A Clinical Trial of Methysergide and Lithium in Mania* **

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Summary. Six manic patients were studied in an open sequential drug trial of placebo and the serotonin antagonist methysergide; lithium was then substituted double-blind. No dramatic change occurred in individual manic item scores or in mean daily mania ratings after 48 hours or seven days of methysergide, although several of the patients showed slight trends toward improvement. However, after a mean duration of 10.3 days of lithium treatment, all manic item scores improved dramatically and significantly, so that complete clinical remission was evident in all patients. In view of the discrepancy between these essentially negative findings and several recent positive reports on the efficacy of methysergide in the treatment of mania, the authors feel that the indolealkylamine hypothesis of affective disorders should be further investigated.

Key-Words: Psychopharmacology — Methysergide — Mania — Lithium.

Several recent reports (Verster, 1963; Dewhurst, 1968; Haškovec and Souček, 1968) have claimed close to a 100% effectiveness within 48 hours when methysergide (1-methyl-D-lysergic-acid butanolamide) was used to treat mania. There is experimental evidence in animals to support the hypothesis that an antiserotonin substance might be effective in clinical mania (Dewhurst and Marley, 1965a and b). A number of biologically active amines, including dextroamphetamine and tryptamine, are known to produce behavioral-alerting effects, which are then reversed by serotonin antagonists such as methysergide. Due to the current theoretical interest in the indolealkylamine hypothesis of

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affective disorders and the need for anti-manic substance with a faster onset than lithium, we undertook the following study.

Methods

Acute mania was diagnosed by the previous criteria used for manic-depressive studies on our Metabolic Research Unit (Fieve et al., 1968). Of critical importance was a current of elation, hyperactivity, decreased total sleep without fatigue upon awakening, and pressure of speech. All patients included in this study had had at least one affective attack during each of the past two years with relatively normal interval functioning.

Four women and two men were studied on the Metabolic Research Service\(^1\). The average age of the six subjects was 51 years; the average duration of the manic attack before admission was one month. Before admission one patient had failed on lithium, one on placebo, and one on imipramine. The three others were newly diagnosed patients on no previous medication.

After admission to the research unit, all six subjects were given placebo for at least nine days, and thereafter were placed openly on methysergide for seven days before being switched to double-blind lithium carbonate. Blindness was established by one physician (not a rater) regulating the dosages of methysergide, placebo, and lithium, all administered in pink capsules. Raters were research nurses trained in the use of the Spitzer et al. (1967) Psychiatric Evaluation Form and Supplement, who knew a methysergide study was taking place but did not know of the double-blind switch to lithium. The dosage of methysergide throughout the trial was eight milligrams per day (although a single patient received 12 mg per day without change in her manic scores). Lithium carbonate was administered in 300 mg pink capsules three to five times a day to achieve a blood level range of 0.8 to 1.2 mEq/l (mean, 1.13 mEq/l).

Independent staff ratings of patient behavior were obtained utilizing the Psychiatric Evaluation Form (PEF) and Supplement for Affective Disorders on the placebo day seven days prior to the introduction of methysergide, on days one, three and seven of the methysergide trial, and on mean lithium day 10.3 (range, 8—14 days). Two to four specially-trained staff members rated each patient on 30 dimensions of psychopathology, ranging in intensity as follows: 1 = none, 2 = minimum, 3 = mild, 4 = moderate, 5 = severe, 6 = extreme; these ratings have been found to be of high reliability. The six scales descriptive of manic behavior are reported here.

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\(^{1}\) Two additional men were studied in less detail on an acute drug evaluation service.
Results

The first two columns of both Table 1 and 2 show a trend of increasing severity of manic behavior in all patients while on placebo from the seventh day prior to methysergide administration until the first day of treatment with this drug. Forty-eight hours after methysergide was substituted for placebo, a small downward trend of behavioral disturbance was recorded. However, this trend reversed itself by the seventh day on methysergide in four of the six categories (Table 1). If mean scores across the six mania scales for individual patients are examined (Table 2), two patients are seen not to have changed after either 48 hours or seven days on methysergide, while the other four patients are seen to have improved only to the extent of a mean drop of one point.

