible reason is that the patient groups, although fulfilling the same diagnostic criteria, in fact differed in composition. The premenstrual tension syndrome may encompass a variety of clinical entities.

The difference in results between the study of Sletten and Gershon and our study is, in fact, more apparent than real. In both studies, good improvement was obtained with lithium. However in our study we also used placebo, with which we also obtained good improvement. Everyone who has studied the premenstrual tension syndrome will testify how easily this condition is influenced, at least temporarily, by new treatments and other psychological factors. We therefore considered it essential to record not only how much patients improved on lithium but also how much they improved on placebo. Our results therefore indicate that the major part of the improvement noted during lithium treatment was due to the psychological effects of the treatment and that the small fraction by which the lithium scores were better than the placebo scores may have been due to random variation.