

Beta blockade in lithium tremor

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SYNOPSIS Practolol, propranolol, and placebo have been tested on an objective test of lithium induced tremor. Both beta-blocking agents produced significantly more tremor than the placebo. It is argued that lithium induced tremor is closer to essential than to physiological tremor.

Lithium salts, although widely accepted as a prophylactic in recurrent affective disorders (Baastrup *et al.*, 1970; Coppen *et al.*, 1971), are estimated to produce a tremor in 80% of patients (Varaflor *et al.*, 1970), and in a few patients it is sufficiently severe to require termination of treatment (Fries, 1969). Propranolol has been reported to be effective in reducing physiological tremor (Marsden *et al.*, 1968, 1969), and more recently there have been reports of a beneficial effect in essential tremor (Pakkenberg, 1972) and lithium tremor (Floru, 1971; Kirk *et al.*, 1973). The object of this investigation is to study further the reported benefits of a beta blocking agent on the tremor induced by lithium. Two compounds were studied: (1) propranolol which enters the central nervous system, and (2) practolol, a beta blocking agent which largely fails to penetrate the blood brain barrier and the actions of which are, therefore, peripheral.

METHOD

The subjects were all patients attending West Park Hospital Lithium Clinic, who had been maintained on lithium carbonate for at least three months as prophylaxis against further affective illness. Of 60 patients screened, 15 were found to have noticeable tremor and entered the trial. Each of the three treatments (40 mg propranolol, 120 mg practolol, and placebo) was given in random order at the same time on three consecutive days. Ninety minutes later the patients completed a test for tremor. This consisted of drawing a line with a ballpoint pen between printed lines at varying distances apart and contour

(see Figure). A score was obtained of the number of times the ballpoint line crossed the printed line (with an extra point for every 5 mm it remained outside these lines). The score was obtained by an assessor unaware of the drug which was taken.

RESULTS

The results are shown in the Table. It can be seen that practolol did not differ from propranolol, but patients receiving either compound recorded a significantly greater tremor score than when taking placebo. This indicates that both beta blocking agents were less effective than the placebo at reducing the tremor.

TABLE
INTENTION TREMOR INDEX

Patient no.	A Propranolol	B Practolol	C Placebo
1	43	49	17
2	15	12	9
3	19	3	10
4	7	9	5
5	14	10	15
6	22	21	18
7	3	8	2
8	22	5	4
9	15	28	7
10	8	6	0
11	2	0	1
12	14	14	22
13	5	7	3
14	16	29	10
15	1	3	2

A v. C $t=2.558$, $P<0.05$ (Less tremor with placebo)
B v. C $t=1.866$, $P<0.1$ (Less tremor with placebo)
A v. B $t=0.061$, P n.s.
Friedman two way analysis of variance $\chi^2=6.44$, $P<0.05$.

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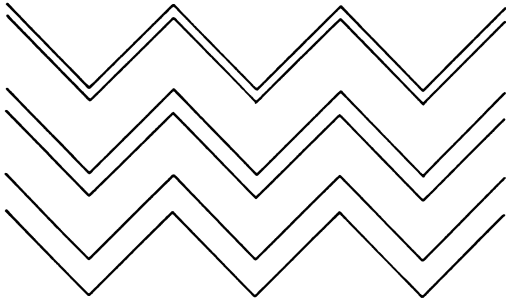
INTENTION TREMOR INDEX


NAME : DATE: TIME : TABLET :


1. _____

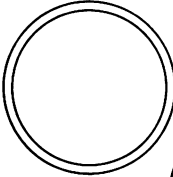
2. _____

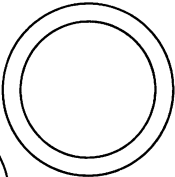
3. _____

1.  _____

2.  _____

3.  _____

1.  _____

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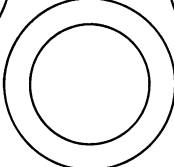
3.  _____

FIGURE Test for tremor.

DISCUSSION

Before concluding that beta blocking agents do not reduce lithium tremor, one must consider the validity of the test used. Lithium tremor is noted to affect handwriting (Fahn, 1972), and a similar measure has been used in the past by Floru (1971). Furthermore, scores on the tests seem to reflect the severity of the tremor observed clinically. The result could not have been explained by a practice effect, since the order of presentation of the drugs was random.

Kirk *et al.* (1973) reported the only other placebo controlled study of lithium tremor in which patient preferences consisted of 13 out of

20 for propranolol, with no preferences for the placebo. It is possible, however, that the patient preference was related to the anxiolytic effect of the propranolol and not its effect on the tremor. Floru (1971) has described an improvement in lithium tremor in eight out of 15 patients on propranolol, but does not record the effects of the drug in the other seven and does not exclude a placebo effect.

Authors differ in the degree to which they distinguish essential from physiological tremor. Marshall (1962) and Marshall and Schneiden (1966) have pointed out that both tremors are exacerbated by adrenaline and have a similar frequency. Others, such as Fahn (1972) consider that the distinction is useful in that essential tremor is intensified by the terminal stage of movement, is often familial, and is more sensitive to the effects of alcohol. While beta blocking agents seem to be effective in relieving physiological tremor, their use in essential tremor is less firmly based. The majority of studies (Gilligan *et al.*, 1972; Murray, 1972; Dupont *et al.*, 1973; Sevt, 1974; Winkler and Young, 1974) show that propranolol is more effective than placebo, though others (Scopa *et al.*, personal communication, 1972; Balla, 1973) do not confirm this. Most investigators can find no improvement in the first 24 hours after starting propranolol, which suggests that the drug is acting at a different site from that concerned with physiological tremor.

A possible explanation for our result could, therefore, be that lithium tremor is closer to essential tremor in type and would not respond to a single dose of a beta blocking agent. The lack of any significant difference between propranolol, which crosses the blood-brain barrier, and practolol, which does not, refutes the possibility that the delay in action is the result of this barrier. While this delay might account for the failure of a single dose of a beta blocking agent to improve lithium tremor, it is difficult to understand how they could have made it worse. Certainly, practolol has intrinsic sympathomimetic activity, but propranolol, without this activity, gave the worse results of the two. The completion of the test in their own home may have diminished the drive to succeed that an observer would have produced, and the anxiolytic effects of the beta blocking agents may have reduced this drive still further to cause a poorer

performance. It is possible that tests of tremor carried out in the more stressful conditions of a laboratory would produce a tremor caused by the anxiety itself. This tremor, being physiological, would improve with a beta blocking agent and thus give a spuriously positive result with lithium tremor. Whatever the explanation, the results support the distinction between physiological and lithium induced tremor, and indicate that lithium tremor is not mediated by an adrenergic mechanism. This suggests that beta blockers are not useful in the management of lithium induced tremor.

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