Table 1
Mean behavioral item scores for six patients on placebo-methysergide-lithium sequence

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Methysergide</th>
<th>Lithium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 1</td>
<td>48 hours</td>
</tr>
<tr>
<td>PEF Scale*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elation</td>
<td>3.0</td>
<td>3.7</td>
<td>3.2</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>2.8</td>
<td>3.7</td>
<td>3.1</td>
</tr>
<tr>
<td>Hypersexuality</td>
<td>2.0</td>
<td>2.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Sleep</td>
<td>4.4</td>
<td>4.8</td>
<td>3.5</td>
</tr>
<tr>
<td>Inappropriate behavior</td>
<td>3.8</td>
<td>3.8</td>
<td>3.0</td>
</tr>
<tr>
<td>Severity</td>
<td>4.2</td>
<td>4.7</td>
<td>4.2</td>
</tr>
</tbody>
</table>

* Graded 1--6 (none to extreme).

Table 2. Mean daily manic behavioral item scores for six patients on placebo-methysergide-lithium sequence

<table>
<thead>
<tr>
<th>Patient</th>
<th>Placebo</th>
<th>Methysergide</th>
<th>Lithium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 1</td>
<td>48 hours</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>4.0</td>
<td>3.7</td>
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<tr>
<td>3</td>
<td>2.7</td>
<td>2.8</td>
<td>2.0</td>
</tr>
<tr>
<td>4</td>
<td>2.7</td>
<td>3.2</td>
<td>3.1</td>
</tr>
<tr>
<td>5</td>
<td>4.8</td>
<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td>6</td>
<td>4.2</td>
<td>4.5</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Upon being transferred to double-blind lithium all patients showed dramatic improvement in manic behavior ratings, which were determined after a mean of 10.3 days (range, 5--14 days) on this drug. In the two male patients on the acute drug service (not included in these data), manic behavior was so severe that both chlorpromazine and seclusion
had to be added to methysergide throughout the seven-day period. Even then, these two patients showed no clinically significant improvement, and only after lithium was substituted for methysergide did they respond.

Discussion

The use of an anti-serotonin substance to treat successfully four cases of acute mania intrathecally was first described by Verster in 1963. Dewhurst (1968) subsequently reported on a dramatically positive clinical trial of methysergide in mania. This open study was prompted by several of his own theoretical considerations, which suggested that the metabolism of indoles, particularly serotonin (5-HT), is disturbed in affective disorders.

Haškovee and Souček (1968), influenced by Dewhurst, studied 10 inpatients with mania, and after a placebo period of two to six days, methysergide was given openly for eight to 14 days (maximum dosage 6 mg per day), and then placebo was reinstated. After 48 hours of methysergide, administered intramuscularly, a marked improvement in manic behavioral scores was evident in eight patients; one patient’s scores remained unchanged, and there was a worsening of manic behavior in the remaining patient. Reinstition of placebo revealed no change in manic scores in one patient and a rapid relapse in five. Two other patients had refused to cooperate, and the remaining two cases had already failed on methysergide during the first 14 days.

Contrary to our expectation from these three studies, none of the eight patients in our own study showed the dramatic results that Dewhurst states “should be quite evident within 48 hours”. The trend noted towards improvement at 48 hours is not significantly greater than trends we have observed in psychiatric patients after the introduction of any physiologically active substance.

We are unable to explain the discrepancy between the results of our work and those of the other authors cited. The strikingly positive results in each of the three studies, and the lack of such immediate and dramatic effects in our own, question the validity of the conclusions drawn from the previous investigations. However, one must consider that methysergide is approved in the United States only when given orally, in contradistinction to other countries where the drug may be administered intrathecally or intramuscularly. Intramuscular methysergide, as used by Haškovee and Souček, might reach the blood stream and central nervous system more rapidly and effectively than that administered orally. In Haškovee’s study, and in our own, a placebo period preceded administration of methysergide. In both studies patients were rated on a six to seven point behavioral rating scale, and from the data it appears
that the two groups began the trial with comparable manic severity. All four trials were subject to the usual problems associated with open studies, i.e., individual bias and a number of other variables. Only in phase three of our study, when lithium was substituted for methysergide, were the raters blind.

In the Haškovec and Souček series, patients had been manic for a mean of 7.4 weeks before entering the study, and many had been treated with other drugs. The longer the manic period before the trial, the greater the chances for a spontaneous remission of the psychosis. In our study no regular side effects of either methysergide or lithium were evident during the trial. Lithium treatment resulted in a statistically significant decrease in all behavioral ratings by the end of the mean of 10.3 days, and a complete clinical remission in these six patients.

In this brief report, results are presented of an open and empirical trial of methysergide$^2$ in mania; several investigators have recently claimed that this drug has dramatic potential physiologically to alter mood. Positive results in our trial would have been a contribution to one of the biochemical theories of affective disorders. However, in view of our essentially negative findings, we feel that the indolealkylamine hypothesis of affective disorders should be subjected to further study.

References


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$^2$ Methysergide maleate (Sansert) was supplied by Sandoz.